DEVELOPMENT OF VERSATILE STRATEGIES FOR ARYNE ANNULATION

APPLICATIONS IN METHODOLOGY AND NATURAL PRODUCT TOTAL SYNTHESIS

VOLUME II

Thesis by

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CHAPTER 5

Expedient Synthesis of 3-Hydroxyisoquinolines and 2-Hydroxy-1,4-Naphthoquinones via One-Pot Aryne Acyl-Alkylation / Condensation

5.1 INTRODUCTION AND BACKGROUND

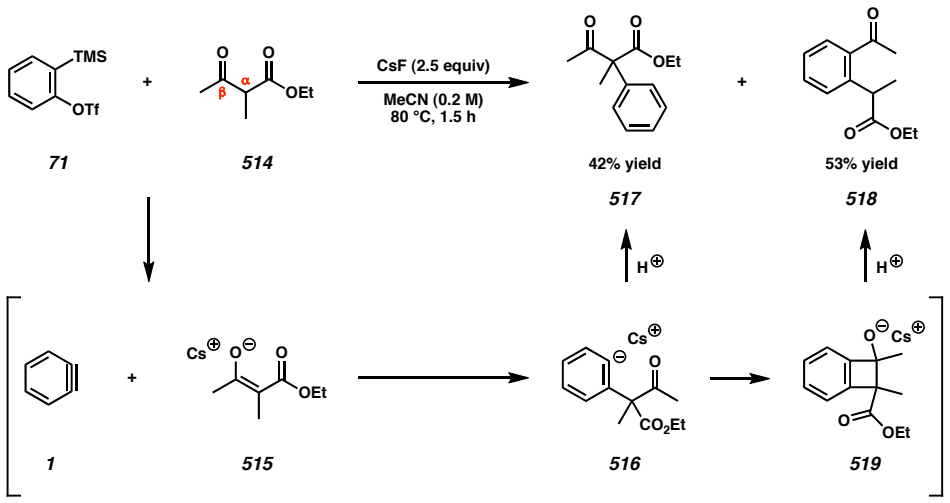
5.1.1 The Direct Acyl-Alkylation of Arynes[†,1,2,3]

Our research group first took an interest in the unique reactivity of benzyne in an attempt to employ this species as an electrophilic arylating agent for the synthesis of α-quaternary β-ketoesters (**517**) (Scheme 5.1). Using a combination of the *ortho*-silyl aryl triflate (**71**) previously developed by Kobayashi[4] and an α-monosubstituted β-ketoester such as ethyl 2-methylacetoacetate (**514**), it was envisioned that treatment with caesium fluoride would accomplish both a fluoride-induced net elimination of TMSOTf from **71** to generate benzyne (**1**) and a deprotonation of the β-ketoester to generate a nucleophilic enolate species (**515**). Attack upon the electrophilic aryne and subsequent protonation of the resulting aryl anion (**516**) would then furnish the desired α-arylated β-ketoester (**517**).

[†] The discovery and development of the aryne acyl-alkylation reaction is the work of a former graduate student in the Stoltz research group, Dr. Uttam K. Tambar.

When this concept was put into practice, however, an interesting *ortho*-disubstituted arene (**518**) was isolated in addition to the expected product. Remarkably, this new product constituted a formal insertion of benzyne into the α,β C–C bond of the β-ketoester. Formation of the acyl-alkylated arene (**518**) presumably results through a divergence from the anticipated path of reactivity. If, instead of undergoing protonation, aryl anion **516** undergoes nucleophilic addition to the proximal ketone, a benzocyclobutenoxide intermediate (**519**) would be formed. This species would then be capable of decomposing to the acyl-alkylated arene (**518**) through fragmentation of the strained four-membered ring and subsequent protonation.

Scheme 5.1. Discovery of the aryne acyl-alkylation reaction



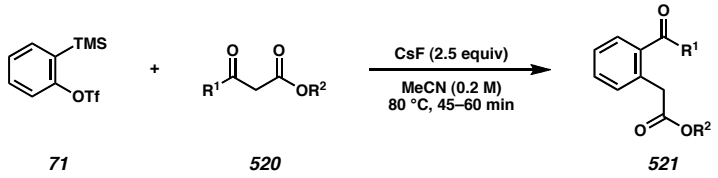
Formal aryne insertions into metal–metal,[5] heteroatom–metal,[6,7] heteroatom–heteroatom,[8–13] carbon–metal,[14] and carbon–heteroatom[15,16] σ-bonds have been reported previously. However, the results of the experiment depicted above are especially intriguing in that they represent the insertion of an aryne into a carbon–carbon

σ-bond under mild conditions without prior formation of an anionic nucleophile.[17–19] Inspired by this realization, our group initiated a more in-depth examination of the scope of the aryne acyl-alkylation reaction.

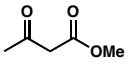
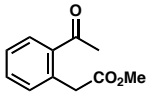
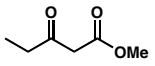
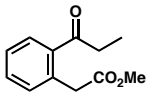
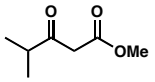
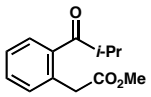
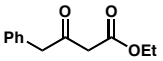
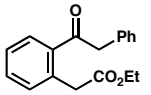
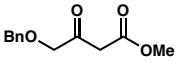
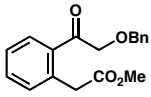
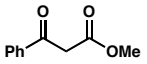
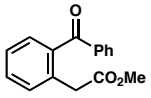
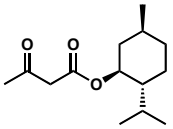
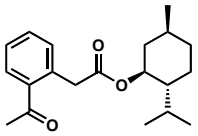
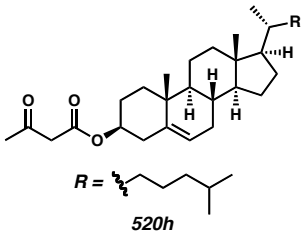
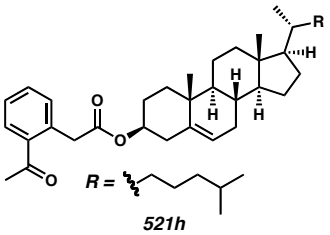
Consideration was first given to the β-ketoester substrate. It was reasoned that a β-ketoester lacking substitution at the α-carbon would contain less steric bulk as the corresponding aryl anion (**516**), and therefore display more rapid closure of the putative benzocyclobutenoxide (**519**). The expected benefits of this modification were two-fold: the yield of the acyl-alkylated arene product (**518**) would likely increase, while the incidence of α-arylation side product **517** would be suppressed. A series of α-unsubstituted β-ketoesters (**520**) bearing varied substitution at the γ-carbon were therefore investigated (Table 5.1). As anticipated, the reaction produced higher yields of the *ortho*-disubstituted arenes (**521**) when substitution was omitted from the α-position. Substrates bearing linear (entries 1 and 2) and branched (entry 3) alkyl chains, as well as aryl substitution (entries 4 and 6) were all well tolerated. Ether substitution could even be incorporated, albeit in lower yield (entry 5). On the other hand, modification of the ester substituent enabled the preparation of acyl-alkylated products derived from more complex alcohol precursors such as menthol (entry 7) and cholesterol (entry 8). Importantly, this reaction has proven to be readily scalable for the production of multi-gram quantities of acyl-alkylated arene **521a**.[3]

Having confirmed that the aryne acyl-alkylation proceeds smoothly with a number of differentially substituted β-ketoester substrates, attention was next given to an examination of the second reaction partner, the aryne. Methyl acetoacetate (**520a**) was chosen as a model β-ketoester for its structural simplicity and employed in the acyl-

Table 5.1. Acyl-alkylation of benzyne with substituted β-ketoesters



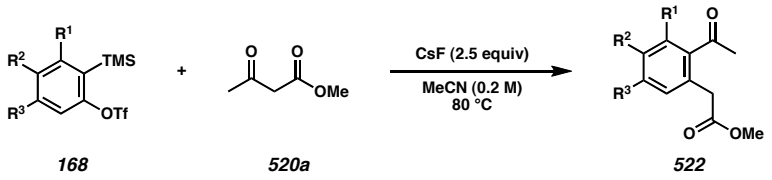
71 ***520*** ***521***

entry	β-ketoester[a]	product	yield
1	 ***520a***	 ***521a***	90%
2	 ***520b***	 ***521b***	78%
3	 ***520c***	 ***521c***	84%
4[b]	 ***520d***	 ***521d***	85%
5	 ***520e***	 ***521e***	53%
6	 ***520f***	 ***521f***	99%
7	 ***520g***	 ***521g***	72%
8	 ***520h***	 ***521h***	75%

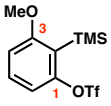
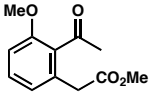
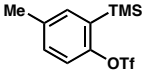
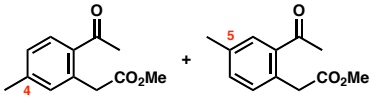
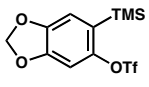
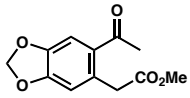
[a] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate **71** relative to β-ketoester **520**.
[b] Reaction performed with 2 equiv *ortho*-silyl aryl triflate **71** relative to β-ketoester **520d**.

alkylation of the arynes derived from mono- and disubstituted *ortho*-silyl aryl triflates (**168**) (Table 5.2). Gratifyingly, each of the three aryne precursors produced the expected tri- (entries 1 and 2) and tetrasubstituted arenes (entry 3) in very good yield. Furthermore, 3-methoxy-2-(trimethylsilyl)phenyl triflate (**108**) was found to react in a completely regioselective manner, furnishing only the product isomer corresponding to nucleophilic attack of the putative caesium enolate (e.g., **515**) at C(1).[20,21] As expected from previous studies,[20e] however, the *meta*-alkyl substituted precursor (**183**) displayed a weaker propensity for polarization of the reactive aryne bond and therefore afforded a mixture of isomers (**522b** and **522c**).

Table 5.2. Acyl-alkylation of substituted arynes



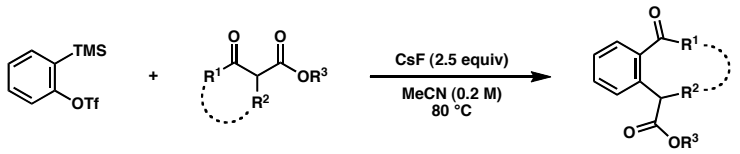
168 ***520a*** ***522***

entry	*ortho*-silyl aryl triflate[a]	product	yield
1	 ***108***	 ***522a***	95%
2[b]	 ***183***	 ***522b*** ***522c***	82% (1 : 1)
3	 ***155***	 ***522d***	75%

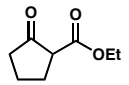
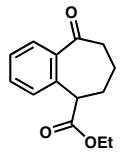
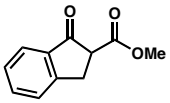
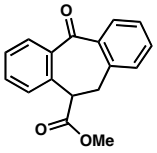
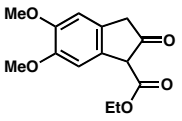
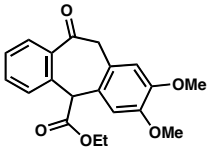
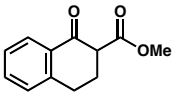
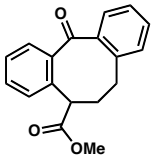
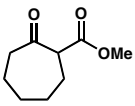
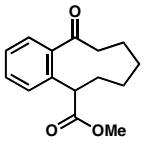
[a] Reaction performed with 2 equiv *ortho*-silyl aryl triflate **168** relative to β-ketoester **520a**.
[b] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate **183** relative to β-ketoester **520a**.

In a final evaluation of the substrate scope, the aryne acyl-alkylation was performed with a series of cyclic β-ketoesters (**523**) that, upon insertion of the aryne into the α,β C–C bond, would undergo two-carbon ring expansion to generate benzannulated medium-sized carbocycles (**524**) (Table 5.3). In each of the substrates examined (**523a–e**), the ester is oriented exo to a ketone-containing ring, thus constituting an analogue of the α-monosubstituted β-ketoester originally examined (**514**). A primary concern was that these compounds would therefore display the same susceptibility toward α-arylation that was observed in that first example. While this indeed proved to be the case with several of the substrates, the ring-expansive aryne acyl-alkylation method was able to provide access to a number of benzannulated 7- (entries 1–3), 8- (entry 4), and 9-membered polycycles (entry 5) in good yield from simple, readily available starting materials. In analogy to the previous screen of β-ketoester reactivity (Table 5.1), the insertion proceeded smoothly when aryl substitution was introduced at the γ-position (entries 2 and 4). 2-Indanone **523c** performed equally well, suggesting that α-aryl substitution of the β-ketoester has no additional negative effect upon reactivity. In full, this technique enables the construction of a number of synthetically useful medium-sized ring-containing products featuring varying degrees of benzannulation around the central ring.

Table 5.3. Ring-expansive aryne acyl-alkylation using cyclic β-ketoesters



71 ***523*** ***524***

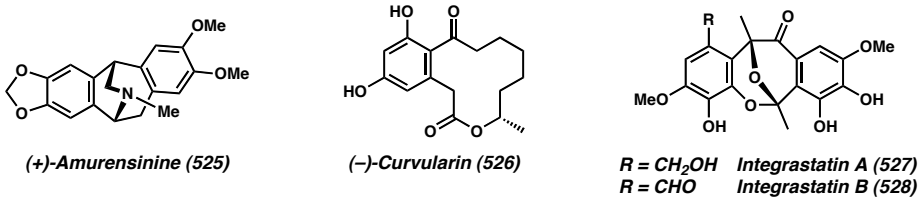
entry	β-ketoester[a]	product	yield[b]
1	 ***523a***	 ***524a***	50%
2[b]	 ***523b***	 ***524b***	61%
3	 ***523c***	 ***524c***	65%
4	 ***523d***	 ***524d***	45%
5	 ***523e***	 ***524e***	69%

[a] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate **71** relative to β-ketoester **523.**
[b] In most cases, the α-arylated β-ketoester was isolated as the major side product.

5.1.2 Applications of Aryne Acyl-Alkylation in Natural Product Total Synthesis

The aryne acyl-alkylation reaction is a powerful tool for the convergent assembly of polycyclic arene-containing frameworks from simple starting materials. As such, it is not at all surprising that this technique has found ready use within the context of total synthesis. Over the past three years, our group has employed the acyl-alkylation reaction as a key transformation in the asymmetric total syntheses of two natural products, (+)-amurensinine (**525**) and (–)-curvularin (**526**), and we are currently investigating its implementation as part of a synthetic approach toward integrastatins A (**527**) and B (**528**) (Figure 5.1). The following sections discuss each of these synthetic efforts in detail.

Figure 5.1. Natural products targeted for application of the aryne acyl-alkylation reaction



(+)-Amurensinine (525) ***(–)-Curvularin (526)*** ***R = CH_2OH Integrastatin A (527)***
R = CHO Integrastatin B (528)

5.1.2.1 Total Synthesis of (+)-Amurensinine[†,2,22,23]

The first natural product to be completed using the aryne acyl-alkylation reaction was (+)-amurensinine (**525**), a member of the isopavine alkaloids (Scheme 5.2).[24] The carbon skeleton of **525** was recognized as being strikingly similar to structures previously prepared using the ring-expansive aryne acyl-alkylation (**524b** and **524c**, Table 5.3), so

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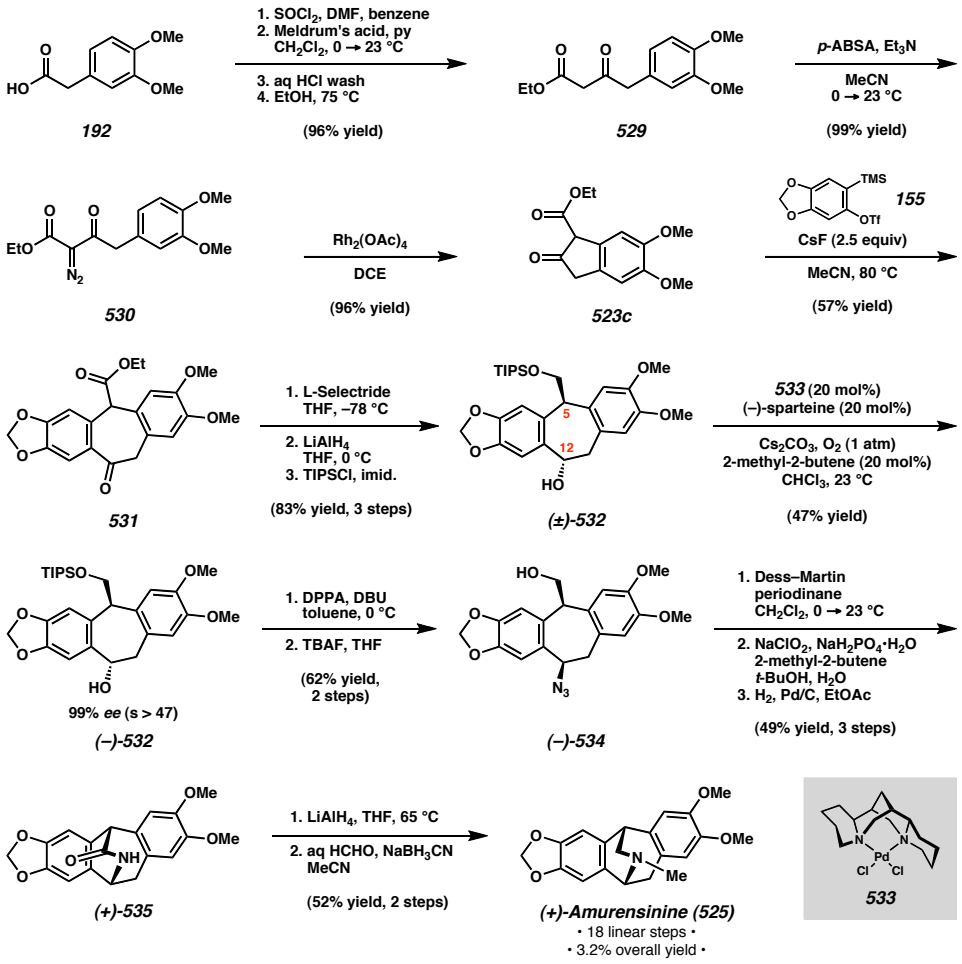
[†] The asymmetric total synthesis of (+)-amurensinine was carried out by two former graduate students in the Stoltz research group, Drs. Uttam K. Tambar and David C. Ebner.

much so that cyclic β-ketoester **523c** was targeted as the precursor to the right hemisphere of the natural product. Construction of this intermediate started from homoveratric acid (**192**), which was advanced to β-ketoester **529** through a four-step procedure entailing conversion to the acid chloride, addition of Meldrum's acid, thermal decomposition of the resulting adduct to an α-ketoketene, and quenching with ethanol. The β-ketoester was then treated with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) to furnish α-diazo-β-ketoester **530**, which underwent subsequent rhodium-catalyzed insertion into the less hindered *ortho*-C–H bond to generate cyclic β-ketoester **523c**.

Scheme 5.2. Total synthesis of (+)-amurensinine



In the key transformation, this compound was combined with *ortho*-silyl aryl triflate **155**—a derivative of sesamol—and heated in the presence of caesium fluoride to generate tetracycle **531**. Following assembly of the carbon framework, the ketone was reduced with L-Selectride to set the trans relationship between the substituents at C(5) and C(12), and the ester was reduced to a primary alcohol and selectively protected as the silyl ether (**(±)-532**). In order to impart asymmetry upon the synthetic sequence, an oxidative kinetic resolution—a reaction methodology previously developed by our research group—was carried out on this racemic material using Pd(sparteine)Cl_2 (**533**) as the chiral catalyst.[25,26] Stereoselective oxidation of the undesired enantiomer of the secondary alcohol (i.e., **(+)-532**) thereby furnished alcohol **(–)-532** in 47% yield and >99% *ee* (s > 47).[27] Mitsunobu inversion using diphenylphosphoryl azide (DPPA) and desilylation provided *syn*-azido alcohol **534**, after which two-step oxidation to the carboxylic acid and reduction of the azide resulted in spontaneous ring closure to form the lactam (**535**). The synthesis was completed through reduction of the lactam to a benzazepine and installation of the *N*-methyl group via reductive amination, thus yielding (+)-amurensinine (**525**) in a total of 18 linear steps. Importantly, the completion of this natural product marked the first application of both the aryne acyl-alkylation and the oxidative kinetic resolution reactions in total synthesis.

5.1.2.2 Total Synthesis of (–)-Curvularin[†,28]

The second natural product targeted was (–)-curvularin,[29,30] a polyketide isolated from the mold *Curvularia* that has recently been shown to inhibit human inducible nitric oxide synthase expression.[31] The primary objective of this synthesis was to examine the feasibility of an aryne acyl-alkylation approach that employed a β-ketolactone—wherein both the ester and ketone functionalities are contained within a single ring—in place of a cyclic β-ketoester bearing an exocyclic ester (e.g., **523a–e**, Table 5.3).

The synthesis of curvularin began from known (*S*)-heptenyl-6-acetate (**536**), which was prepared as a single enantiomer through the addition of the Grignard reagent of 4-bromo-1-butene to the terminus of (*S*)-propylene oxide followed by acetylation of the resulting alcohol (Scheme 5.3).[32] Aldol addition of the lithium enolate of **536** to acrolein formed allylic alcohol **537**. This intermediate was then carried forward through silylation, ring closing metathesis using ruthenium catalyst **538**,[33] and desilylation to furnish unsaturated lactone **539** as a mixture of diastereomers and olefin isomers. Hydrogenation of the olefin and oxidation of the secondary alcohol then generated β-ketolactone **540**, the substrate for the key aryne acyl-alkylation. Heating this substrate with dibenzyloxy *ortho*-silyl aryl triflate **541**[34] in the presence of caesium fluoride produced the desired ring-expansion product in 30% yield, accompanied by a 20% yield of the α-arylated isomer (not shown). Hydrogenolysis of the benzyl protecting groups then provided (–)-curvularin (**526**) in 7.2% yield over 6 linear steps from acetate **536**.

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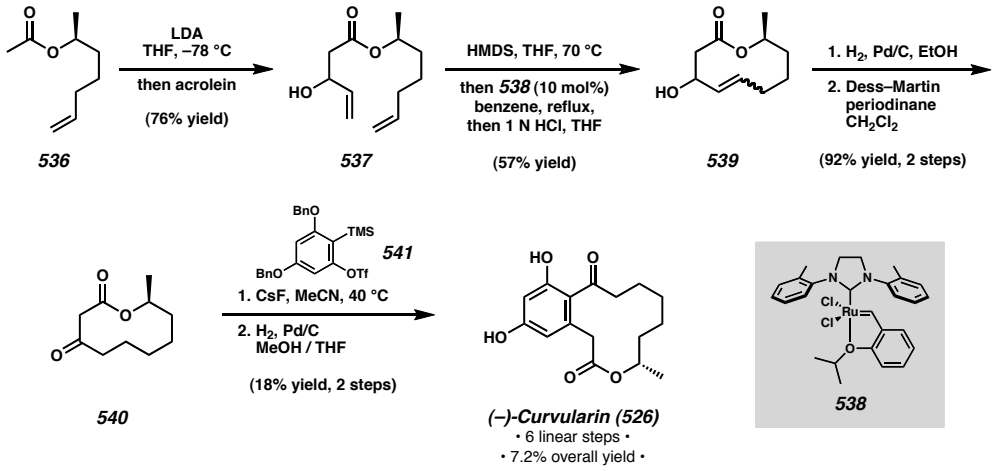
† The asymmetric total synthesis of (–)-curvularin was carried out by Pamela M. Tadross, a graduate student in the Stoltz research group.

Scheme 5.3. Total synthesis of (–)-curvularin



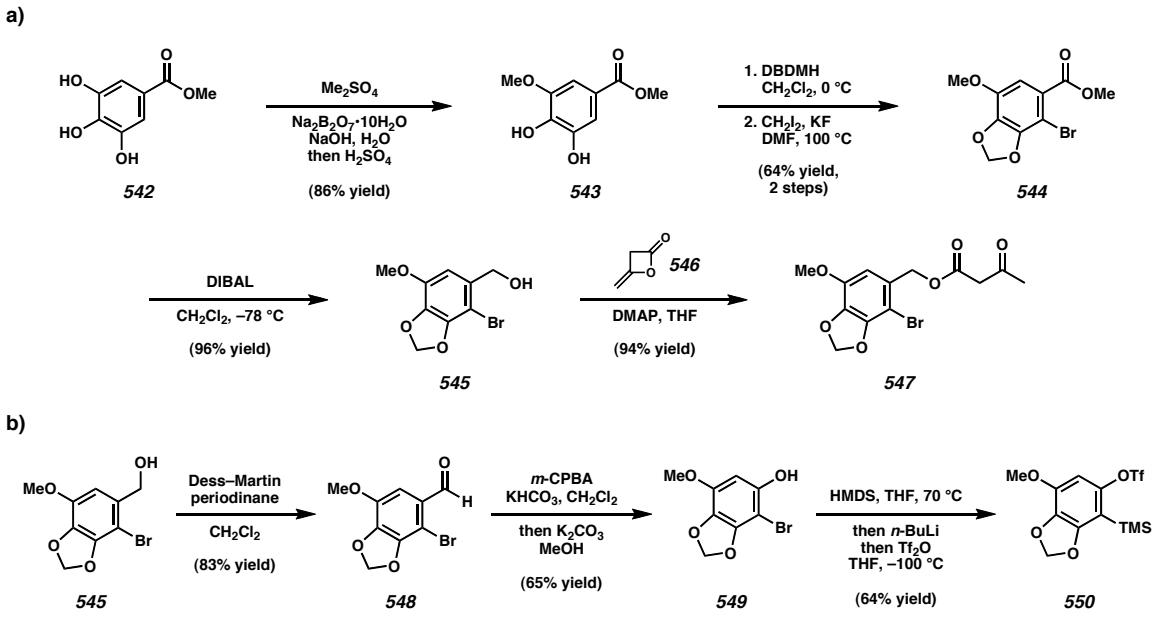
5.2.1.3 Progress Toward the Total Synthesis of Integrastatins A and B[†]

Our research group is currently pursuing the total syntheses of integrastatins A (**527**) and B (**528**), isolates from an unidentified fungus found in New Mexico that have been shown to inhibit the strand transfer reaction of recombinant HIV-1 integrase (IC_{50} = 1.1 and 2.5 μM, respectively).[35] The present strategy calls for early construction of the left and right hand arene rings as precursors to the key aryne acyl-alkylation, after which the central bridging acetal will be assembled to complete the synthesis. Beginning from methyl gallate (**542**), selective mono-methylation, bromination, and installation of a methylene dioxolane provided ester **544** (Scheme 5.4a). Reduction to the primary alcohol (**545**) and addition to diketene (**546**) then yielded β-ketoester **547**. Alternatively, the aryne precursor can be prepared by diverting from alcohol **545** to generate bromophenol **549** through conversion to the aldehyde (**548**), Baeyer–Villiger oxidation,

[†] The total syntheses of integrastatins A and B are being pursued by Pradeep Bugga, a baccalaureate researcher, and Pamela M. Tadross, a graduate student, both of whom are members of the Stoltz research group.

and deformylation (Scheme 5.4b). Advancement to *ortho*-silyl aryl triflate **550** was then accomplished through silylation of the phenol, lithium-halogen exchange, migration of the silyl group from oxygen to the lithiated *ortho*-carbon, and quenching of the resultant phenoxide with trifluoromethanesulfonic anhydride (Tf_2O).[36]

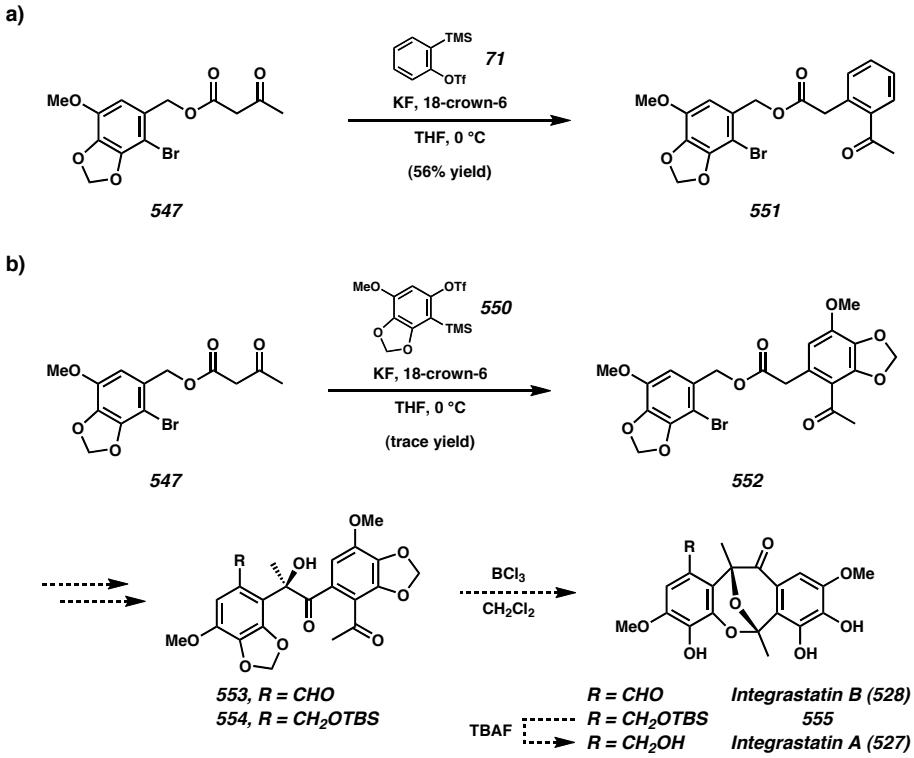
*Scheme 5.4. a) Synthesis of β-ketoester **547**. b) Synthesis of ortho-silyl aryl triflate **550**.*



With β-ketoester **547** in hand, the aryne acyl-alkylation was first examined using *ortho*-silyl aryl triflate **71** as a model substrate (Scheme 5.5a). Because the β-ketoester decomposes above room temperature in the presence of several fluoride sources, an alternative set of conditions was developed to promote comparable reactivity at lower temperatures. Replacing caesium fluoride with potassium fluoride activated by a crown ether promotes the reaction in tetrahydrofuran at 0 °C, thus suppressing thermal decomposition of β-ketoester **547** and providing benzylic ester **551** in 56% yield. When this same reaction was attempted with *ortho*-silyl aryl triflate **550**, however, the

corresponding benzylic ester (**552**) could only be isolated in trace quantities (Scheme 5.5b). Current efforts are therefore focused upon gaining a better understanding of the shortcomings of this particular reaction in order to optimize the yield of **552**. With greater quantities of this intermediate in hand, attention will be turned toward its advancement to one of two α-hydroxyketones (**553** or **554**). In the final steps, removal of the two dioxolanes using boron trichloride will reveal a pair of catechols capable of forming the central acetal to generate integrastatin B (**528**), or a silyl ether (**555**) one step removed from integrastatin A (**527**).

*Scheme 5.5. a) Model acyl-alkylation using ortho-silyl aryl triflate **71**. b) Aryne acyl-alkylation and strategy for the completion of integrastatins A and B.*

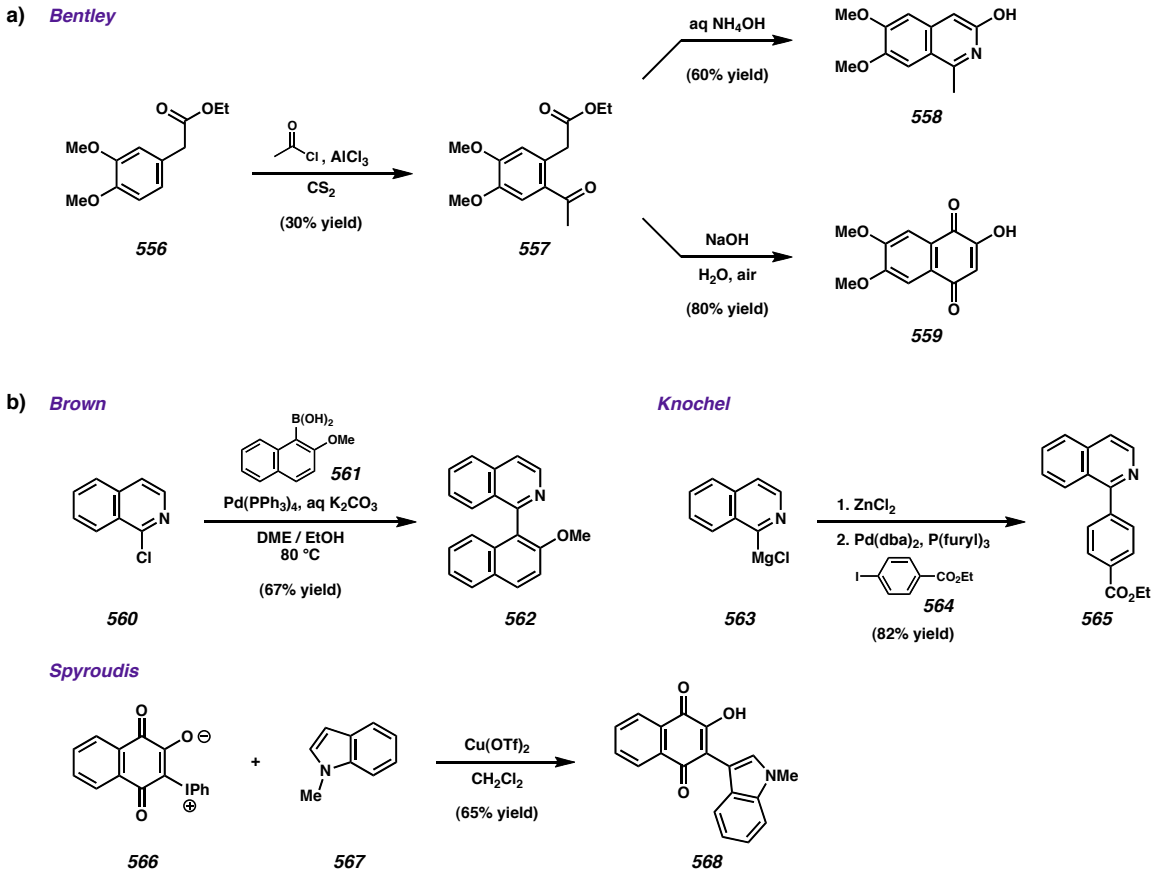


5.2 EXPEDIENT SYNTHESIS OF 3-HYDROXYISOQUINOLINES AND 2-HYDROXY-1,4-NAPHTHOQUINONES VIA ONE-POT ARYNE ACYL-ALKYLATION / CONDENSATION[37]

5.2.1 Previous Synthetic Methods

Following our development of the fluoride-induced insertion reaction between β-ketoesters and arynes derived from *ortho*-silyl aryl triflates,[1] we began to investigate avenues along which the acyl-alkylated arene products could be advanced toward more complex ring systems.[22] Our interest in nitrogen-containing heterocycles[38] led us to a communication by Bentley *et al.*, which reported the synthesis of both 3-hydroxyisoquinolines (**558**) and 2-hydroxy-1,4-naphthoquinones (**559**) through exposure of 1,5-ketoesters such as **557**—prepared by Friedel–Crafts acylation of homoveratric esters (**556**)—to either aqueous ammonia or alkaline base under an ambient atmosphere, respectively (Scheme 5.6a).[39] We found this strategy particularly inspiring given that traditional approaches to the incorporation of these aromatic groups within larger molecular scaffolds typically rely upon transition metal-catalyzed cross coupling reactions employing $C(sp^2)$–X substrates.[40] Select examples of such approaches include Brown's employment of a Suzuki coupling between isoquinoline chloride **560** and naphthyl boronic acid **561** to prepare naphthyl isoquinoline **562**,[41] Knoechel's synthesis of arylisoquinline **565** via Negishi coupling,[42] and the copper-catalyzed coupling between naphthoquinone phenyliodonium ylide **566** and *N*-methylindole (**567**) utilized by Spyroudis (Scheme 5.6b).[43]

Scheme 5.6. a) Bentley's synthesis of 3-hydroxyisoquinolines and 2-hydroxy-1,4-naphthoquinones from 2-acylhomoveratric esters. b) Selected previous syntheses of functionalized isoquinoline and naphthoquinone motifs via transition metal-catalyzed cross coupling.

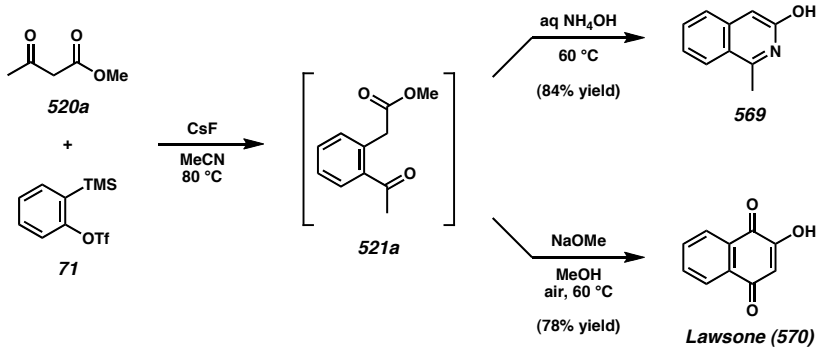


5.2.2 Proof of Principle

The ability to extend our aryne acyl-alkylation technology to the preparation of isoquinoline and naphthoquinone motifs would represent a new synthetic approach employing materials ultimately derived from carboxylic acids. Combining Bentley's condensation with our own aryne methodology, we found that treatment of a crude acyl-alkylation reaction mixture containing methyl (2-acetylphenyl)acetate (**521a**) with aqueous ammonium hydroxide furnished 1-methyl-3-hydroxyisoquinoline (**569**) in 84%

yield directly from methyl acetoacetate (**520a**) and 2-(trimethylsilyl)phenyl triflate (**71**) (Scheme 5.7). Alternatively, the addition of sodium methoxide to intermediate **521a** with concomitant exposure to air generated lawsone (**570**)—an isolate from the henna plant *Lawsonia inermis*[44]—in 78% yield.

Scheme 5.7. Aryne acyl-alkylation followed by condensation with ammonia or intramolecular condensation and aerobic oxidation

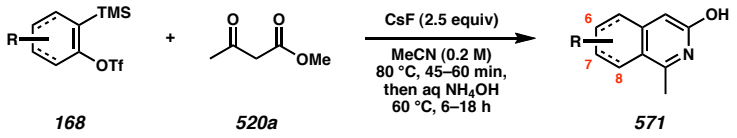


5.2.3 Development of a One-Pot Aryne Acyl-Alkylation / Ammonia Condensation Reaction Sequence for the Synthesis of 3-Hydroxyisoquinolines

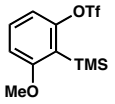
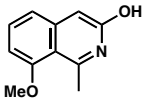
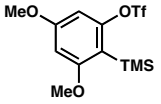
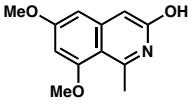
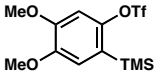
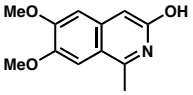
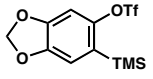
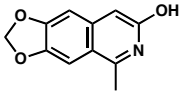
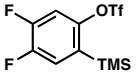
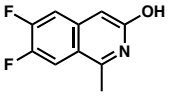
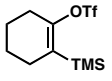
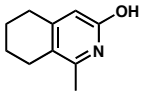
Focusing on the first of these two transformations, we investigated the reaction between methyl acetoacetate (**520a**) and a number of functionalized aryne precursors (**168**) (Table 5.4). The sequence proved quite general, providing rapid access to a number of 3-hydroxyisoquinoline products (**571**) featuring substitution at carbons 6, 7, and 8. The reaction proceeded well with both electron-rich (entries 1–4) and electron-deficient arynes (entry 5), as well as with cyclohexyne[45] (entry 6). Notably, the use of unsymmetrically substituted arynes (entries 1 and 2) provided single product isomers

originating from regioselective addition of the β-ketoester to the inductively activated carbon *meta* to the heteroatom.[20,21]

Table 5.4. Synthesis of 3-hydroxyisoquinolines via one-pot aryne acyl-alkylation and condensation with ammonia



168 ***520a*** ***571***

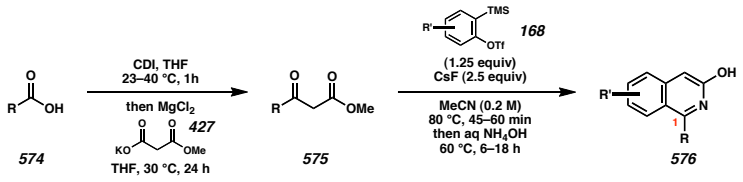
entry	substrate[a]	product	yield
1	 ***108***	 ***571a***	70%
2	 ***572***	 ***571b***	81%
3	 ***184***	 ***571c***	75%
4	 ***155***	 ***571d***	77%
5	 ***185***	 ***571e***	73%
6	 ***573***	 ***571f***	54%

[a] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate **168** relative to β-ketoester **520a**.

Next, we considered alternative β-ketoesters for the introduction of substitution at C(1) of the hydroxyisoquinoline scaffold (Table 5.5). Though methyl acetoacetate and a handful of other β-ketoesters are commercially available, we found it necessary to prepare additional substrates in order to probe the scope of the reaction. While there are a number of methods known to generate β-ketoesters from the corresponding carboxylic acids (**574**), we selected a procedure reported by Masamune *et al.*, which employs the addition of a magnesium monomethylmalonate to a preformed acyl imidazole.[46] Both simple and high yielding, this method facilitated the synthesis of a small library of differentially substituted methyl β-ketoesters (**575**) from readily available carboxylic acids in a single step.[48]

With a collection of substrates in hand, we set about testing the steric and electronic tolerances of our acyl-alkylation/condensation reaction sequence. Under optimized conditions, the β-ketoester (**575**) and *ortho*-silyl aryl triflate (**168**) are combined and heated in the presence of caesium fluoride. Following formation of the acyl-alkylated arene (e.g., **521a**), ammonium hydroxide is added and heating is continued in a sealed environment. We were delighted to find that the reaction proceeds quite well with a variety of alkyl (entries 1 and 2), aryl (entries 3–5), and heteroaryl groups (entries 6–8) located at the γ-position of the β-ketoester. In addition, naphthyl isoquinoline (entry 9) and bis-isoquinoline (entry 10) scaffolds—structures central to many ligand frameworks—are accessible.[47] Interestingly, this sequence proves quite effective at rapidly appending isoquinoline motifs on to biological substrates such as arachidonic acid (entry 11) and 3β-acetoxy-5-etienic acid (entry 12) without epimerization of existing stereocenters. The reaction can even be performed bidirectionally with a diacid to

Table 5.5. Two-step synthesis of 3-hydroxyisoquinolines from carboxylic acids[48]



entry	β-ketoester[a]	yield (***575***)	product	yield (***576***)
1	***575a***, R = CH_2OMe	71%	***576a***, R = CH_2OMe	82%
2	***575b***, R = *c*-Hex	69%	***576b***, R = *c*-Hex	81%
3	***575c***, R = Ph	88%	***576c***, R = Ph	79%
4	***575d***	85%	***576d***, R = H	68%
5			***576e***, R = OCH_2O	73%
6	***575e***	89%	***576f***	85%
7	***575f***	76%	***576g***, R = H	72%
8			***576h***, R = OMe	94%
9	***575g***	91%	***576i***	69%
10	***575h***	64%	***576j***	68%
11	***575i***	90%	***576k***	81%
12	***575j***	96%	***576l***	62%
13	***575k***	92%	***576m***	66%

[a] Acyl-alkylation/condensation reaction performed with 1.25 equiv **168** relative to β-ketoester **575**.

generate a bis(3-hydroxyisoquinoline) product (entry 13).

The hydroxyl group on this molecular scaffold provides an excellent functional handle for the introduction of additional substitution at C(3) of the isoquinoline. As a demonstration of this fact, we carried out the triflation of 3-hydroxyisoquinoline **576f** (Table 5.5, entry 6) followed by a palladium-catalyzed Suzuki coupling with 4-methoxyphenylboronic acid (**577**) to furnish diarylisoquinoline **578** in high yield (Scheme 5.8a). Thus, this method provides avenues not only to C(1) functionalized hydroxyisoquinolines, but toward 1,3-disubstituted isoquinolines as well.

As previously mentioned, our aryne acyl-alkylation/condensation reaction sequence enables rapid assembly of structural motifs that are key to several chiral ligand frameworks. In particular, we envisioned that naphthyl isoquinoline **576i** (Table 5.5, entry 9) could be employed toward the synthesis of 1-(2'-diphenylphosphino-1'-naphthyl)-isoquinoline (QUINAP, **582**),[49] an axially chiral *P*,*N*-ligand that has found widespread application in asymmetric catalysis, including enantioselective hydroboration,[50] allylic alkylation,[51] and hydrogenation[52] (Scheme 5.8b).[†] Having developed an expedient method for the construction of naphthyl 3-hydroxyisoquinoline **576i**, we set out to demonstrate the feasibility of our synthetic approach. Following the acyl-alkylation/condensation sequence, the resulting hydroxyisoquinoline (**576i**) was subjected to triflation. Next, reduction of triflate **579** yielded naphthyl isoquinoline **580**, which was subsequently brominated via nitrogen-directed palladium-catalyzed C–H activation to furnish bromide **581**.[53] Finally, implementation of a modified version of

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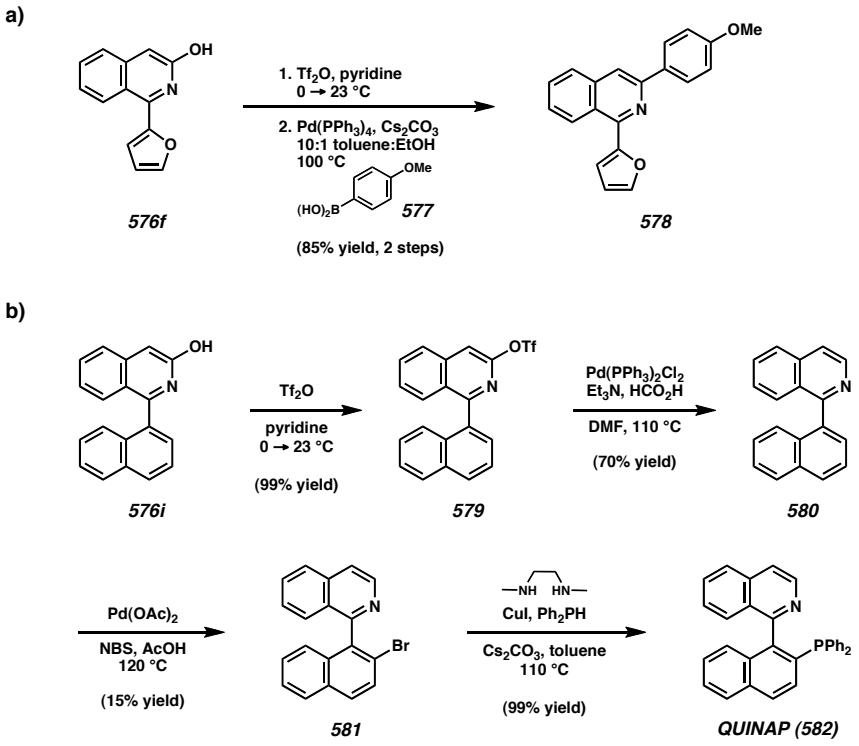
[†] The synthesis of QUINAP was carried out by Boram D. Hong, a graduate student in the Stoltz research group.

Buchwald's phosphine–aryl bromide coupling[54] afforded the desired target, QUINAP (**582**). Whereas the majority of previous approaches to this ligand rely on transition metal-catalyzed cross coupling reactions to form the axial C–C bond,[55] our synthetic route represents a novel disconnection that ultimately builds the isoquinoline ring system on to the existing framework of naphthoic acid.

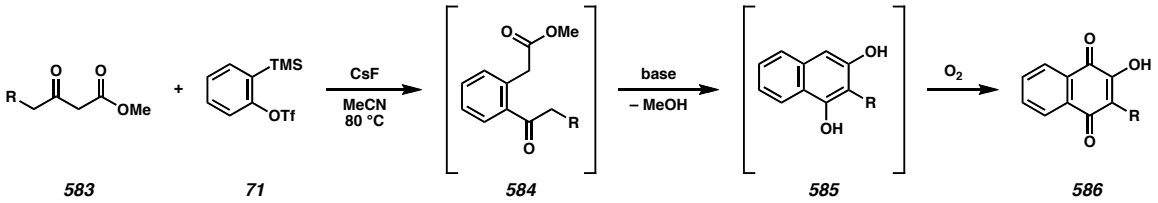
*Scheme 5.8. a) Synthesis of 1,3-diarylisoquinoline **578**. b) Synthesis of QUINAP.*



5.2.4 Development of a One-Pot Aryne Acyl-Alkylation / Intramolecular Condensation Reaction Sequence for the Synthesis of 2-Hydroxy-1,4-naphthoquinones

The second class of compounds we investigated comprised a series of 2-hydroxy-1,4-naphthoquinones (**586**) (Scheme 5.9). These compounds are generated via intramolecular condensation of the acyl-alkylated arene (**584**) to form an intermediate 1,3-naphthalenediol (**585**), which then autooxidizes under an ambient atmosphere. We first encountered these compounds while working toward 3-hydroxyisoquinolines when we noticed that β-ketoester substrates bearing an acidic γ-methylene (**583**) preferentially formed the hydroxynaphthoquinone, albeit in low yield, through the action of NH_4OH as a base. When aqueous potassium carbonate was added in its place and the mixture was heated while open to air, the reaction proceeded cleanly to provide exclusively the hydroxynaphthoquinone (**586**).[56]

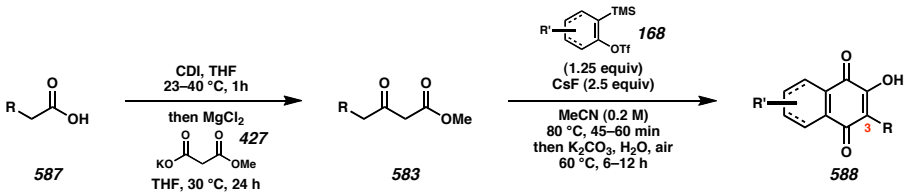
Scheme 5.9. Synthesis of 2-hydroxy-1,4-naphthoquinones via one-pot aryne acyl-alkylation, intramolecular condensation, and aerobic oxidation



Using these optimized conditions, we are able to generate a variety of hydroxynaphthoquinones (**588**) possessing alkoxy (entry 1), aryl (entries 2–5), and even indole (entries 6 and 7) substitution at C(3) (Table 5.6). However, having optimized the

reaction for β-ketoesters bearing electron-withdrawing functionality at the γ-position, it was necessary to select a stronger base in order to target alkyl substituted products (**588i–k**). Fortunately, sodium methoxide provided a suitable alternative in such cases, giving rise to simple natural product scaffolds such as phthiocol[57] (entry 9) and *O*-des-methyl-stoechadone[58] (entry 10), as well as a derivative of arachidonic acid (entry 11). Under both conditions, differentially substituted arynes (entries 4, 8, and 10) and cyclohexyne (entry 5) performed comparably to benzyne (derived from **71**).

Table 5.6. Two-step synthesis of 2-hydroxy-1,4-naphthoquinones from carboxylic acids[48]



587 ***583*** ***588***

entry	β-ketoester[a]	yield (***583***)	product	yield (***588***)
1	***583a***, R = OMe	69%	***588a***, R = OMe	86%
2	***583b***, R = Ph	93%	***588b***, R = Ph	92%
3			***588c***, R = H	78%
4			***588d***, R = OMe	84%
5	***583c***	96%	***588e***	61%
6	***583d***	85%	***588f***	70%
7			***588g***, R = H	84%
8	***583e***	93%	***588h***, R = OCH_2O	88%
9[b]			***588i***, R = H	80%
10[b]	***583f***	N/A[c]	***588j***, R = OMe	63%
11[b]	***583g***	90%	***588k***	66%

[a] Acyl-alkylation/condensation reaction performed with 1.25 equiv **168** relative to β-ketoester **583**.
[b] NaOMe (5 equiv) in MeOH (1.0 M) was used in place of K_2CO_3 in H_2O.
[c] Methyl 3-oxovalerate (**583f**) is commercially available.

5.3 CONCLUSION

The aryne acyl-alkylation reaction has enabled the synthesis of a wide array of structural motifs ranging from simple *ortho*-disubstituted arenes to complex polycyclic benzannulated scaffolds. This methodology has provided the key bond-forming transformation in routes toward two separate natural products, and progress toward a third target is currently underway. In an effort to extend the synthetic utility of this technology, we have developed an extremely concise procedure for the preparation of 3-hydroxyisoquinolines and 2-hydroxy-1,4-naphthoquinones directly from β-ketoesters using a novel one-pot aryne acyl-alkylation/condensation sequence. By employing this procedure in conjunction with a one-step synthesis of β-ketoesters from carboxylic acids, we are able to build these bicyclic aromatic structures in only two steps from commercially available materials. Furthermore, this two-step sequence is capable of joining a variety of differentially functionalized β-ketoester and *ortho*-silyl aryl triflate substrates to generate products bearing sterically and electronically diverse substitution. The utility of this approach has been demonostrated in the synthesis of the axially chiral *P*,*N*-ligand, QUINAP. Given the proven scalability of the aryne acyl-alkylation step, this approach is expected to enable the preparation of multigram quantities of either of these product structures. Further investigation of this methodology, including its utilization toward more complex natural product targets, is currently underway in our laboratories.

5.4 EXPERIMENTAL SECTION

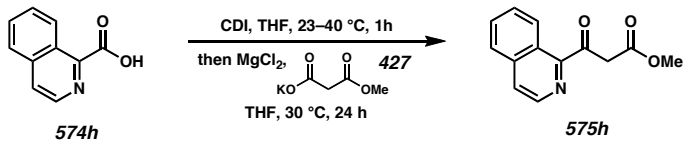
5.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. 3-Methoxy-2-(trimethylsilyl)phenyl triflate (**108**),[59] 3,5-dimethoxy-2-(trimethylsilyl)phenyl triflate (**572**),[34] 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate (**184**),[60] 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl triflate (**155**),[1] 4,5-difluoro-2-(trimethylsilyl)phenyl triflate (**185**),[36] and 2-(trimethylsilyl)cyclohexene triflate (**573**)[45] were prepared according to literature procedures. Reaction temperatures were controlled by an IKAmag temperature modulator. Brine solutions are saturated aqueous sodium chloride solutions. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or ceric ammonium molybdate staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical

ionization (APCI) or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility (FAB+).

5.4.2 Preparative Procedures and Spectroscopic Data

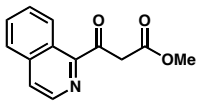
5.4.2.1 Representative Procedure for the Synthesis of β-Ketoesters From Carboxylic Acids



This procedure is based on the method of Masamune, *et al.*[46] A flame-dried 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with magnesium chloride (0.469 g, 4.93 mmol, 1.0 equiv) and potassium monomethyl malonate (**427**) (1.02 g, 6.53 mmol, 1.3 equiv). A reflux condenser was attached and the flask was subsequently evacuated and back-filled with argon. Tetrahydrofuran (7.5 mL) was added and the suspension was heated to 65 °C for 3 h. After the above reaction had proceeded for 2 h, a separate flame-dried 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with isoquinoline-1-carboxylic acid (**574h**) (0.852 g, 4.92 mmol, 1.0 equiv) and tetrahydrofuran (5 mL). To this solution was added carbonyl diimidazole (0.957 g, 5.90 mmol, 1.2 equiv) in portions, allowing for effervescence to subside between additions. **Warning:** vigorous gas evolution. The reaction was stirred at 23 °C until bubbling ceased (30 min), and then heated to 40 °C (at which point bubbling renewed) for an additional 30 min. The magnesium malonate suspension was cooled to 30 °C and the acyl-imidazole solution was added dropwise via syringe (NOTE: a white precipitate forms rapidly during this addition; vigorous stirring is necessary to avoid

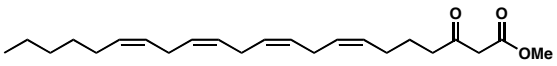
clumping). The resulting milky white suspension was stirred at 30 °C for 24 h. The reaction was cooled to 0 °C when TLC analysis showed complete consumption of the intermediate acyl imidazole. The reaction was quenched by the addition of 1.0 N HCl (15 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were sequentially washed with water (80 mL), saturated aqueous sodium bicarbonate (80 mL), and brine (80 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography over silica gel.

5.4.2.2 Spectroscopic Data for β-Ketoesters[61]



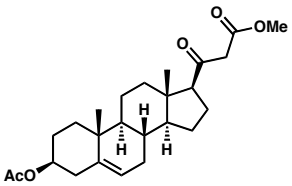
β-Ketoester 575h (Table 5.5, Entry 10)

Purified via flash chromatography (SiO_2, 10:90 EtOAc/hexanes) to yield a clear colorless oil (64% yield). R_f = 0.70 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14–9.11 (m, 1H), 8.59 (d, *J* = 5.4 Hz, 1H), 7.89 (dd, *J* = 5.9, 2.4 Hz, 1H), 7.86 (dd, *J* = 5.9, 1.0 Hz, 1H), 7.76–7.70 (comp m, 2H), 4.38 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 169.0, 150.5, 141.0, 137.1, 130.5, 129.6, 127.0, 126.7, 126.3, 125.4, 52.2, 46.8; IR (Neat Film, NaCl) 3055, 2952, 1744, 1698, 1580, 1436, 1323, 1104, 1089 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{13}H_{11}NO_3$ $[M+H]^+$: 230.0812, found 230.0815.



β-Ketoester 575i (Table 5.5, Entry 11)

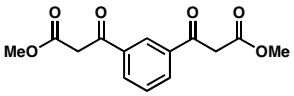
Purified via flash chromatography (SiO_2, 5:95 → 8:92 EtOAc/hexanes) to yield a waxy white solid (90% yield). R_f = 0.64 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45–5.32 (comp m, 8H), 3.75 (s, 3H), 3.45 (s, 2H), 2.84 (comp m, 6H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.10 (dt, *J* = 7.3, 6.6 Hz, 2H), 2.07 (dt, *J* = 7.1, 7.1 Hz, 2H), 1.69 (tt, *J* = 7.6, 7.3 Hz, 2H), 1.41–1.26 (comp m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 167.6, 130.5, 129.0, 128.9, 128.6, 128.3, 128.1, 127.8, 127.5, 52.3, 49.0, 42.3, 31.5, 29.3, 27.2, 26.3, 25.7, 25.6, 25.6, 23.2, 22.6, 14.1; IR (Neat Film, NaCl) 3434, 2928, 2858, 1743, 1716, 1438, 1321, 1175, 1083, 1002 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{23}H_{36}O_3$ $[M+H]^+$: 361.2737, found 361.2735.



β-Ketoester 575j (Table 5.5, Entry 12)

Purified via flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield a white solid (96% yield). R_f = 0.42 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (d, *J* = 5.1 Hz, 1H), 4.64–4.57 (m, 1H), 3.73 (s, 3H), 3.45 (s, 2H), 2.62 (t, *J* = 9.0 Hz, 1H), 2.33 (dd, *J* = 3.7, 1.5 Hz, 1H), 2.31 (dd, *J* = 2.7, 2.2 Hz, 1H), 2.22–2.15 (m, 1H), 2.05–2.00 (comp m, 2H), 2.03 (s, 3H), 1.98 (td, *J* = 5.4, 2.0 Hz, 1H), 1.87 (app dd, *J* = 9.3, 2.4 Hz, 2H), 1.76–1.67 (comp m, 2H), 1.66–1.54 (comp m, 4H), 1.54–1.44 (comp m, 2H), 1.28–1.12 (comp m, 3H), 1.02 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

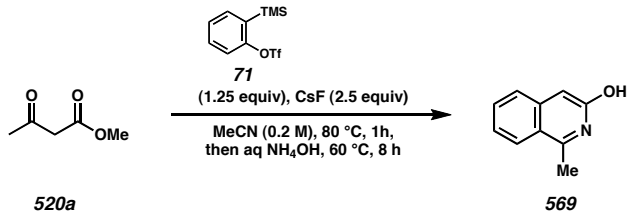
δ 203.5, 170.5, 167.7, 139.7, 122.2, 73.8, 63.1, 56.8, 52.2, 50.4, 49.8, 44.5, 38.6, 38.1, 37.0, 36.6, 31.9, 31.7, 27.7, 24.4, 23.1, 21.4, 21.0, 19.3, 13.4; IR (Neat Film, NaCl) 2945, 2903, 1748, 1732, 1709, 1438, 1374, 1310, 1245, 1032 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{25}H_{36}O_5$ $[M–H]^-$: 415.2490, found 415.2516.



β-Ketoester 575k (Table 5.5, Entry 13)[62]

Purified via flash chromatography (SiO_2, 15:85 → 25:75 EtOAc/hexanes) to yield a clear colorless oil (92% yield). R_f = 0.20 (25:75 EtOAc/hexanes); product is isolated as a 1:0.8:0.3 mixture of bis(β-ketoester), *E*-mono-enolized, and *Z*-mono-enolized tautomers, respectively. ^1H NMR (500 MHz, $CDCl_3$) δ 12.54 (s, 0.8H), 12.52 (s, 0.3H), 8.50 (t, *J* = 1.8 Hz, 1H), 8.35 (t, *J* = 1.8 Hz, 0.8H), 8.19 (dd, *J* = 7.5, 1.8 Hz, 2H), 8.03 (tt, *J* = 7.5, 1.8 Hz, 1H), 8.02 (tt, *J* = 7.5, 1.8 Hz, 0.8H), 7.88 (dd, *J* = 7.5, 1.8 Hz, 0.3H), 7.65 (t, *J* = 8.1 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 0.8H), 7.49 (t, *J* = 7.8 Hz, 0.3H), 5.75 (s, 0.8H), 5.74 (s, 0.3H), 4.06 (s, 4H), 4.05 (s, 1.6H), 3.83 (s, 2.4H), 3.83 (s, 0.9H), 3.78 (s, 6H), 3.77 (s, 2.4H), 3.77 (s, 0.9H); ^{13}C NMR (125 MHz, $CDCl_3$) bis(β-ketoester): δ191.5, 167.5, 133.3, 131.0, 129.6, 128.5, 52.6, 45.7; combination of *E*- and *Z*-mono-enolized tautomers: δ 191.8, 173.3, 170.5, 169.8, 167.7, 167.1, 136.5, 136.3, 134.2, 133.9, 130.9, 129.2, 128.9, 128.7, 126.1, 123.8, 88.1, 87.7, 52.6, 52.5, 51.6, 51.5, 48.7, 45.7; IR (Neat Film, NaCl) 2955, 1742, 1689, 1654, 1625, 1438, 1327, 1268, 1199, 1150, 1012 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{14}H_{14}O_6$ $[M+H]^+$: 279.0863, found 279.0863.

5.4.2.3 Representative Procedure for the Synthesis of 3-Hydroxyisoquinolines From β-Ketoesters

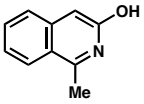


520a *569*

A flame-dried 10 mL Schlenk flask with a septum-covered side arm equipped with a magnetic stir bar was charged with cesium fluoride (0.152 g, 1.00 mmol, 2.5 equiv). The flask was evacuated and back-filled with argon (×2). Acetonitrile (2 mL), methyl acetoacetate (**520a**) (0.043 mL, 0.4 mmol, 1.0 equiv) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**71**) (0.121 mL, 0.498 mmol, 1.25 equiv) were sequentially added. The screw valve was sealed and the reaction was heated to 80 °C while stirring for 1 h. The reaction was cooled to room temperature when TLC analysis showed complete consumption of methyl acetoacetate (**520a**) (NOTE: at this point, the major component of the reaction is the acyl-alkylated arene). The screw valve was removed under positive argon pressure and aqueous ammonium hydroxide (28% w/w, 2 mL) was added via syringe. The screw valve was replaced and tightened, and the reaction was heated to 60 °C while stirring for 8 h. The reaction was cooled to room temperature when TLC analysis showed complete consumption of the intermediate acyl-alkylated arene. The mixture was diluted with brine (5 mL) and extracted with EtOAc (2 × 15 mL). The aqueous layer was neutralized to pH 7 with 2.0 N HCl and extracted again with EtOAc (2 × 15 mL). The aqueous layers were discarded and the combined organic layers were extracted with 2.0 N HCl (3 × 20 mL) (NOTE: this process separates nitrogen containing products capable of forming HCl salts (in aqueous phase) from other organic

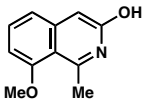
products (in organic phase)). The organic layers were discarded and the combined aqueous layers were neutralized to pH 7 with 2.0 N NaOH and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified either by recrystallization or flash chromatography over silica gel.

5.4.2.4 Spectroscopic Data for 3-Hydroxyisoquinolines



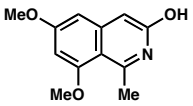
1-Methyl-3-hydroxyisoquinoline (569)[63]

Purified via recrystallization from boiling EtOAc to yield a yellow solid (84% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.18 (br s, 1H), 7.99 (dd, J = 8.5, 1.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.51 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H), 7.26 (ddd, J = 8.3, 6.8, 1.0 Hz, 1H), 6.67 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.8, 157.2, 140.4, 130.6, 126.3, 126.1, 123.5, 122.1, 99.2, 21.3; IR (Neat Film, NaCl) 3384, 3244, 2641, 1668, 1627, 1454, 1382, 1234 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{10}H_9NO$ $[M+H]^+$: 160.0757, found 160.0765.



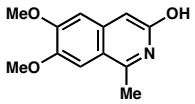
3-Hydroxyisoquinoline 571a (Table 5.4, Entry 1)

Purified via recrystallization from boiling EtOAc to yield a yellow solid (70% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (br s, 1H), 7.33 (dd, J = 8.1, 7.6 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.52 (s, 1H), 3.88 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.7, 158.6, 155.5, 143.7, 131.2, 118.4, 114.1, 102.4, 100.2, 56.0, 26.6; IR (Neat Film, NaCl) 2590, 1651, 1627, 1587, 1502, 1438, 1388 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{11}H_{11}NO_2$ [M+H]$^+$: 190.0863, found 190.0886.



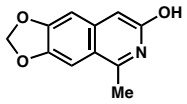
3-Hydroxyisoquinoline 571b (Table 5.4, Entry 2)[64]

Purified via recrystallization from boiling EtOAc to yield a yellow solid (81% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.40 (s, 1H), 6.29 (s, 1H), 6.10 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.8, 160.2, 160.0, 159.9, 157.9, 140.8, 122.2, 106.7, 98.8, 56.1, 55.7, 20.1; IR (Neat Film, NaCl) 2921, 2719, 1666, 1641, 1624, 1560, 1497, 1430, 1178 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{12}H_{13}NO_3$ [M+H]$^+$: 220.0968, found 220.0963.



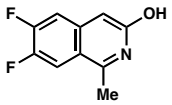
3-Hydroxyisoquinoline 571c (Table 5.4, Entry 3)[65]

Purified via recrystallization from boiling EtOAc to yield a yellow solid (75% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.64 (s, 1H), 6.58 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 155.1, 147.7, 146.4, 142.0, 113.5, 104.8, 102.9, 102.5, 56.3, 56.1, 17.5; IR (Neat Film, NaCl) 3251, 2939, 2836, 1645, 1488, 1433, 1245, 1161, 1029 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{12}H_{13}NO_3$ $[M^{\bullet}]^{-}$: 219.0895, found 219.0884.



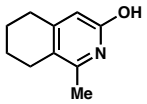
3-Hydroxyisoquinoline 571d (Table 5.4, Entry 4)[64]

Purified via recrystallization from boiling EtOAc to yield a yellow solid (77% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 (s, 1H), 6.96 (s, 1H), 6.50 (s, 1H), 6.08 (s, 2H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.6, 151.3, 145.7, 139.9, 131.6, 106.9, 105.0, 101.8, 101.4, 101.1, 20.8; IR (Neat Film, NaCl) 3306, 2918, 1658, 1651, 1620, 1478, 1433, 1231 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{11}H_9NO_3$ $[M+H]^{+}$: 204.0655, found 204.0656.



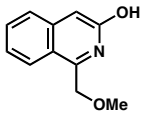
3-Hydroxyisoquinoline 571e (Table 5.4, Entry 5)

Purified via recrystallization from boiling EtOAc to yield a pale yellow solid (73% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.86 (br s, 1H), 8.04 (dd, J = 12.0, 8.3 Hz, 1H), 7.71 (dd, J = 12.0, 8.1 Hz, 1H), 6.73 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.3 (d, $J_{C–F}$ = 2.3 Hz), 153.5 (d, $J_{C–F}$ = 16.6 Hz), 151.5 (d, $J_{C–F}$ = 16.6 Hz), 148.0 (d, $J_{C–F}$ = 16.6 Hz), 146.1 (d, $J_{C–F}$ = 16.6 Hz), 138.3 (d, $J_{C–F}$ = 9.7 Hz), 113.1 (d, $J_{C–F}$ = 15.2 Hz), 111.8 (d, $J_{C–F}$ = 17.5 Hz), 99.2, 21.7; ^{19}F NMR (282 MHz, DMSO-d_6) δ –132.5 (app quintet, J = 11.0 Hz), –140.5 (app q, J = 11.0 Hz); IR (Neat Film, NaCl) 2613, 1679, 1656, 1516, 1488, 1454, 1336 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{10}H_7F_2NO$ $[M+H]^+$: 196.0568, found 196.0573.



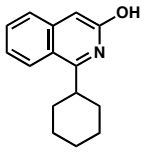
3-Hydroxyisoquinoline 571f (Table 5.4, Entry 6)[66]

Purified via flash chromatography (SiO_2, 20:80 EtOAc/hexanes) to yield a white solid (54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (s, 1H), 2.64 (t, J = 6.1 Hz, 2H), 2.44 (t, J = 6.5 Hz, 2H), 2.27 (s, 3H), 1.80–1.74 (comp m, 2H), 1.73–1.67 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 154.3, 142.3, 114.3, 114.2, 30.2, 24.2, 23.0, 22.2, 16.5; IR (Neat Film, NaCl) 2942, 1651, 1609, 1536, 1450, 1251, 1172, 1103 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{10}H_{13}NO$ $[M+H]^+$: 164.1070, found 164.1065.



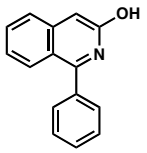
3-Hydroxyisoquinoline 576a (Table 5.5, Entry 1)

Purified via flash chromatography (SiO_2, 40:60 → 50:50 EtOAc/hexanes) to yield a yellow solid (82% yield). R_f = 0.20 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.53 (ddd, *J* = 8.5, 6.8, 1.2 Hz, 1H), 7.29 (ddd, *J* = 8.8, 6.8, 1.2 Hz, 1H), 6.99 (s, 1H), 5.02 (s, 2H), 3.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 153.3, 141.8, 131.0, 126.1, 125.6, 123.9, 121.2, 104.0, 71.5, 58.7; IR (Neat Film, NaCl) 2929, 2670, 2595, 1629, 1562, 1514, 1457, 1326, 1103 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{11}H_{11}NO_2$ $[M+H]^+$: 190.0863, found 190.0860.



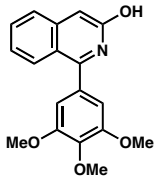
3-Hydroxyisoquinoline 576b (Table 5.5, Entry 2)

Purified via flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a yellow solid (81% yield). R_f = 0.20 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.37 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1H), 7.09 (ddd, *J* = 8.8, 6.6, 1.0 Hz, 1H), 6.73 (s, 1H), 3.46 (tt, *J* = 11.8, 3.4 Hz, 1H), 2.04–1.76 (comp m, 7H), 1.54–1.42 (comp m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 159.8, 143.2, 131.0, 126.3, 125.1, 122.5, 117.5, 104.4, 39.8, 31.5, 26.7, 25.6; IR (Neat Film, NaCl) 3208, 2930, 2855, 1694, 1651, 1602, 1452, 1374, 1258, 1066 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{15}H_{17}NO$ $[M+H]^+$: 228.1383, found 228.1382.



3-Hydroxyisoquinoline 576c (Table 5.5, Entry 3)[67]

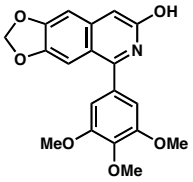
Purified via flash chromatography (SiO_2, 40:60 EtOAc/hexanes) to yield a yellow solid (79% yield). R_f = 0.27 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.61–7.58 (m, 2H), 7.56–7.52 (comp m, 3H), 7.49 (ddd, *J* = 8.8, 6.6, 1.2 Hz, 1H), 7.18 (ddd, *J* = 8.8, 6.6, 1.2 Hz, 1H), 6.93 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 157.1, 142.0, 136.4, 130.7, 130.0, 129.2, 128.4, 127.8, 125.9, 123.7, 121.2, 103.1; IR (Neat Film, NaCl) 3151, 3058, 2883, 1662, 1639, 1552, 1450 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{15}H_{11}NO$ $[M+H]^+$: 222.0913, found 222.0917.



3-Hydroxyisoquinoline 576d (Table 5.5, Entry 4)

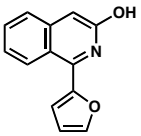
Purified via flash chromatography (SiO_2, 30:70 EtOAc/hexanes) to yield a yellow solid (68% yield). R_f = 0.14 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.50 (ddd, *J* = 8.5, 6.6, 1.2 Hz, 1H), 7.19 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1H), 6.93 (s, 1H), 6.80 (s, 2H), 3.95 (s, 3H), 3.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 156.0, 153.0, 142.4, 138.8, 131.1, 130.9, 127.7, 126.0, 123.7, 120.5, 107.3, 103.5, 60.9, 56.1; IR (Neat Film, NaCl) 3191, 2940, 1711, 1694,

1679, 1640, 1585, 1505, 1454, 1414, 1354, 1335, 1236, 1127 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{18}H_{17}NO_4$ $[M+H]^+$: 312.1230, found 312.1249.



3-Hydroxyisoquinoline 576e (Table 5.5, Entry 5)

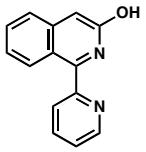
Purified via flash chromatography (SiO_2, 40:60 → 80:20 EtOAc/hexanes) to yield a yellow-orange solid (73% yield). R_f = 0.15 (70:30 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.80 (s, 1H), 6.72 (app s, 3H), 6.01 (s, 2H), 3.92 (s, 3H), 3.82 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 153.1, 152.1, 150.5, 146.4, 142.6, 138.7, 130.2, 115.7, 106.9, 105.5, 101.8, 101.5, 100.6, 60.9, 56.1; IR (Neat Film, NaCl) 3181, 2938, 1643, 1612, 1584, 1455, 1236, 1126 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{19}H_{17}NO_6$ $[M+H]^+$: 356.1129, found356.1126.



3-Hydroxyisoquinoline 576f (Table 5.5, Entry 6)

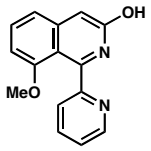
Purified via flash chromatography (SiO_2, 25:75 → 35:65 EtOAc/hexanes) to yield a red-orange solid (85% yield). R_f = 0.13 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.8 Hz, 1H), 7.66 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 3.4 Hz, 1H), 6.97 (s, 1H), 6.60 (dd, *J* = 3.4, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 150.3, 144.4, 144.1, 142.5, 130.8, 126.9,

126.1, 124.4, 119.7, 114.0, 112.1, 104.6; IR (Neat Film, NaCl) 3057, 2893, 1634, 1551, 1444, 1300, 1152 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{13}H_9NO_2$ $[M+H]^+$: 212.0706, found 212.0717.



3-Hydroxyisoquinoline 576g (Table 5.5, Entry 7)

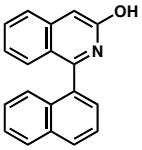
Purified via flash chromatography (SiO_2, 40:60 → 70:30 EtOAc/hexanes) to yield a yellow solid (72% yield). R_f = 0.20 (50:50 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (ddd, *J* = 4.9, 1.0, 0.7 Hz, 1H), 8.22 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.90 (td, *J* = 7.6, 1.7 Hz, 1H), 7.85 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.51 (ddd, *J* = 8.6, 6.6, 1.0 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.27 (ddd, *J* = 8.9, 6.6, 1.0 Hz, 1H), 7.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 155.2, 154.0, 149.3, 142.1, 136.8, 130.7, 127.4, 125.9, 125.4, 124.5, 123.7, 121.4, 104.3; IR (Neat Film, NaCl) 3056, 2665, 1626, 1587, 1555, 1445, 1312, 1132 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{14}H_{10}N_2O$ $[M+H]^+$: 223.0866, found 223.0870.



3-Hydroxyisoquinoline 576h (Table 5.5, Entry 8)

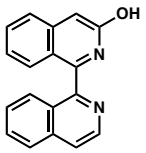
Purified via flash chromatography (SiO_2, 60:40 EtOAc/hexanes → 80:15:5 EtOAc/hexanes/CH_2Cl_2) to yield a yellow solid (94% yield). R_f = 0.13 (70:30

EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.73 (td, *J* = 7.6, 1.7 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.30 (ddd, *J* = 7.3, 4.9, 1.0 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.70 (br s, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 3.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 156.9, 148.3, 144.2, 135.3, 131.6, 130.1, 124.0, 122.8, 121.6, 118.4, 115.0, 113.0, 102.3, 55.2; IR (Neat Film, NaCl) 3062, 2937, 1643, 1638, 1556, 1434, 1390, 1281, 1147 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{15}H_{12}N_2O_2$ $[M+H]^+$: 253.0972, found 253.0843.



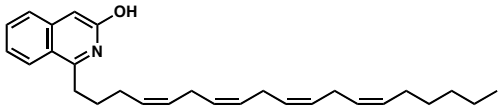
3-Hydroxyisoquinoline 576i (Table 5.5, Entry 9)

Purified via flash chromatography (SiO_2, 20:80 EtOAc/hexanes → 80:10:10 EtOAc/hexanes/CH_2Cl_2) to yield a yellow solid (69% yield). R_f = 0.15 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.64 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.58 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.3, 6.6, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1H), 7.41 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.37 (dd, *J* = 6.6, 1.2 Hz, 1H), 7.35 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.05 (ddd, *J* = 8.6, 6.6, 1.2 Hz, 1H), 6.96 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 156.4, 141.5, 134.2, 133.6, 132.0, 130.9, 129.5, 128.4, 127.8, 126.7, 126.2, 125.8, 125.7, 125.1, 123.8, 122.8, 105.0, 103.0; IR (Neat Film, NaCl) 2968, 2665, 2582, 1626, 1601, 1558, 1449, 1317 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{19}H_{13}NO$ $[M+H]^+$: 272.1070, found 272.1082.



3-Hydroxyisoquinoline 576j (Table 5.5, Entry 10)

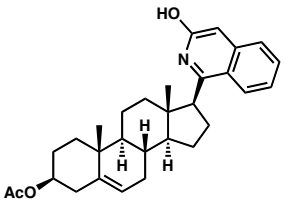
Purified via flash chromatography (SiO_2, 50:50 → 60:40 EtOAc/hexanes) to yield a yellow solid (68% yield). R_f = 0.30 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.9 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.85 (dd, *J* = 5.9, 1.0 Hz, 1H), 7.72 (ddd, *J* = 8.3, 6.6, 1.0 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.64 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.52 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1H), 7.47 (ddd, *J* = 8.5, 6.8, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.6, 6.8, 1.2), 7.02 (d, *J* = 0.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 156.4, 155.4, 142.2, 141.2, 136.6, 130.7, 130.5, 127.7, 127.6, 127.2, 127.0, 126.9, 125.9, 124.4, 123.4, 121.4, 102.7; IR (Neat Film, NaCl) 3053, 2665, 2586, 1624, 1554, 1448, 1318, 1136 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{18}H_{12}N_2O$ $[M+H]^+$: 273.1022, found 273.1033.



3-Hydroxyisoquinoline 576k (Table 5.5, Entry 11)

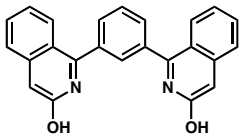
Purified via flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a pale yellow oil (81% yield). R_f = 0.16 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.40 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.8, 6.6, 1.0 Hz, 1H), 6.76 (s, 1H), 5.49–5.31 (comp m, 8H), 3.26 (dd, *J* = 8.1, 7.8 Hz, 2H), 2.86–2.78 (comp m, 6H), 2.28 (dd, *J* = 7.1, 6.8 Hz, 2H), 2.05 (dd, *J* = 7.1, 7.1 Hz, 2H), 1.92 (tt, *J* = 7.8, 7.6 Hz, 2H), 1.38–1.24 (comp m, 6H), 0.88 (t, *J* = 6.8 Hz,

3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 156.4, 143.1, 131.3, 130.5, 129.1, 129.0, 128.6, 128.2, 128.1, 127.9, 127.6, 126.1, 125.7, 122.7, 118.3, 104.6, 31.5, 31.3, 30.4, 29.4, 27.2, 27.1, 25.7, 25.6, 25.5, 22.6, 14.1; IR (Neat Film, NaCl) 3265, 2930, 1697, 1602, 1458, 1284 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{28}H_{37}NO$ $[M+H]^+$: 404.2948, found 404.2951.



3-Hydroxyisoquinoline 576l (Table 5.5, Entry 12)

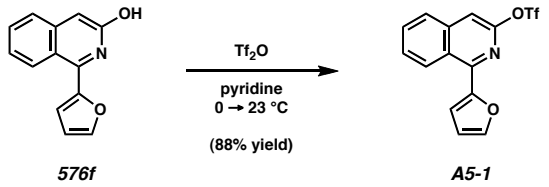
Purified via flash chromatography (SiO_2, 15:85 → 50:50 EtOAc/hexanes) to yield a yellow oil (62% yield). R_f = 0.20 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.36 (ddd, *J* = 8.5, 6.6, 1.0 Hz, 1H), 7.05 (ddd, *J* = 8.8, 6.6, 1.2 Hz, 1H), 6.72 (s, 1H), 5.42 (d, *J* = 5.1 Hz, 1H), 4.62 (dddd, *J* = 5.9, 5.6, 5.4, 4.1 Hz, 1H), 3.72 (app t, *J* = 9.5 Hz, 1H), 2.67 (ddd, *J* = 11.2, 9.5, 2.5 Hz, 1H), 2.38–2.28 (comp m, 2H), 2.14–2.02 (comp m, 2H), 2.05 (s, 3H), 1.96–1.81 (comp m, 3H), 1.71–1.40 (comp m, 8H), 1.32 (app qd, *J* = 12.5, 4.8 Hz, 1H), 1.14 (app td, *J* = 13.4, 3.9 Hz, 1H), 1.06 (app td, *J* = 12.0, 4.8 Hz, 1H), 0.99 (s, 3H), 0.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.6, 159.9, 154.9, 143.0, 139.7, 130.9, 126.1, 122.4, 122.3, 119.9, 104.7, 73.8, 57.2, 50.5, 50.1, 47.0, 38.6, 38.1, 37.0, 36.7, 32.2, 31.9, 27.7, 26.4, 25.0, 21.5, 21.0, 19.3, 13.5; IR (Neat Film, NaCl) 3221, 2943, 1729, 1711, 1600, 1438, 1375, 1365, 1249, 1033 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{30}H_{37}NO_3$ $[M+H]^+$: 460.2846, found 460.2845.



3-Hydroxyisoquinoline 576m (Table 5.5, Entry 13)[68]

Purified via flash chromatography (SiO_2, 50:50 → 75:25 EtOAc/hexanes) to yield a yellow solid (66% yield). R_f = 0.46 (70:30 EtOAc/hexanes); ^{1}H NMR (500 MHz, CD_3OD) δ 7.93 (t, J = 8.5 Hz, 2H), 7.91 (t, J = 1.2 Hz, 1H), 7.85 (dd, J = 8.1, 1.2 Hz, 2H), 7.79 (dd, J = 8.5, 7.1 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.56 (ddd, J = 8.5, 6.8, 1.2 Hz, 2H), 7.27 (ddd, J = 8.5, 6.6, 1.2 Hz, 2H), 6.95 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.9, 160.0, 141.1, 139.1, 131.5, 130.6, 130.4, 128.6, 127.2, 126.4, 124.6, 122.0, 100.5; IR (Neat Film, NaCl) 3181, 3063, 2958, 1671, 1639, 1624, 1555, 1446, 1343, 1281, 1152, 1024 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{24}H_{16}N_2O_2$ $[M+H]^+$: 365.1285, found 365.1293.

5.4.2.5 Synthesis of a 1,3-diarylisoquinoline via Suzuki coupling

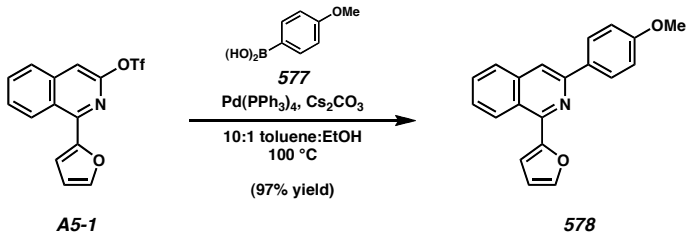


576f *A5-1*

Isoquinoline triflate A5-1

A flame-dried 1 dram vial equipped with a magnetic stir bar and a screw cap with PTFE septum was charged with 3-hydroxyisoquinoline **576f** (0.028 g, 0.133 mmol) and pyridine (0.7 mL). The mixture was cooled to 0 °C in an ice bath while stirring, and Tf_2O (0.033 mL, 0.196 mmol, 1.5 equiv) was then added dropwise via syringe. The reaction was stirred at 0 °C for 5 minutes, after which the ice bath was removed. The resulting brown solution was allowed to warm to room temperature while stirring for 11 hours. When TLC analysis showed complete consumption of the 3-hydroxyisoquinoline **576f**, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography over silica gel (SiO_2, 10:90 EtOAc/hexanes) to yield triflate **A5-1** as a pale yellow oil (0.040 g, 88% yield). $R_f = 0.70$ (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (dd, J = 8.6, 0.7 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.77 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.75 (d, J = 0.73 Hz, 1H), 7.70 (ddd, J = 8.6, 6.8, 1.5 Hz, 1H), 7.44 (s, 1H), 7.40 (dd, J = 3.4, 0.7 Hz, 1H), 6.67 (dd, J = 3.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 151.0, 148.2, 144.9, 140.3, 131.3, 128.5, 127.5, 127.4, 124.8, 118.8 (q, $J_{C–F}$ = 320.8 Hz), 115.0, 112.4, 109.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ –72.8; IR (Neat Film, NaCl) 3141, 3077, 2923, 1593, 1547,

1484, 1420, 1321, 1224, 1212, 1139, 1109, 1016 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_8F_3NO_4S$ $[M^{\bullet}]^+$: 343.0126, found 343.0131.



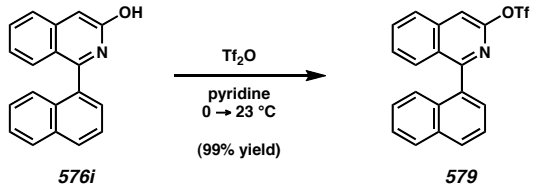
Diarylisoquinoline 578

A flame-dried 1 dram vial equipped with a magnetic stir bar and a screw cap with a PTFE septum was charged with $Pd(PPh_3)_4$ (0.0035 g, 0.003 mmol, 0.05 equiv), caesium carbonate (0.0220 g, 0.068 mmol, 1.2 equiv), and 4-methoxyphenylboronic acid (**577**) (0.0142 g, 0.093 mmol, 1.6 equiv). The vial was evacuated and backfilled with argon (×2). Isoquinoline triflate **A5-1** (0.020 g, 0.058 mmol) in toluene (0.6 mL) was added *via* syringe followed by ethanol (0.06 mL). The vial was sealed and heated to 100 °C. After stirring for 18 h, the reaction was cooled to room temperature and filtered through a plug of silica under EtOAc elution. The solvents were removed under vacuum and the crude yellow residue was purified via flash chromatography (SiO_2, 3:97 EtOAc/hexanes) to yield 1,3-diarylisoquinoline **578** as a colorless oil (0.0169 g, 97% yield). R_f = 0.37 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.94 (s, 1H), 7.87 (ddd, *J* = 8.1, 0.7, 0.5 Hz, 1H), 7.74 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.67 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.37 (dd, *J* = 3.4, 0.7 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.67 (dd, *J* = 3.4, 2.0 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 155.0, 149.8, 148.4, 143.7, 138.3, 132.0, 130.0, 128.2, 127.4, 127.0, 126.9, 124.2, 114.9, 114.1, 112.6, 111.8, 55.4; IR (Neat Film, NaCl)

3052, 2958, 2933, 2835, 1607, 1554, 1514, 1487, 1439, 1334, 1289, 1249, 1173, 1033, 1012 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{15}NO_2$ $[M^{\bullet}]^+$: 301.1103, found 301.1099.

5.4.2.6 Synthesis of QUINAP

Spectroscopic data is provided only for those compounds that have not been previously reported in the literature (i.e., **579**). Spectroscopic data for compounds **580**,[69] **581**,[55b] and QUINAP (**582**)[55a] match those previously reported in all respects.

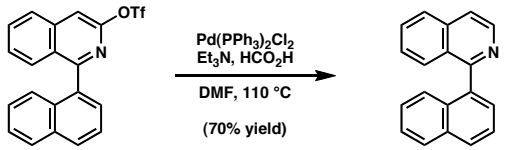


576i *579*

Isoquinoline triflate 579

A flame-dried 10 mL round-bottomed flask equipped with a magnetic stir bar was charged with 3-hydroxyisoquinoline **576i** (0.053 g, 0.195 mmol) and pyridine (1.2 mL). The mixture was cooled to 0 °C in an ice bath while stirring, and Tf_2O (0.056 mL, 0.333 mmol, 1.7 equiv) was then added dropwise via syringe. The reaction was stirred at 0 °C for 5 minutes, after which the ice bath was removed. The resulting orange brown solution was allowed to warm to room temperature while stirring for 12 hours. When TLC analysis showed complete consumption of the 3-hydroxyisoquinoline **576i**, the reaction was quenched by the addition of water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography over

silica gel (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield triflate **579** as a colorless oil (0.0782 g, 99% yield). R_f = 0.70 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.78 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.72 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.69 (d, *J* = 0.7 Hz, 1H), 7.63 (dd, *J* = 7.0, 8.1 Hz, 1H), 7.58 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.49 (ddd, *J* = 8.5, 6.8, 1.0 Hz, 1H), 7.45 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.38 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 151.3, 139.2, 134.7, 133.7, 131.9, 131.6, 129.7, 128.4, 128.3, 128.2, 128.2, 127.3, 126.7, 126.2, 125.6, 125.0, 118.8 (q, *J* = 320.8 Hz), 110.4; ^{19}F (282 MHz, $CDCl_3$) δ –72.9; IR (Neat Film, NaCl) 3066, 1622, 1594, 1553, 1509, 1504, 1422, 1321, 1244, 1227, 1212, 1138, 1110 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{12}F_3NO_3S$ $[M^{\bullet}]^+$: 403.0490, found 403.0504.

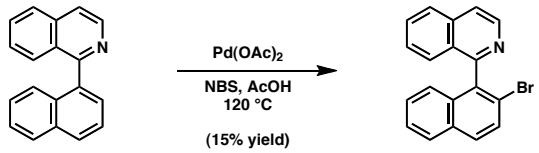


579 ***580***

Naphthyl isoquinoline 580

A flame-dried 1 dram vial equipped with a magnetic stir bar and a screw cap with a PTFE septum was charged with 1-(1'-naphthyl)-3-(trifluoromethanesulfonyloxy)-isoquinoline **579** (0.020 g, 0.0496 mmol) and DMF (0.6 mL). The mixture was stirred for approximately 5 minutes at room temperature, after which $Pd(PPh_3)_2Cl_2$ (0.075 g, 0.0107 mmol, 20 mol%), Et_3N (0.040 mL, 0.287 mmol, 5.8 equiv), and formic acid (0.020 mL, 0.530 mmol, 10.6 equiv) were added sequentially. The resulting mixture was heated to 110 °C for 90 minutes. The reaction was then cooled to room temperature

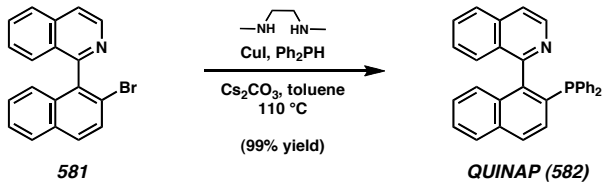
when TLC analysis showed complete consumption of triflate **579**, diluted with water (2 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified via flash chromatography over silica gel (SiO_2, 5:95 → 20:80 EtOAc/hexanes) to yield napthyl isoquinoline **580** as a white solid (0.0087 g, 70% yield). Spectroscopic data matched those reported in the literature.[69]



580 ***581***

1-(2'-bromo-1'-naphthyl)isoquinoline 581

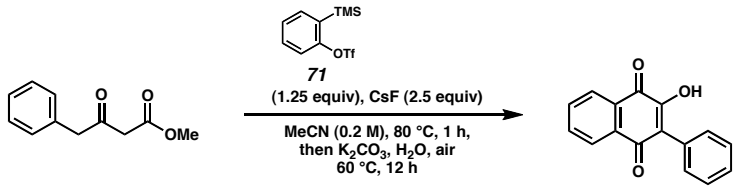
This procedure is based on the method of Sanford *et al.*[53b] A flame-dried 1 dram vial equipped with a magnetic stir bar and a screw cap with a PTFE septum was charged with naphthyl isoquinoline **580** (0.021 mg, 0.081 mmol), $Pd(OAc)_2$ (0.063 g, 0.028 mmol, 35 mol%), NBS (0.016 g, 0.090 mmol, 1.1 equiv), and AcOH (0.8 mL). The vial was sealed with a Teflon-lined screw cap, and the mixture was heated to 120 °C while stirring for 17 hours. The solvent was then evaporated under reduced pressure and the crude residue was purified by flash chromatography over silica gel (SiO_2, 5:95 → 20:80 EtOAc/hexanes) to yield bromonaphthyl isoquinoline **581** as a colorless film (0.0039 g, 15% yield). Spectroscopic data matched those reported in the literature.[55b]



1-(2'-diphenylphosphino-1'-naphthyl)isoquinoline (QUINAP, 582)

This procedure is based on our previously reported variant of Buchwald's copper-catalyzed phosphine–aryl halide coupling reaction.[54] A flame-dried 1 dram vial equipped with a magnetic stir bar and a screw cap with a PTFE septum was charged with copper(I) iodide (0.0022 g, 0.012 mmol, 70 mol%), diphenylphosphine (0.0061 mL, 0.035 mmol, 2.1 equiv), *N,N'*-dimethylethylenediamine (0.002 mL, 0.019 mmol, 1.1 equiv), and toluene (0.1 mL). The mixture was stirred for 30 minutes at room temperature. Following this, caesium carbonate (0.0221 g, 0.068 mmol, 4 equiv), 1-(2-bromo-1-naphthyl)isoquinoline (**581**) (0.0055 g, 0.017 mmol, 1 equiv), and toluene (0.15 mL) were added, and the vial was sealed and heated to 110 °C. After stirring for 14 hours, the reaction mixture was allowed to cool to room temperature and filtered through celite under dichloromethane elution (20 mL). The solution was concentrated under reduced pressure and the crude residue was purified via flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield QUINAP (**582**) as a colorless film (0.0075 g, 99% yield). Spectroscopic data matched those reported in the literature.[55a]

5.4.2.7 Representative Procedure for the Synthesis of 2-Hydroxy-1,4-naphthoquinones From β-Ketoesters

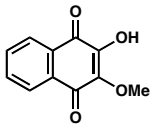


583b *588b*

A flame-dried 15 mL reaction tube equipped with a magnetic stir bar was charged with cesium fluoride (0.152 g, 1.00 mmol, 2.5 equiv). The reaction tube was sealed with a rubber septum, evacuated, and back-filled with argon (×2). Acetonitrile (2 mL), methyl 3-oxo-4-phenylbutanoate (**583b**) (0.077 g, 0.4 mmol, 1.0 equiv) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**71**) (0.121 mL, 0.498 mmol, 1.25 equiv) were sequentially added. The reaction was then heated to 80 °C while stirring for 1 h. The reaction was cooled to room temperature when TLC analysis showed complete consumption of methyl 3-oxo-4-phenylbutanoate (**583b**) (NOTE: at this point, the major component of the reaction is the acyl-alkylated arene). Potassium carbonate (0.276 g, 5.0 equiv) in water (2 mL) was added via syringe and the biphasic mixture was vigorously stirred at room temperature for 30 min. The septum was then removed and the reaction was heated to 60 °C while open to air for 12 h. The reaction was cooled to room temperature when TLC analysis showed complete consumption of the acyl-alkylated arene intermediate. The reaction was diluted with EtOAc (10 mL) and extracted with 1.0 N K_2CO_3 (5 × 15 mL). The organic layer was discarded. The combined aqueous layers were acidified to pH 1 with 2.0 N HCl (**Warning:** vigorous gas evolution) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL)

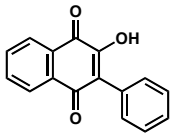
and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified via flash chromatography over silica gel.

5.4.2.8 Spectroscopic Data for 2-Hydroxy-1,4-naphthoquinones



2-Hydroxy-1,4-naphthoquinone 588a (Table 5.6, Entry 1)[70]

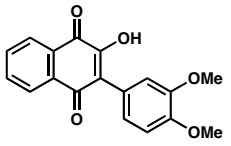
Purified via flash chromatography (SiO_2, 40:60 EtOAc/hexanes) to yield an orange solid (86% yield). R_f = 0.11 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 8.06 (ddd, *J* = 7.6, 1.2, 0.5 Hz, 1H), 7.74 (td, *J* = 7.6, 1.5 Hz, 1H), 7.69 (td, *J* = 7.6, 1.5 Hz, 1H), 6.91 (br s, 1H), 4.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.2, 181.1, 142.5, 140.5, 134.7, 133.4, 131.3, 129.1, 126.8, 126.1, 60.7; IR (Neat Film, NaCl) 3370, 2967, 1673, 1639, 1592, 1461, 1276, 1203 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{11}H_8O_4$ $[M+H]^+$: 205.0495, found 205.0498.



2-Hydroxy-1,4-naphthoquinone 588b (Table 5.6, Entry 2)[71]

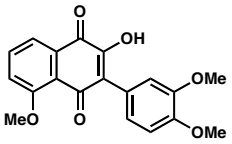
Purified via flash chromatography (SiO_2, 10:90 EtOAc/hexanes) to yield a bright yellow solid (92% yield). R_f = 0.37 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.17 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.83 (td, *J* = 7.6, 1.5 Hz, 1H), 7.76 (td, *J* = 7.6, 1.5 Hz, 1H), 7.60 (br s, 1H), 7.52 (d, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 2H), 7.42 (tt, *J* = 7.3, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9, 182.1,

152.4, 135.5, 133.4, 133.1, 130.9, 130.2, 129.5, 128.9, 128.2, 127.5, 126.4, 122.4; IR (Neat Film, NaCl) 3345, 3057, 1651, 1594, 1365, 1332, 1282, 1000 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{16}H_{10}O_3$ $[M+H]^+$: 251.0703, found 251.0705.



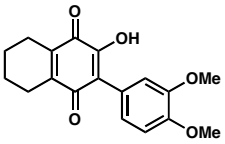
2-Hydroxy-1,4-naphthoquinone 588c (Table 5.6, Entry 3)[72]

Purified via flash chromatography (SiO_2, 15:85 → 25:75 EtOAc/hexanes) to yield a dark red solid (78% yield). R_f = 0.45 (50:50 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (ddd, *J* = 7.6, 1.2, 0.5 Hz, 1H), 8.16 (ddd, *J* = 7.6, 1.2, 0.5 Hz, 1H), 7.82 (td, *J* = 7.6, 1.2 Hz, 1H), 7.74 (td, *J* = 7.6, 1.2 Hz, 1H), 7.61 (br s, 1H), 7.17 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 181.8, 151.9, 149.4, 148.4, 135.2, 133.1, 132.9, 129.3, 127.3, 126.1, 124.0, 122.4, 121.9, 114.0, 110.6, 56.0, 55.9; IR (Neat Film, NaCl) 3363, 2938, 1712, 1655, 1594, 1516, 1364, 1260, 1145, 1026 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{18}H_{14}O_5$ $[M+H]^+$: 311.0914, found 311.0914.



2-Hydroxy-1,4-naphthoquinone 588d (Table 5.6, Entry 4)

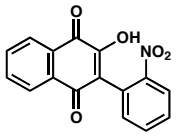
Purified via flash chromatography (SiO_2, 30:70 → 70:30 EtOAc/hexanes) to yield a dark red solid (84% yield). R_f = 0.10 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.67 (dd, *J* = 8.6, 7.6 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.13 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.7, 182.2, 159.9, 150.5, 149.3, 148.2, 134.1, 131.6, 124.1, 123.4, 122.9, 120.1, 119.9, 119.0, 114.2, 110.5, 56.6, 56.0, 55.9; IR (Neat Film, NaCl) 3347, 2937, 2838, 1650, 1585, 1516, 1472, 1369, 1280, 1256, 1016 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{19}H_{16}O_6$ $[M+H]^+$: 341.1020, found 341.1022.



2-hydroxy-5,6,7,8-tetrahydronaphtha-1,4-quinone 588e (Table 5.6, Entry 5)

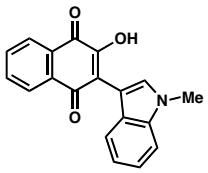
Purified via flash chromatography (SiO_2, 20:80 EtOAc/hexanes) to yield a red solid (61% yield). R_f = 0.53 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (br s, 1H), 7.07 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.52 (ddd, *J* = 12.5, 4.4, 2.0 Hz, 4H), 1.75 (comp m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.6, 183.6, 149.5, 149.2, 148.3, 145.3, 138.1, 123.7, 122.4, 118.7, 113.9, 110.6, 55.9, 55.8, 23.4, 22.1, 21.2, 21.0; IR (Neat Film, NaCl) 3347, 2937, 1639,

1516, 1346, 1257, 1143, 1026 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{18}H_{18}O_5$ $[M+H]^+$: 315.1227, found 315.1228.



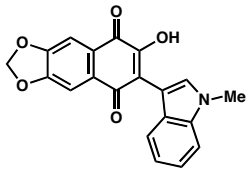
2-Hydroxy-1,4-naphthoquinone 588f (Table 5.6, Entry 6)[73]

Purified via flash chromatography (SiO_2, 50:50 → 70:30 EtOAc/hexanes) to yield a red-orange solid (70% yield). R_f = 0.37 (70:30 EtOAc/hexanes); ^1H NMR (500 MHz, CD_3OD) δ 8.15 (dd, *J* = 7.3, 1.5 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.07 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.83 (td, *J* = 7.5, 1.5 Hz, 1H), 7.79 (td, *J* = 7.5, 1.5 Hz, 1H), 7.74 (td, *J* = 7.6, 1.2 Hz, 1H), 7.60 (td, *J* = 7.6, 1.5 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 183.0, 181.5, 151.3, 149.3, 135.5, 134.2, 133.7, 133.5, 132.2, 130.5, 129.9, 127.0, 126.6, 126.5, 124.6, 105.0; IR (Neat Film, NaCl) 3325, 2923, 1674, 1639, 1523, 1363, 1303, 1286, 1263 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_9NO_5$ $[M+H]^+$: 296.0553, found 296.0564.



2-Hydroxy-1,4-naphthoquinone 588g (Table 5.6, Entry 7)[74]

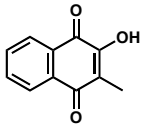
Purified via flash chromatography (SiO_2, 5:95 → 15:85 EtOAc/hexanes) to yield a dark blue solid (84% yield). R_f = 0.17 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 8.16 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 7.79 (td, *J* = 7.6, 1.5 Hz, 1H), 7.73 (td, *J* = 7.6, 1.2 Hz, 1H), 7.68 (br s, 1H), 7.65 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.64 (s, 1H), 7.38 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.29 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4, 181.2, 150.4, 136.9, 134.7, 133.2, 133.1, 133.0, 129.8, 127.2, 126.8, 125.9, 122.4, 122.1, 120.1, 118.1, 109.6, 104.2, 33.3; IR (Neat Film, NaCl) 3350, 3052, 2928, 1651, 1627, 1525, 1474, 1362, 1332, 1287, 1240, 1104 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{19}H_{13}NO_3$ $[M+H]^+$: 304.0968, found 304.0968.



2-Hydroxy-1,4-naphthoquinone 588h (Table 5.6, Entry 8)

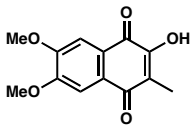
Purified via flash chromatography (SiO_2, 15:85 → 20:80 EtOAc/hexanes) to yield a dark blue solid (88% yield). R_f = 0.60 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (br s, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.61 (s, 1H), 7.58 (s, 1H), 7.53 (s, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.28 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 6.17 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.5, 180.1, 153.1, 151.6,

150.1, 136.8, 132.8, 130.6, 126.8, 126.0, 122.3, 122.0, 120.0, 116.9, 109.5, 107.2, 105.4, 104.1, 102.7, 33.2; IR (Neat Film, NaCl) 3346, 2911, 1706, 1647, 1595, 1478, 1330, 1306, 1239, 1035 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{13}NO_5$ $[M^{\bullet}]^+$: 347.0794, found 347.0804.



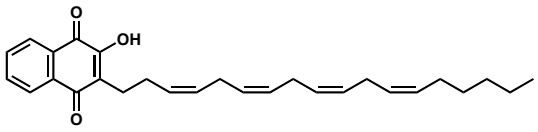
2-Hydroxy-1,4-naphthoquinone 588i (Phthiocol) (Table 5.6, Entry 9)[75,76]

Purified via flash chromatography (SiO_2, 10:90 → 15:85 EtOAc/hexanes) to yield a yellow solid (80% yield). R_f = 0.37 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (ddd, *J* = 7.8, 1.2, 0.5 Hz, 1H), 8.09 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 7.76 (td, *J* = 7.8, 1.5 Hz, 1H), 7.69 (td, *J* = 7.6, 1.2 Hz, 1H), 7.31 (br s, 1H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.0, 181.2, 153.1, 134.8, 133.0, 132.9, 129.4, 126.7, 126.1, 120.5, 8.9; IR (Neat Film, NaCl) 3336, 1658, 1592, 1395, 1349, 1305, 1278, 1208, 1181, 1072 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{11}H_8O_3$ $[M+H]^+$: 189.0546, found 189.0539.



2-Hydroxy-1,4-naphthoquinone 588j
(*O*-des-methyl-Stoechadone) (Table 5.6, Entry 10)[75,77]

Purified via flash chromatography (SiO_2, 15:85 → 25:75 EtOAc/hexanes) to yield a yellow-orange solid (63% yield). R_f = 0.63 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.48 (s, 1H), 7.28 (br s, 1H), 4.03 (s, 3H), 4.01 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.8, 180.5, 154.3, 152.9, 152.5, 128.1, 123.5, 119.2, 108.7, 107.6, 56.6, 56.5, 8.6; IR (Neat Film, NaCl) 3371, 2964, 1638, 1579, 1375, 1321, 1126, 1018 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{13}H_{12}O_5$ $[M+H]^+$: 249.0757, found 249.0764.



2-Hydroxy-1,4-naphthoquinone 588k (Table 5.6, Entry 11)[75]

Purified via flash chromatography (SiO_2, 5:95 EtOAc/hexanes) to yield a yellow oil (66% yield). R_f = 0.33 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 8.09 (ddd, *J* = 7.6, 1.2, 0.5 Hz, 1H), 7.76 (td, *J* = 7.6, 1.2 Hz, 1H), 7.69 (td, *J* = 7.6, 1.5 Hz, 1H), 7.35 (br s, 1H), 5.50 (ddt, *J* = 18, 7.5, 1.5 Hz, 1H), 5.45–5.27 (comp m, 7H), 2.85–2.77 (comp m, 6H), 2.70 (app t, *J* = 7.5 Hz, 2H), 2.36 (dt, *J* = 7.3, 7.1 Hz, 2H), 2.05 (dt, *J* = 7.3, 6.8 Hz, 2H), 1.38–1.24 (comp m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 181.4, 153.2, 134.9, 132.9, 132.8, 130.5, 129.4, 128.9, 128.8, 128.5, 128.2, 128.1, 127.9, 127.6, 126.8, 126.1, 123.8, 31.5,

29.3, 27.2, 25.9, 25.6, 25.6, 25.5, 23.3, 22.6, 14.1; IR (Neat Film, NaCl) 3377, 3012, 2928, 2857, 1774, 1664, 1648, 1594, 1371, 1348, 1276, 1216 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{28}H_{34}O_3$ $[M+H]^+$: 419.2581, found 419.2580.

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(62) The molar equivalents of carbonyl diimidazole, magnesium chloride, and potassium monomethyl malonate (**427**) were doubled for this substrate (i.e., 2.4 equiv carbonyl diimidazole, 2.0 equiv magnesium chloride, and 2.6 equiv potassium monomethyl malonate (**427**)).

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APPENDIX 5

Spectra Relevant to Chapter 5:

Expedient Synthesis of 3-Hydroxyisoquinolines and 2-Hydroxy-1,4-Naphthoquinones via One-Pot Aryne Acyl-Alkylation / Condensation

Figure A5.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of β-ketoester **575h** (Table 5.5, entry 10).

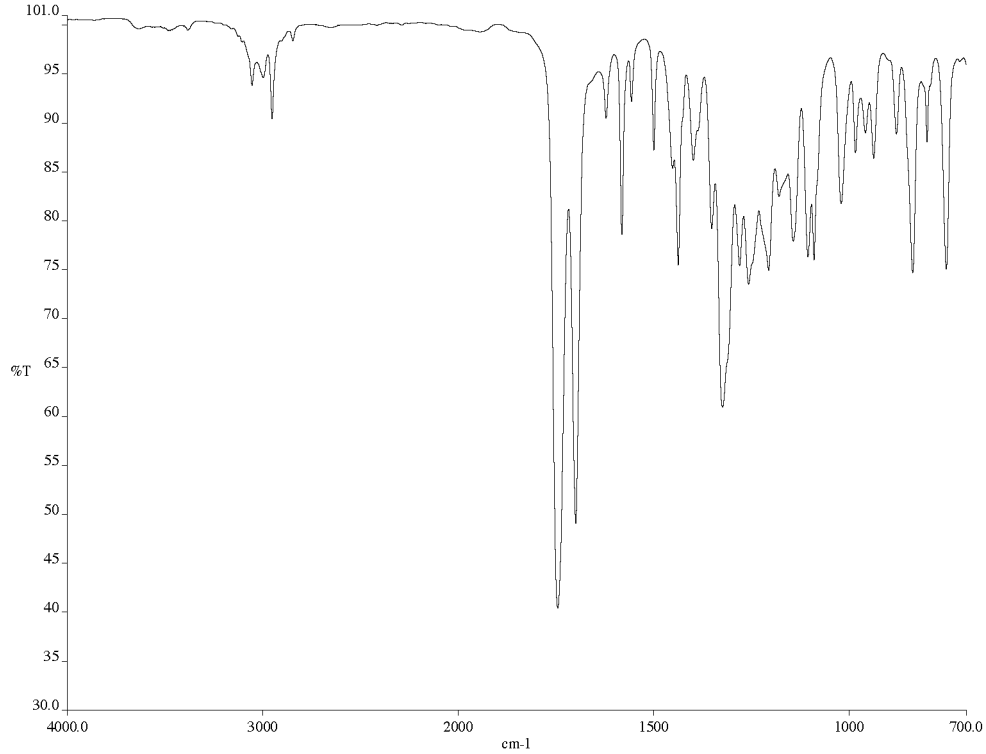


Figure A5.1.2 Infrared spectrum (thin film/NaCl) of β-ketoester **575h** (Table 5.5, entry 10).

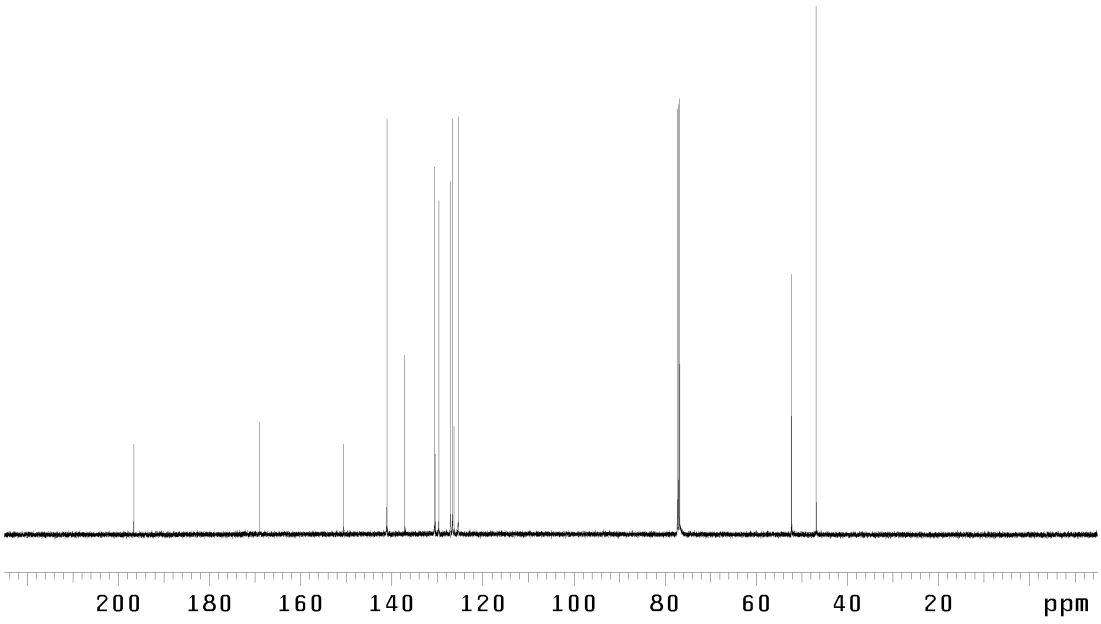


Figure A5.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of β-ketoester **575h** (Table 5.5, entry 10).

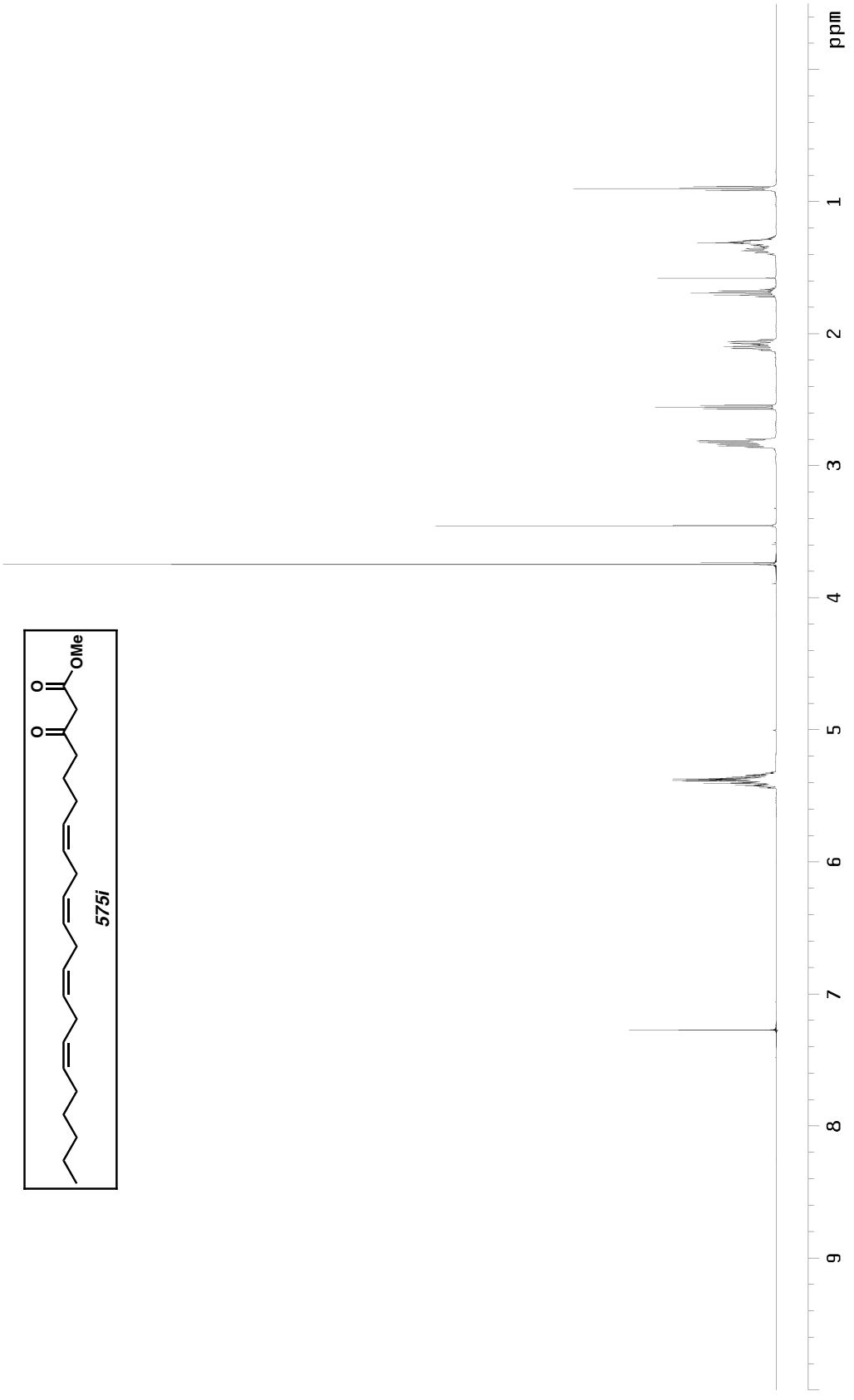


Figure A5.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of β-ketoester **575i** (Table 5.5, entry 11).

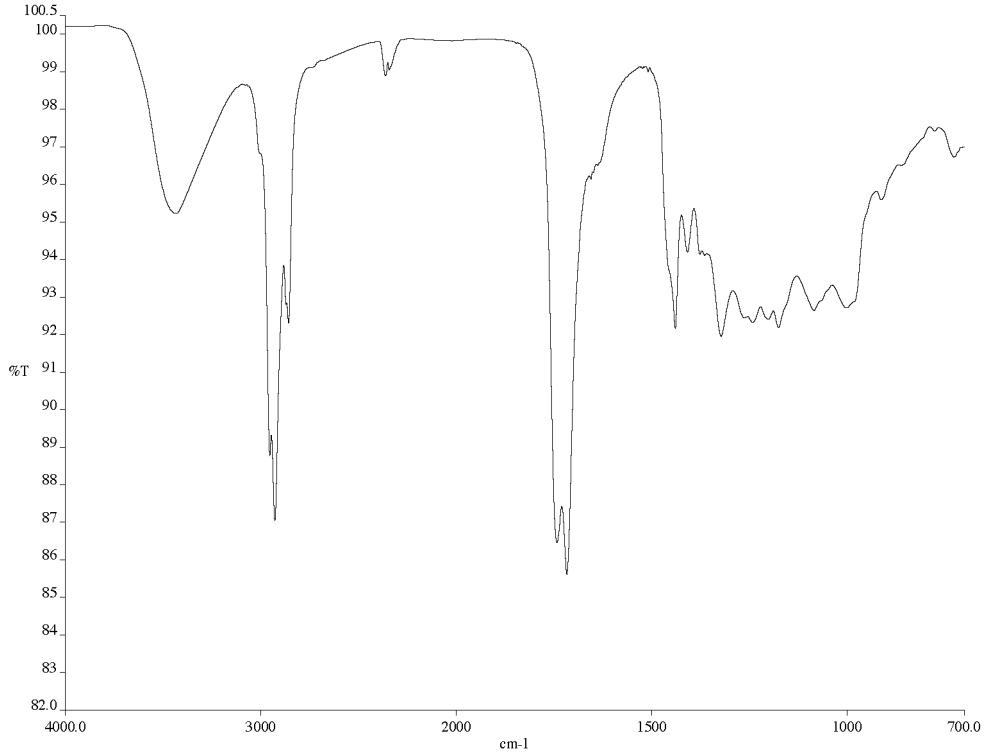


Figure A5.2.2 Infrared spectrum (thin film/NaCl) of β-ketoester **575i** (Table 5.5, entry 11).

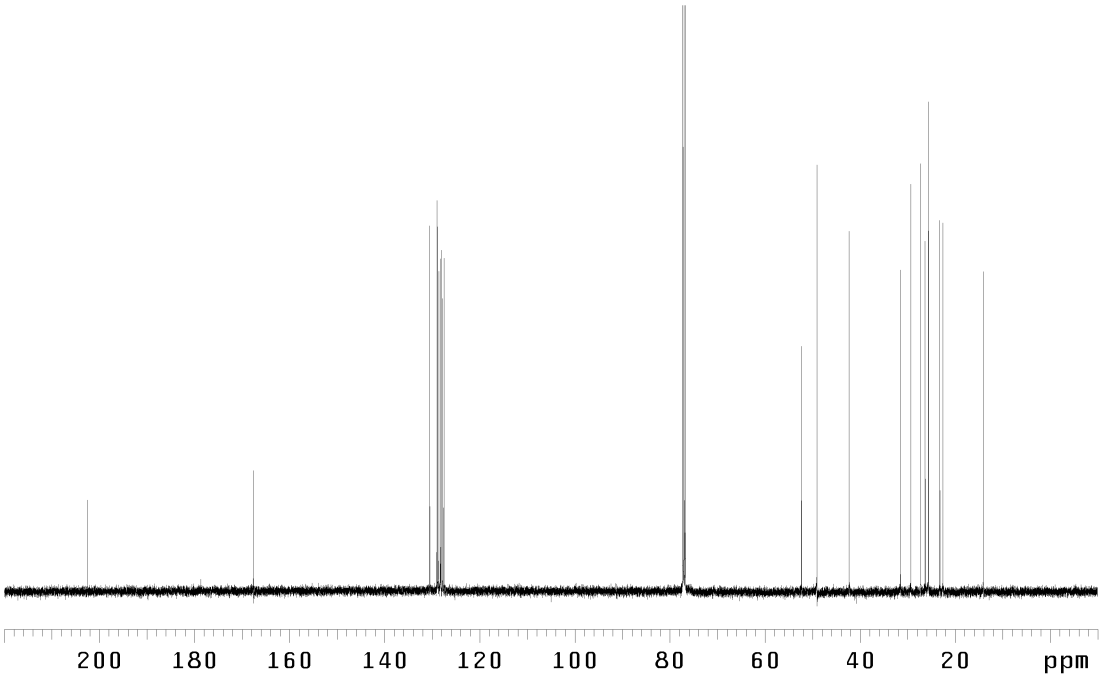


Figure A5.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of β-ketoester **575i** (Table 5.5, entry 11).

Figure A5.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of β-ketoester **575j** (Table 5.5, entry 12).

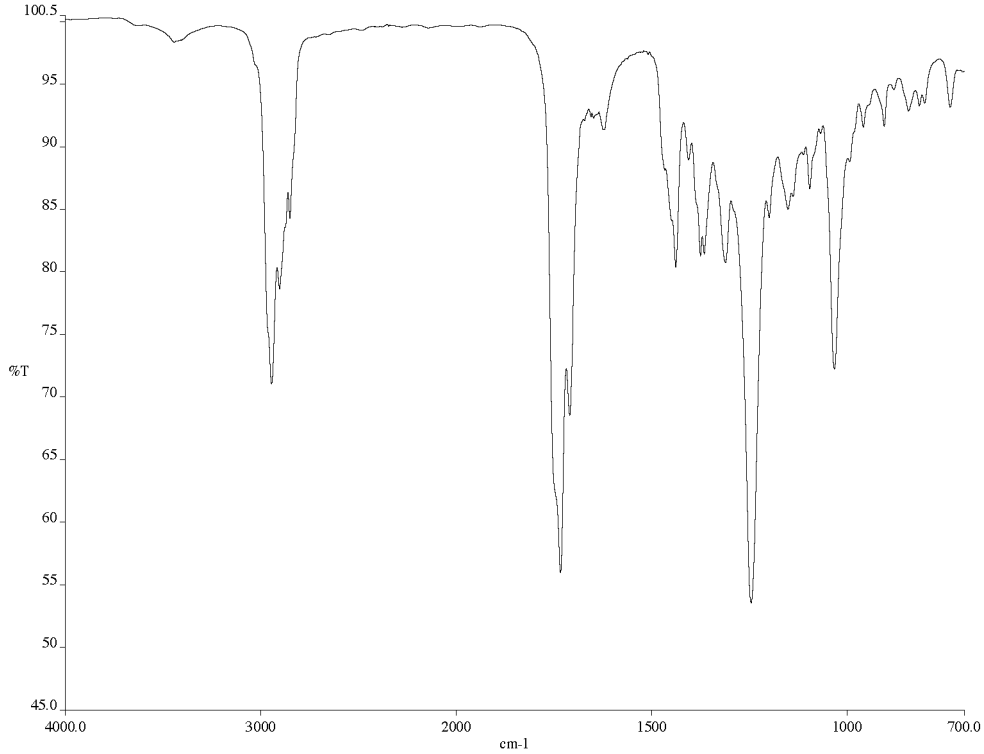


Figure A5.3.2 Infrared spectrum (thin film/NaCl) of β-ketoester **575j** (Table 5.5, entry 12).

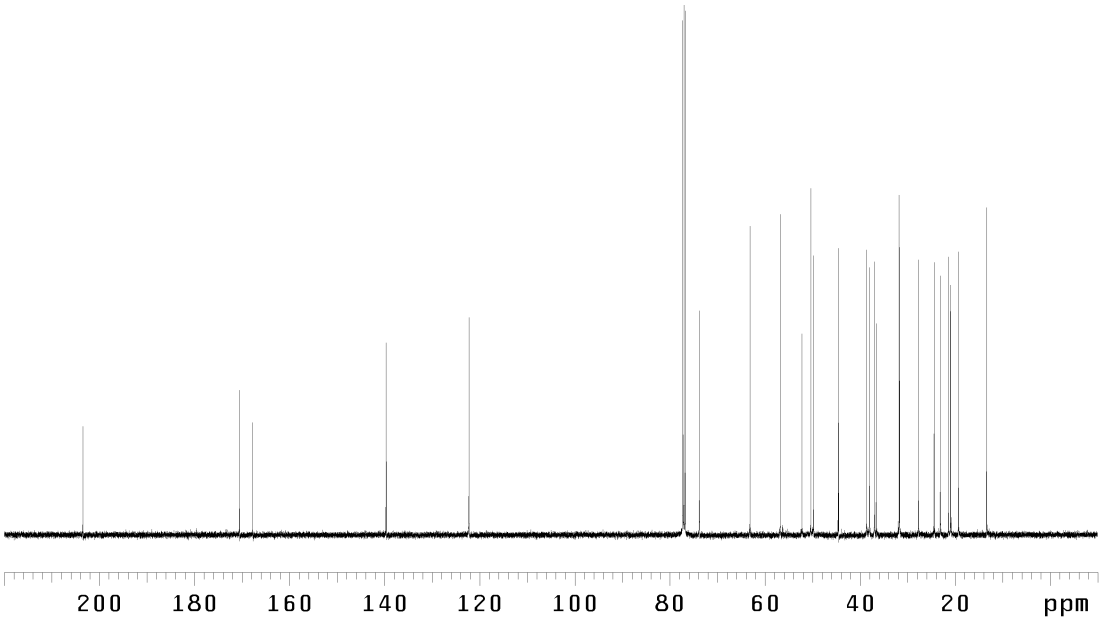


Figure A5.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of β-ketoester **575j** (Table 5.5, entry 12).

Figure A5.4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of β-ketoester **575k** (Table 5.5, entry 13).

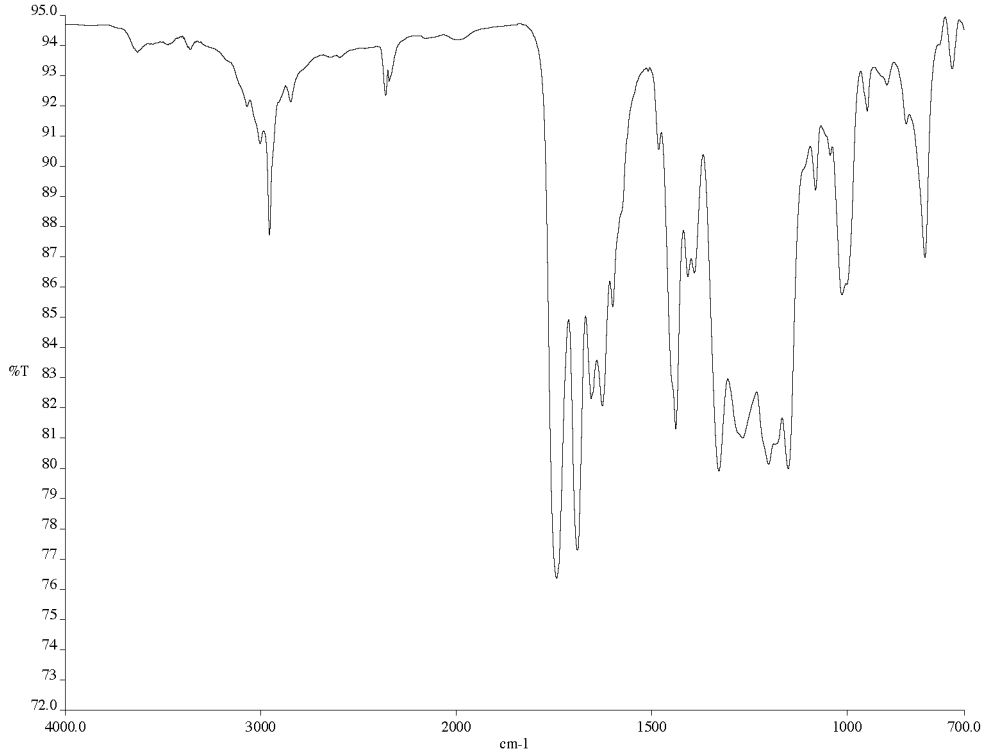


Figure A5.4.2 Infrared spectrum (thin film/NaCl) of β-ketoester **575k** (Table 5.5, entry 13).

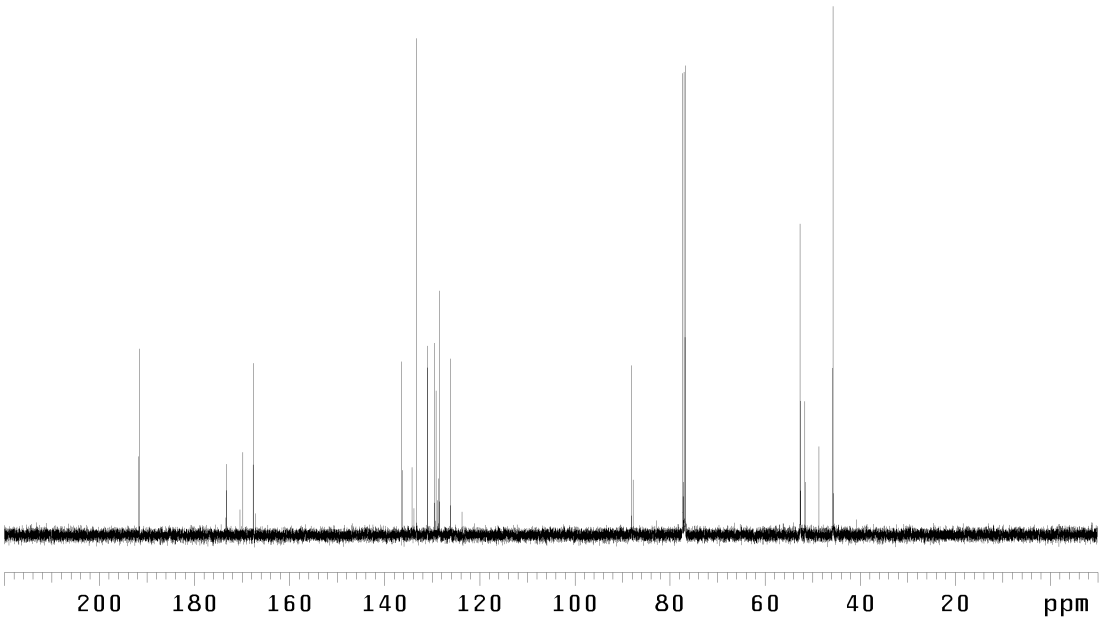


Figure A5.4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of β-ketoester **575k** (Table 5.5, entry 13).

Figure A5.5.1 ^{1}H NMR (500 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **569**.

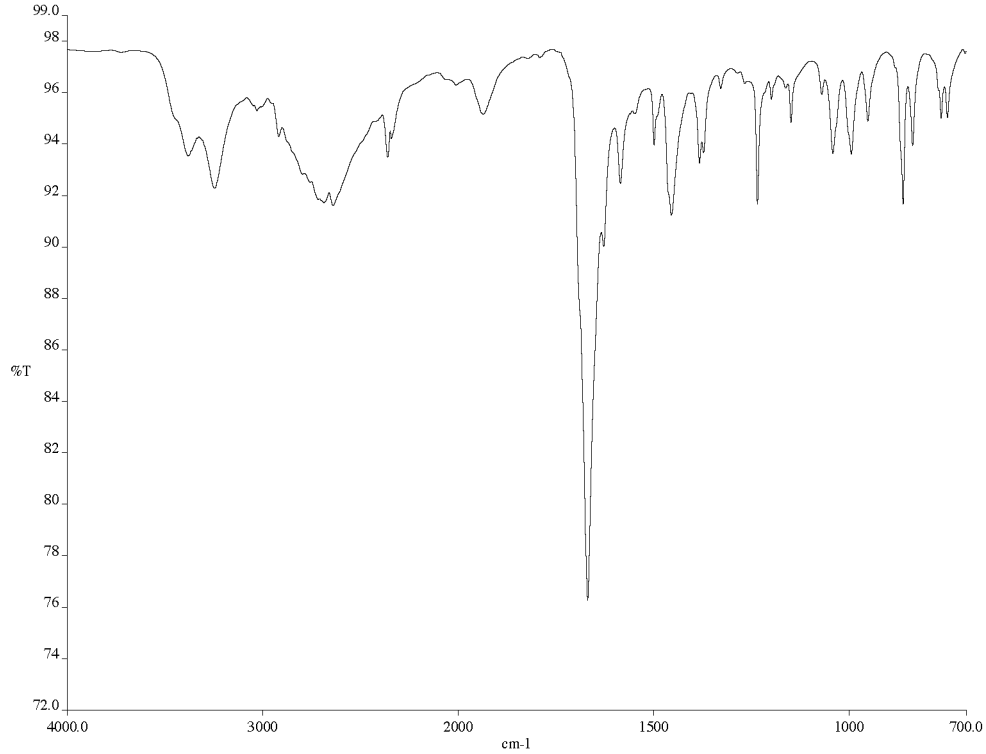


Figure A5.5.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **569**.

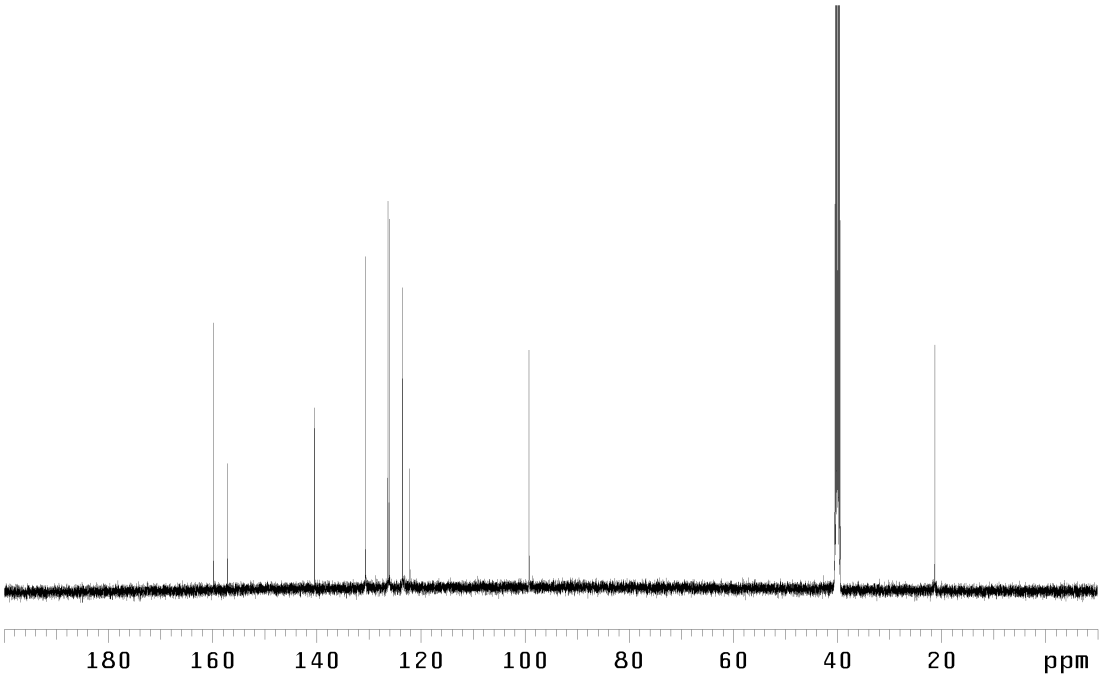


Figure A5.5.3 ^{13}C NMR (125 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **569**.

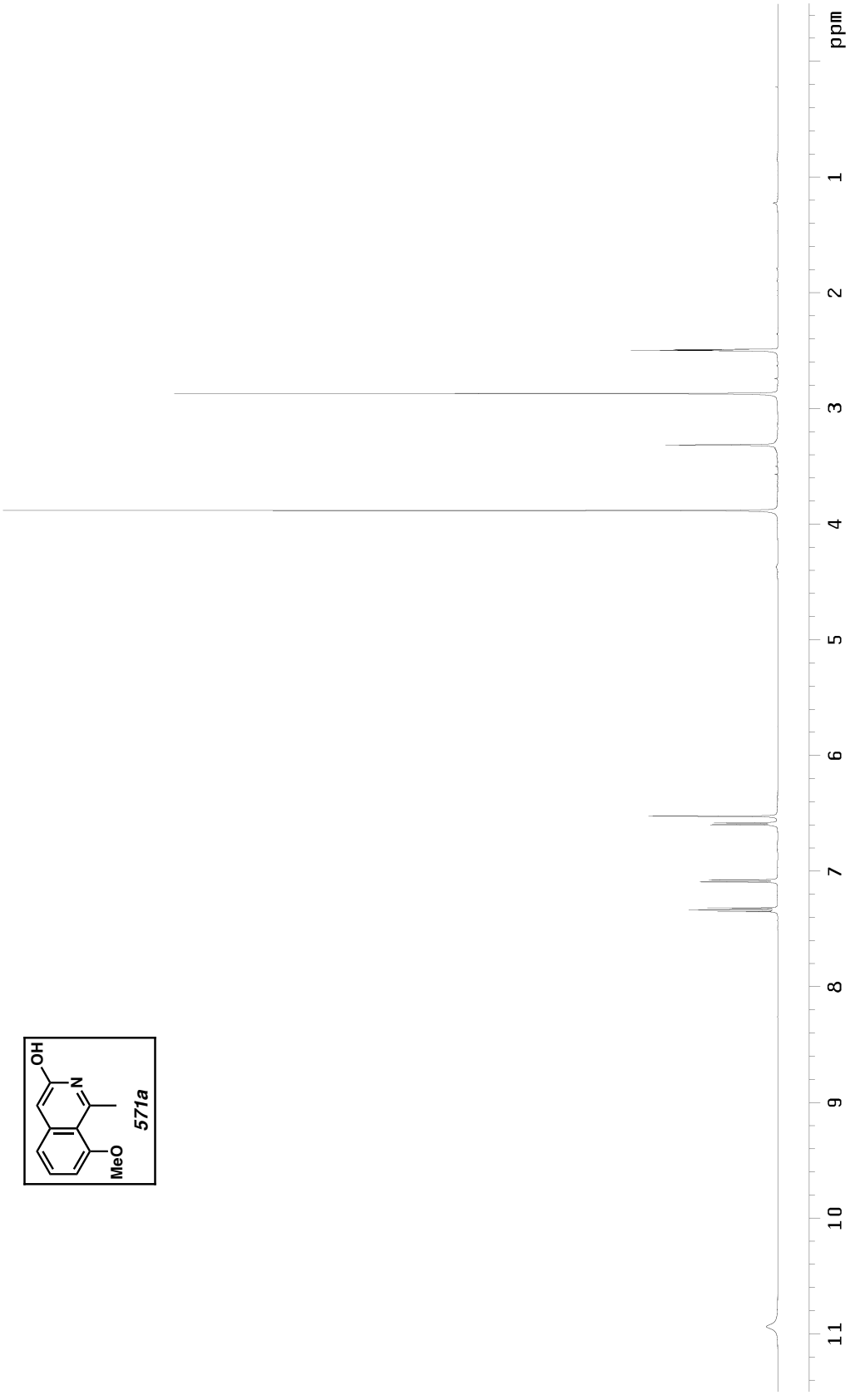


Figure A5.6.1 ^{1}H NMR (500 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571a** (Table 5.4, entry 1).

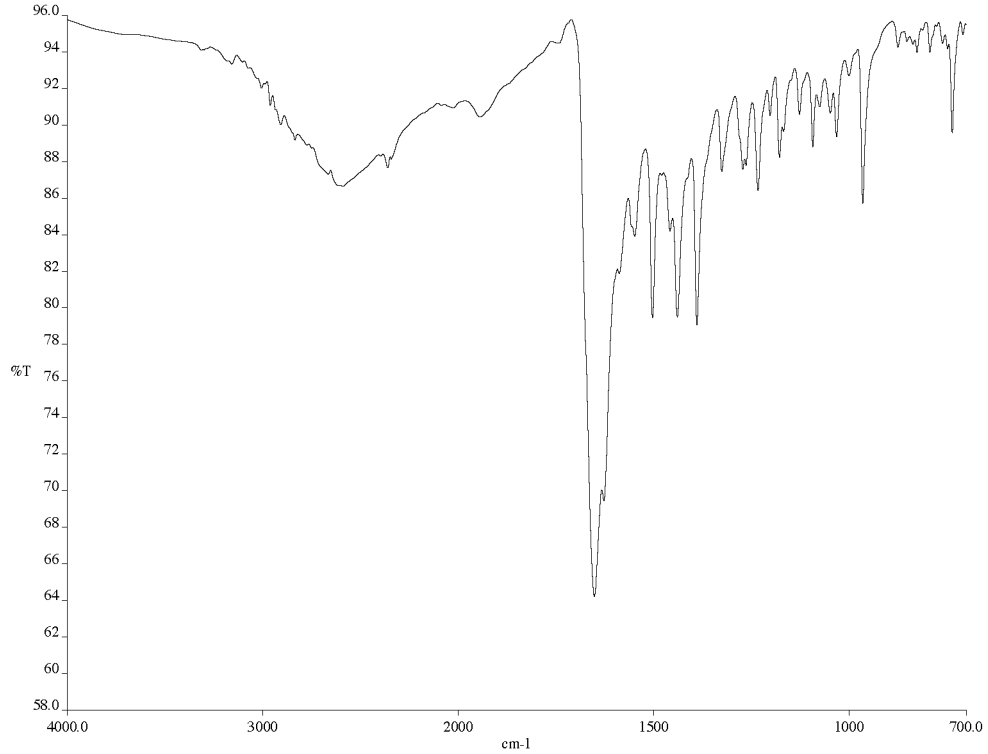


Figure A5.6.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **571a** (Table 5.4, entry 1).

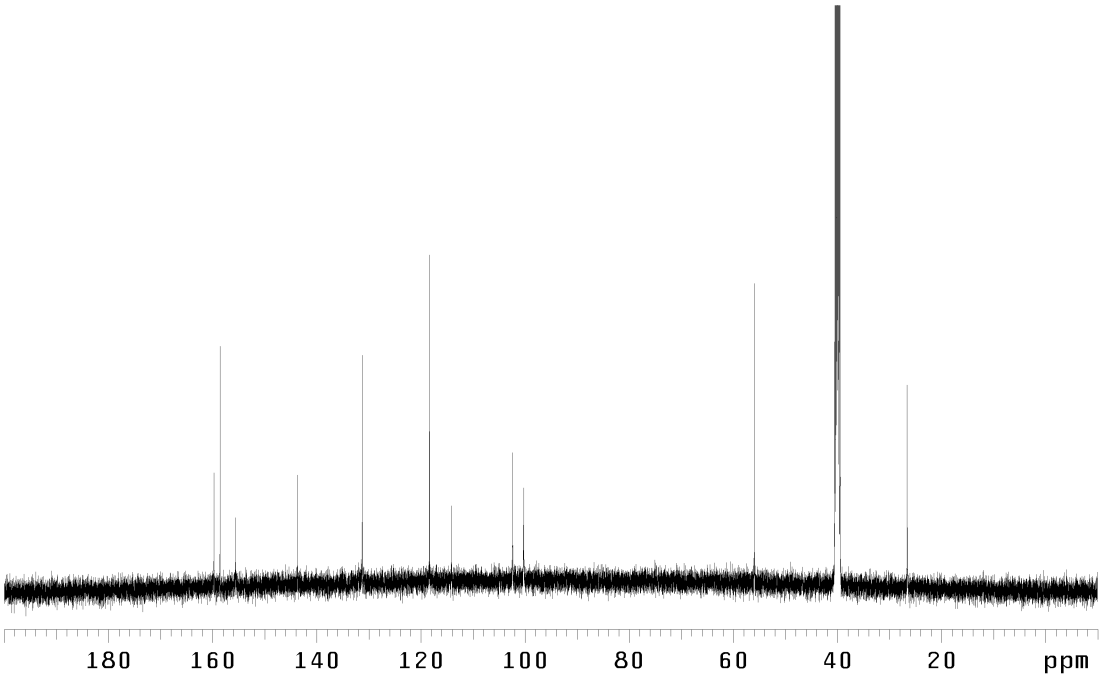


Figure 6.3 ^{13}C NMR (125 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571a** (Table 5.4, entry 1).

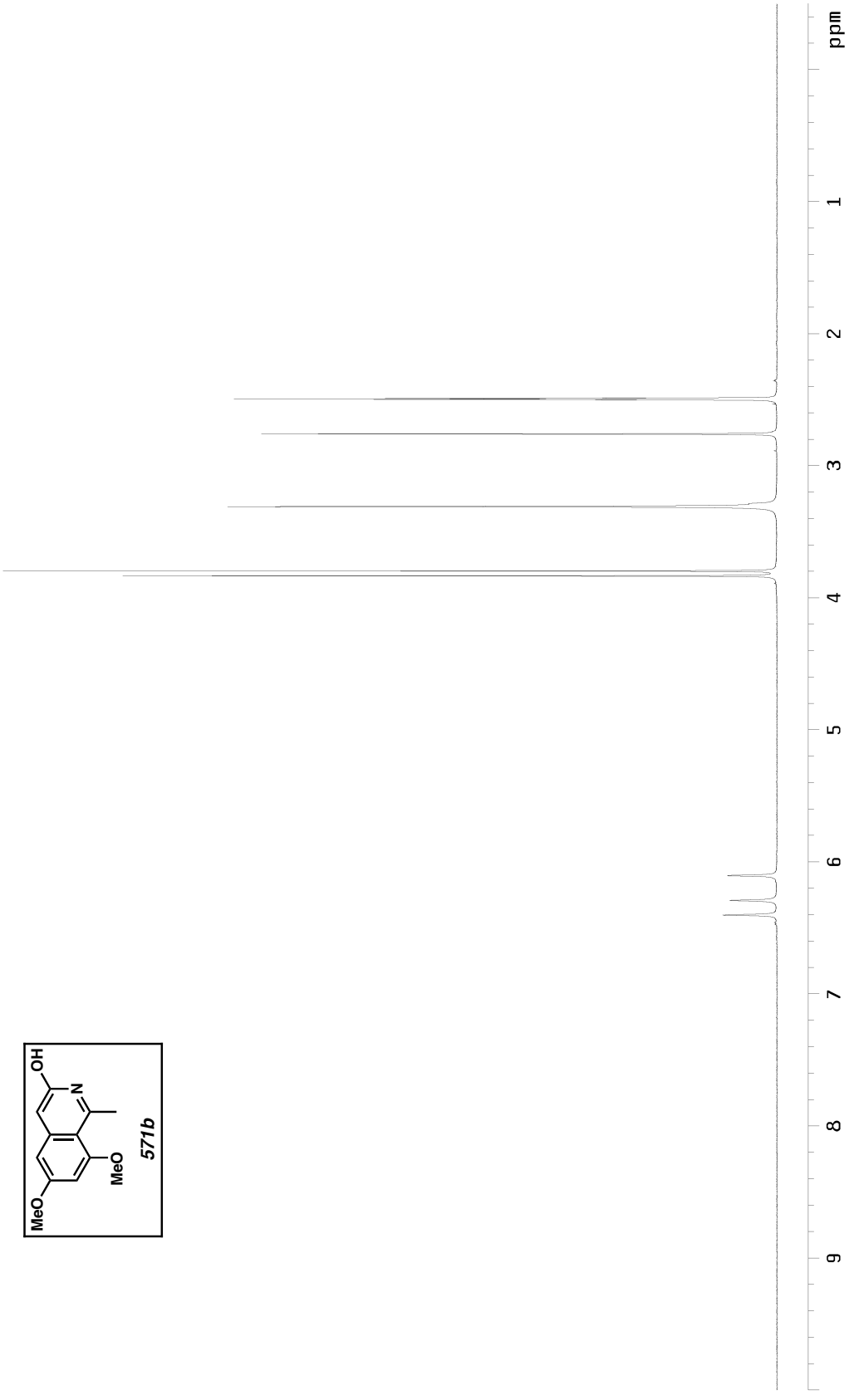


Figure A5.7.1 ^{1}H NMR (500 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571b** (Table 5.4, entry 2).

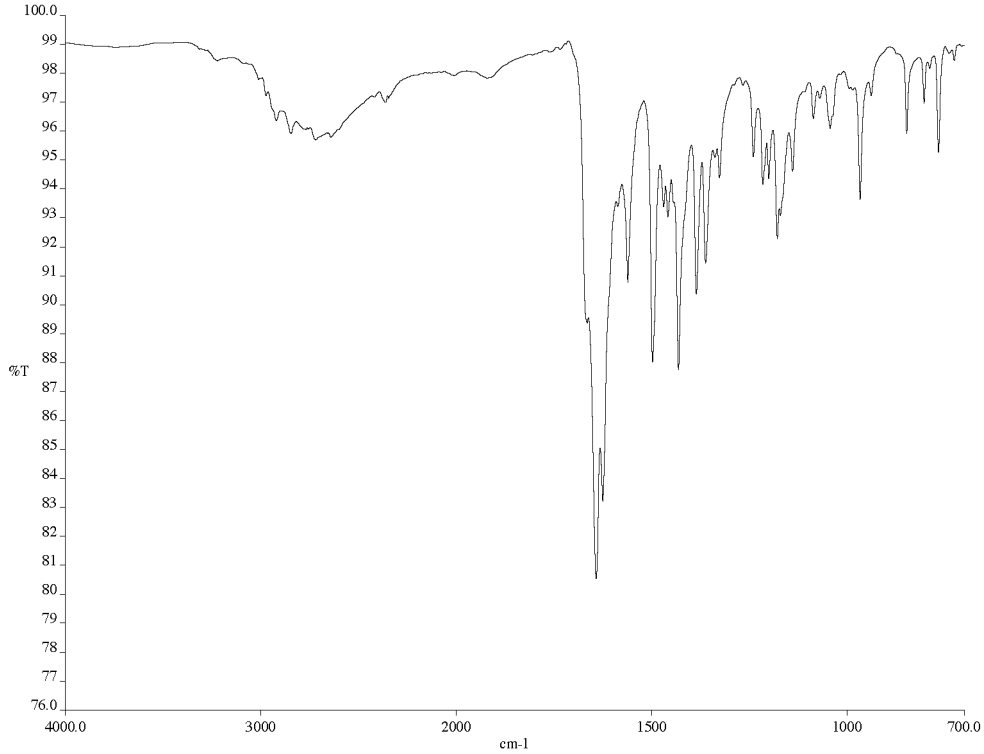


Figure A5.7.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **571b** (Table 5.4, entry 2).

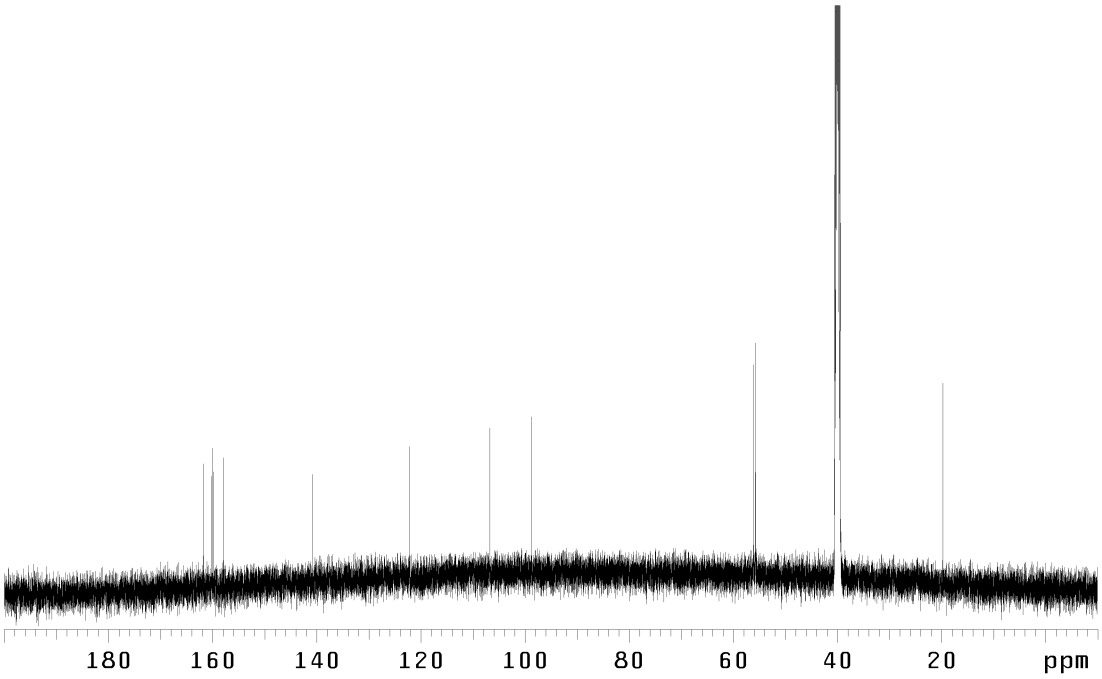


Figure A5.7.3 ^{13}C NMR (125 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571b** (Table 5.4, entry 2).

Figure A5.8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **571c** (Table 5.4, entry 3).

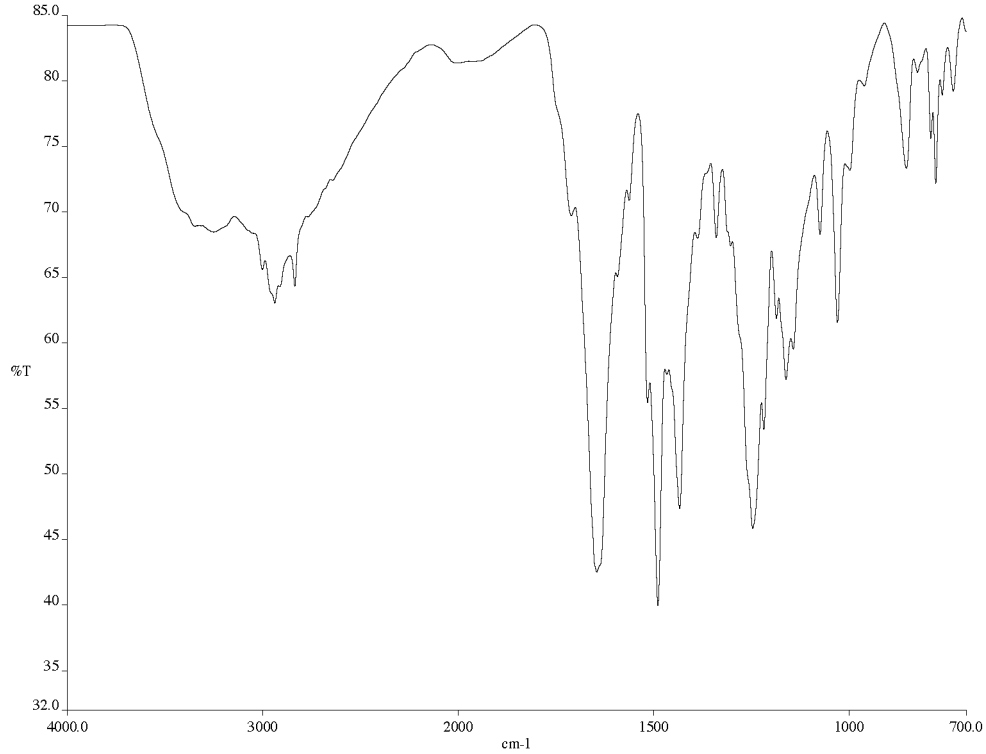


Figure A5.8.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **571c** (Table 5.4, entry 3).

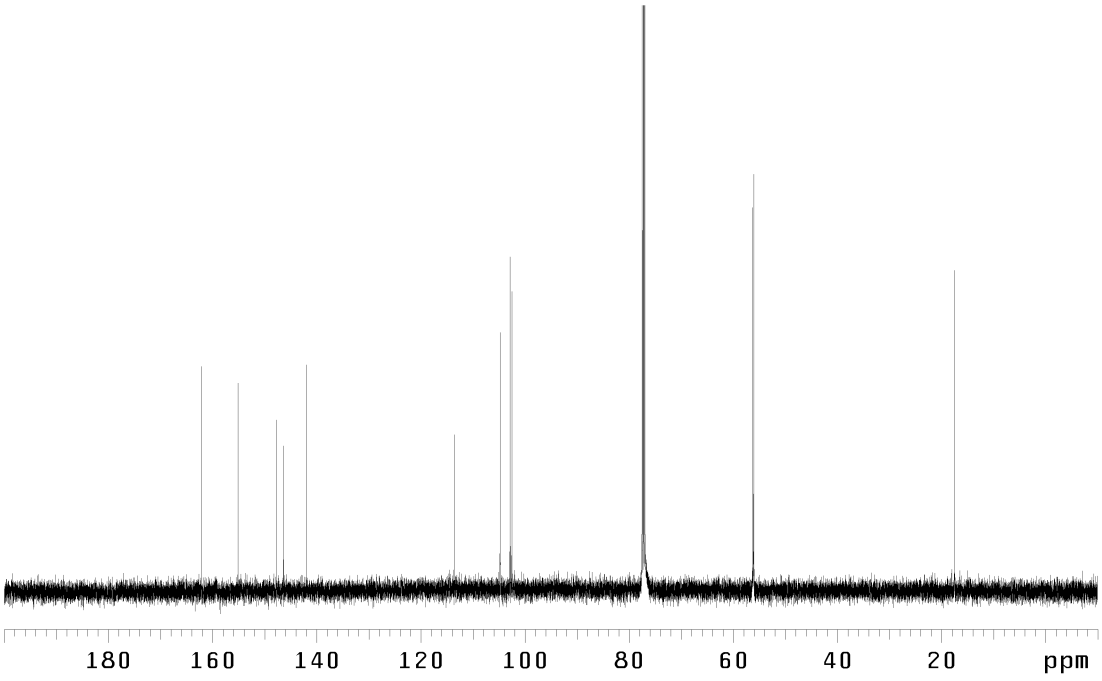


Figure A5.8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **571c** (Table 5.4, entry 3).

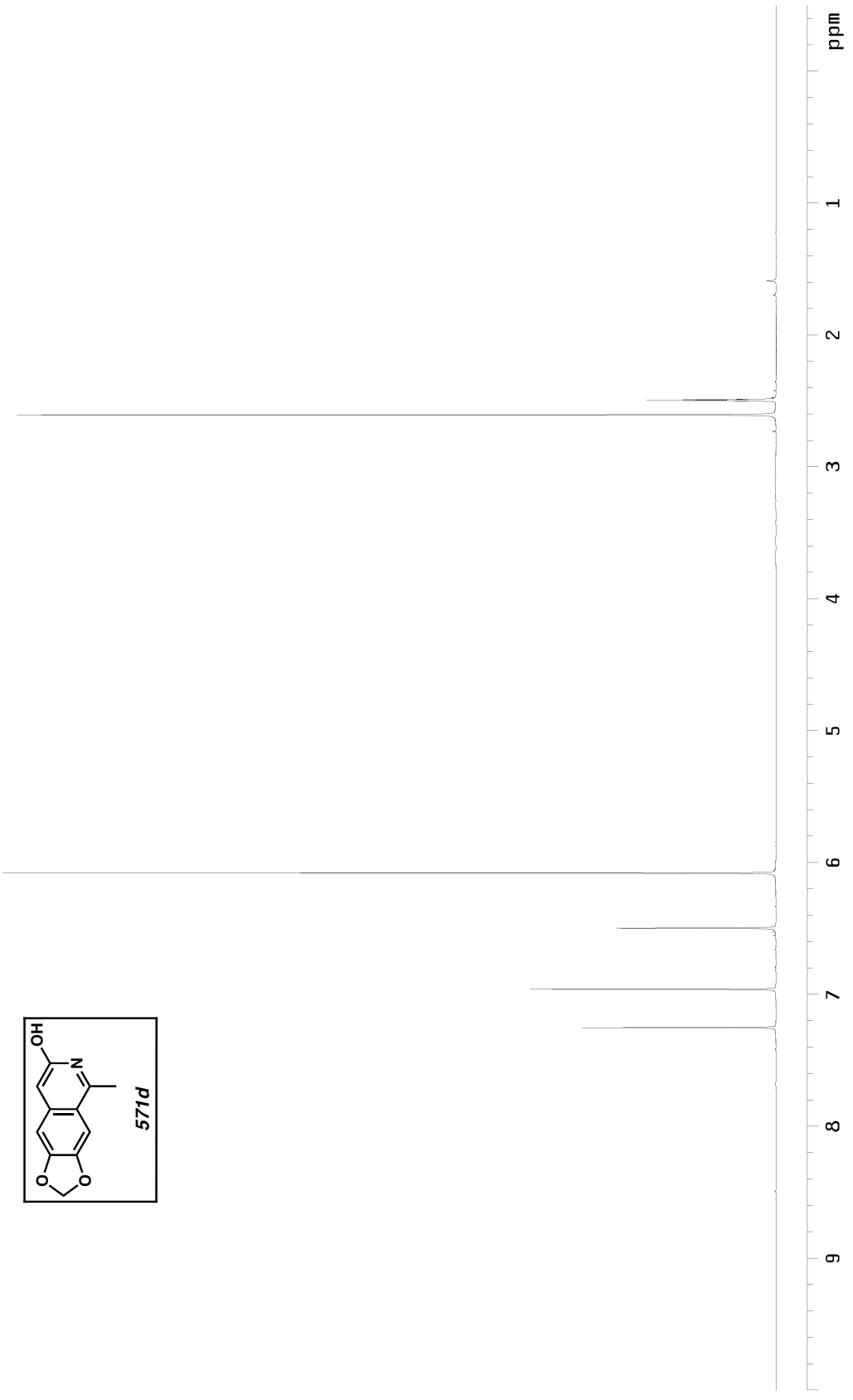


Figure A5.9.1 ^{1}H NMR (500 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571d** (Table 5.4, entry 4).

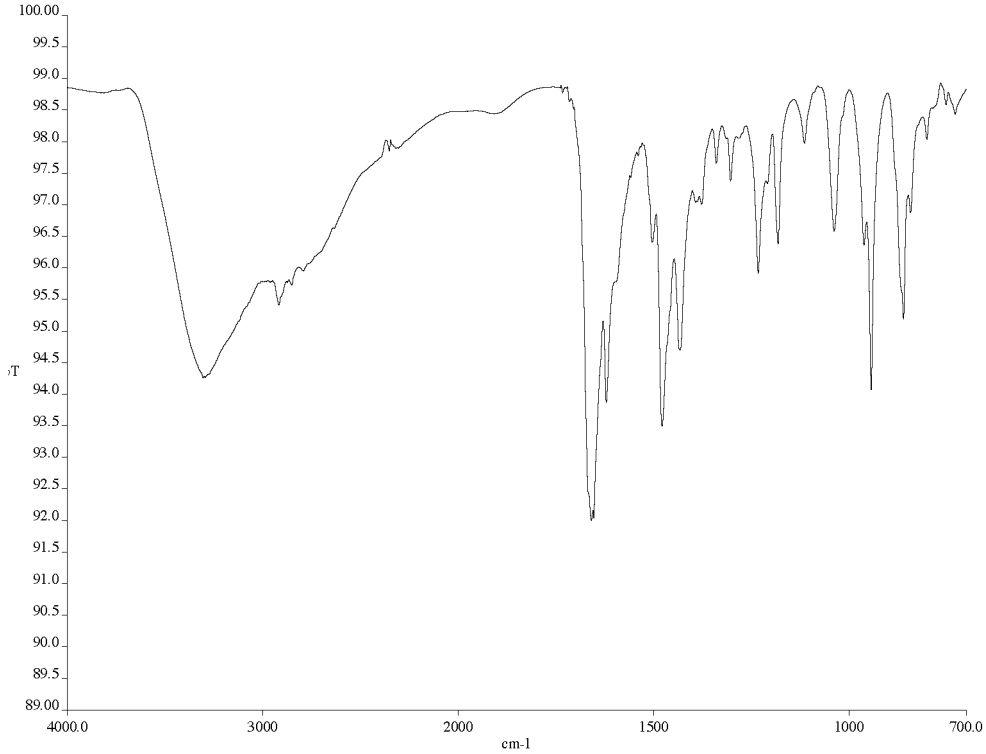


Figure A5.9.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **571d** (Table 5.4, entry 4).

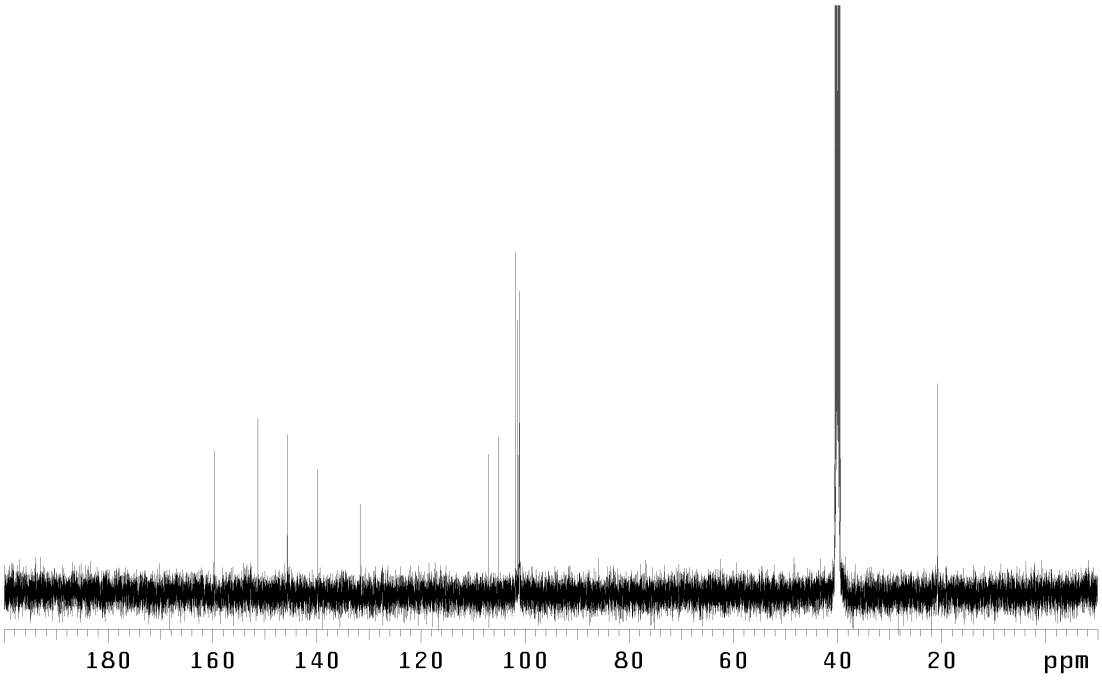


Figure A5.9.3 ^{13}C NMR (125 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571d** (Table 5.4, entry 4).

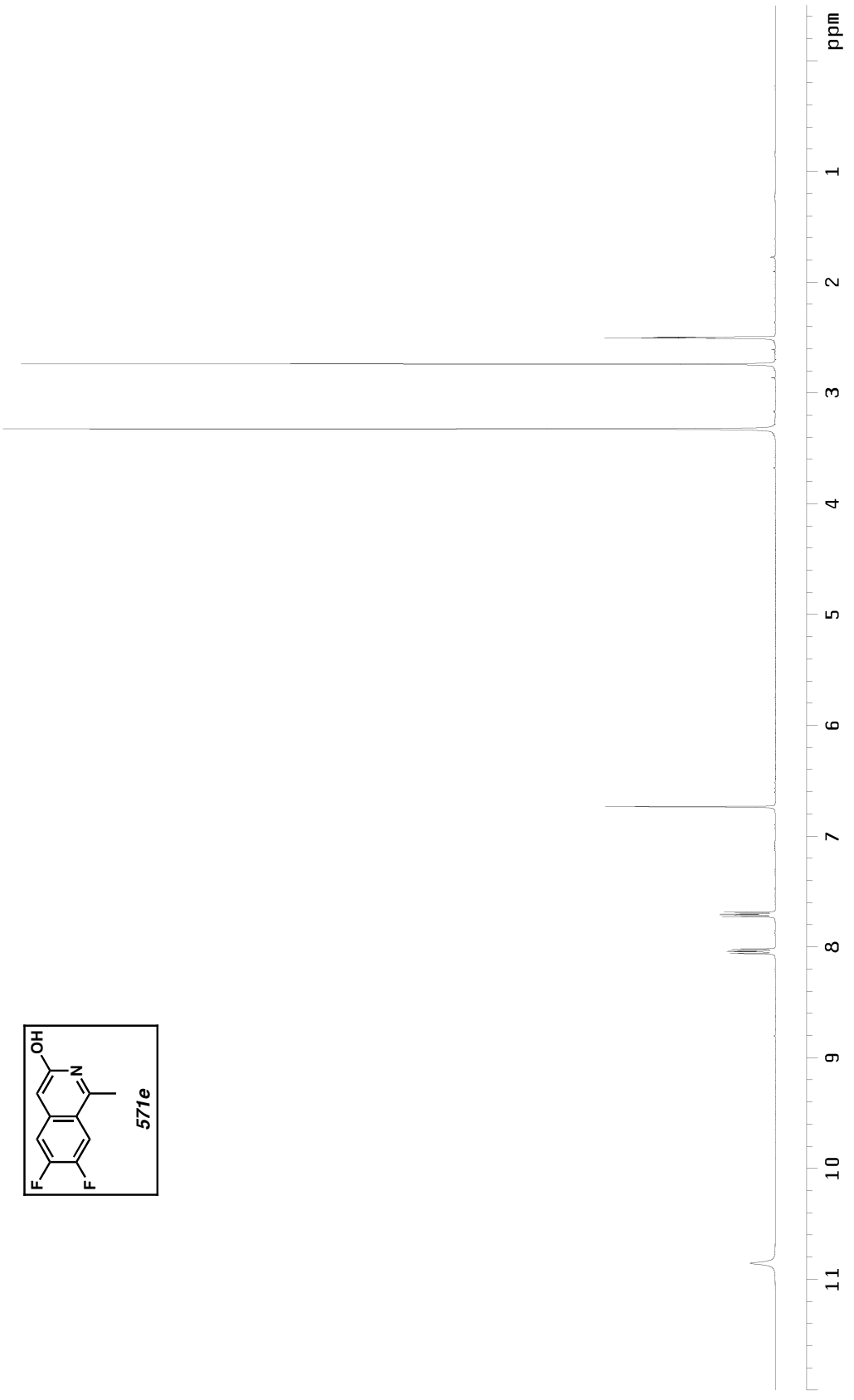


Figure A5.10.1 ^{1}H NMR (500 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571e** (Table 5.4, entry 5).

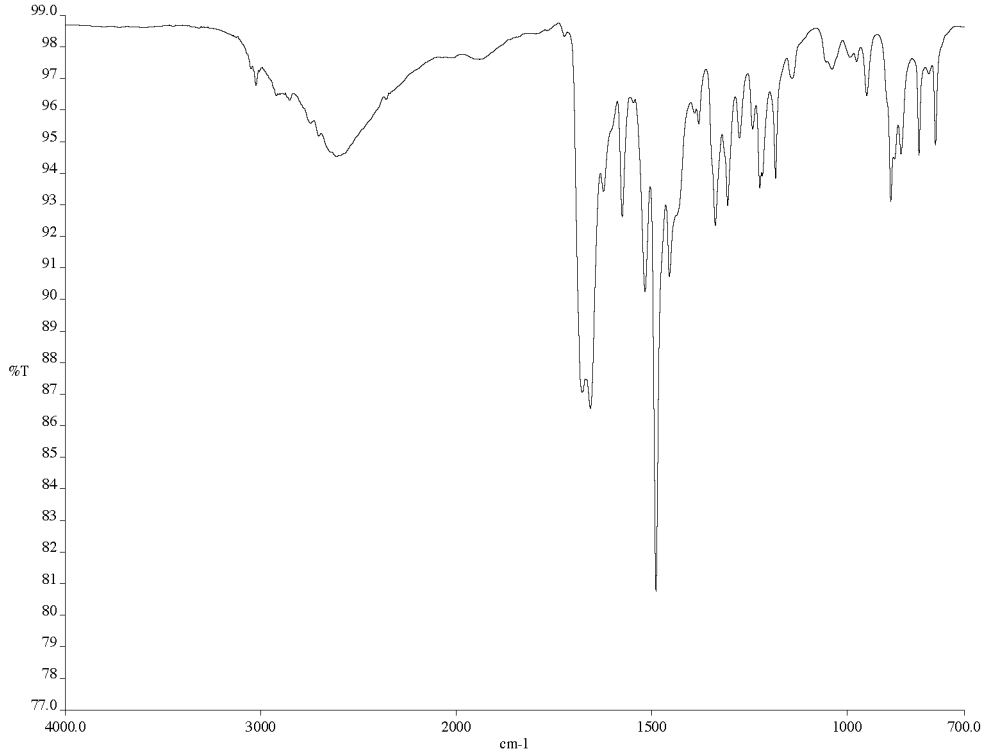


Figure A5.10.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **571e** (Table 5.4, entry 5).

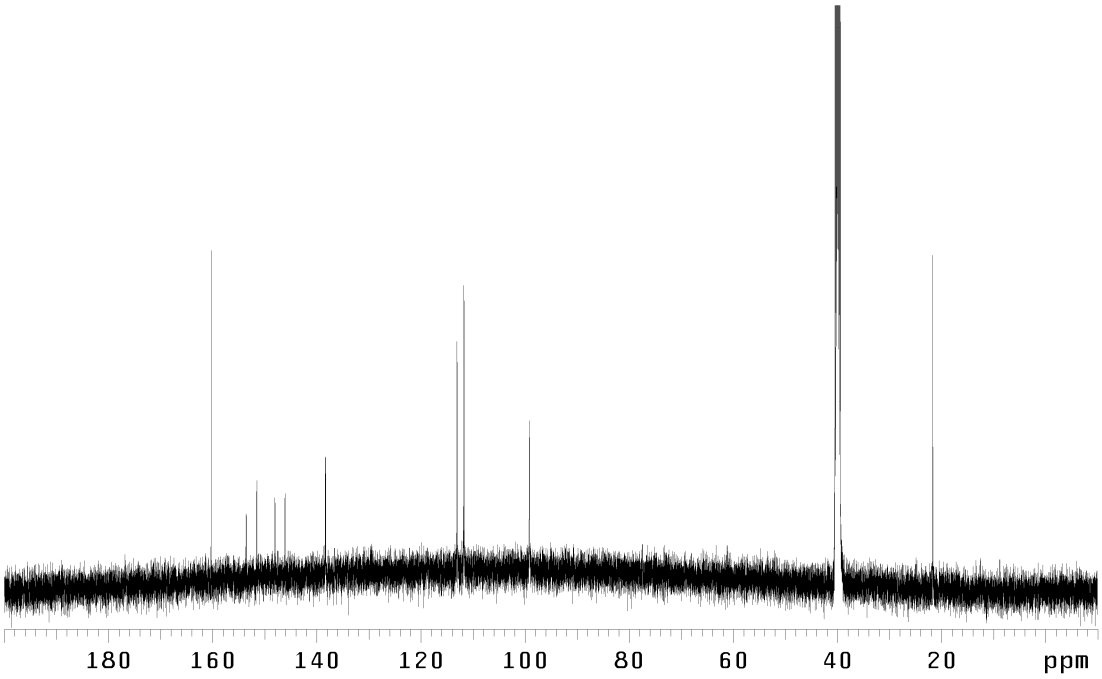


Figure A5.10.3 ^{13}C NMR (125 MHz, DMSO-d_6) of 3-hydroxyisoquinoline **571e** (Table 5.4, entry 5).

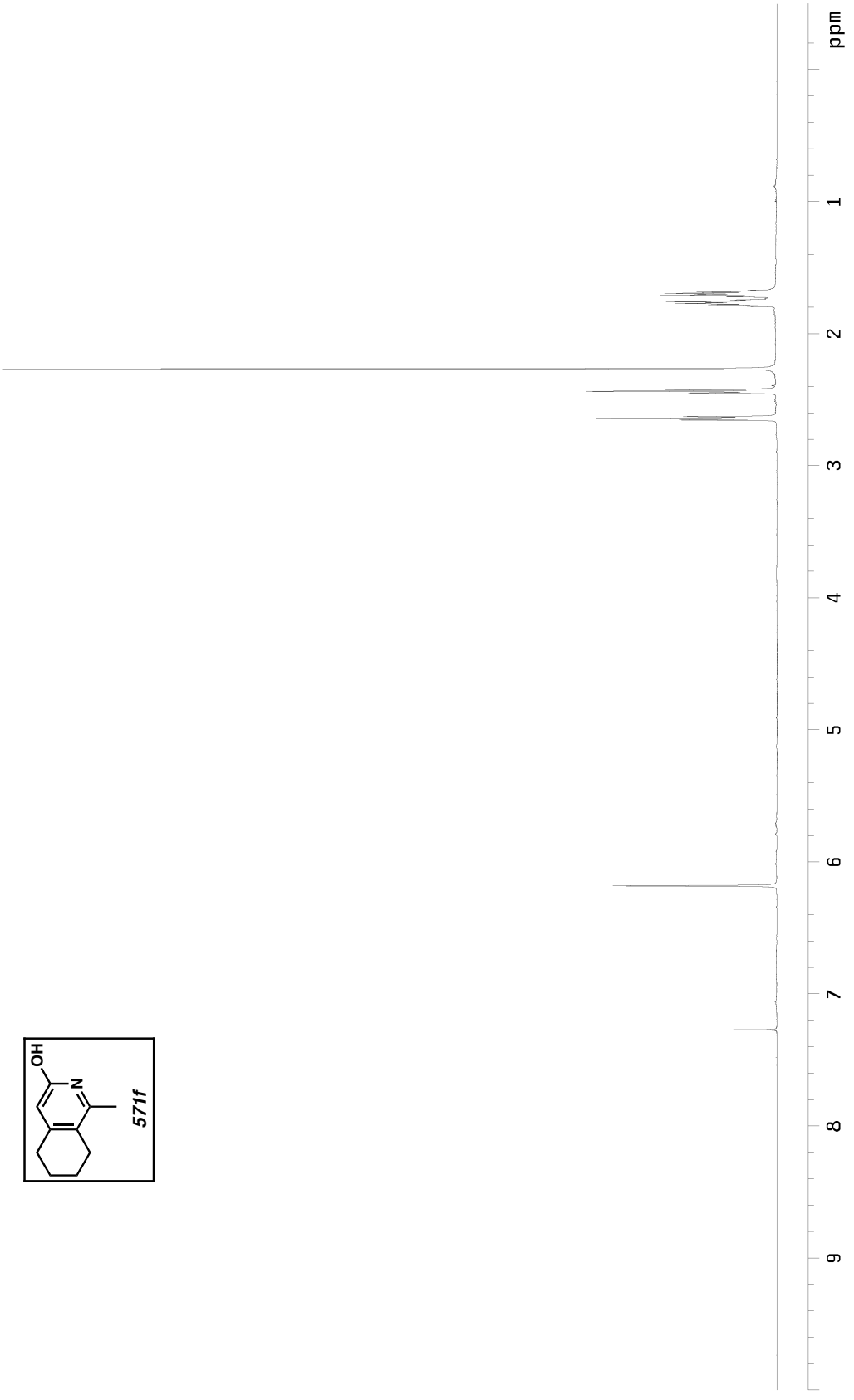


Figure A5.11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxy-5,6,7,8-tetrahydroisoquinoline **571f** (Table 5.4, entry 6).

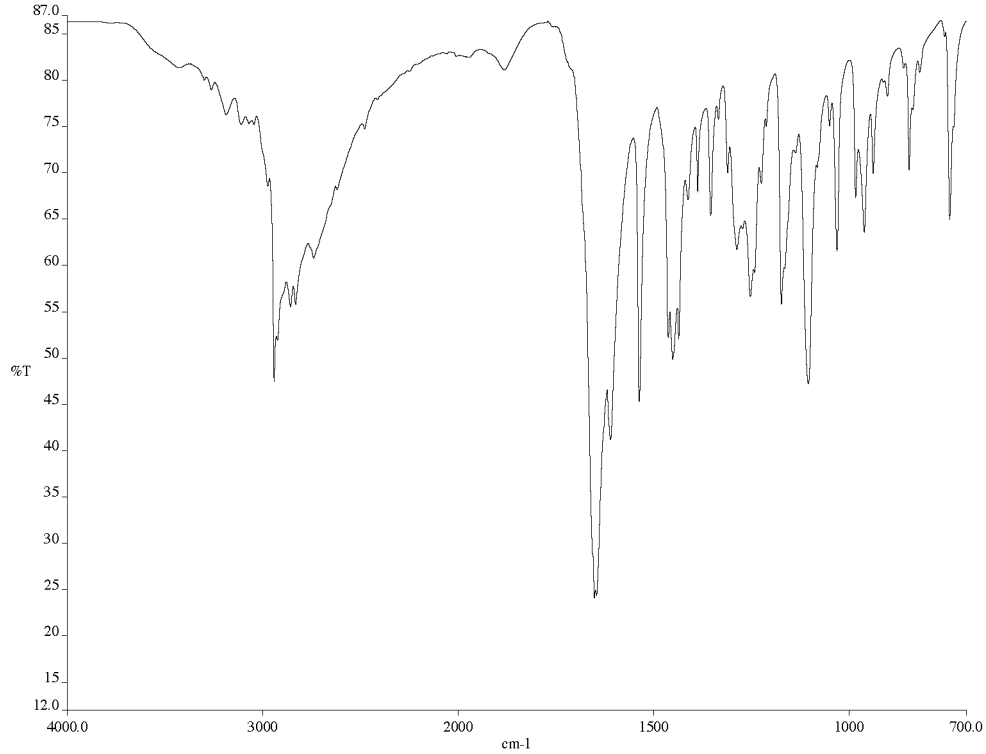


Figure A5.11.2 Infrared spectrum (thin film/NaCl) of 3-hydroxy-5,6,7,8-tetrahydroisoquinoline **571f** (Table 5.4, entry 6).

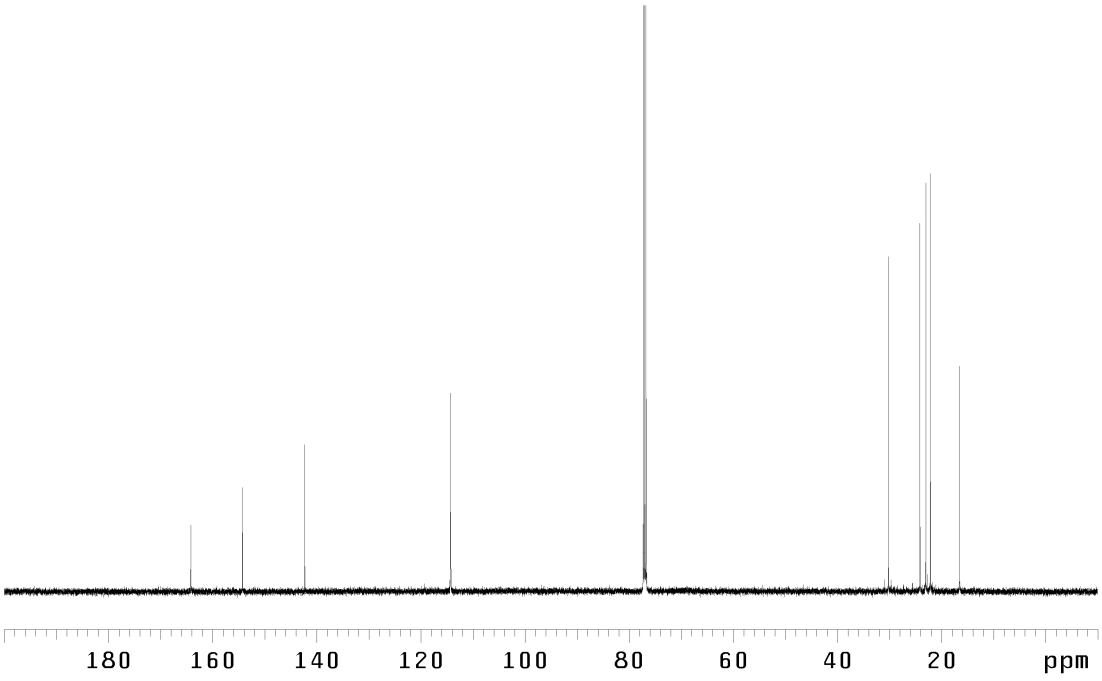


Figure A5.11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxy-5,6,7,8-tetrahydroisoquinoline **571f** (Table 5.4, entry 6).

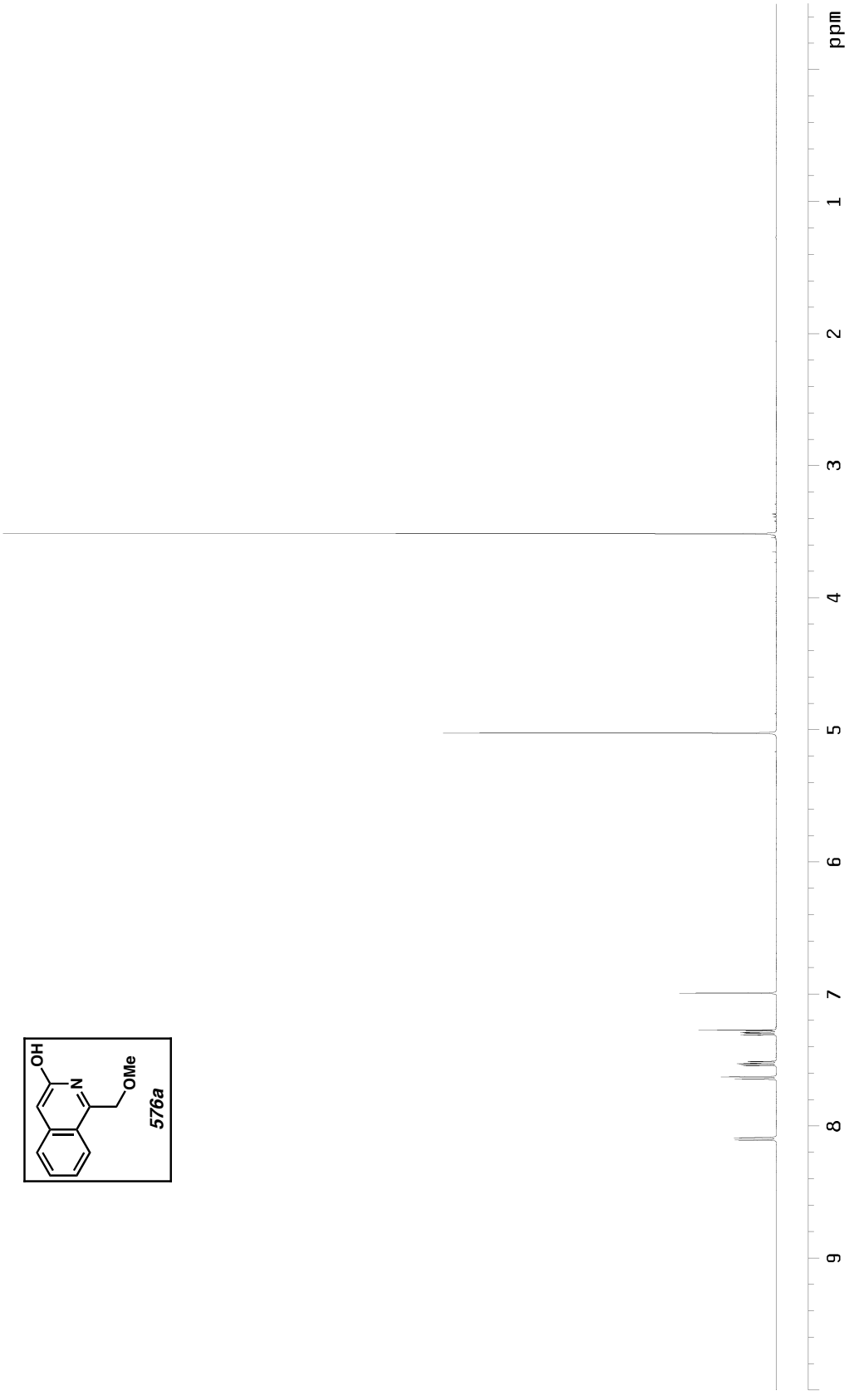


Figure A5.12.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576a** (Table 5.5, entry 1).

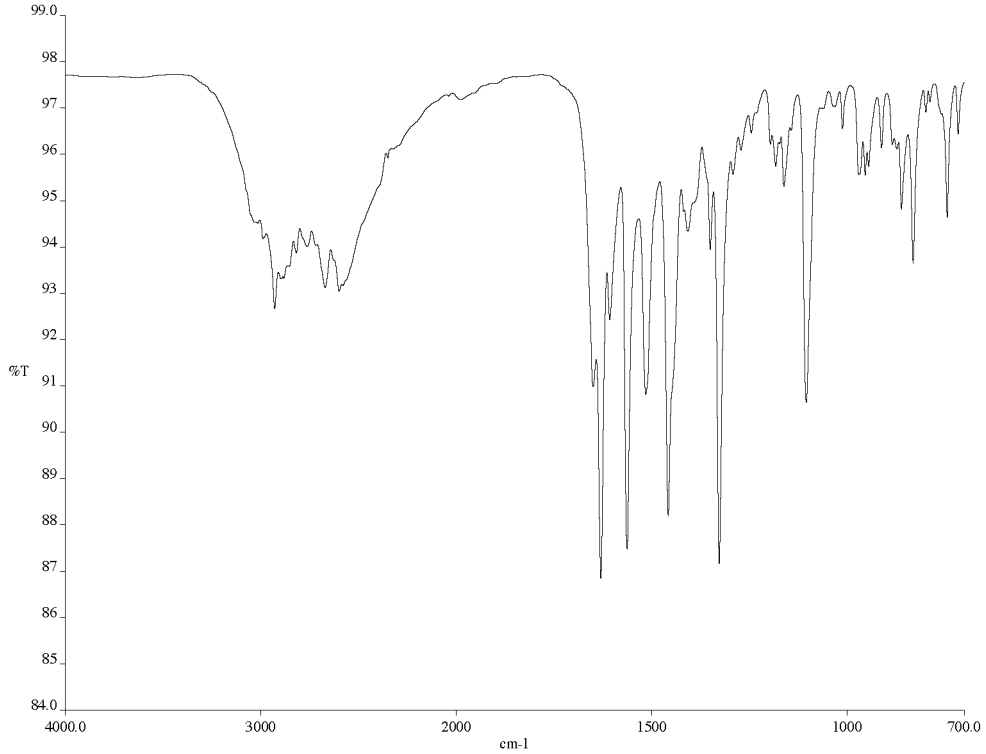


Figure A5.12.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576a** (Table 5.5, entry 1).

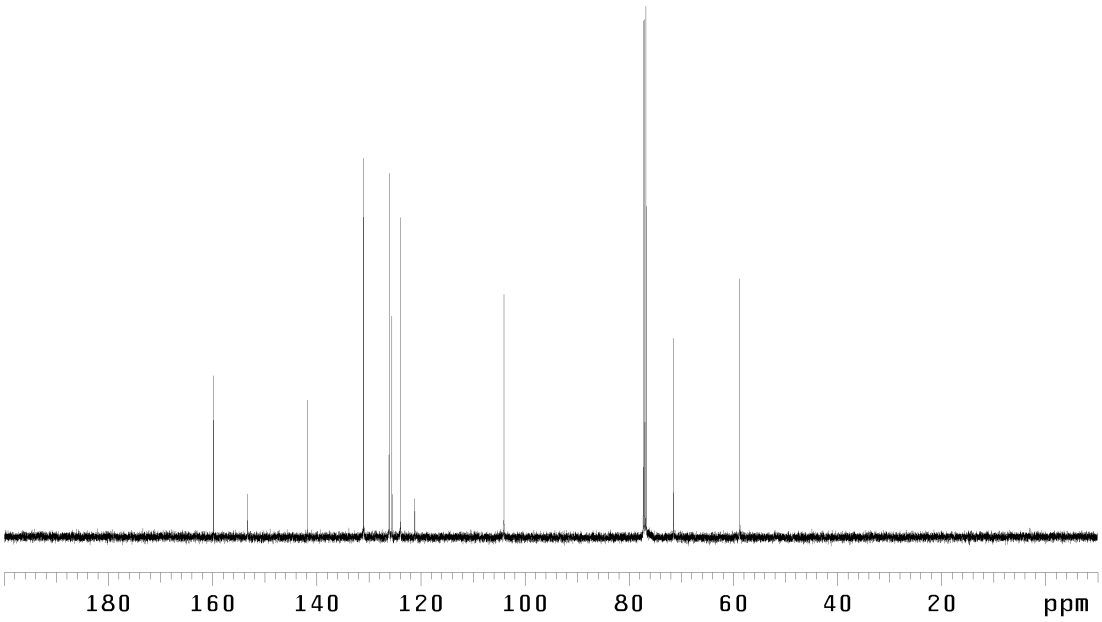


Figure A5.12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576a** (Table 5.5, entry 1).

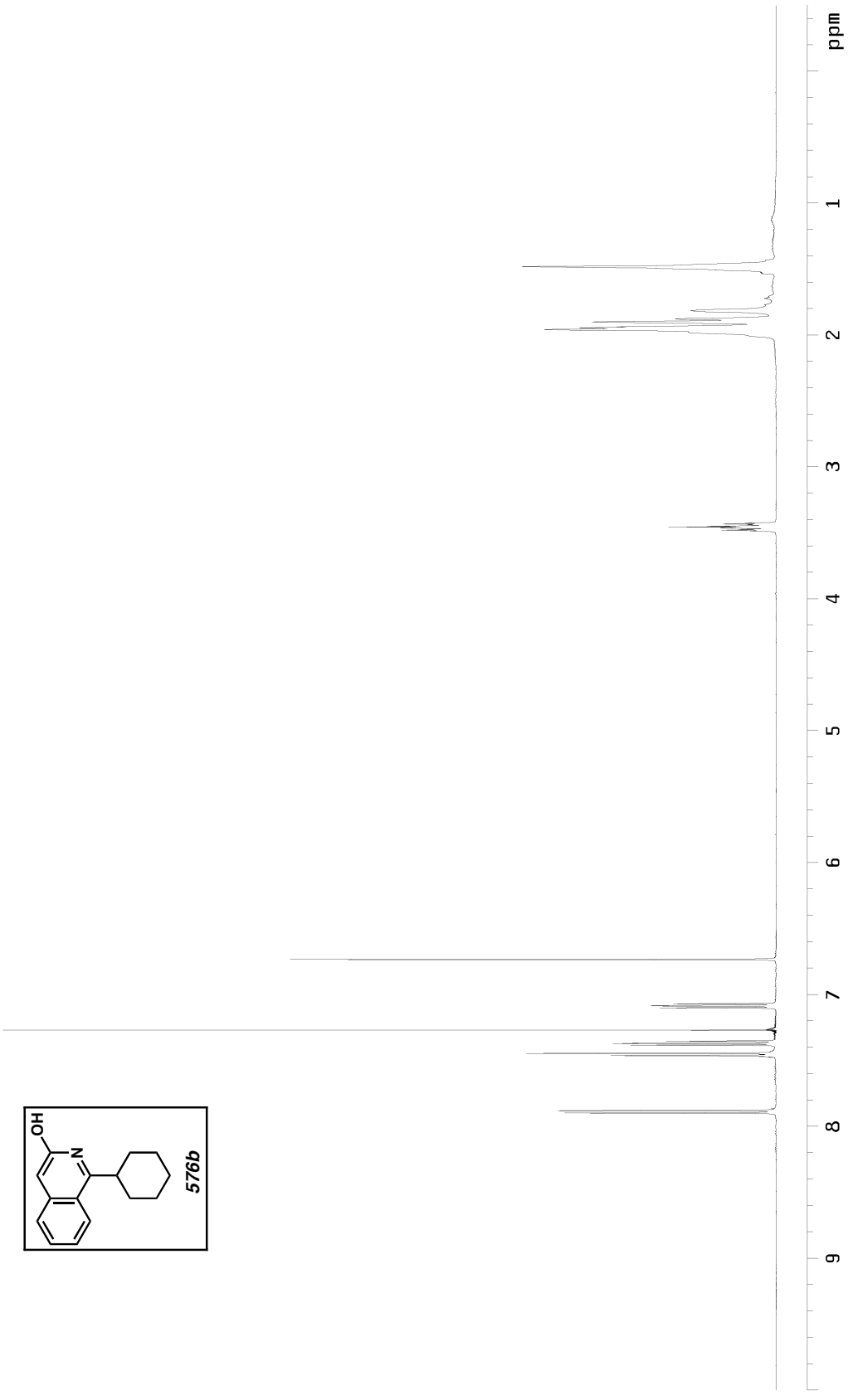


Figure A5.13.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576b** (Table 5.5, entry 2).

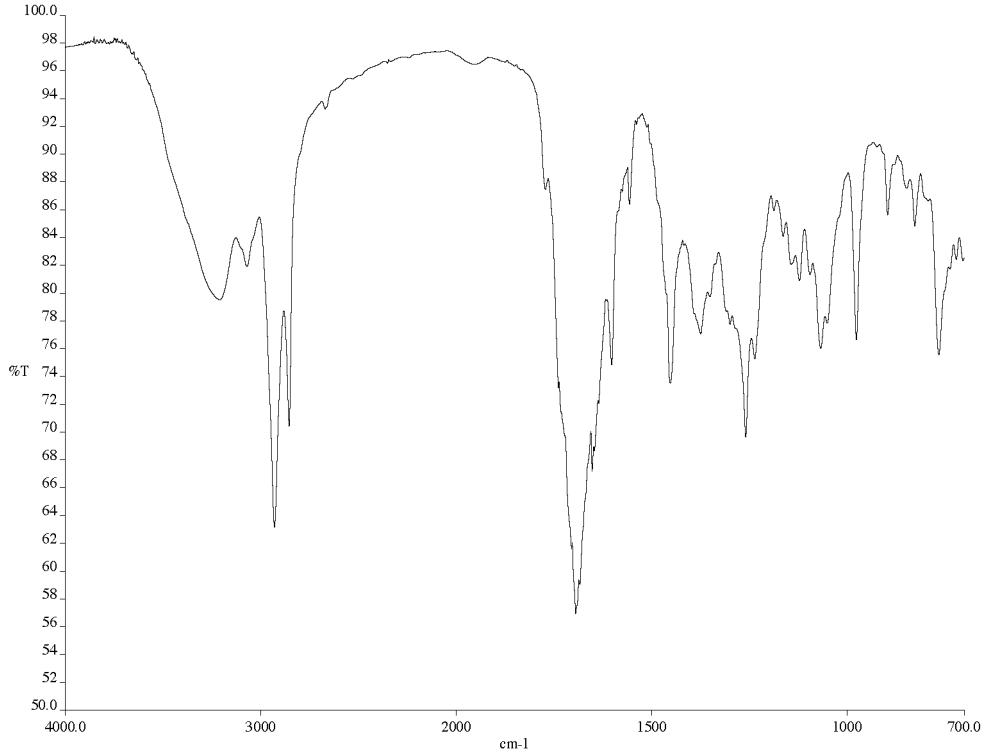


Figure A5.13.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576b** (Table 5.5, entry 2).

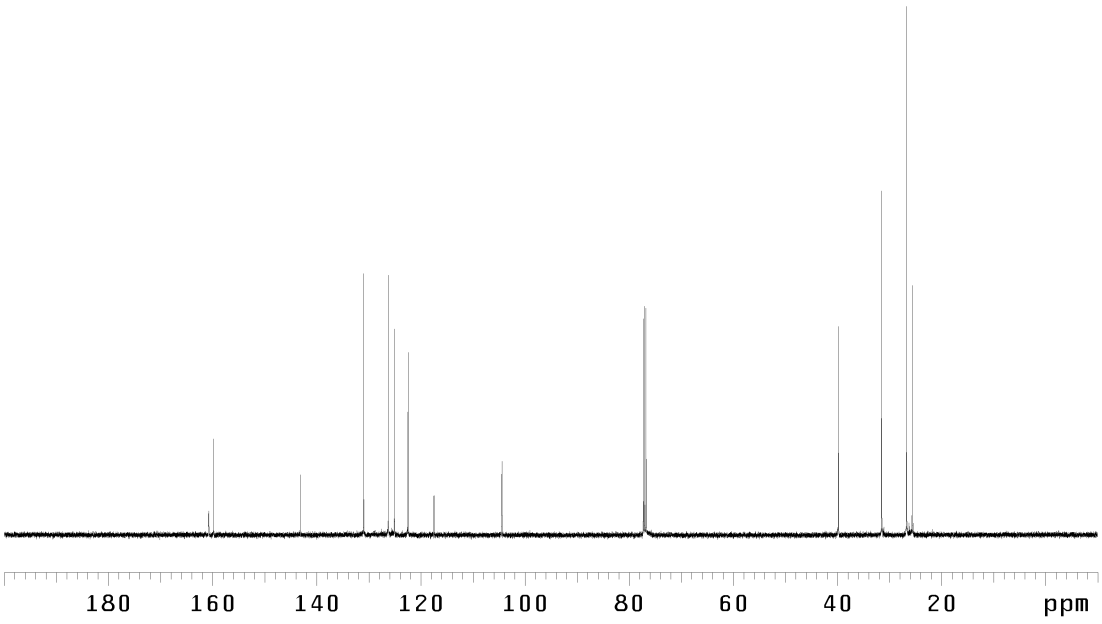


Figure A5.13.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576b** (Table 5.5, entry 2).

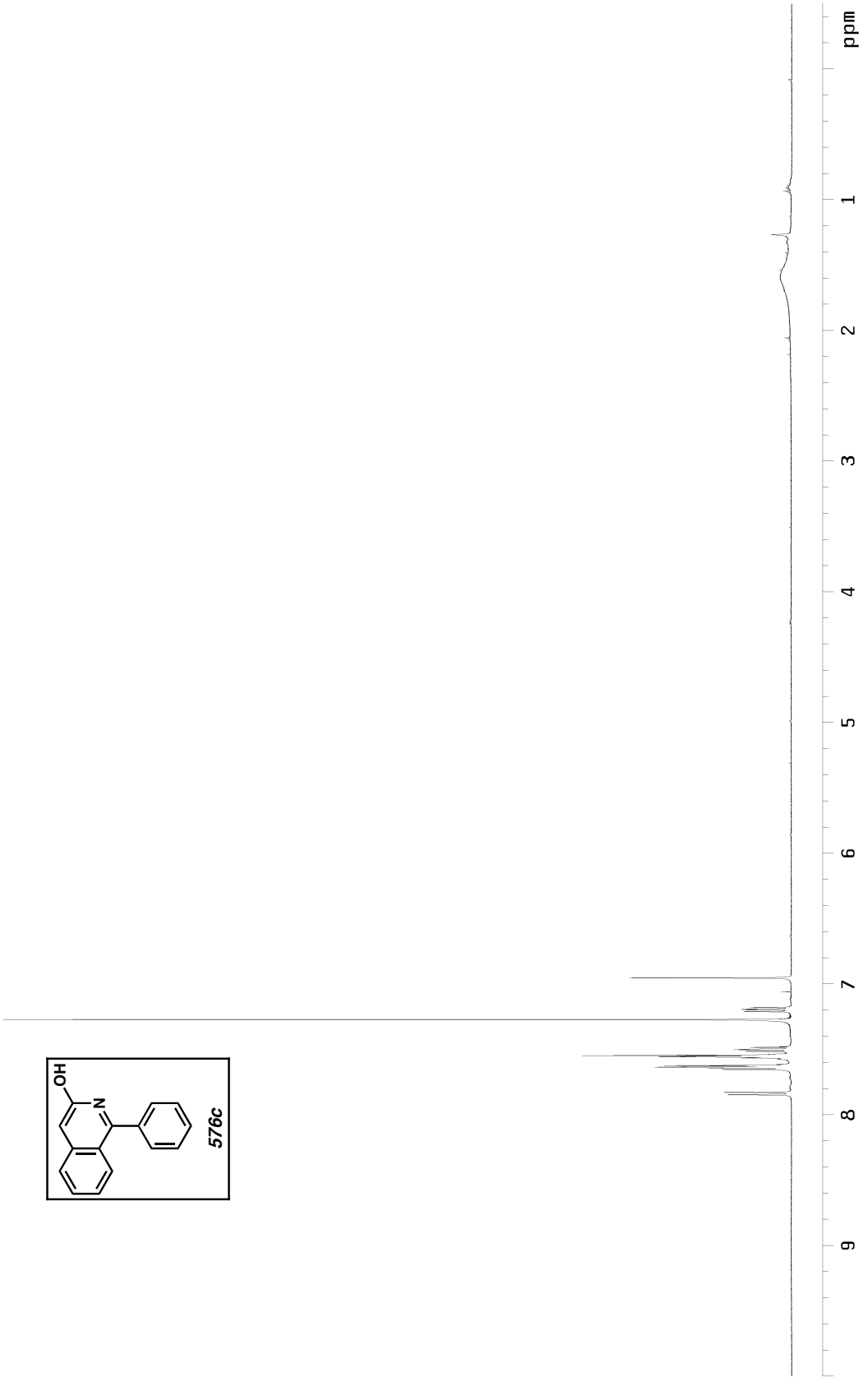


Figure A5.14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576c** (Table 5.5, entry 3).

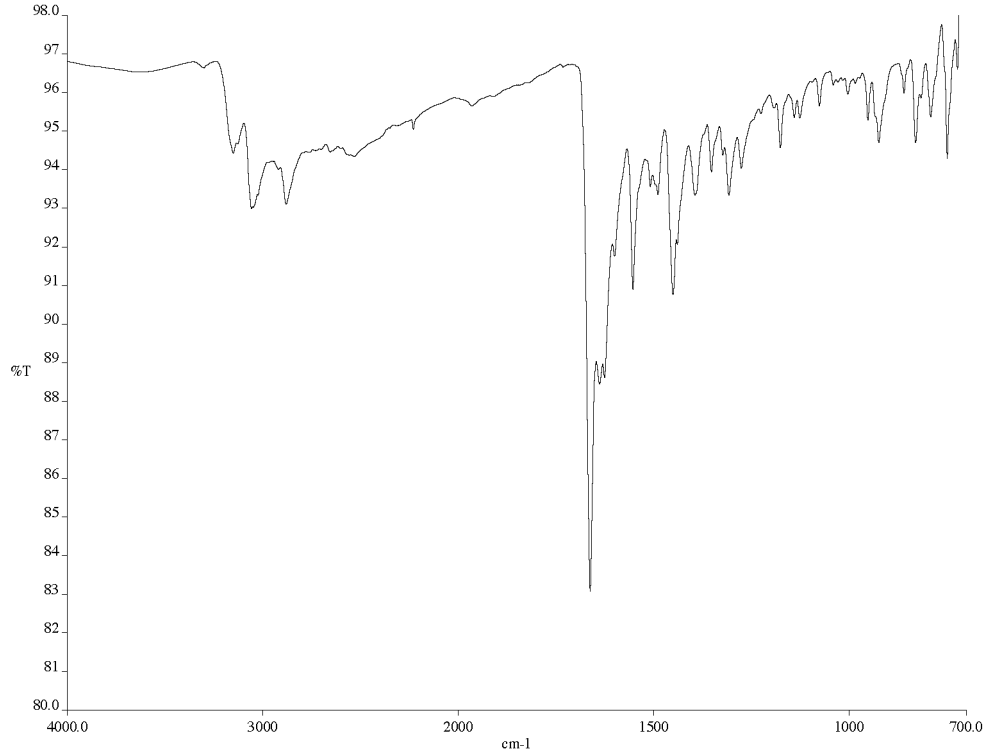


Figure A5.14.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576c** (Table 5.5, entry 3).

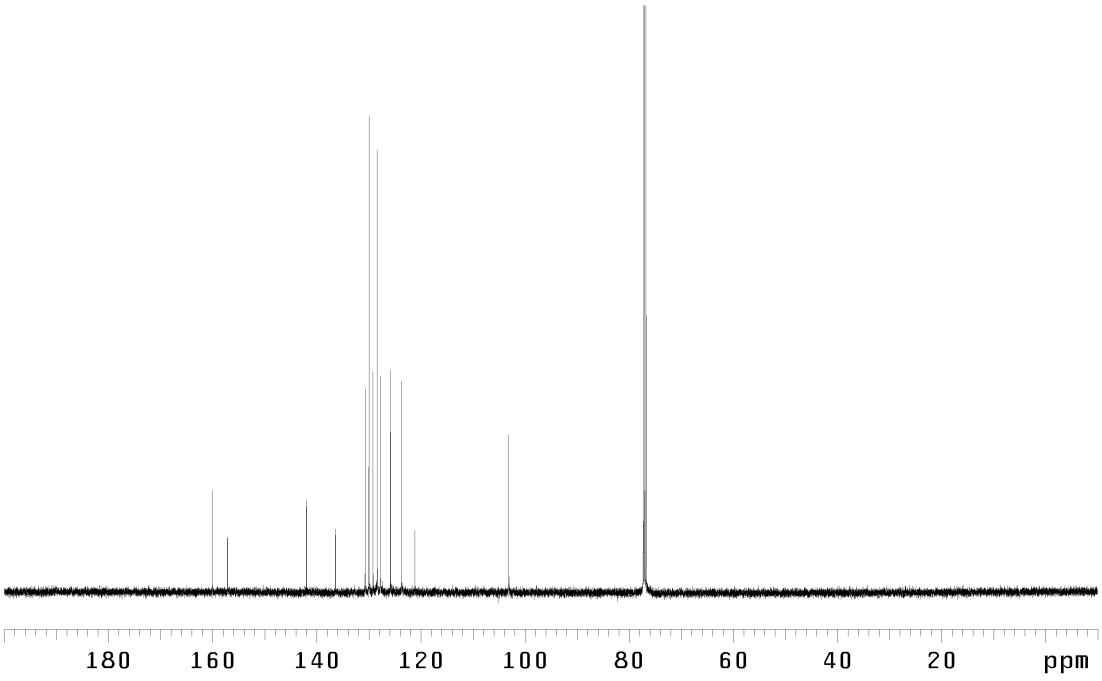


Figure A5.14.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576c** (Table 5.5, entry 3).

Figure A5.15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576d** (Table 5.5, entry 4).

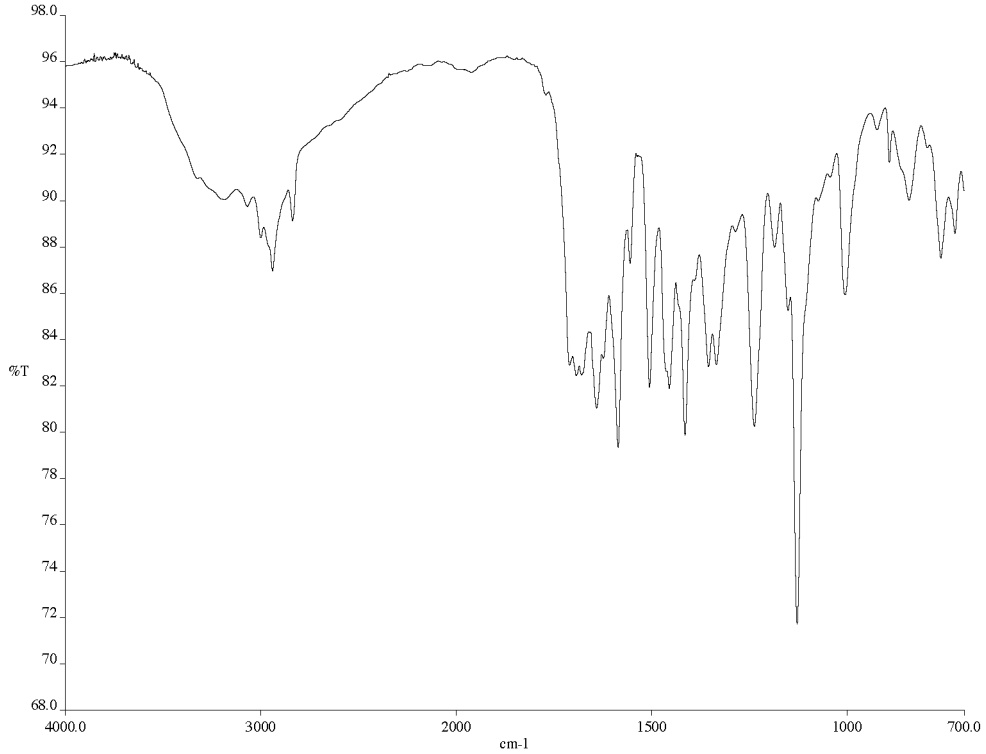


Figure A5.15.2 Infrared spectrum (thin film/NaCl) of of 3-hydroxyisoquinoline **576d** (Table 5.5, entry 4).

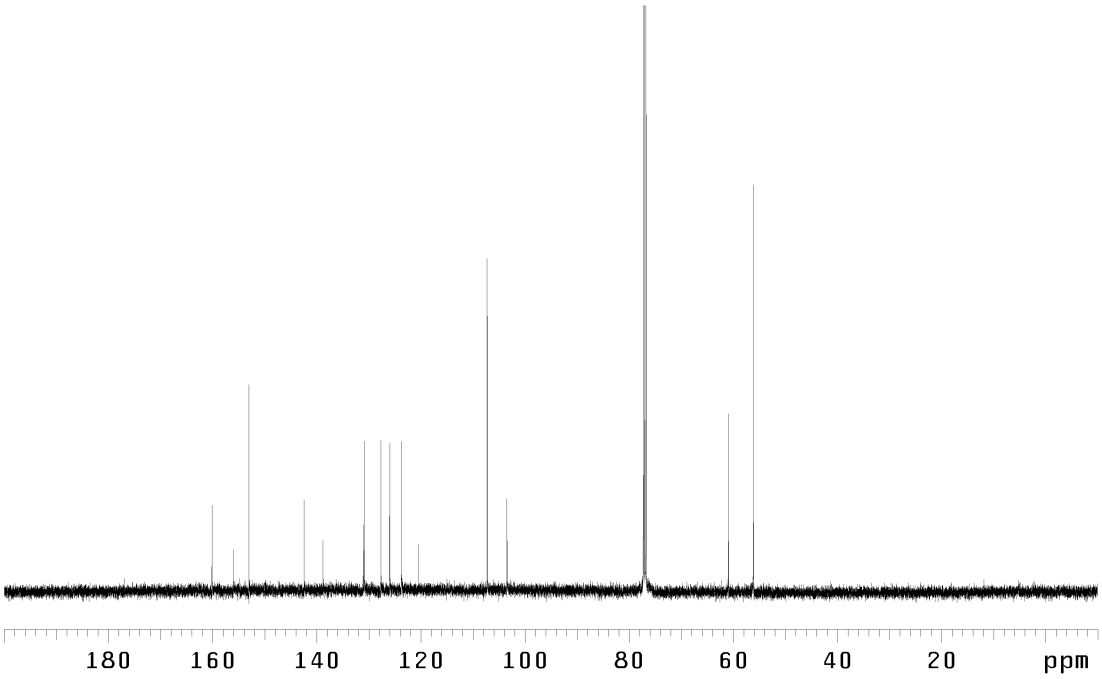


Figure A5.15.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576d** (Table 5.5, entry 4).

Figure A5.16.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576e** (Table 5.5, entry 5).

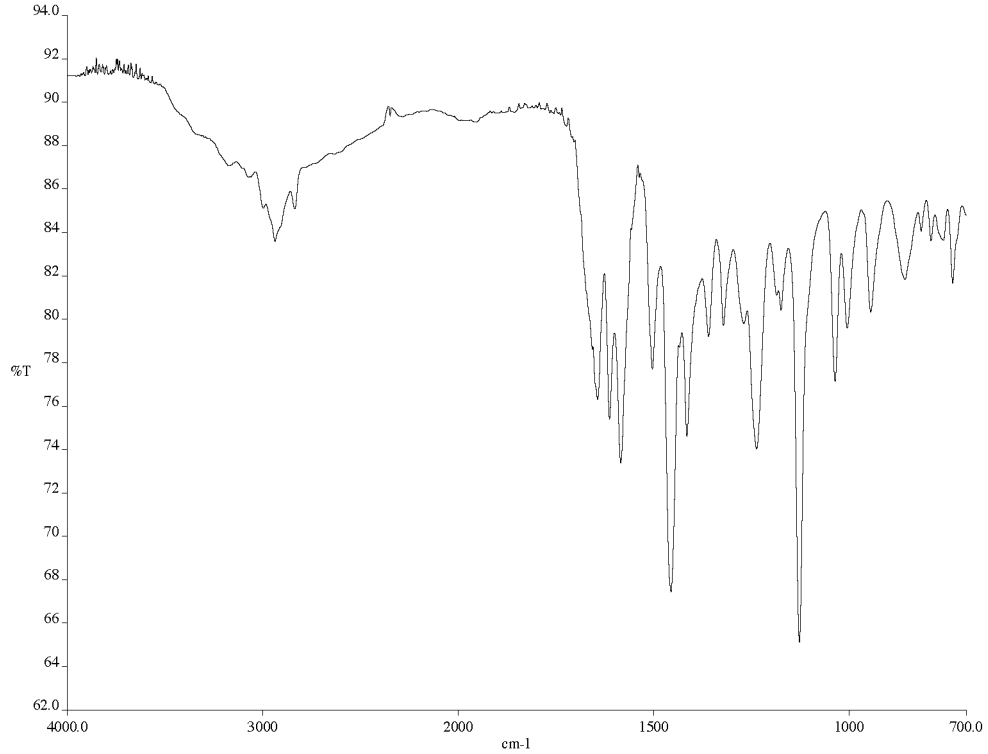


Figure A5.16.2 Infrared spectrum (thin film/NaCl) of of 3-hydroxyisoquinoline **576e** (Table 5.5, entry 5).

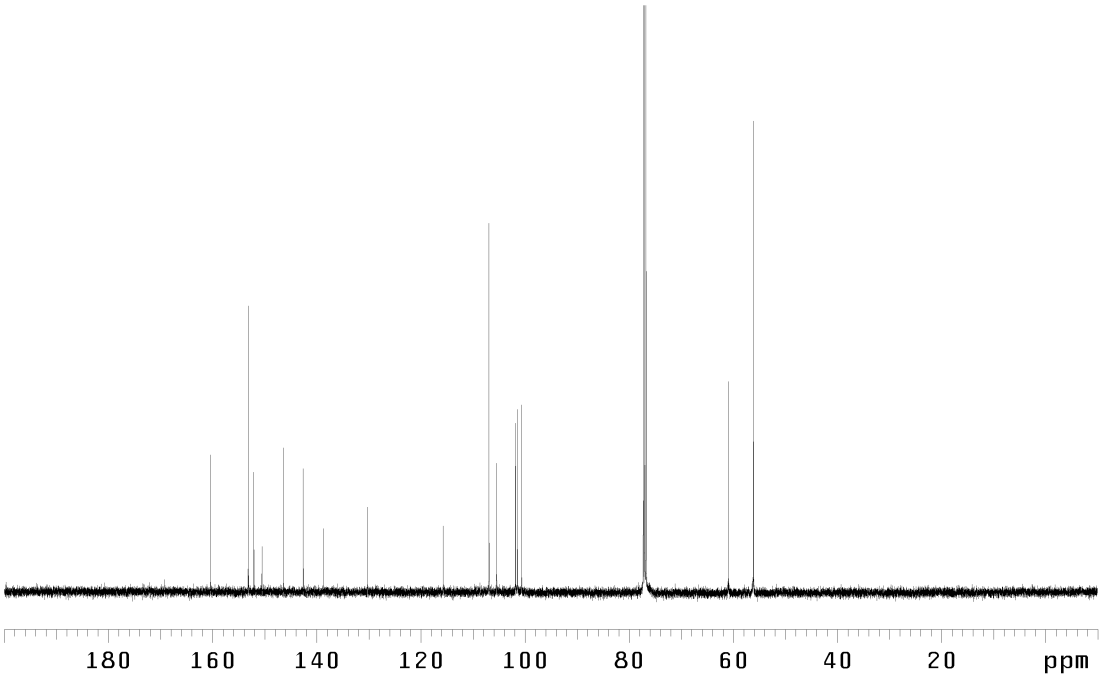


Figure A5.16.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576e** (Table 5.5, entry 5).

Figure A5.17.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576f** (Table 5.5, entry 6).

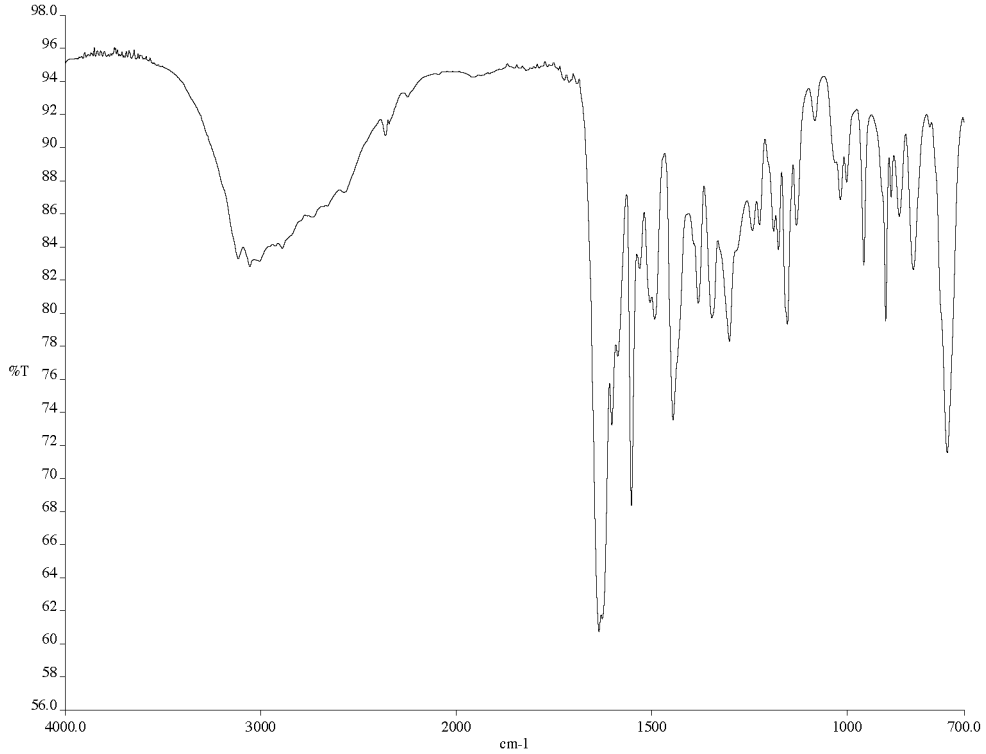


Figure A5.17.2 Infrared spectrum (thin film/NaCl) 3-hydroxyisoquinoline **576f** (Table 5.5, entry 6).

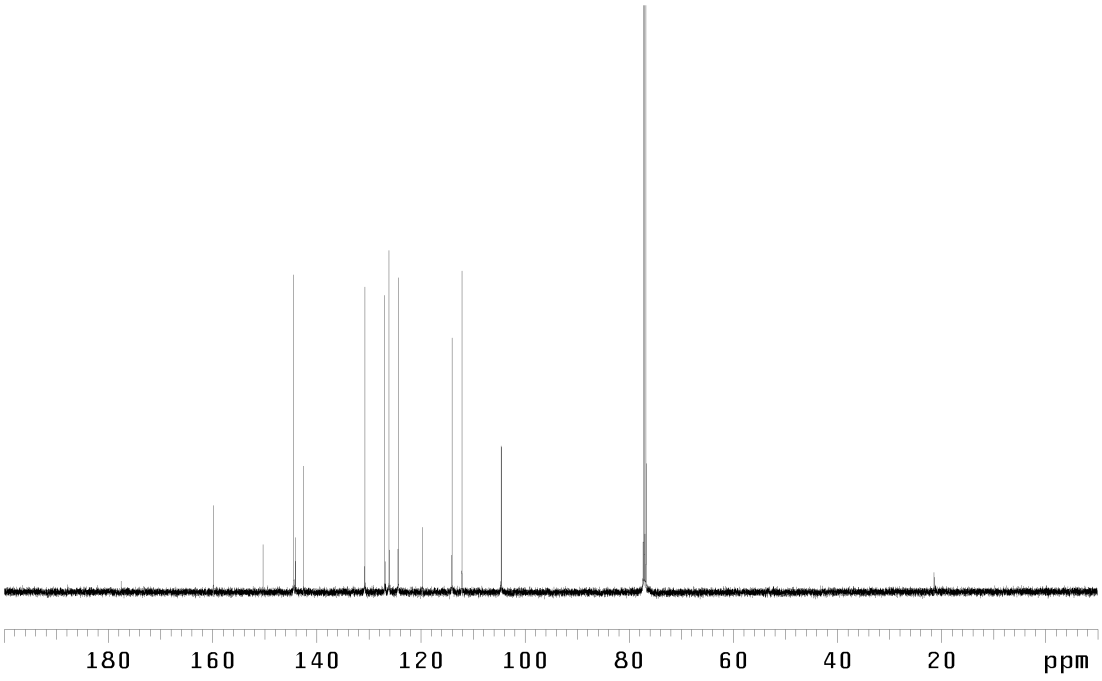


Figure A5.17.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576f** (Table 5.5, entry 6).

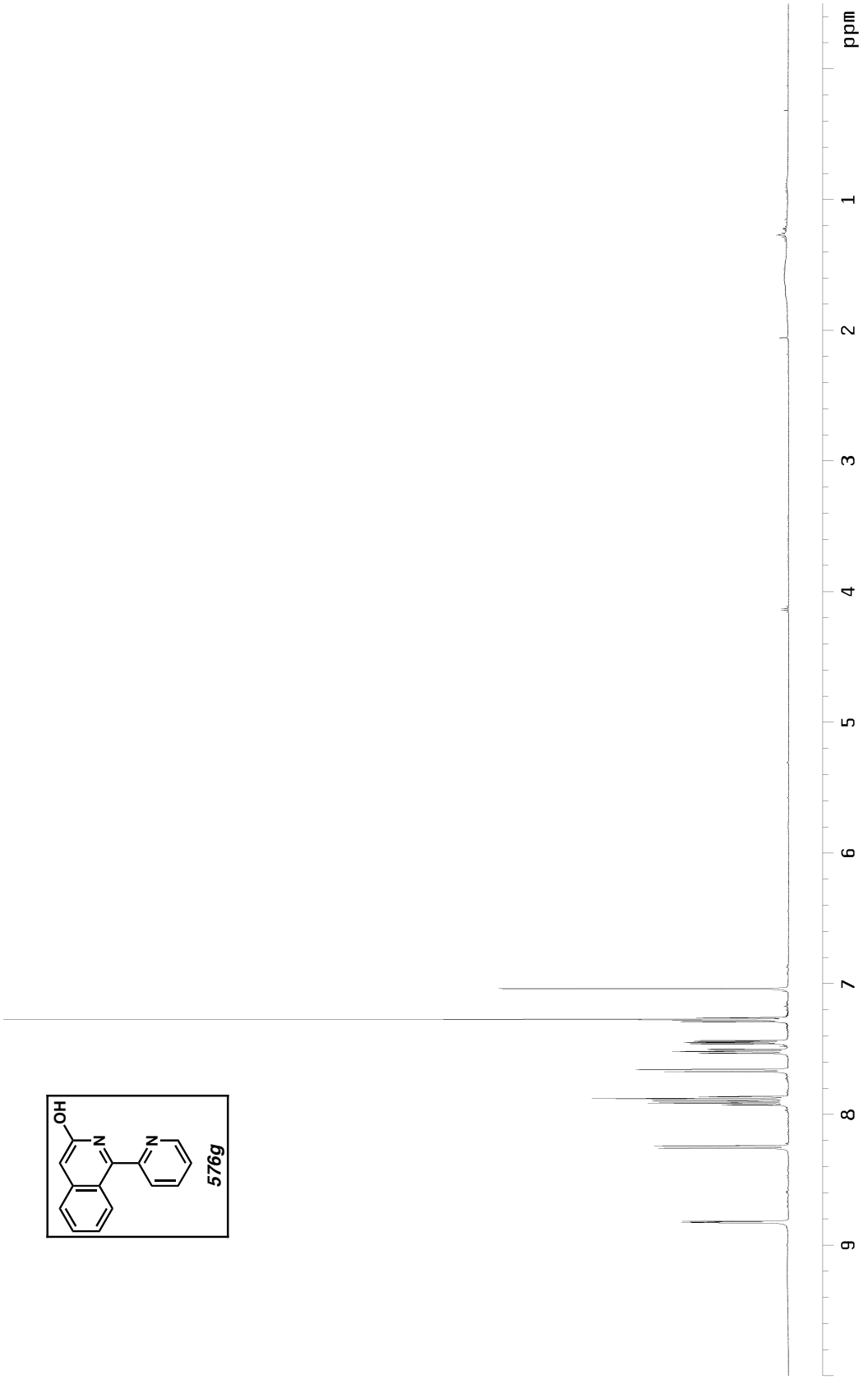


Figure A5.18.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576g** (Table 5.5, entry 7).

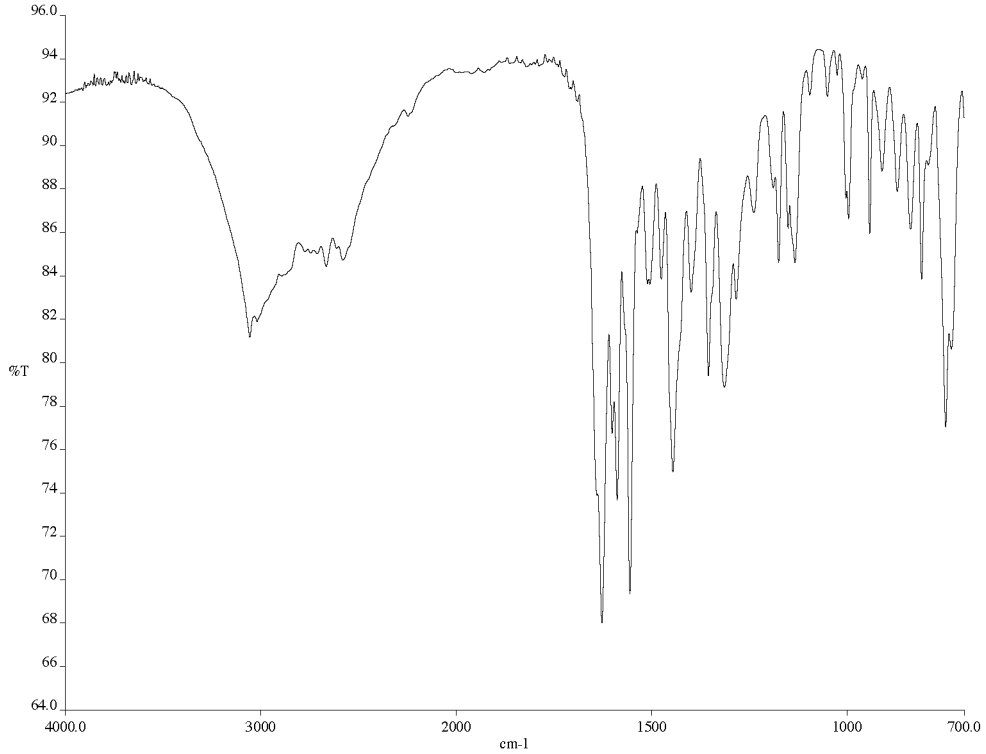


Figure A5.18.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576g** (Table 5.5, entry 7).

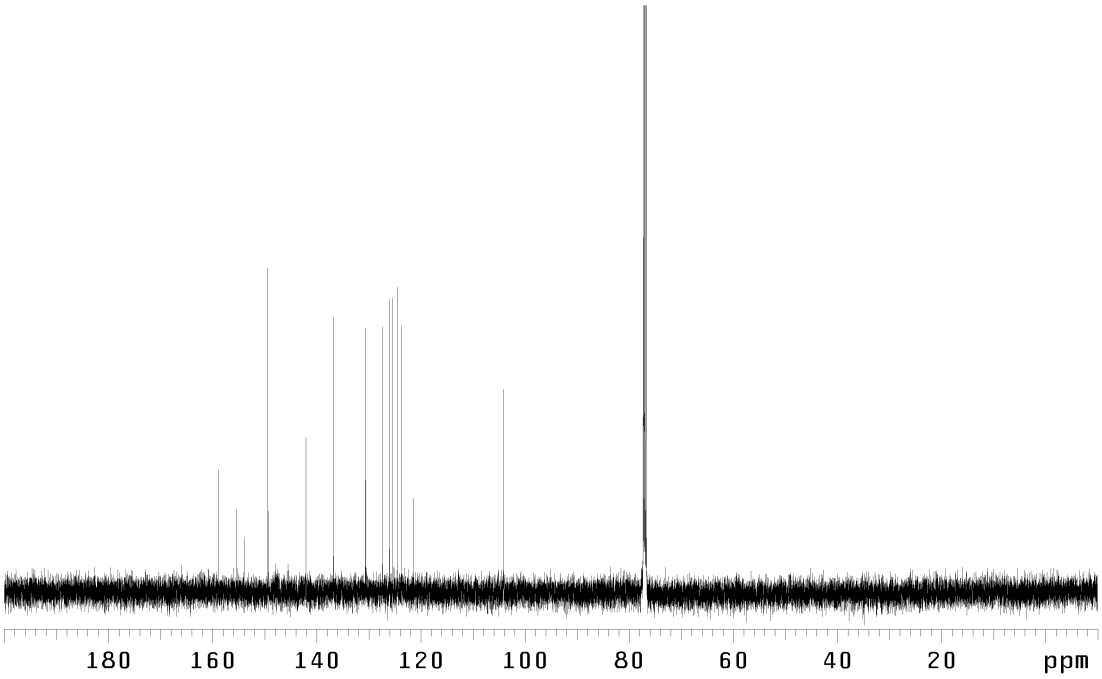


Figure A5.18.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576g** (Table 5.5, entry 7).

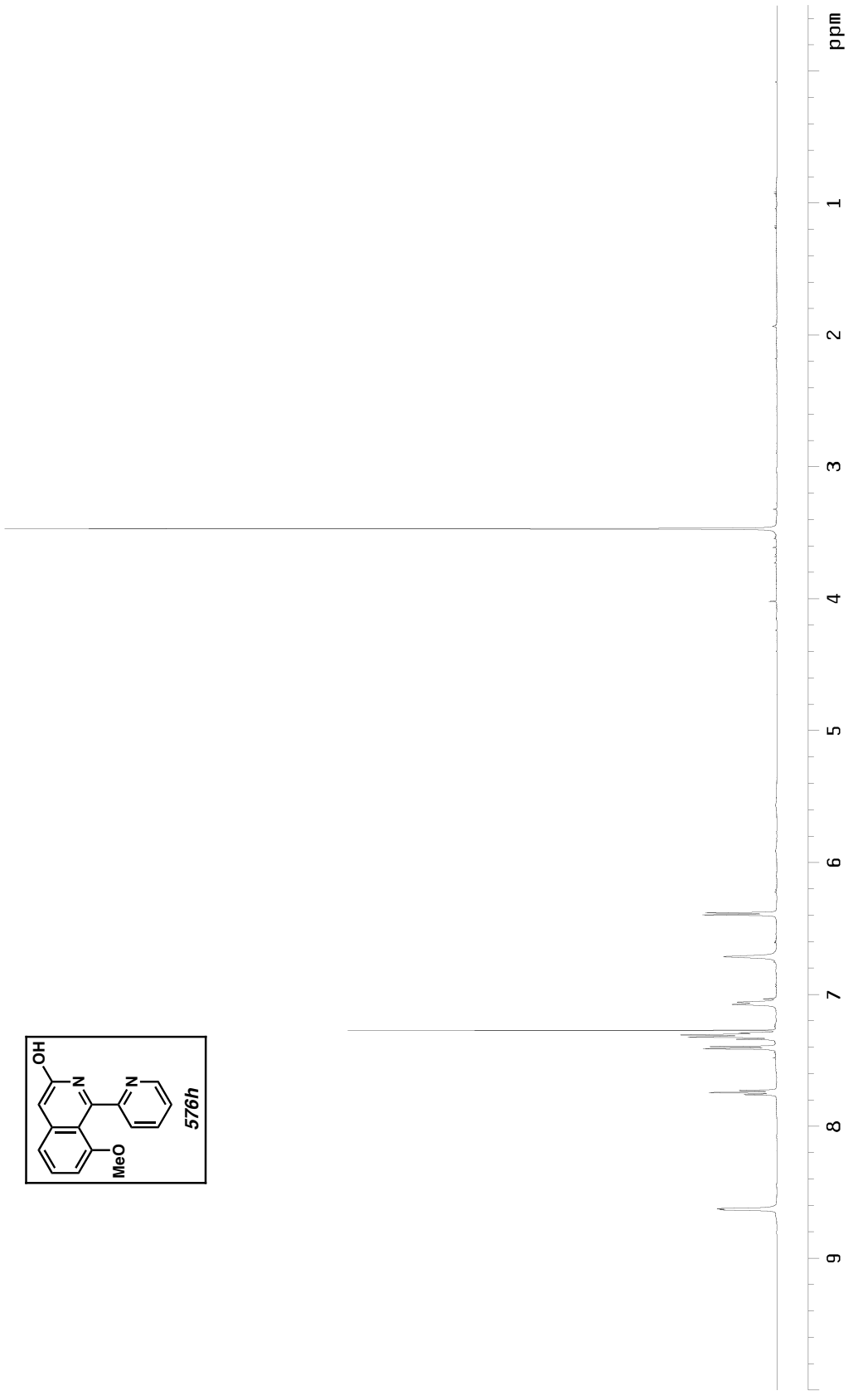


Figure A5.19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576h** (Table 5.5, entry 8).

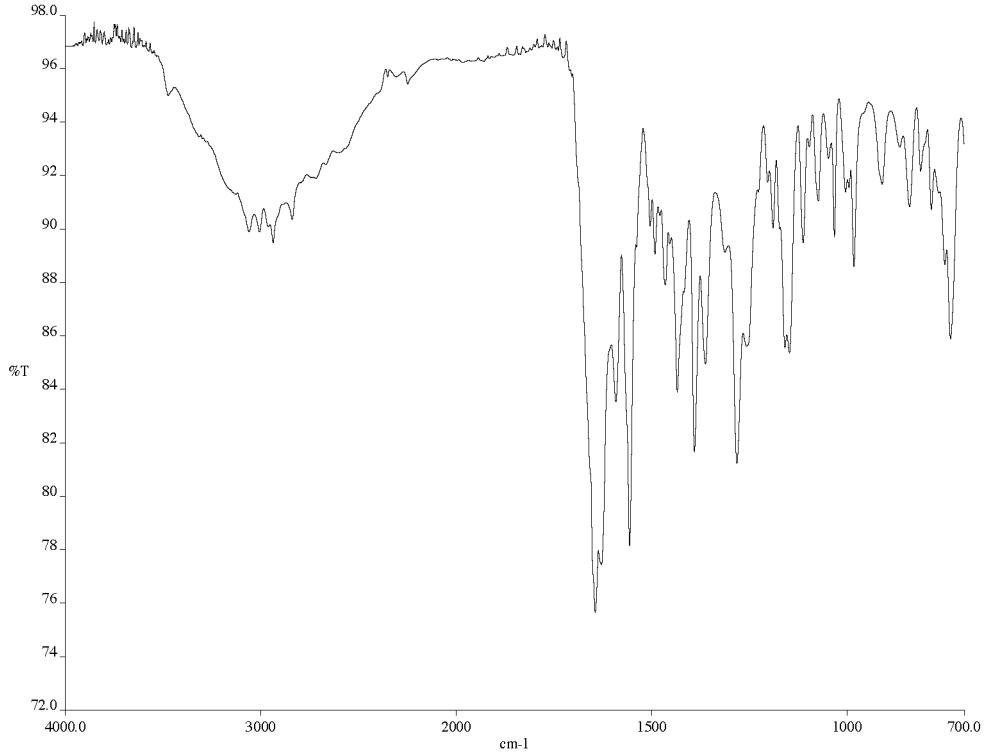


Figure A5.19.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576h** (Table 5.5, entry 8).

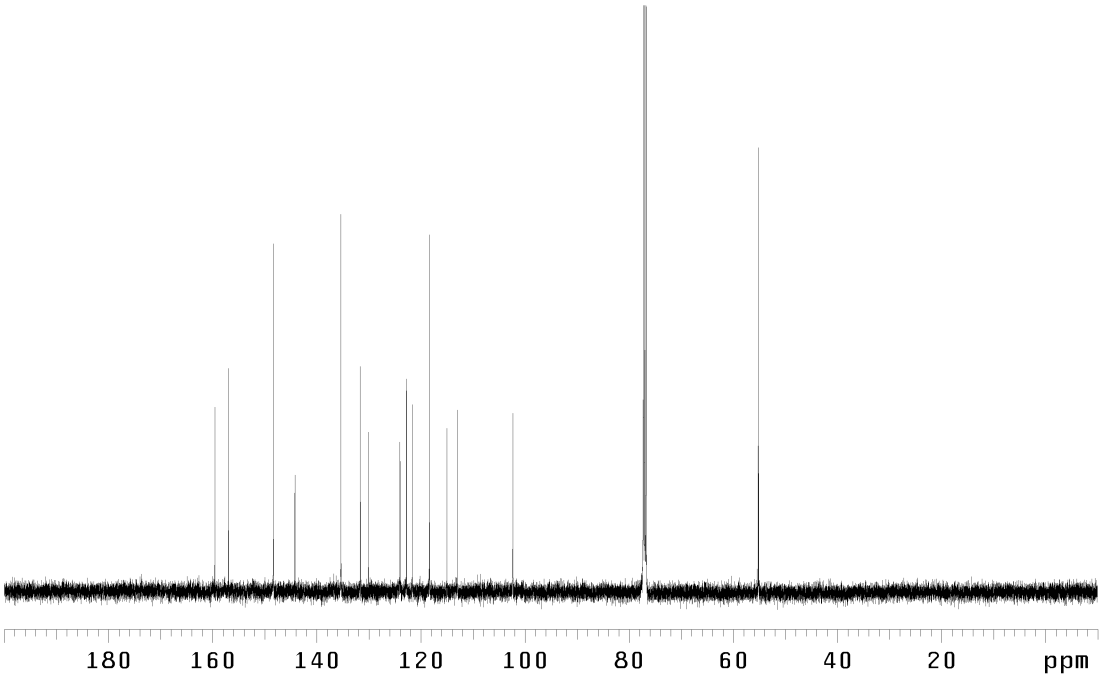


Figure A5.19.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576h** (Table 5.5, entry 8).

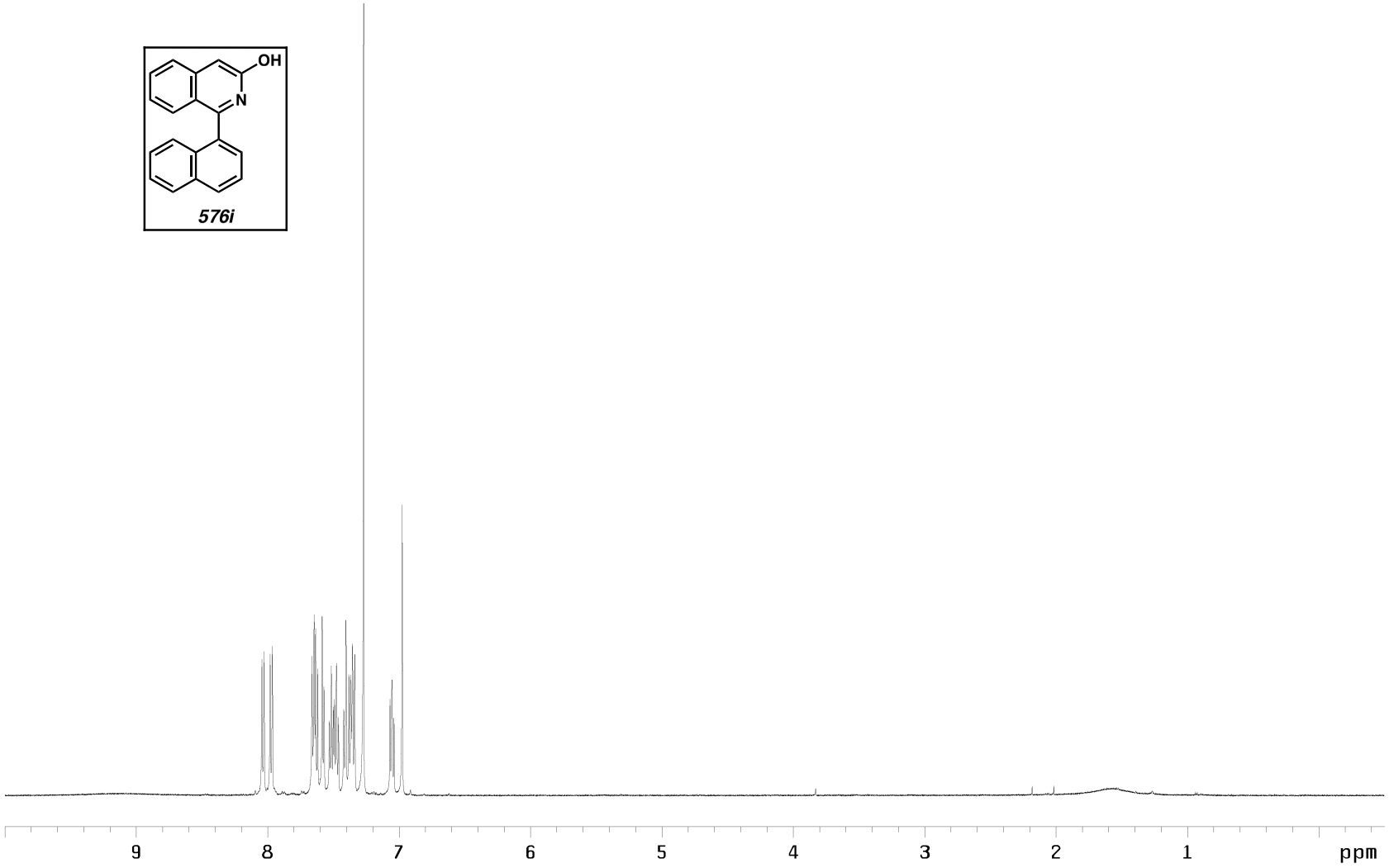


Figure A5.20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576i** (Table 5.5, entry 9).

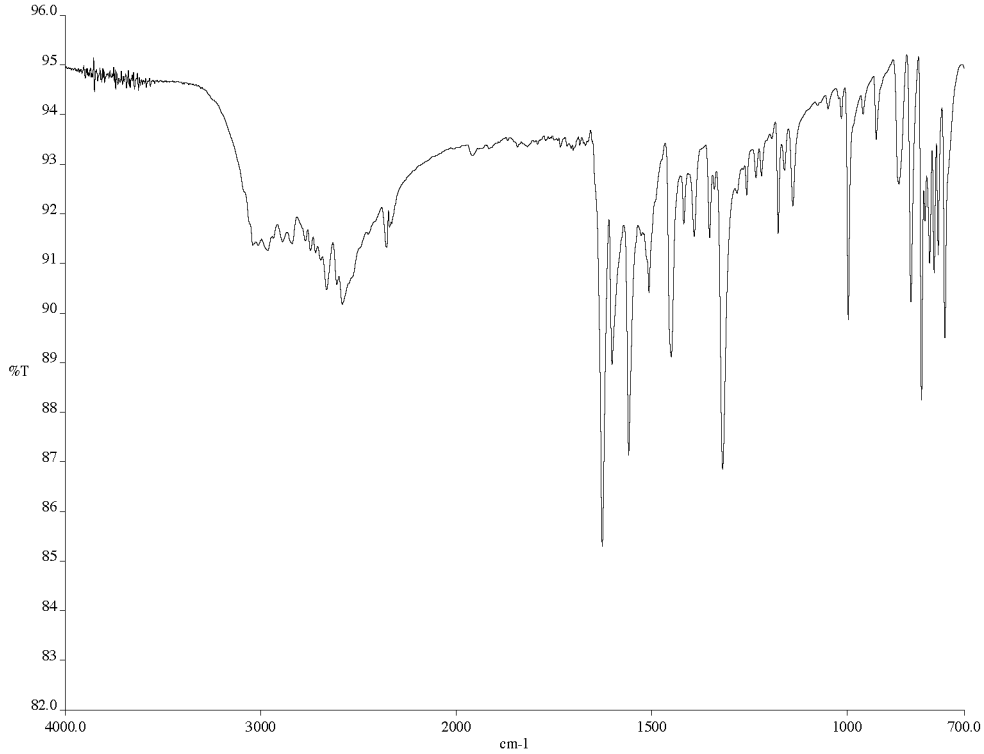


Figure A5.20.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576i** (Table 5.5, entry 9).

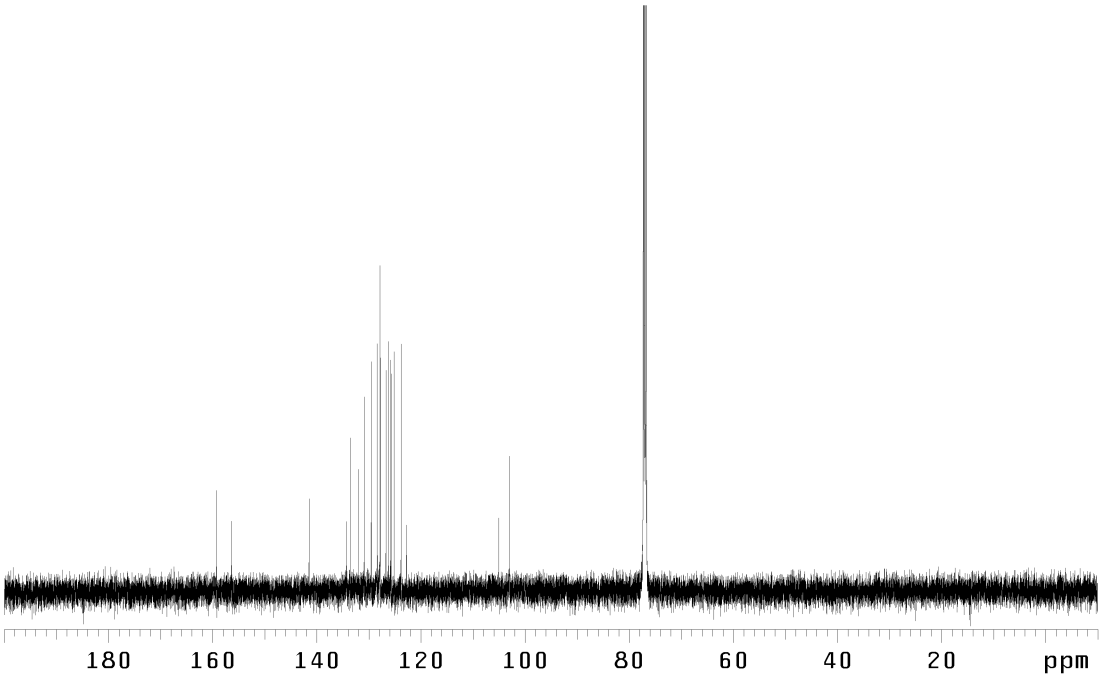


Figure A5.20.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576i** (Table 5.5, entry 9).

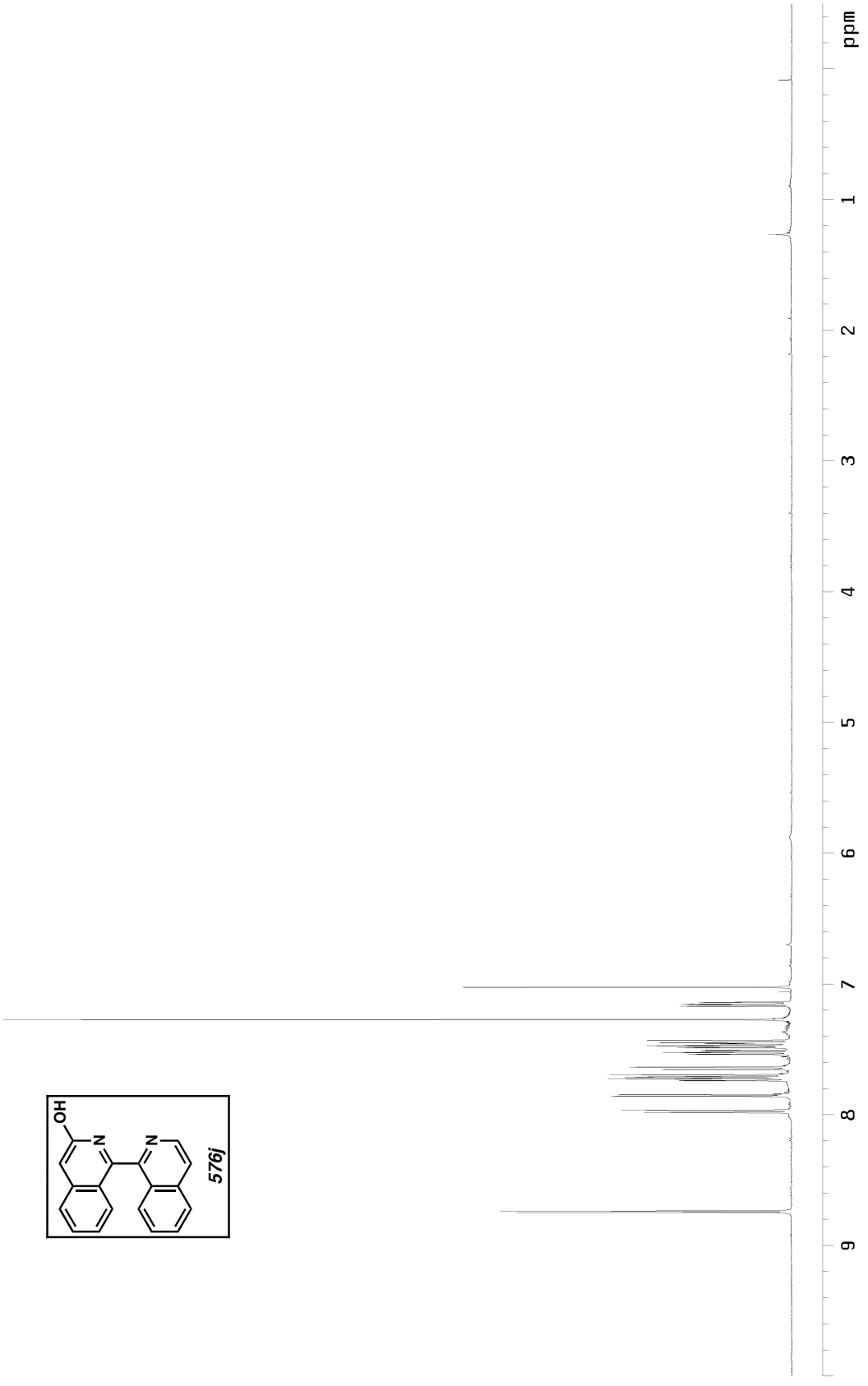


Figure A5.21.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576j** (Table 5.5, entry 10).

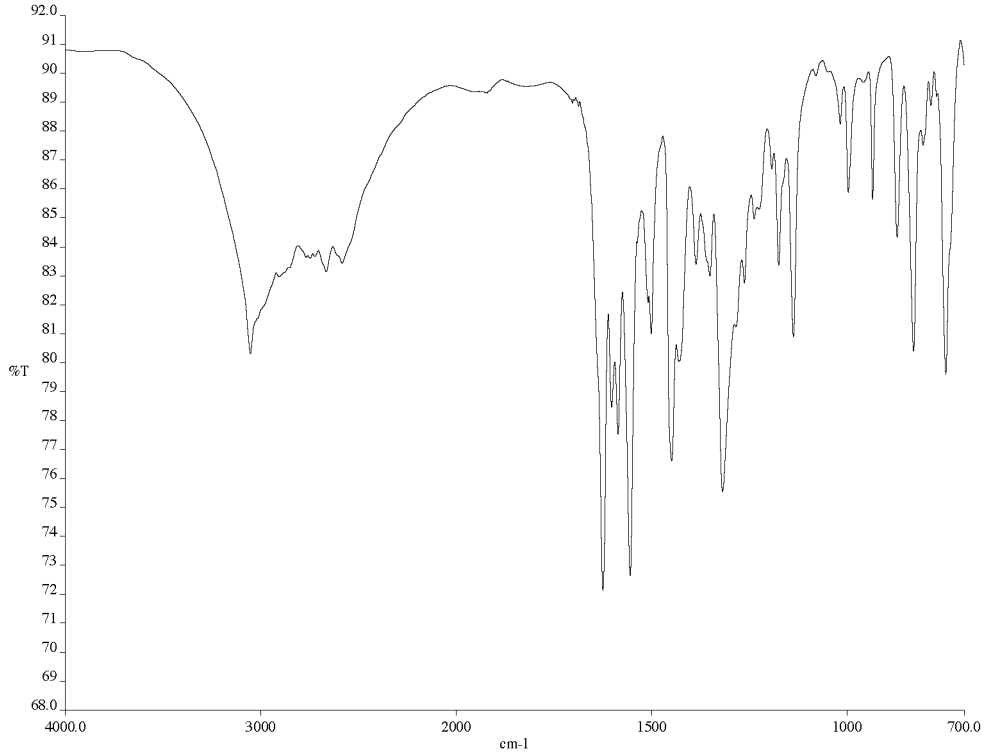


Figure A5.21.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576j** (Table 5.5, entry 10).

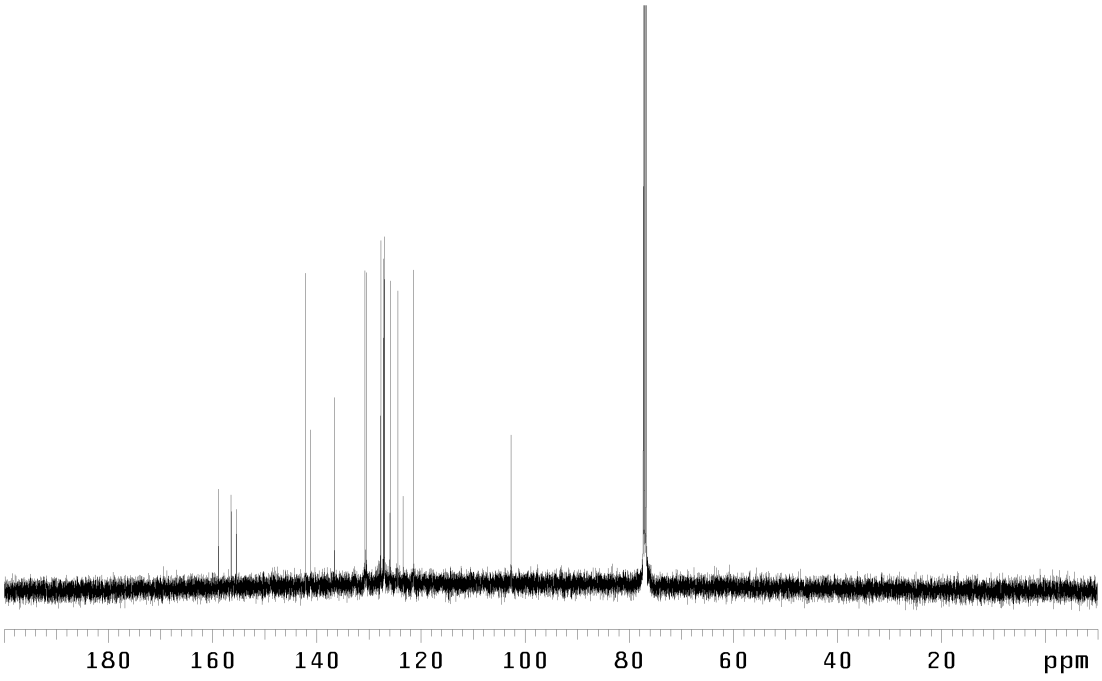


Figure A5.21.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576j** (Table 5.5, entry 10).

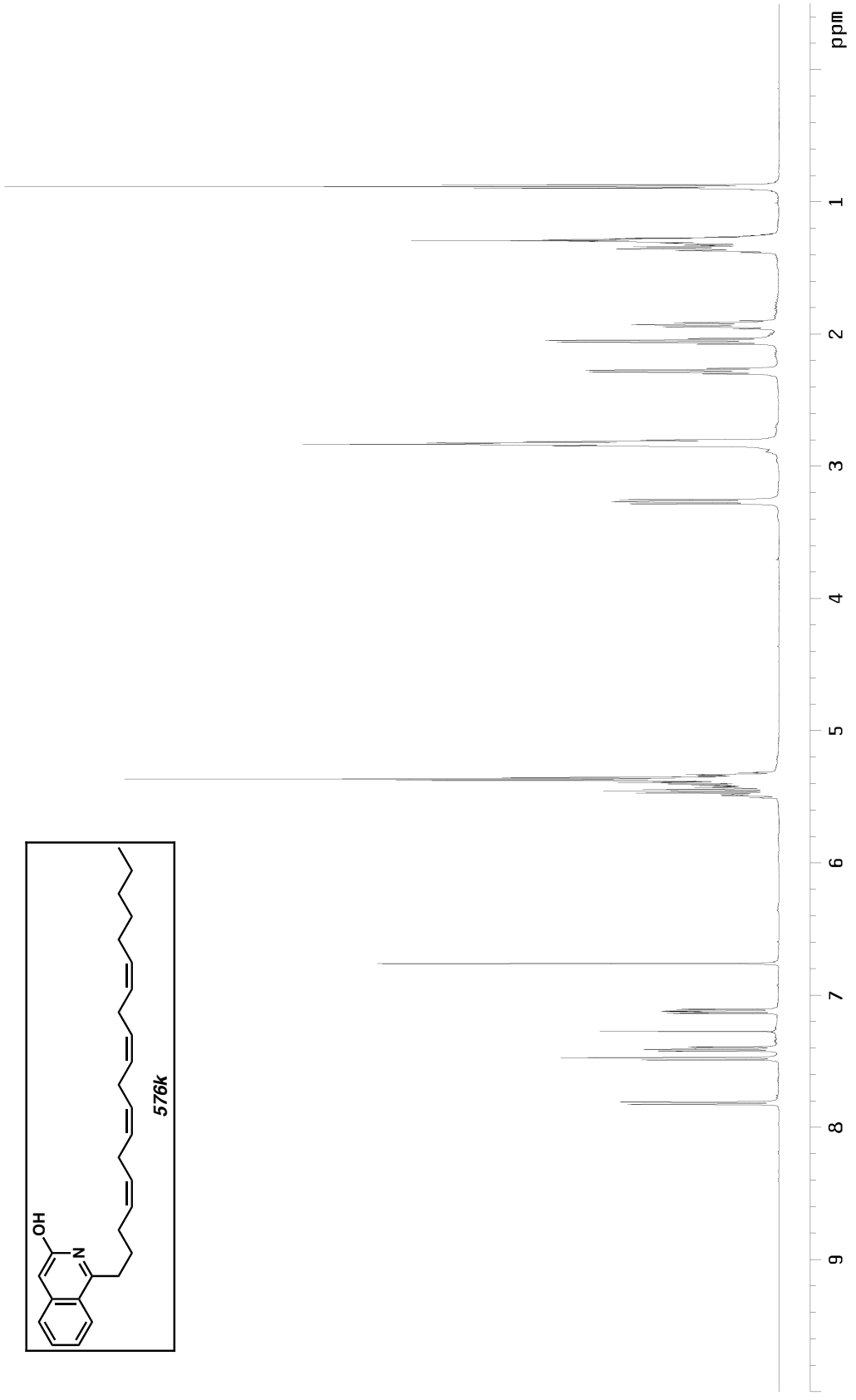


Figure A5.22.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576k** (Table 5.5, entry 11).

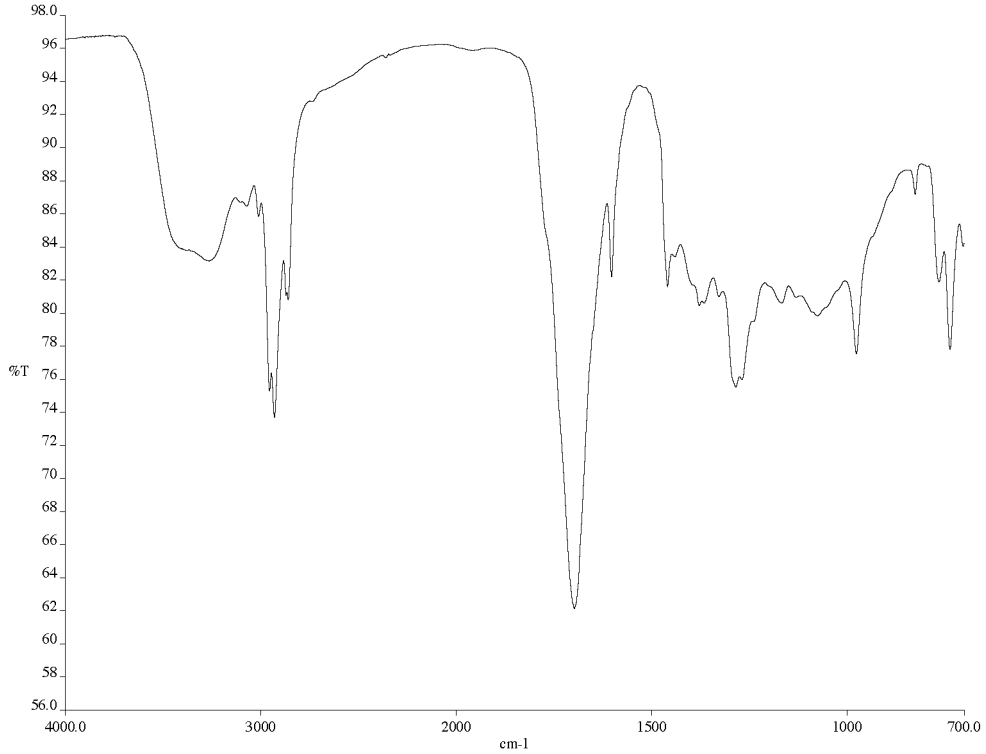


Figure A5.22.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576k** (Table 5.5, entry 11).

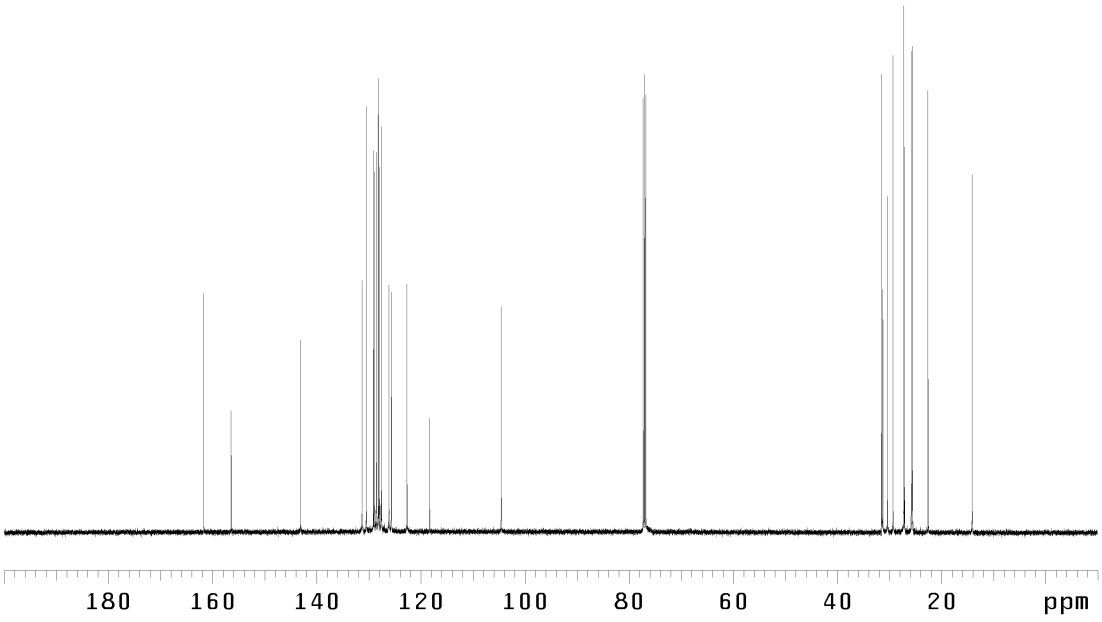


Figure A5.22.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576k** (Table 5.5, entry 11).

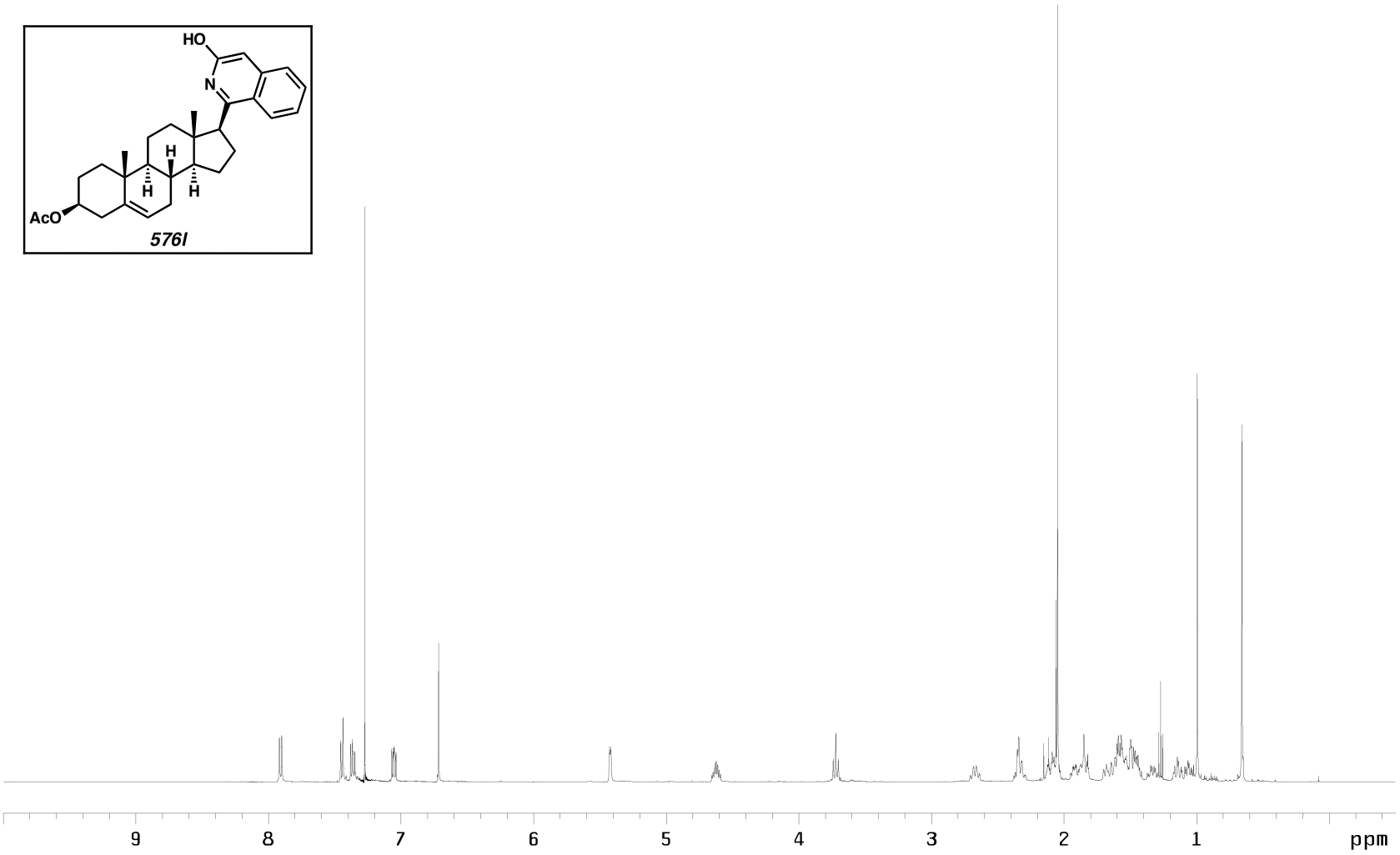


Figure A5.23.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576l** (Table 5.5, entry 12).

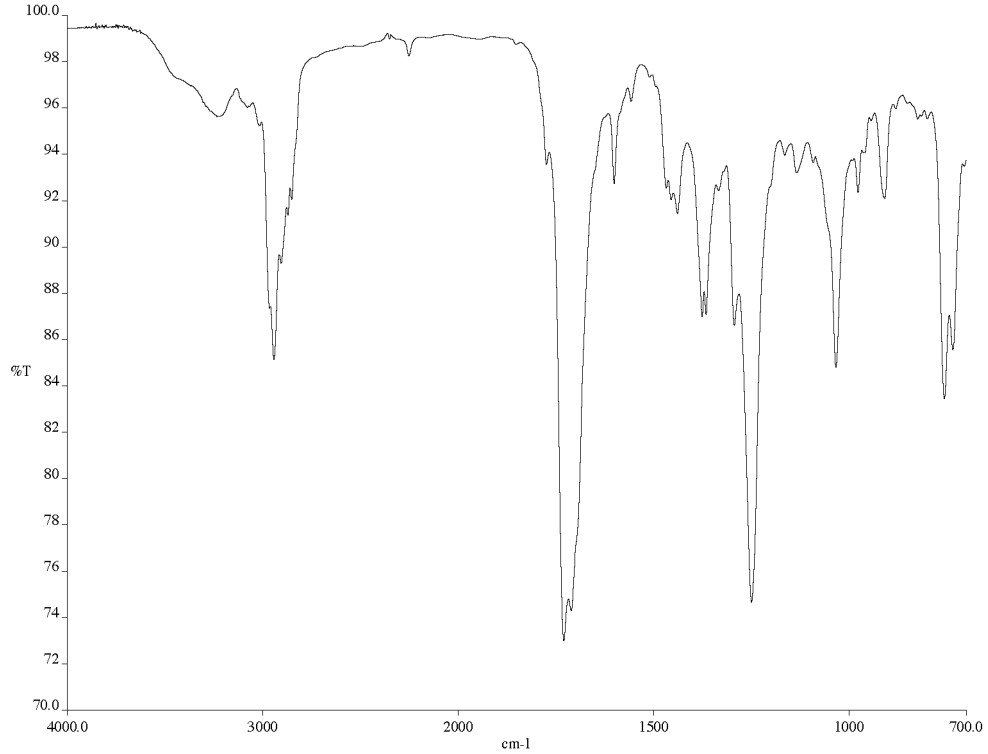


Figure A5.23.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576l** (Table 5.5, entry 12).

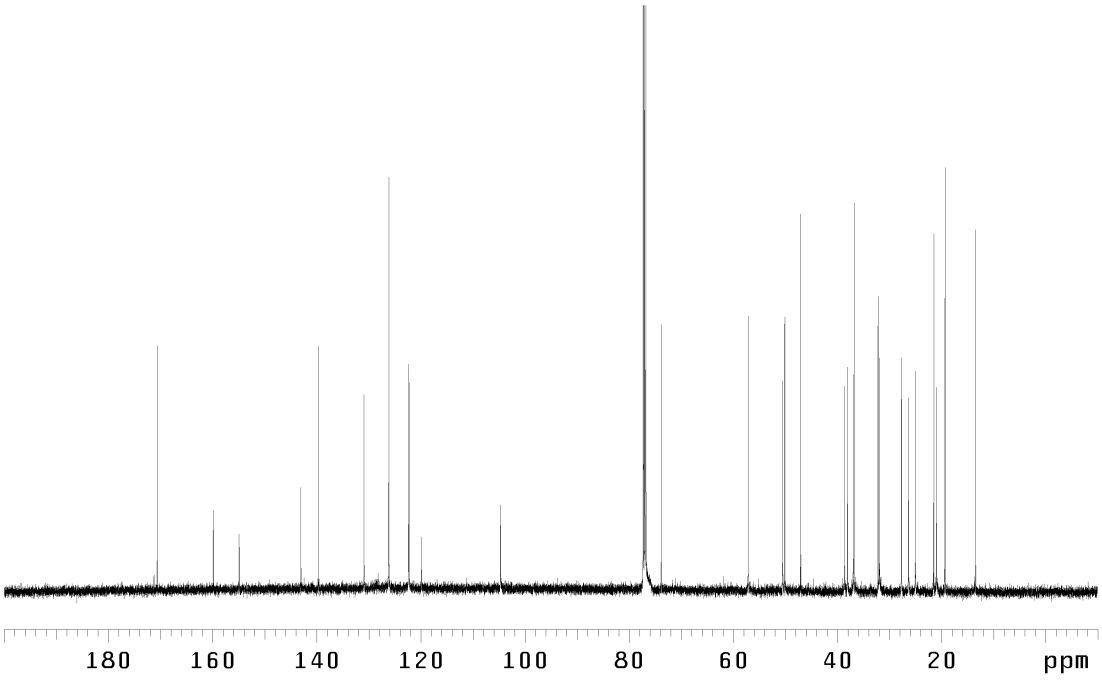


Figure A5.23.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 3-hydroxyisoquinoline **576l** (Table 5.5, entry 12).

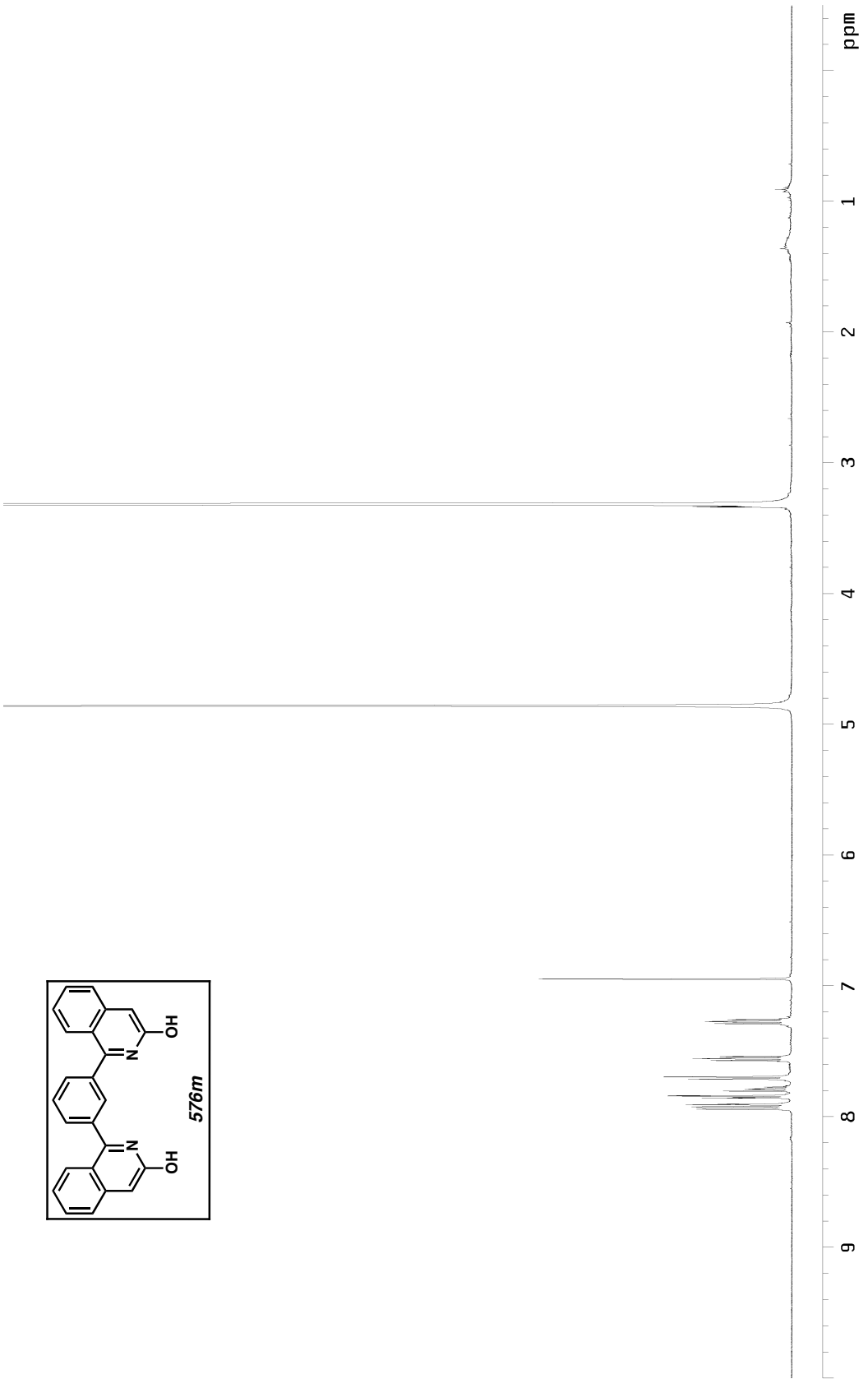


Figure A5.24.1 ^{1}H NMR (500 MHz, CD_3OD) of 3-hydroxyisoquinoline **576m** (Table 5.5, entry 13).

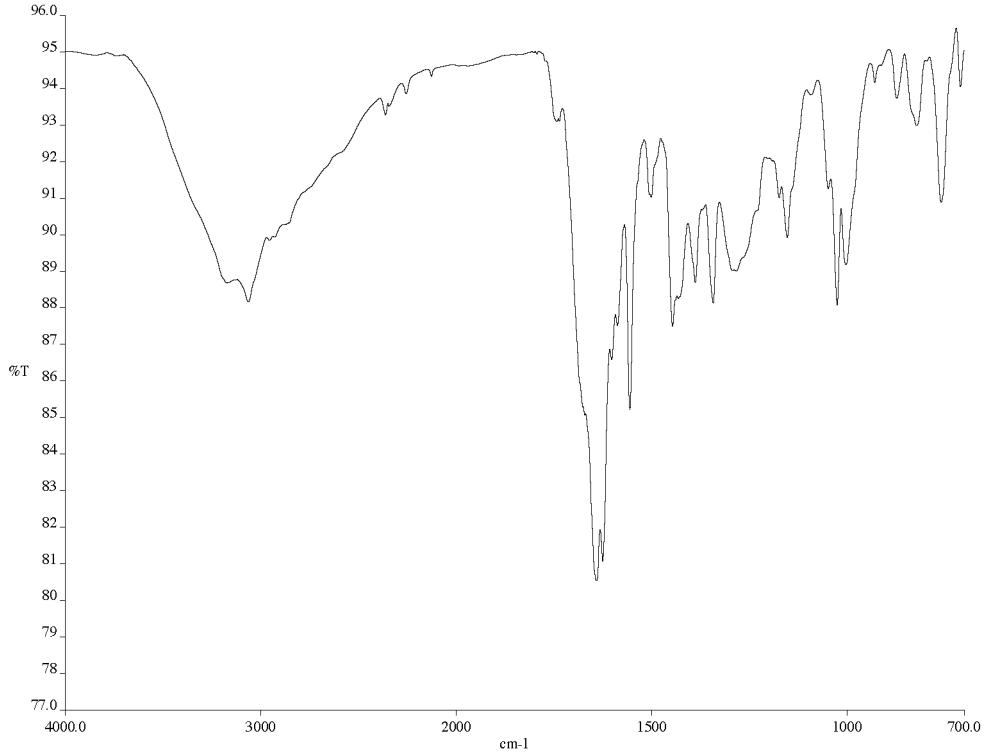


Figure A5.24.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576m** (Table 5.5, entry 13).

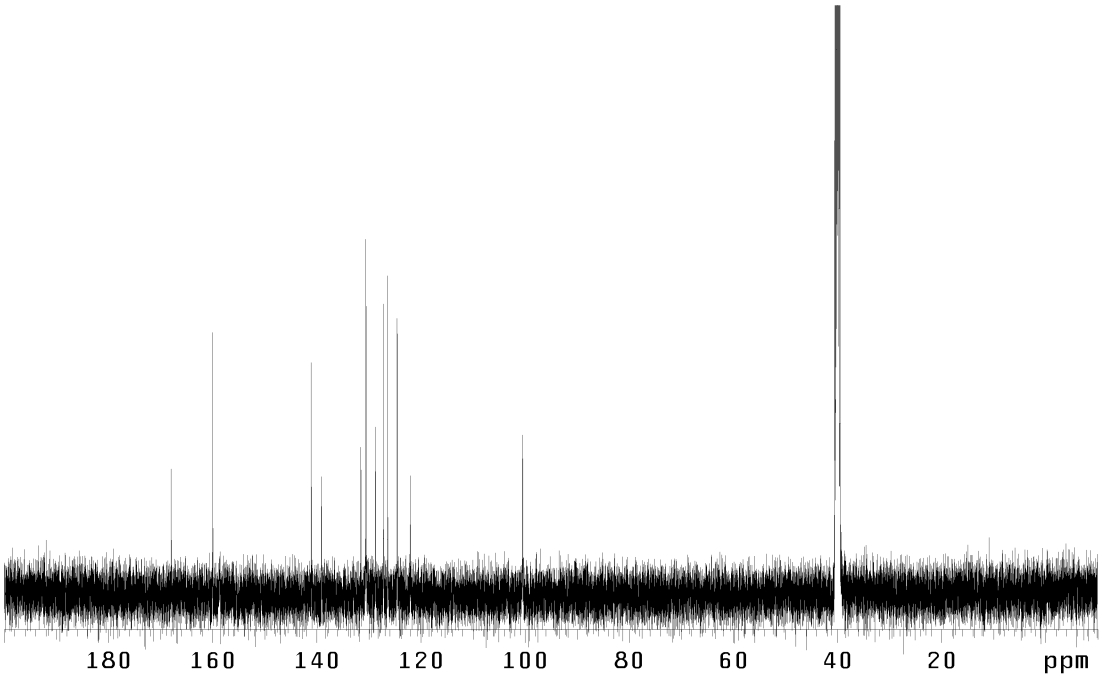


Figure A5.24.2 Infrared spectrum (thin film/NaCl) of 3-hydroxyisoquinoline **576m** (Table 5.5, entry 13).

Figure A5.25.1 ^{1}H NMR (500 MHz, $CDCl_3$) of isoquinoline triflate **A5-1**.

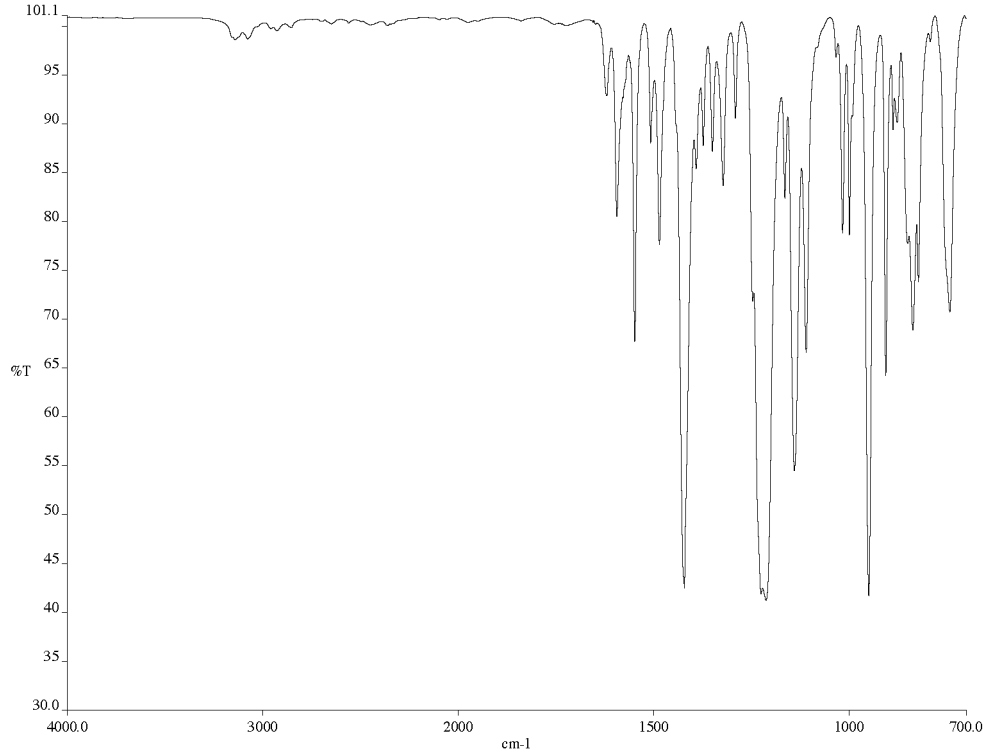


Figure A5.25.2 Infrared spectrum (thin film/NaCl) of isoquinoline triflate **A5-1**.

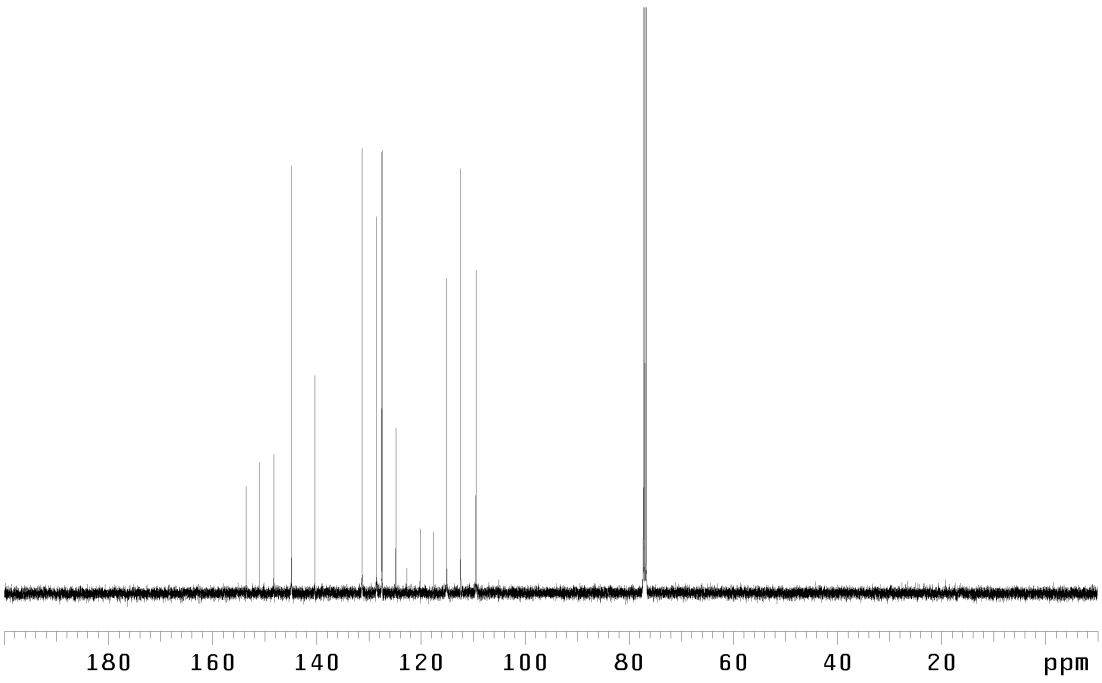


Figure A5.25.3 ^{13}C NMR (125 MHz MHz, $CDCl_3$) of isoquinoline triflate **A5-1**.

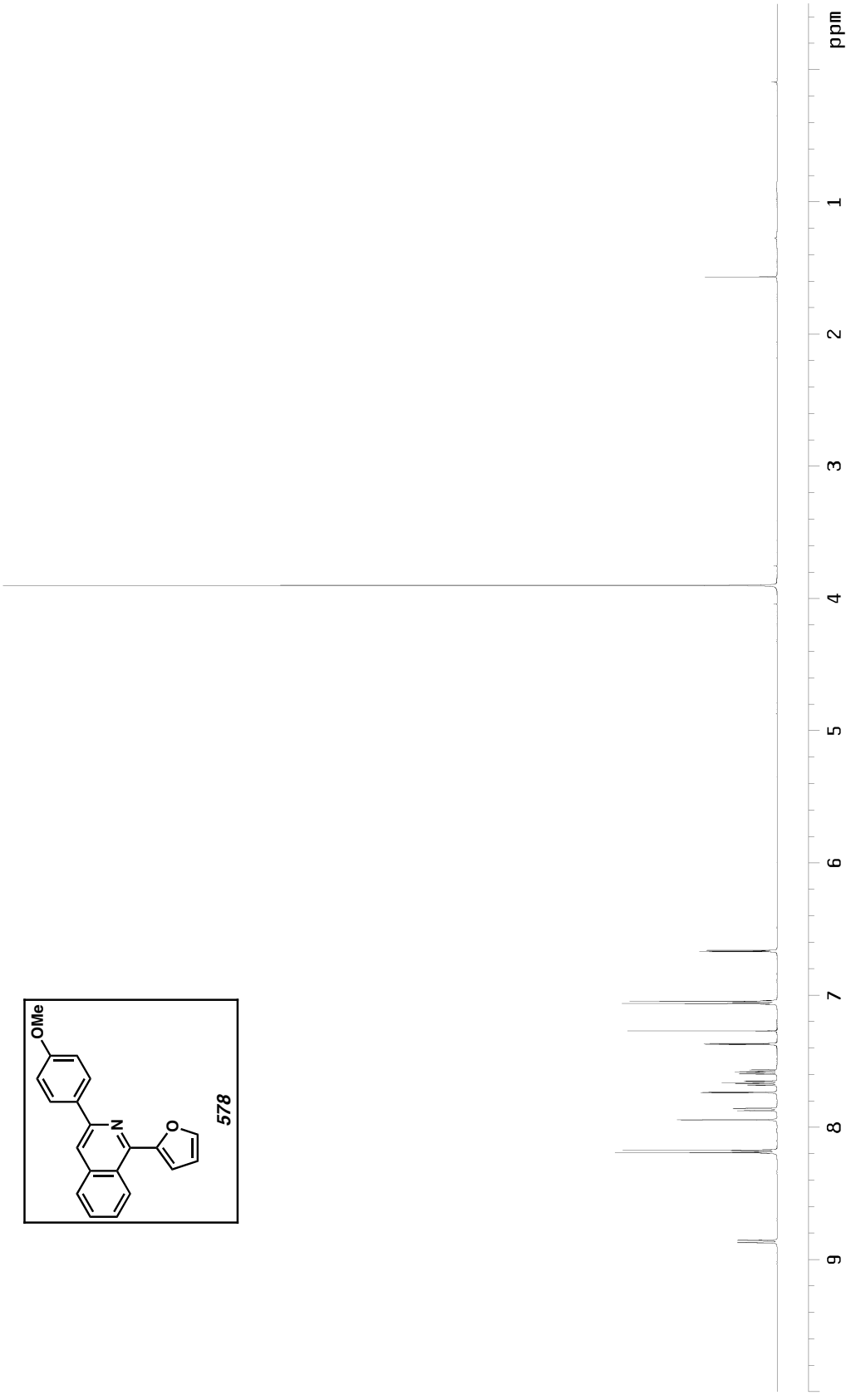


Figure A5.26.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 1,3-diarylisoquinoline **578**.

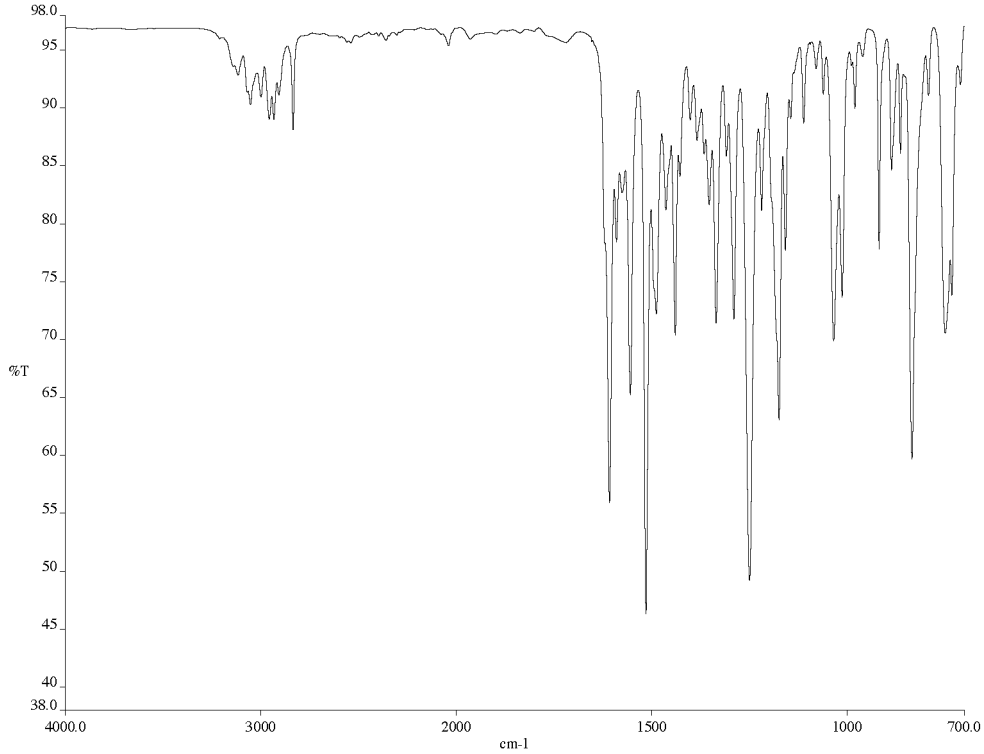


Figure A5.26.2 Infrared spectrum (thin film/NaCl) of 1,3-diarylisoquinoline **578**.

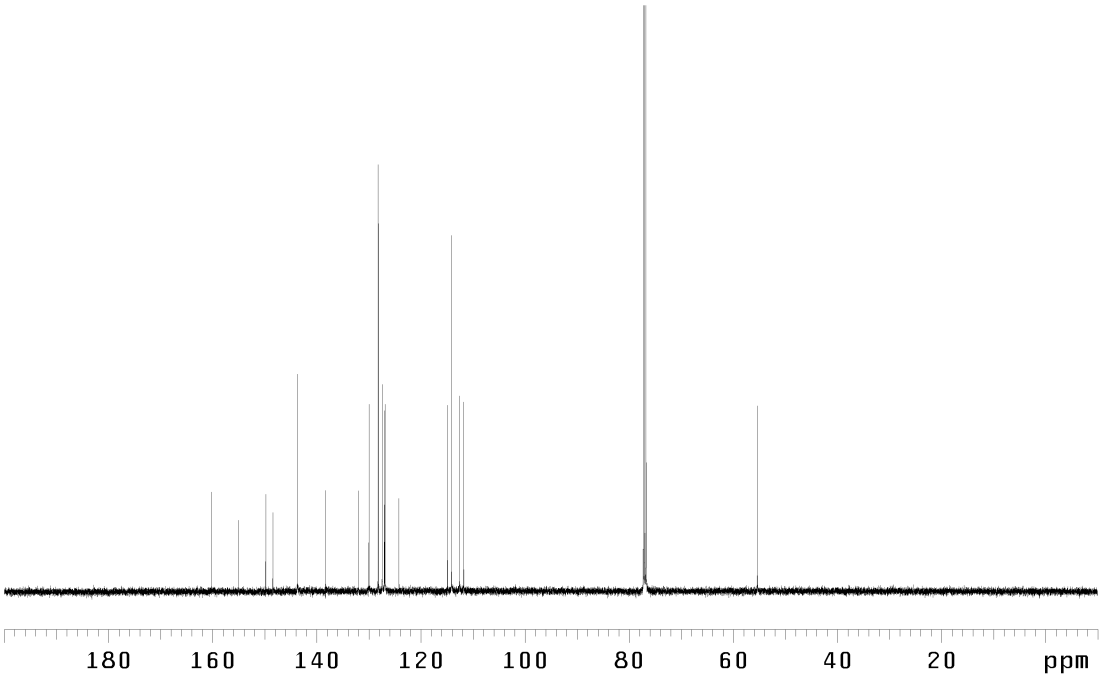


Figure A5.26.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 1,3-diarylisoquinoline **578**.

Figure A5.27.1 ^{1}H NMR (500 MHz, $CDCl_3$) of isoquinoline triflate **579**.

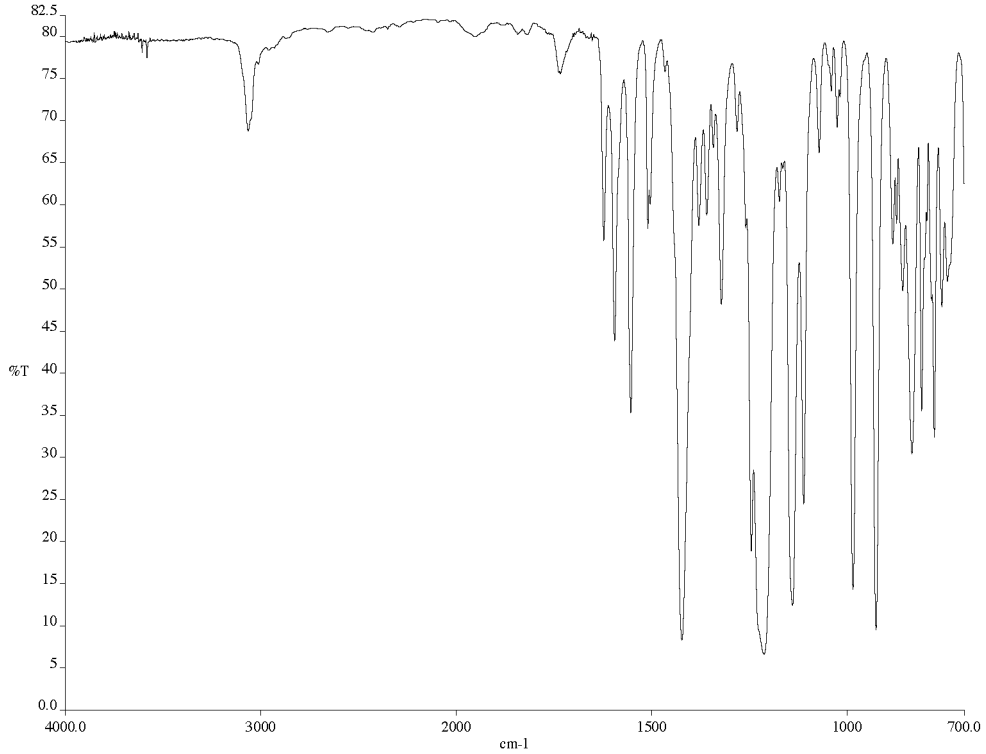


Figure A5.27.2 Infrared spectrum (thin film/NaCl) of isoquinoline triflate **579**.

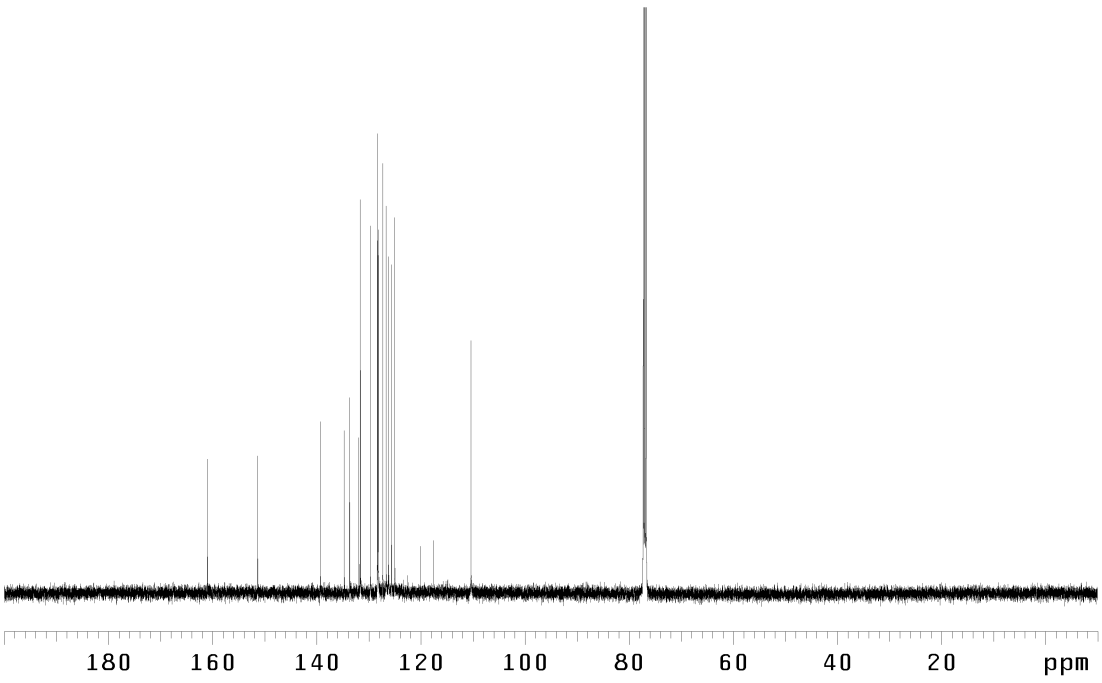


Figure A5.27.3 ^{13}C NMR (125 MHz, $CDCl_3$) of isoquinoline triflate **579**.

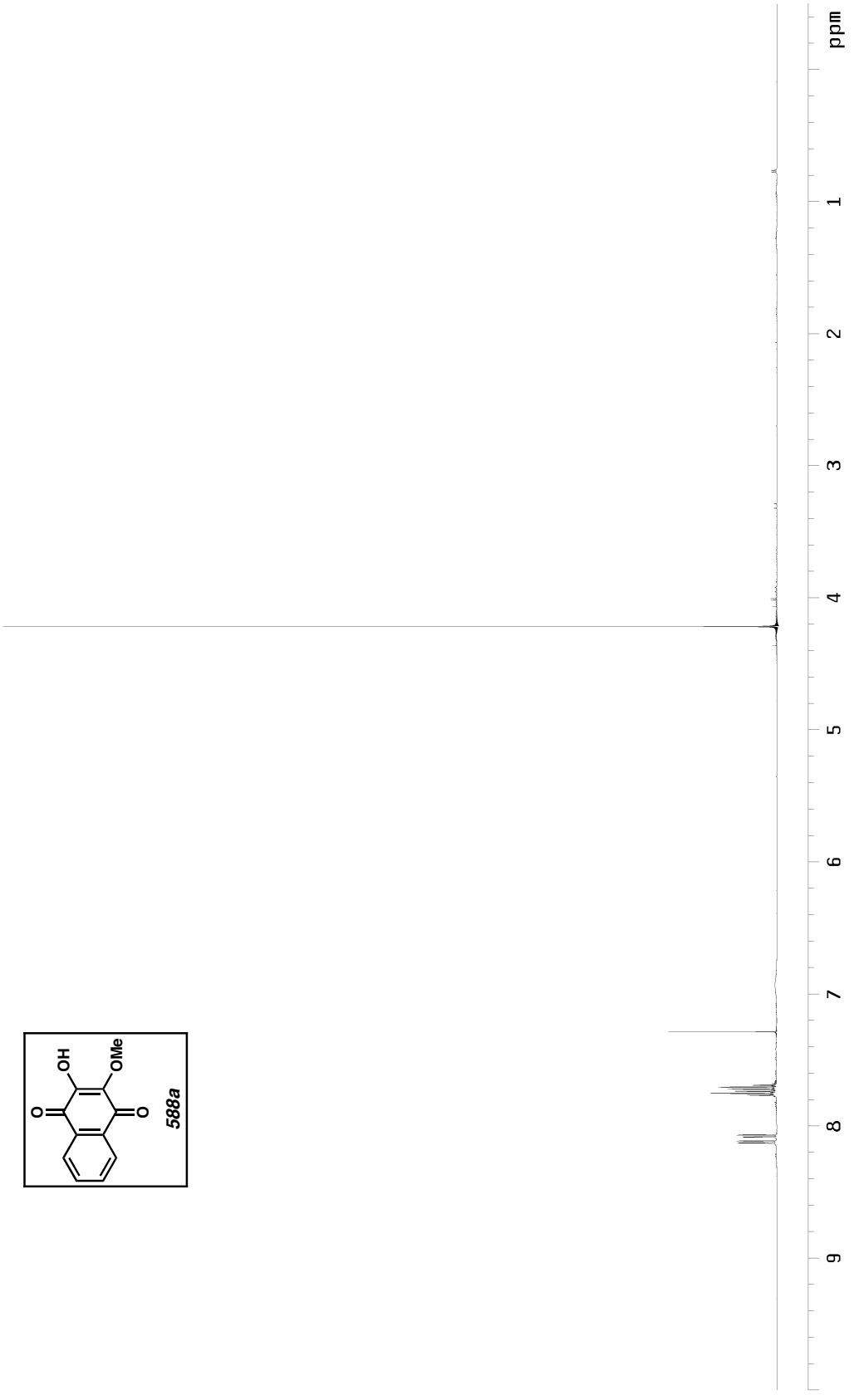


Figure A5.28.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588a** (Table 5.6, entry 1).

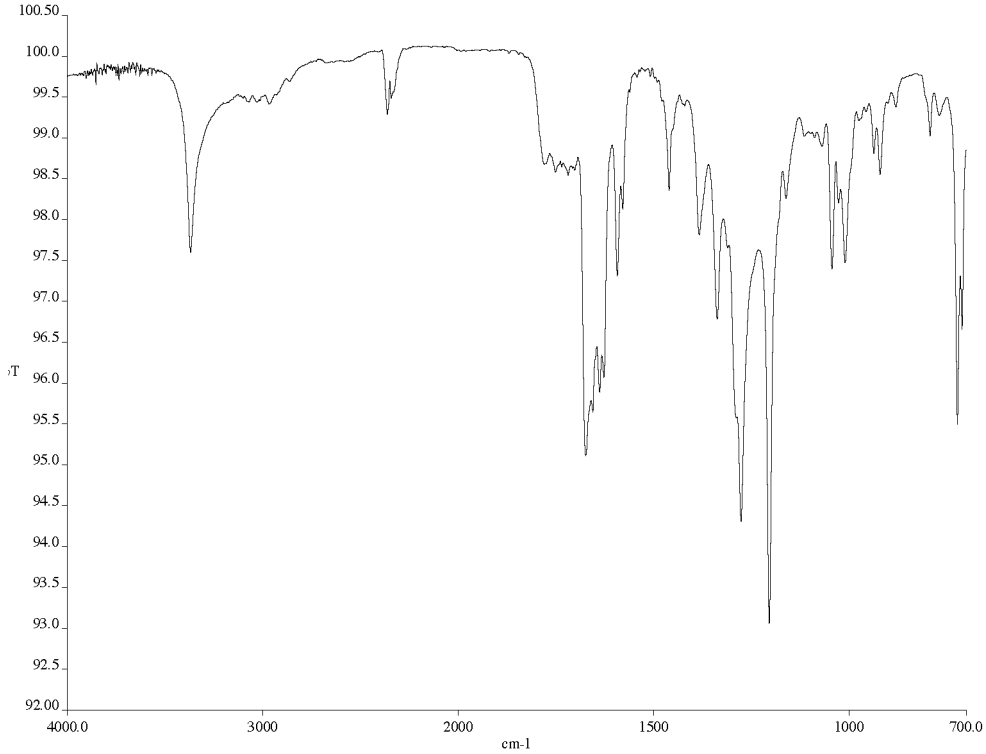


Figure A5.28.2 Infrared spectrum (thin film/NaCl) 2-hydroxy-1,4-naphthaquinone **588a** (Table 5.6, entry 1).

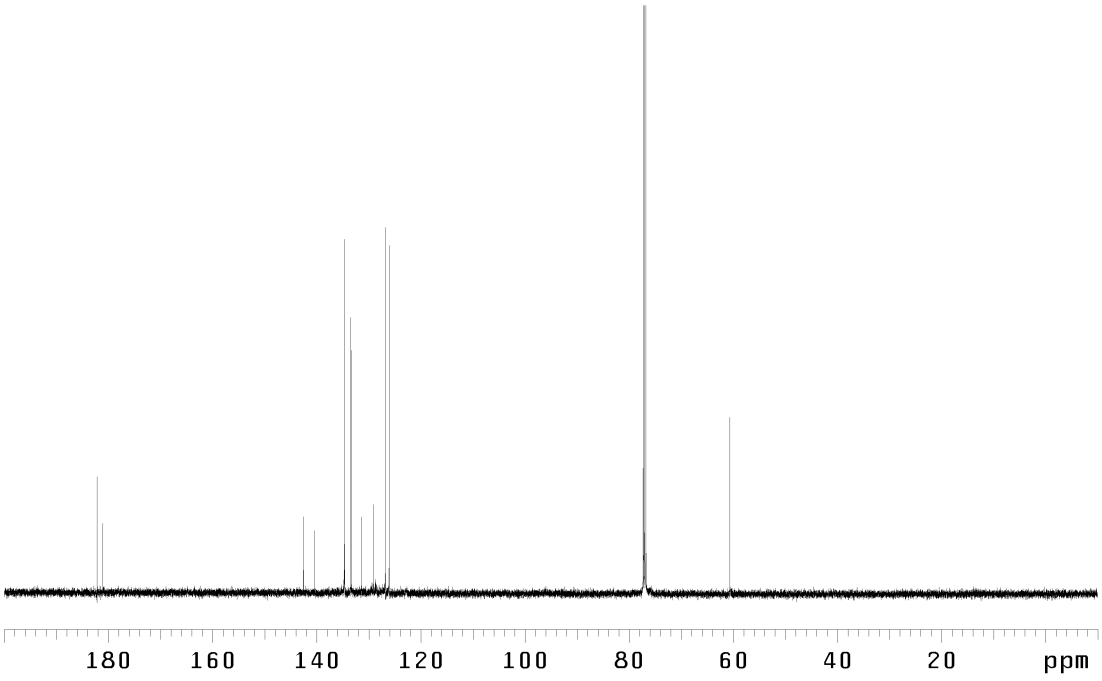
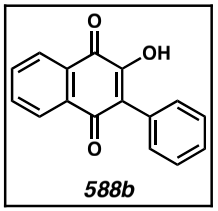


Figure A5.28.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588a** (Table 5.6, entry 1).



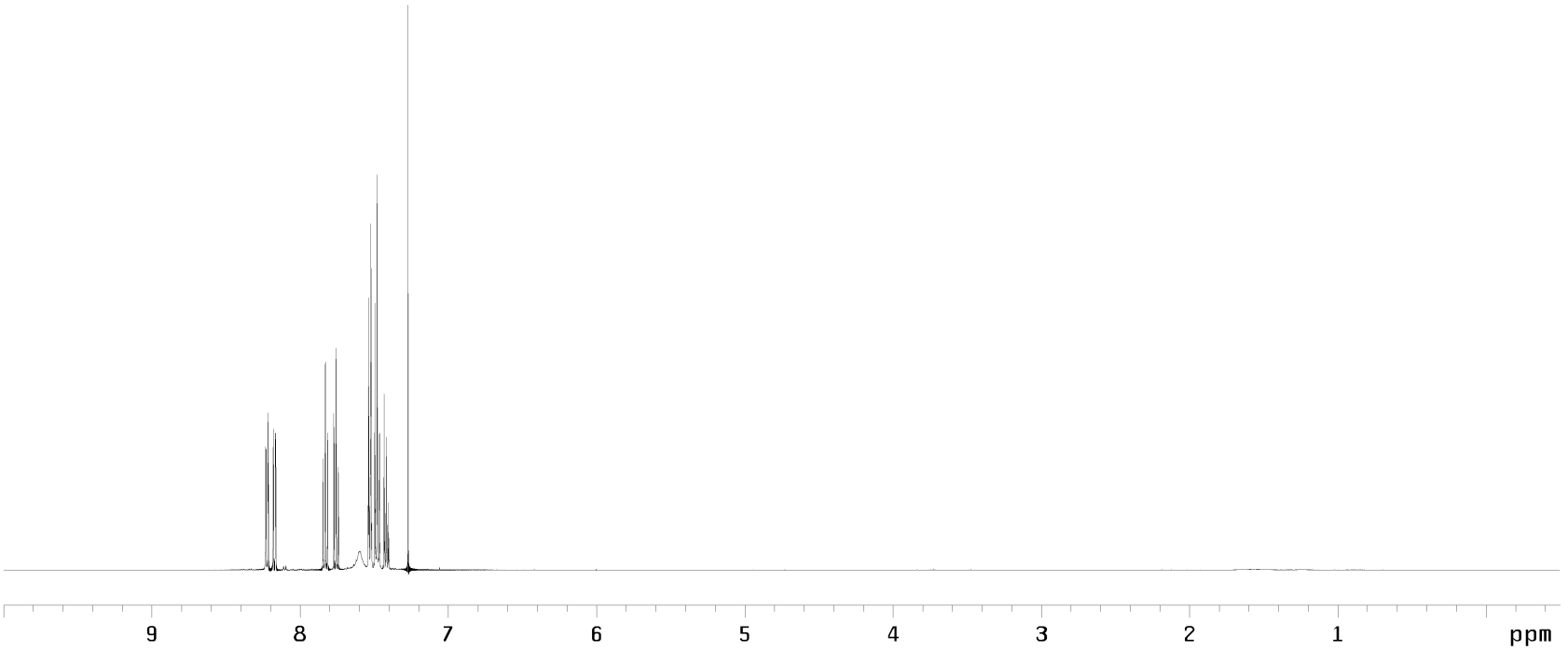


Figure A5.29.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588b** (Table 5.6, entry 2).

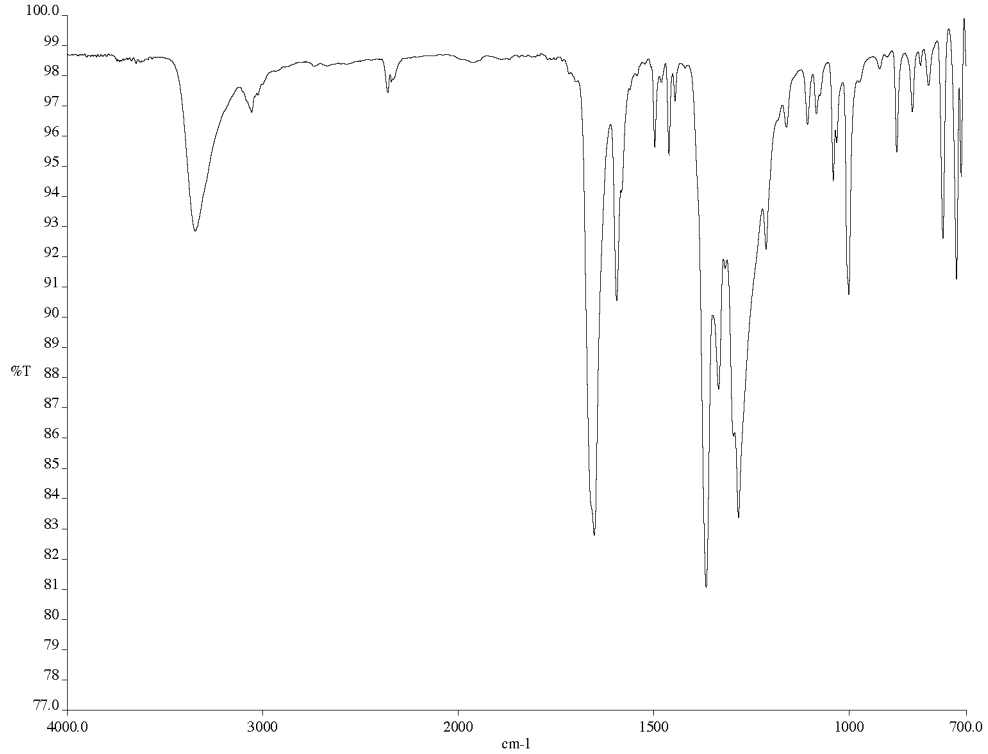


Figure A5.29.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588b** (Table 5.6, entry 2).

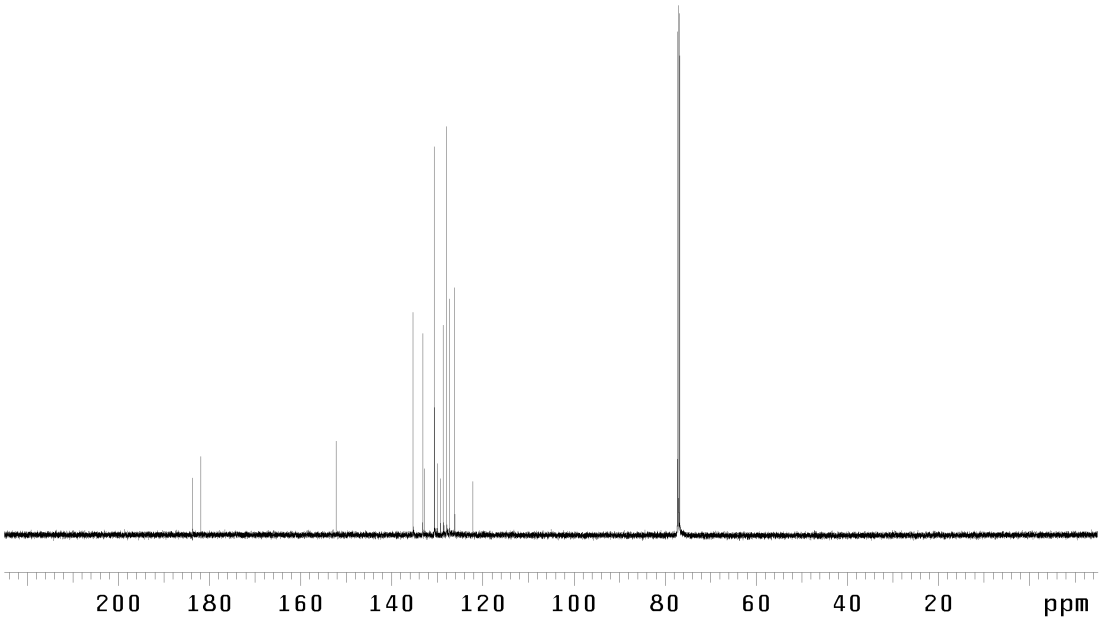


Figure A5.29.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588b** (Table 5.6, entry 2).

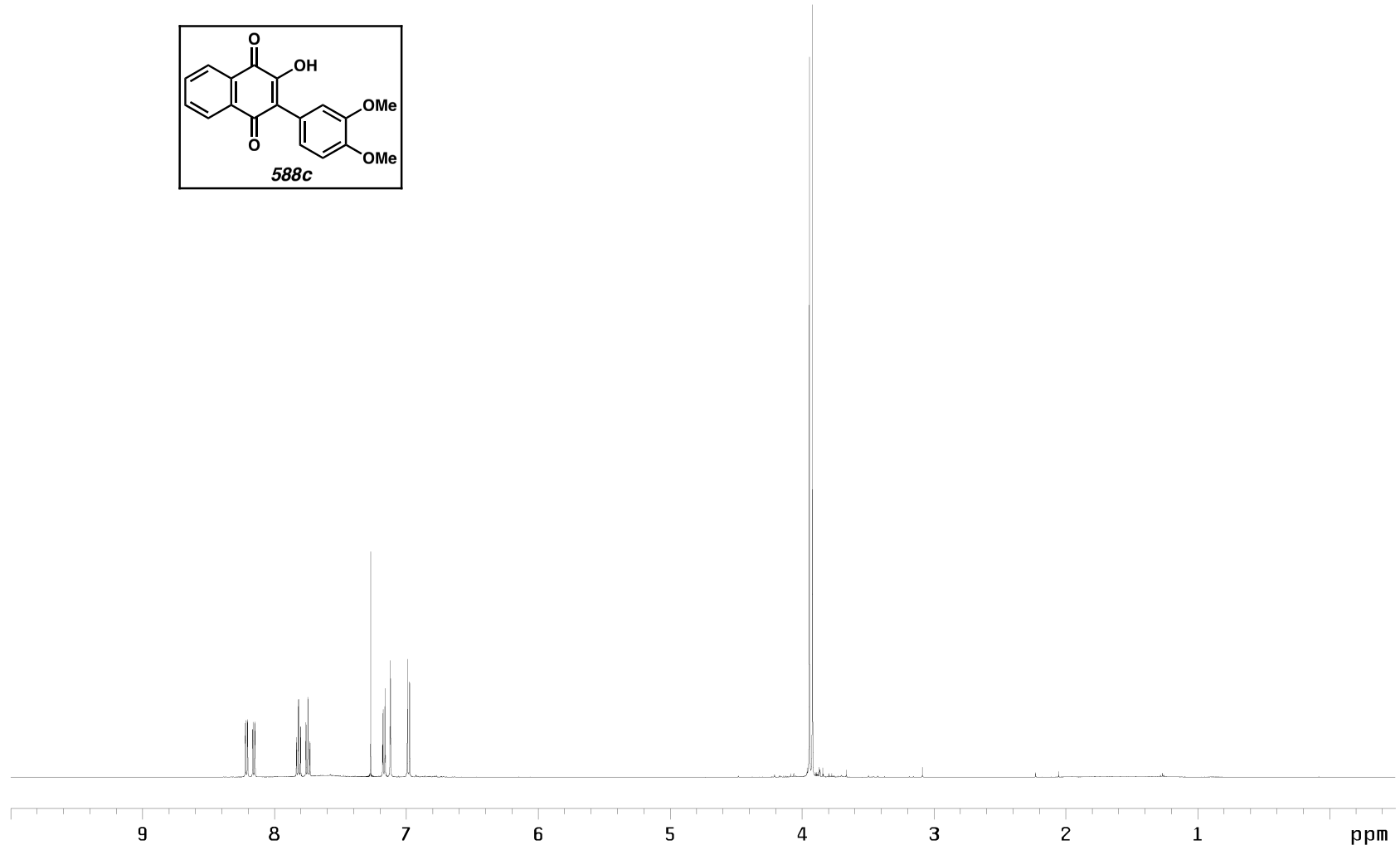


Figure A5.30.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588c** (Table 5.6, entry 3).

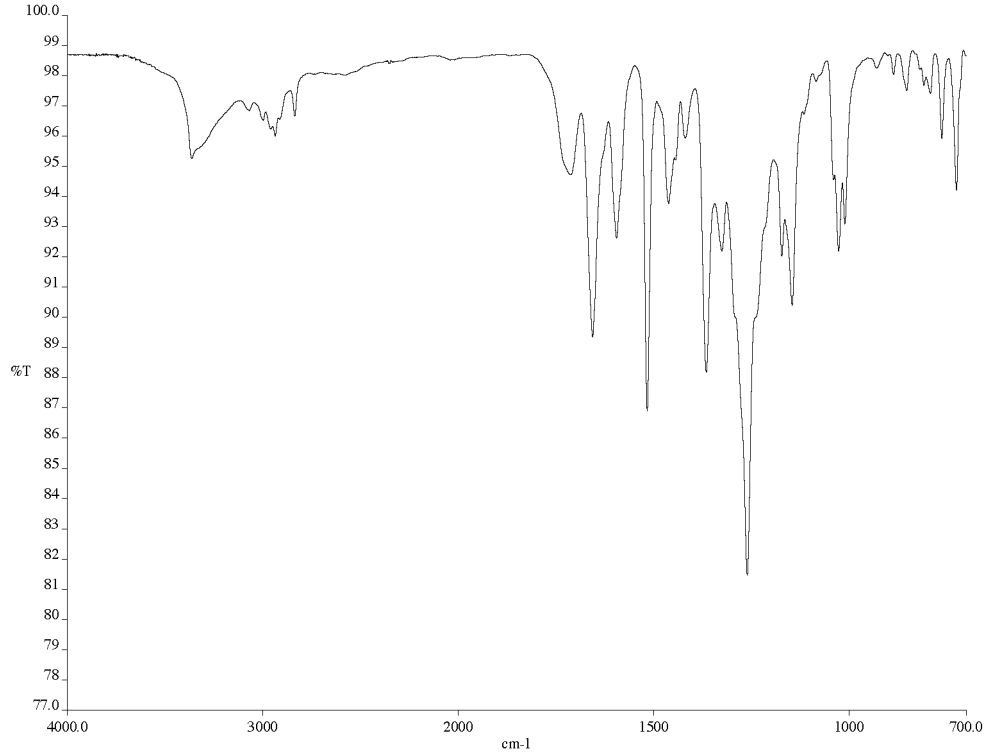


Figure A5.30.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588c** (Table 5.6, entry 3).

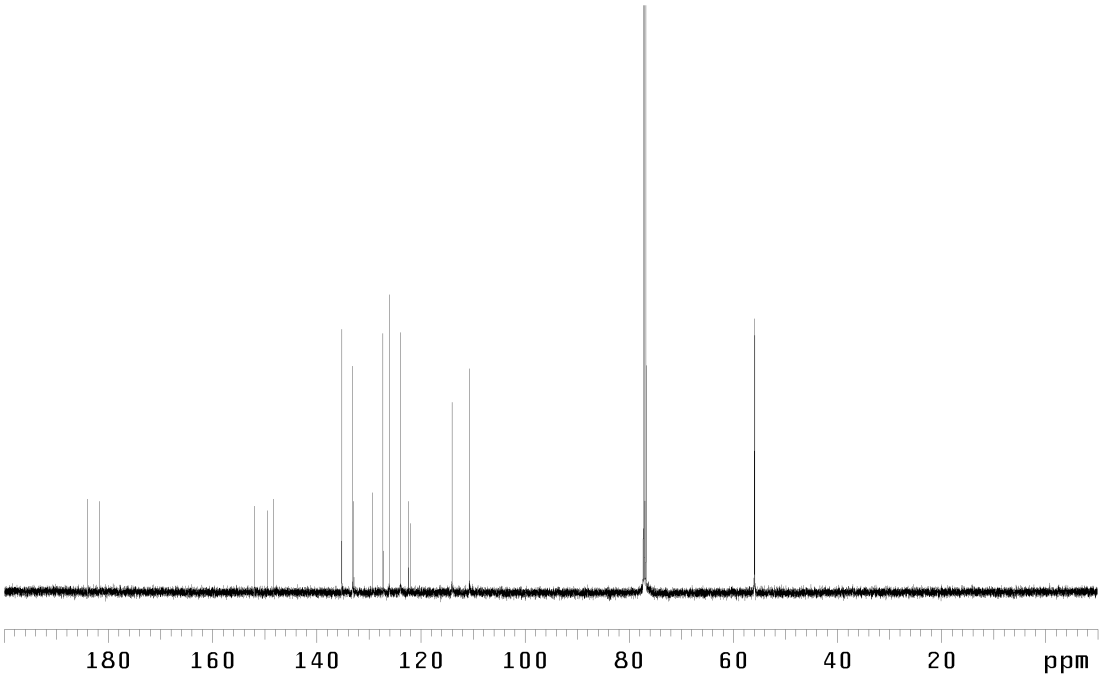


Figure A5.30.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588c** (Table 5.6, entry 3).

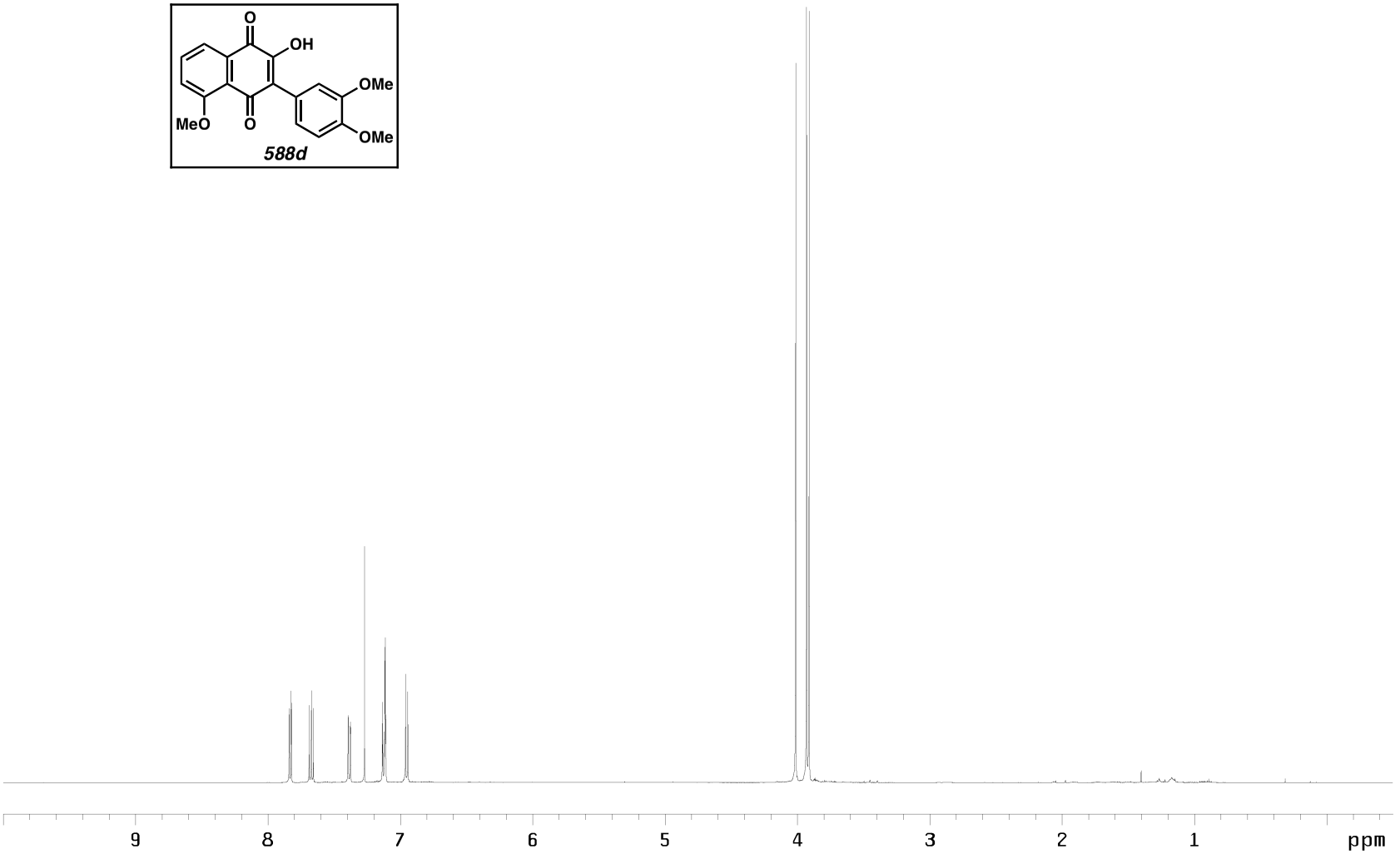


Figure A5.31.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588d** (Table 5.6, entry 4).

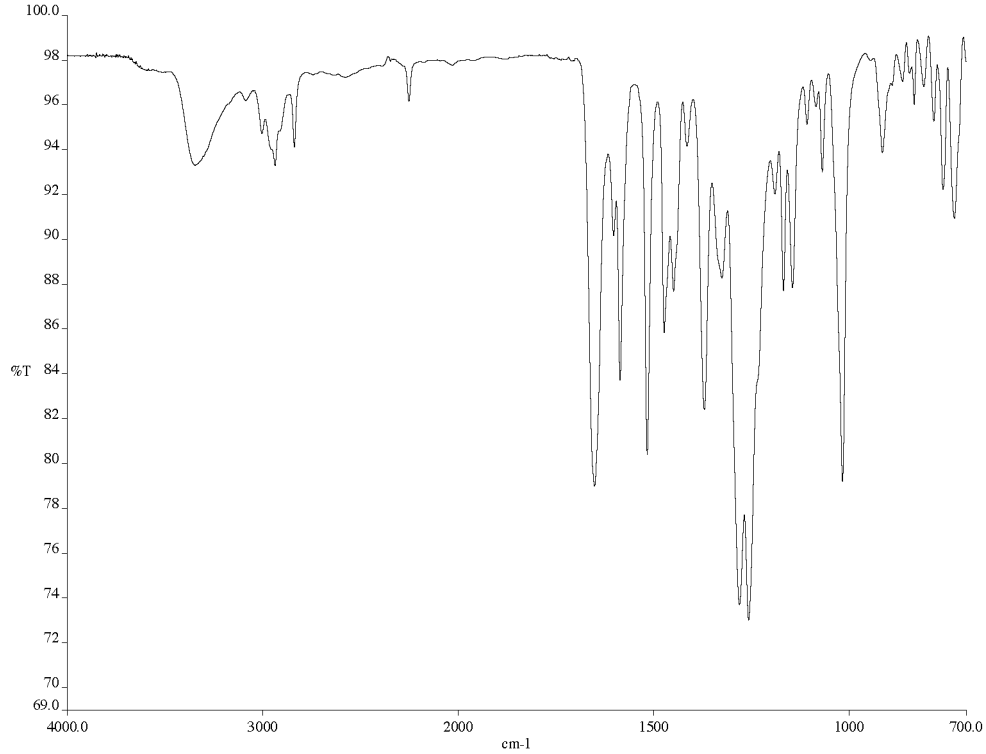


Figure A5.31.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588d** (Table 5.6, entry 4).

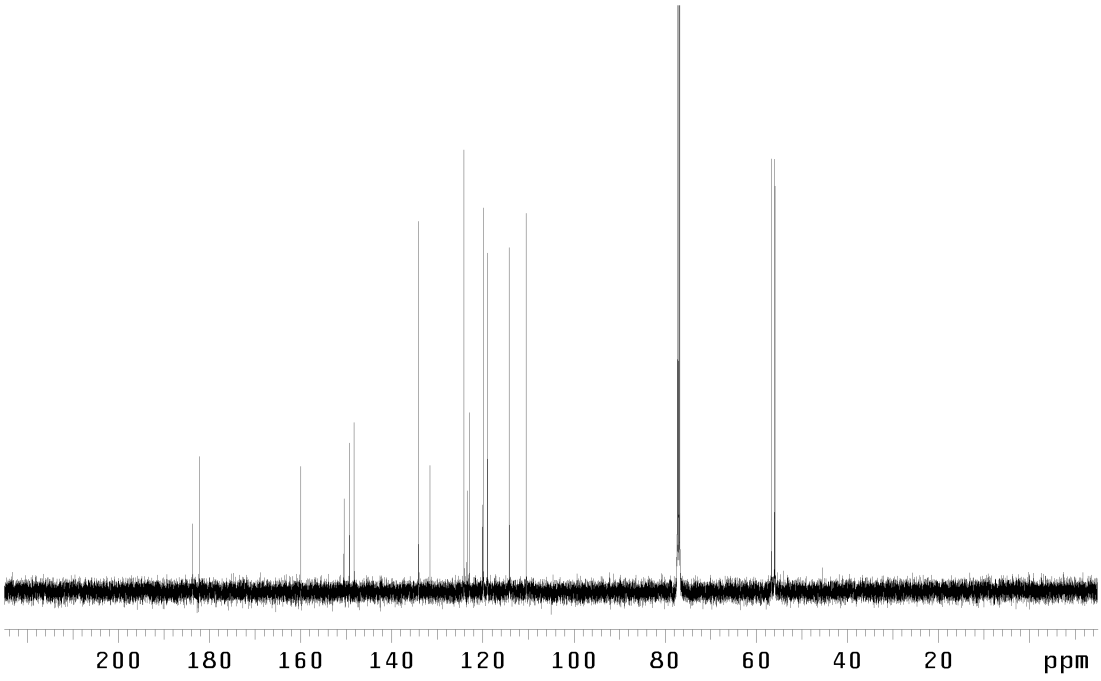


Figure A5.31.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588d** (Table 5.6, entry 4).

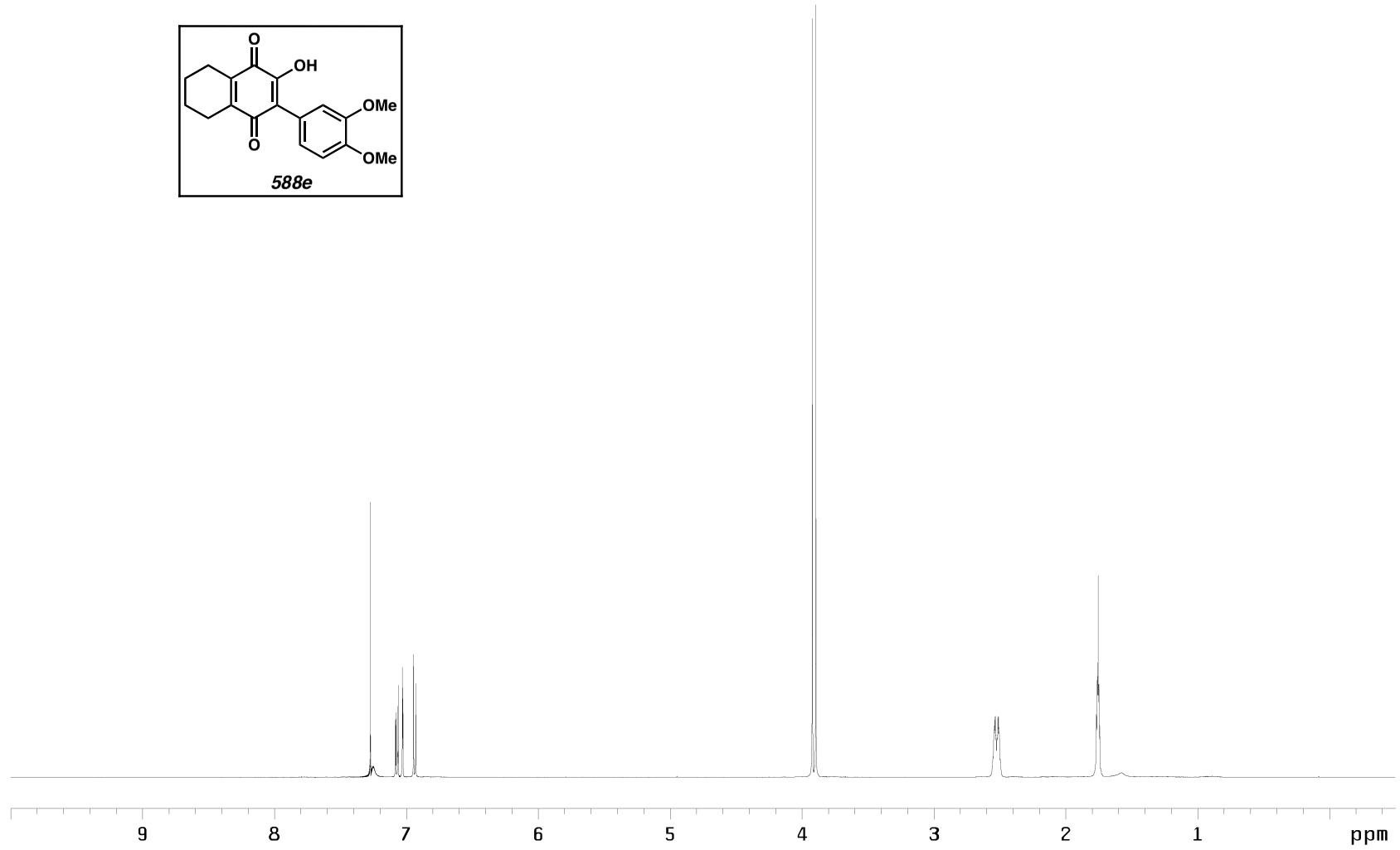


Figure A5.32.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-5,6,7,8-tetrahydronaphtha-1,4-quinone **588e** (Table 5.6, entry 5).

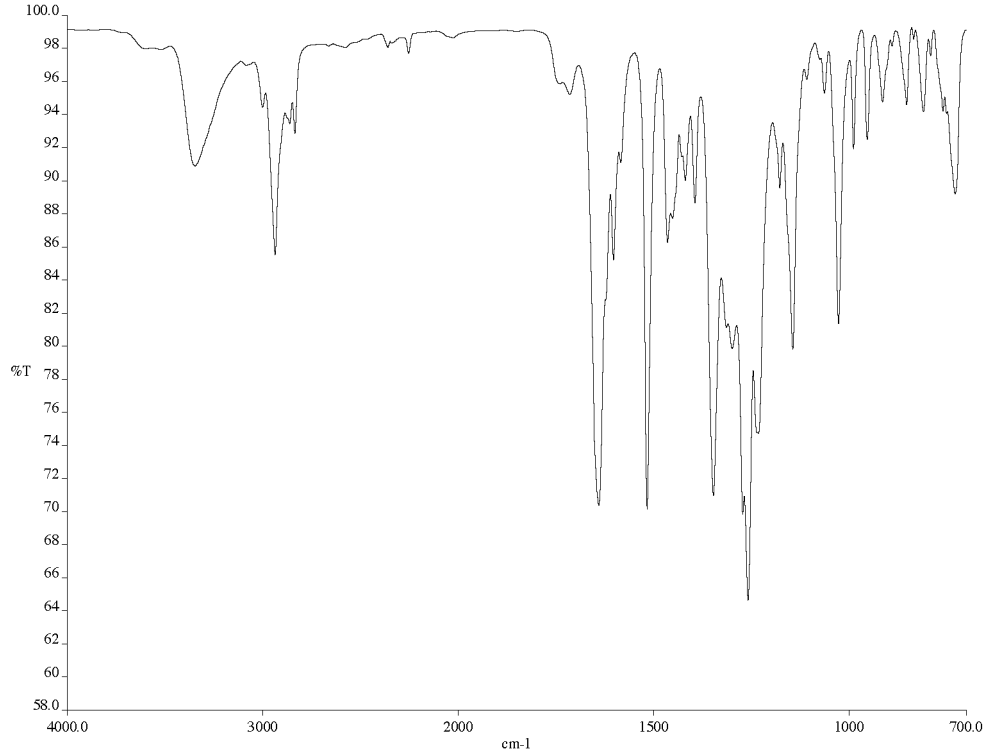


Figure A5.32.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-5,6,7,8-tetrahydronaphtha-1,4-quinone **588e** (Table 5.6, entry 5).

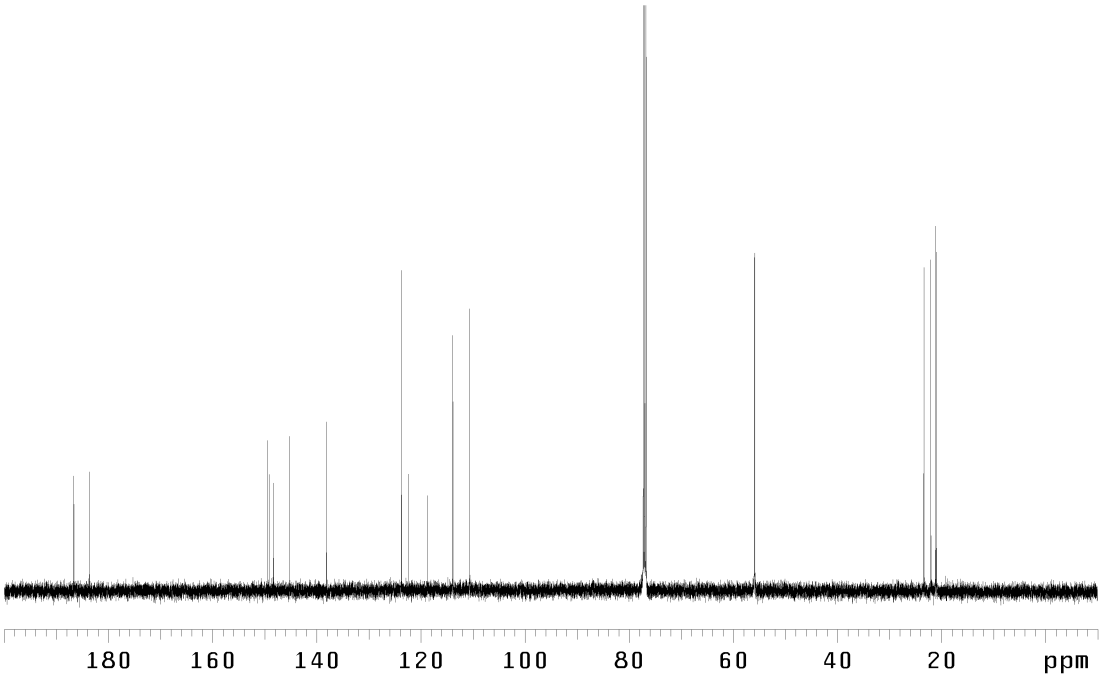


Figure A5.32.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-5,6,7,8-tetrahydronaphtha-1,4-quinone **588e** (Table 5.6, entry 5).

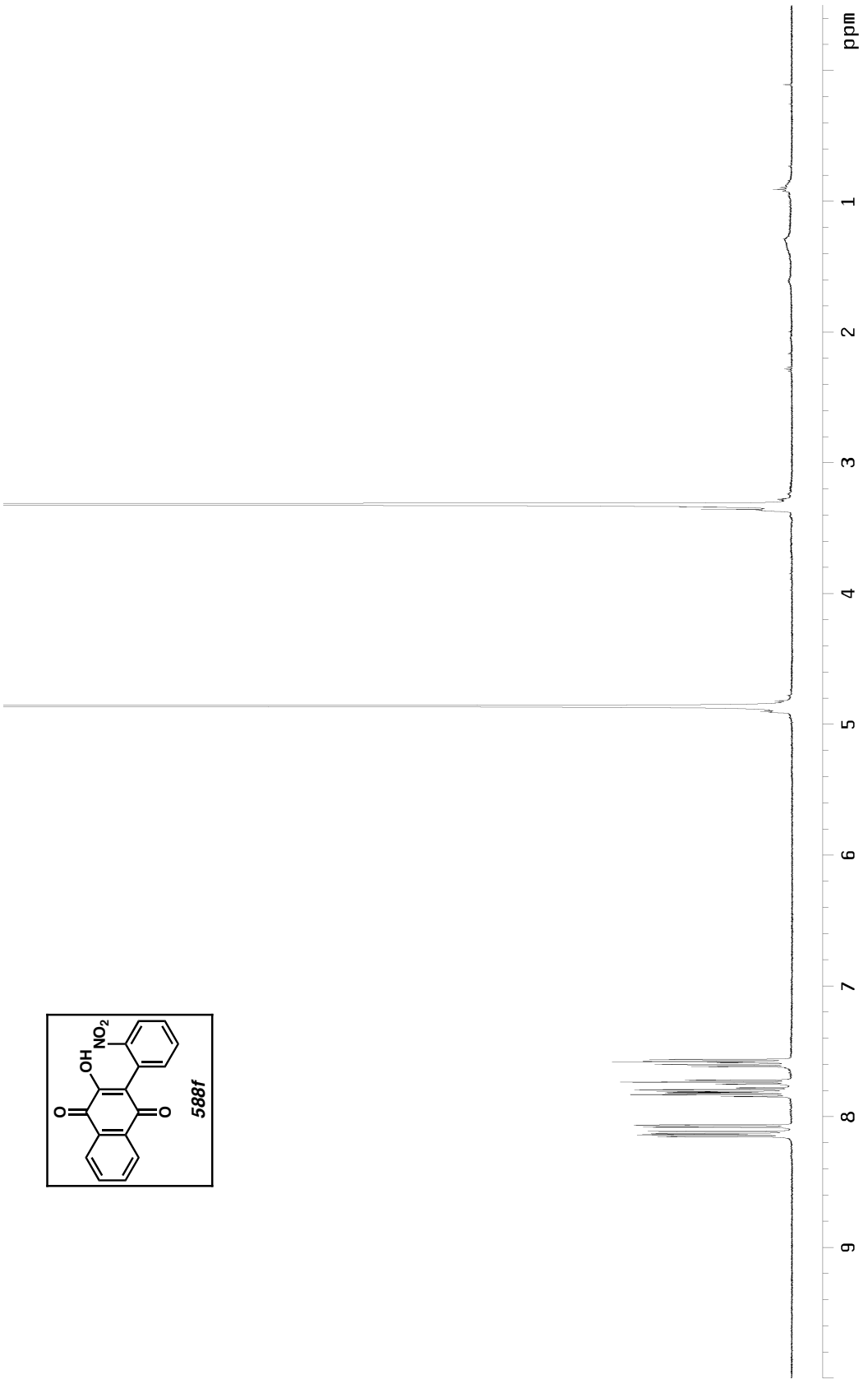


Figure A5.33.1 ^{1}H NMR (500 MHz, CD_3OD) of 2-hydroxy-1,4-naphthaquinone **588f** (Table 5.6, entry 6).

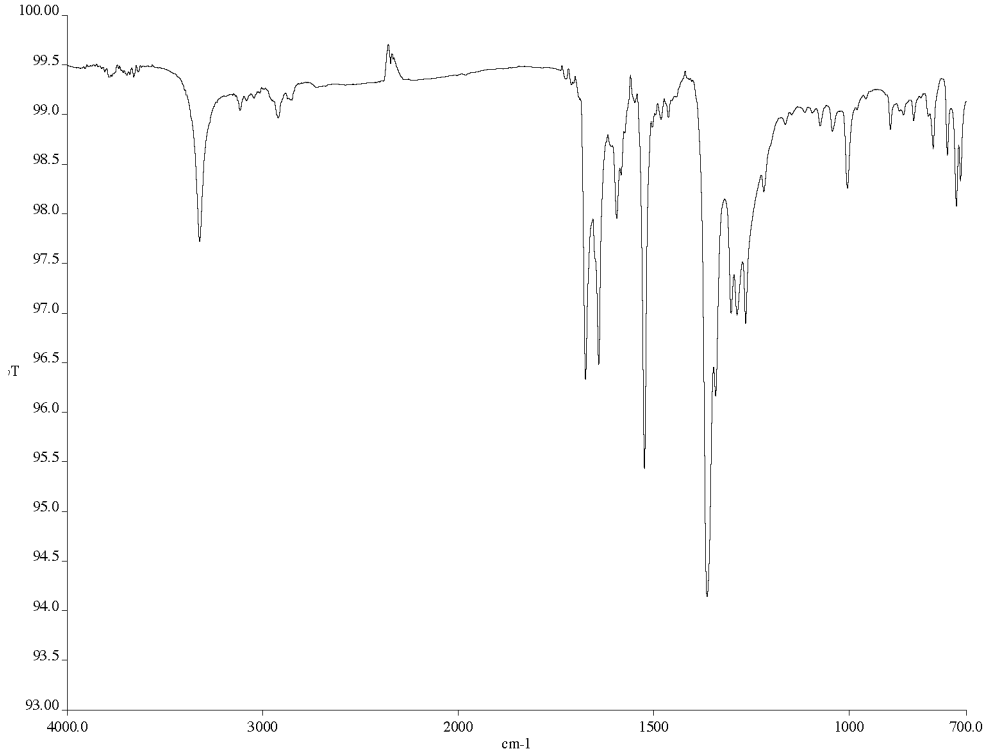


Figure A5.33.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588f** (Table 5.6, entry 6).

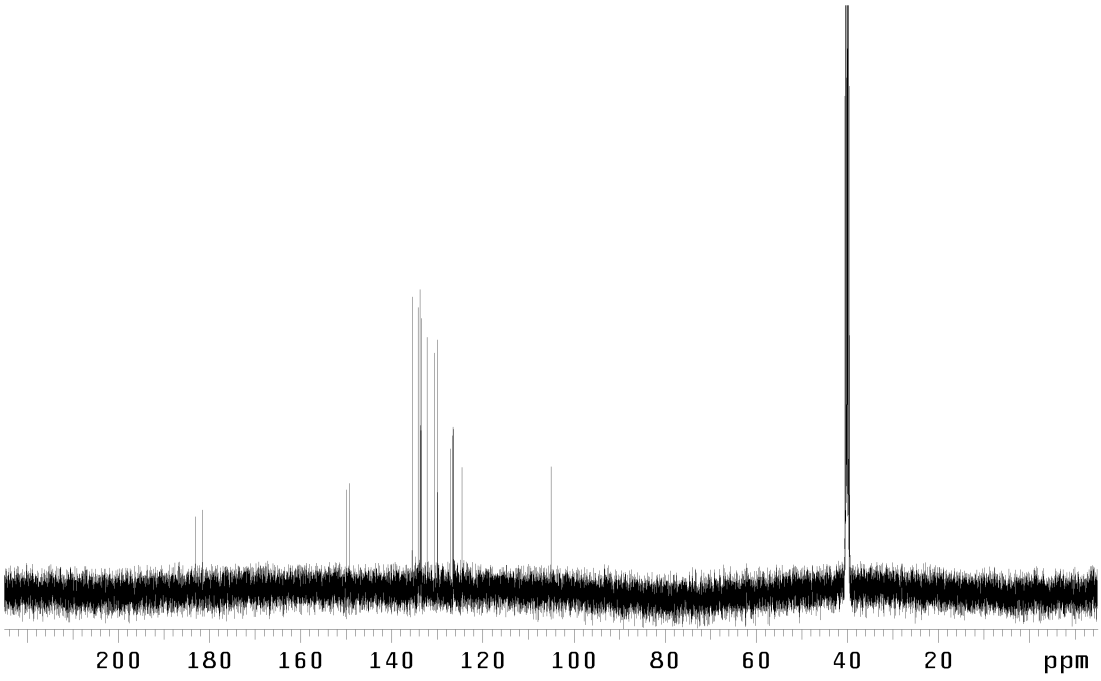


Figure A5.33.3 ^{13}C NMR (125 MHz, DMSO-d_6) of 2-hydroxy-1,4-naphthaquinone **588f** (Table 5.6, entry 6).

Figure A5.34.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588g** (Table 5.6, entry 7).

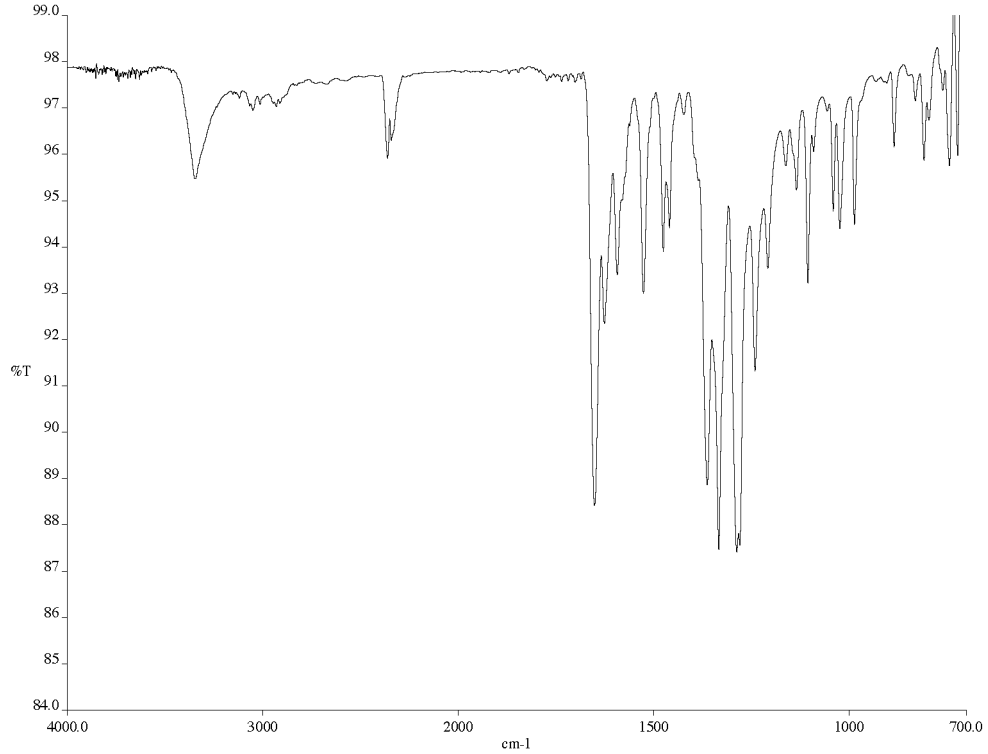


Figure A5.34.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588g** (Table 5.6, entry 7).

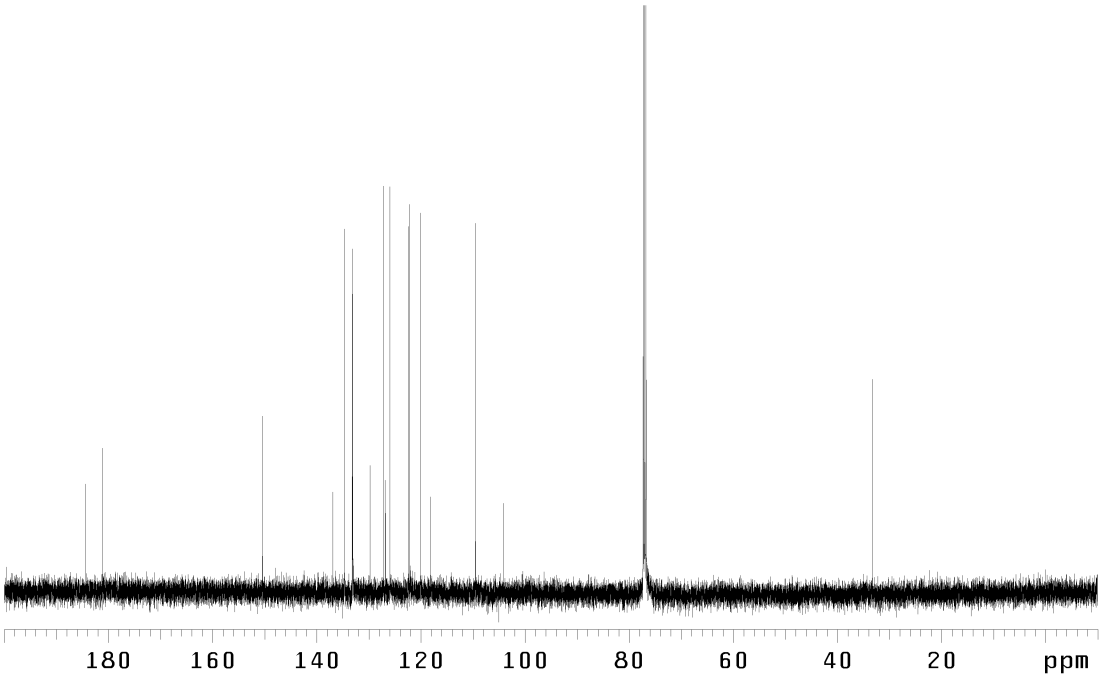


Figure A5.34.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588g** (Table 5.6, entry 7).

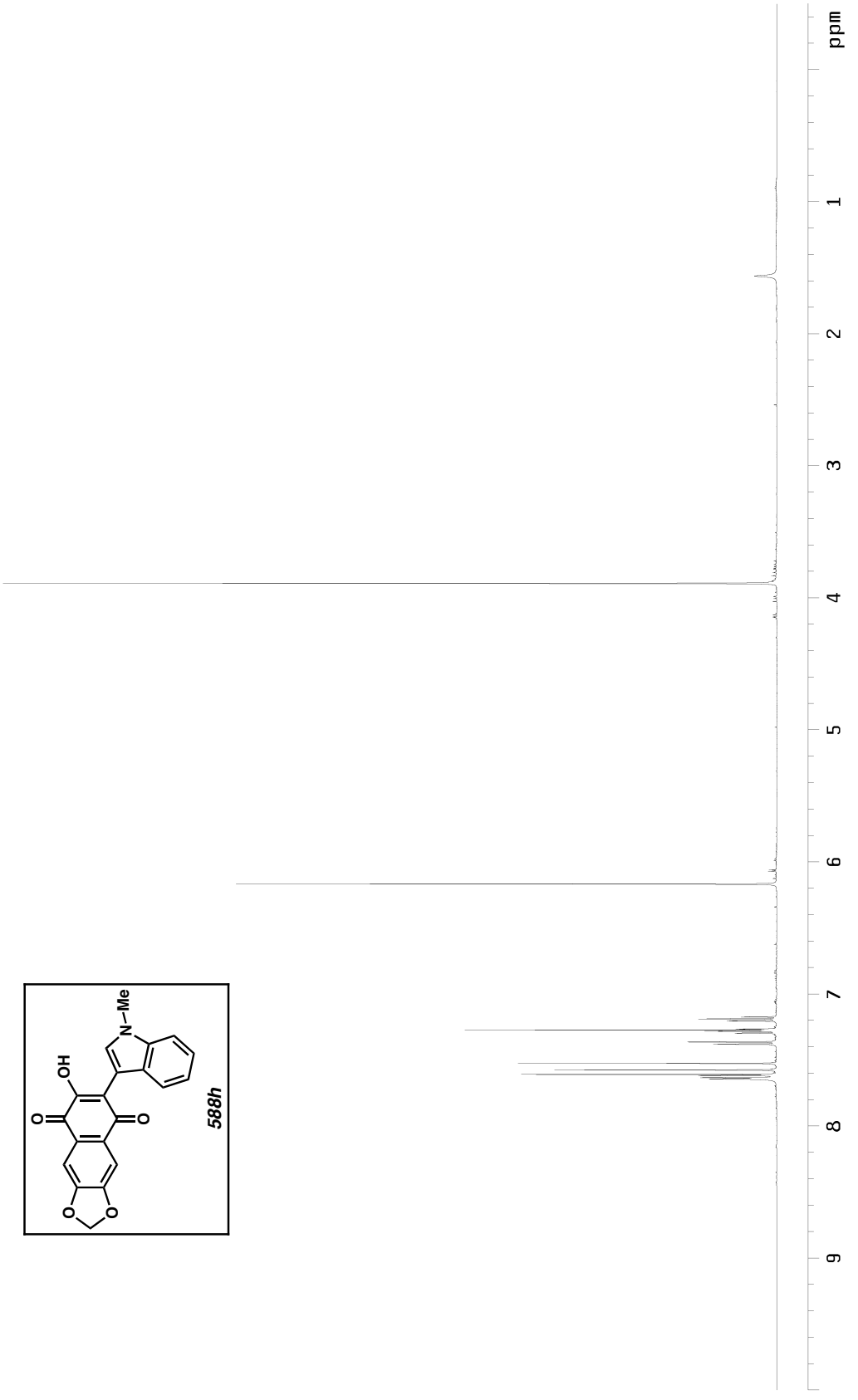


Figure A5.35.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588h** (Table 5.6, entry 8).

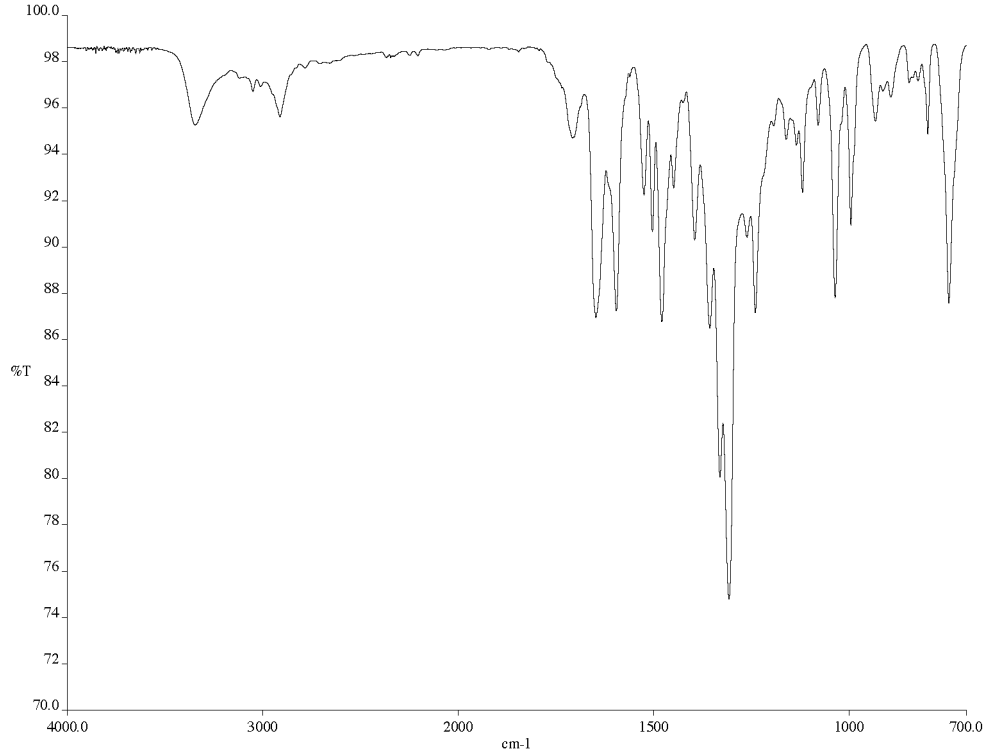


Figure A5.35.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588h** (Table 5.6, entry 8).

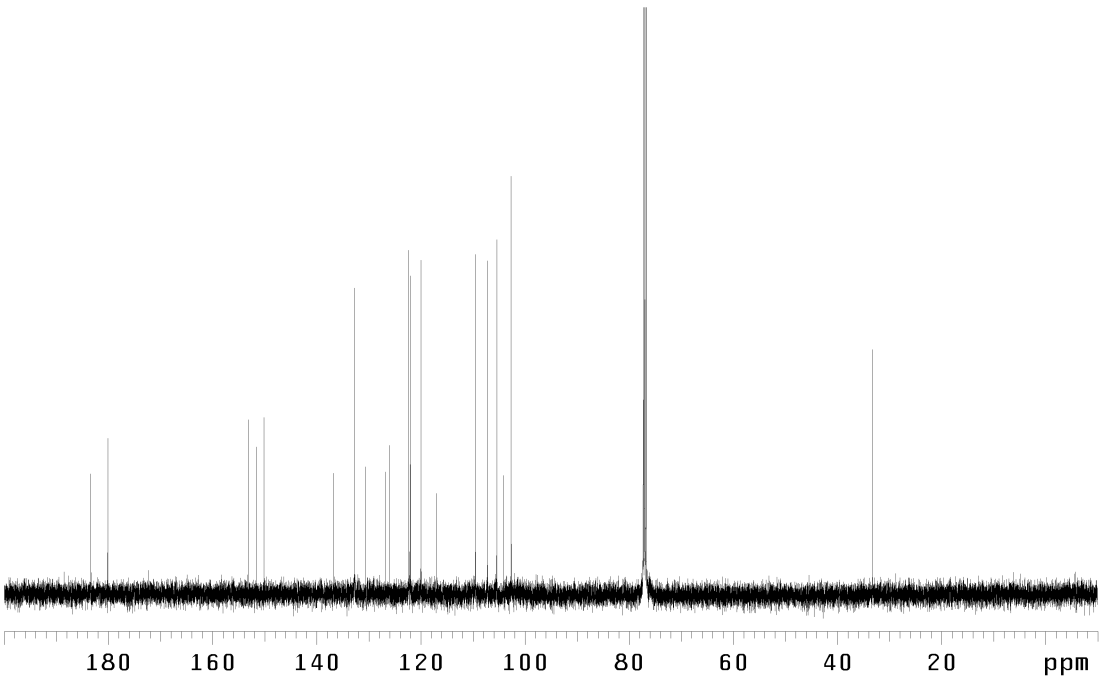


Figure A5.35.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588h** (Table 5.6, entry 8).

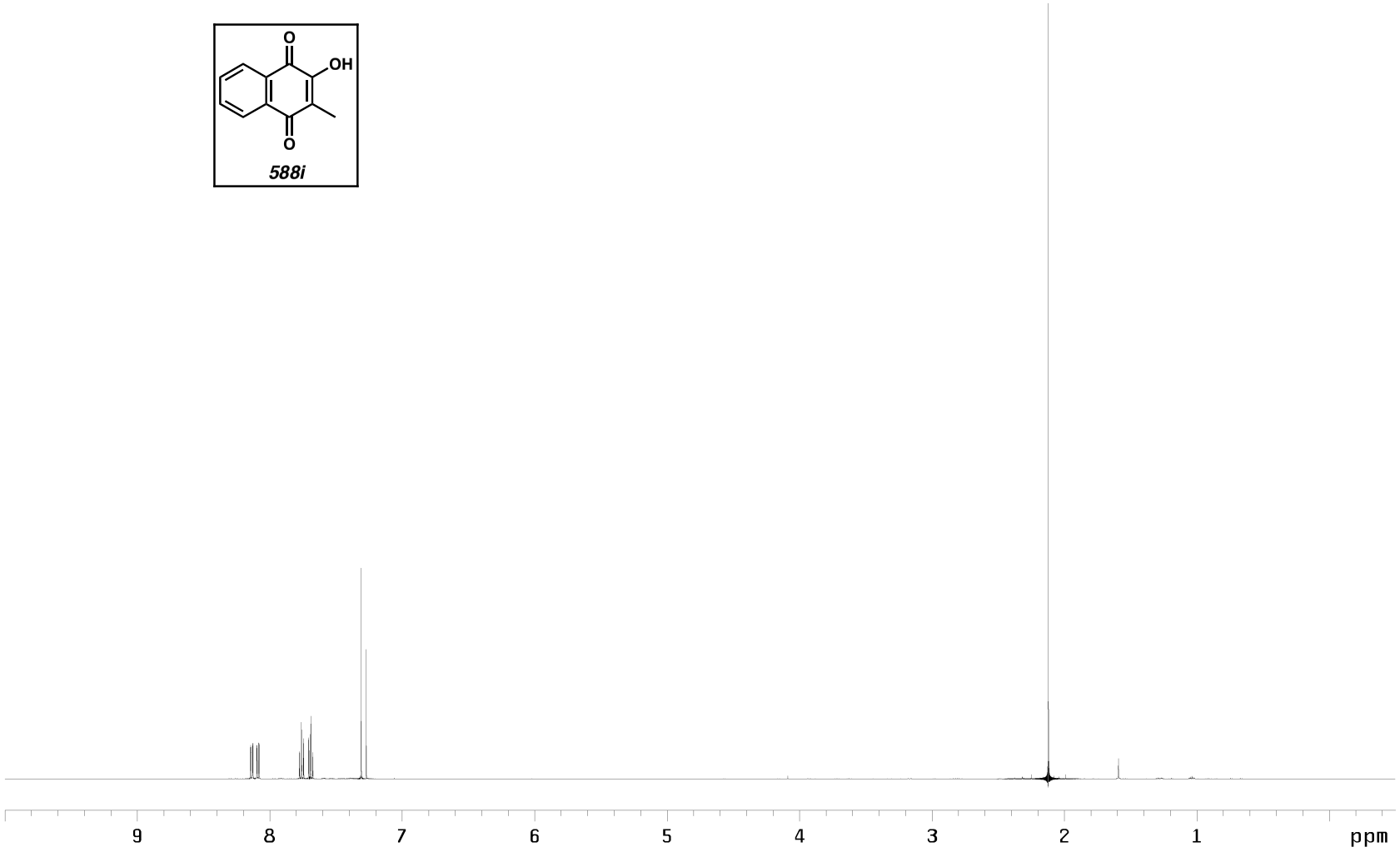


Figure A5.36.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588i** (Table 5.6, entry 9).

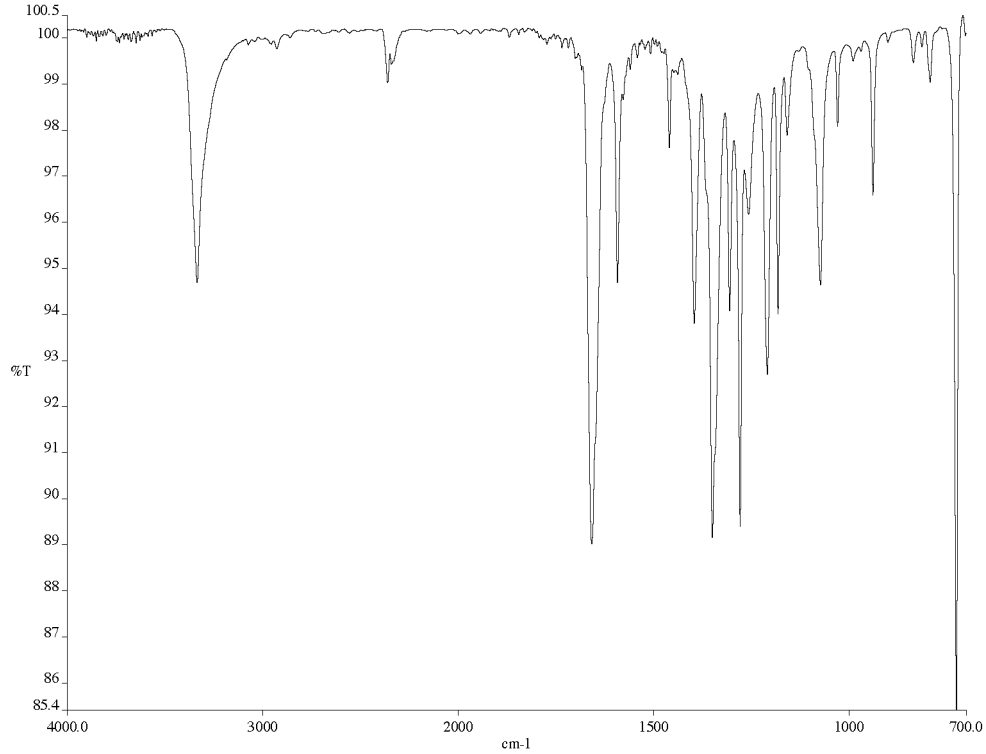


Figure A6.36.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588i** (Table 5.6, entry 9).

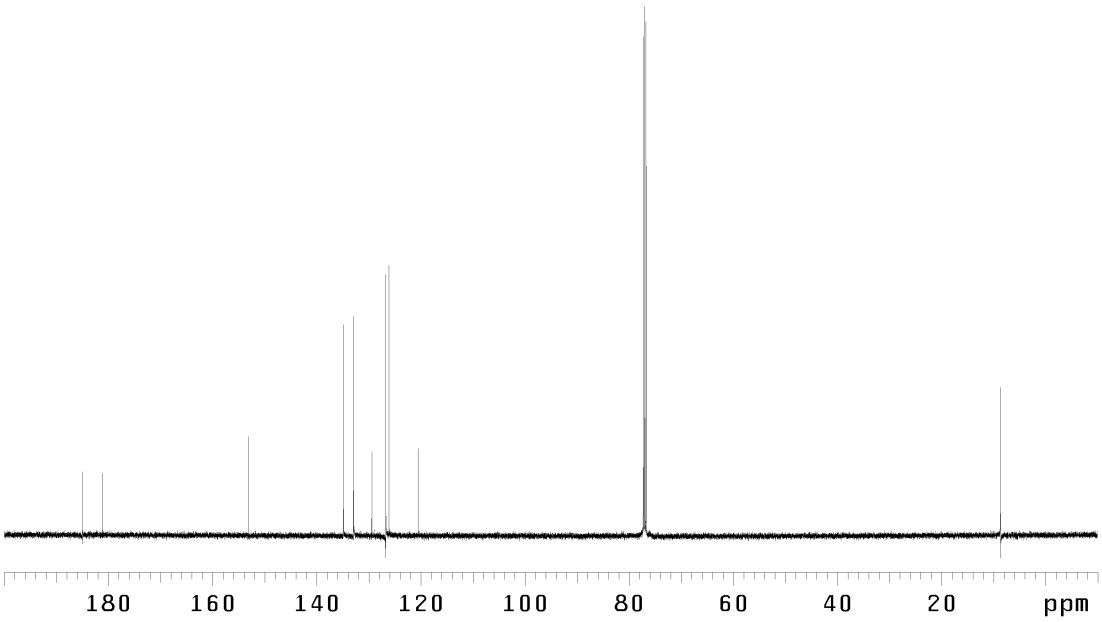


Figure A5.36.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588i** (Table 5.6, entry 9).

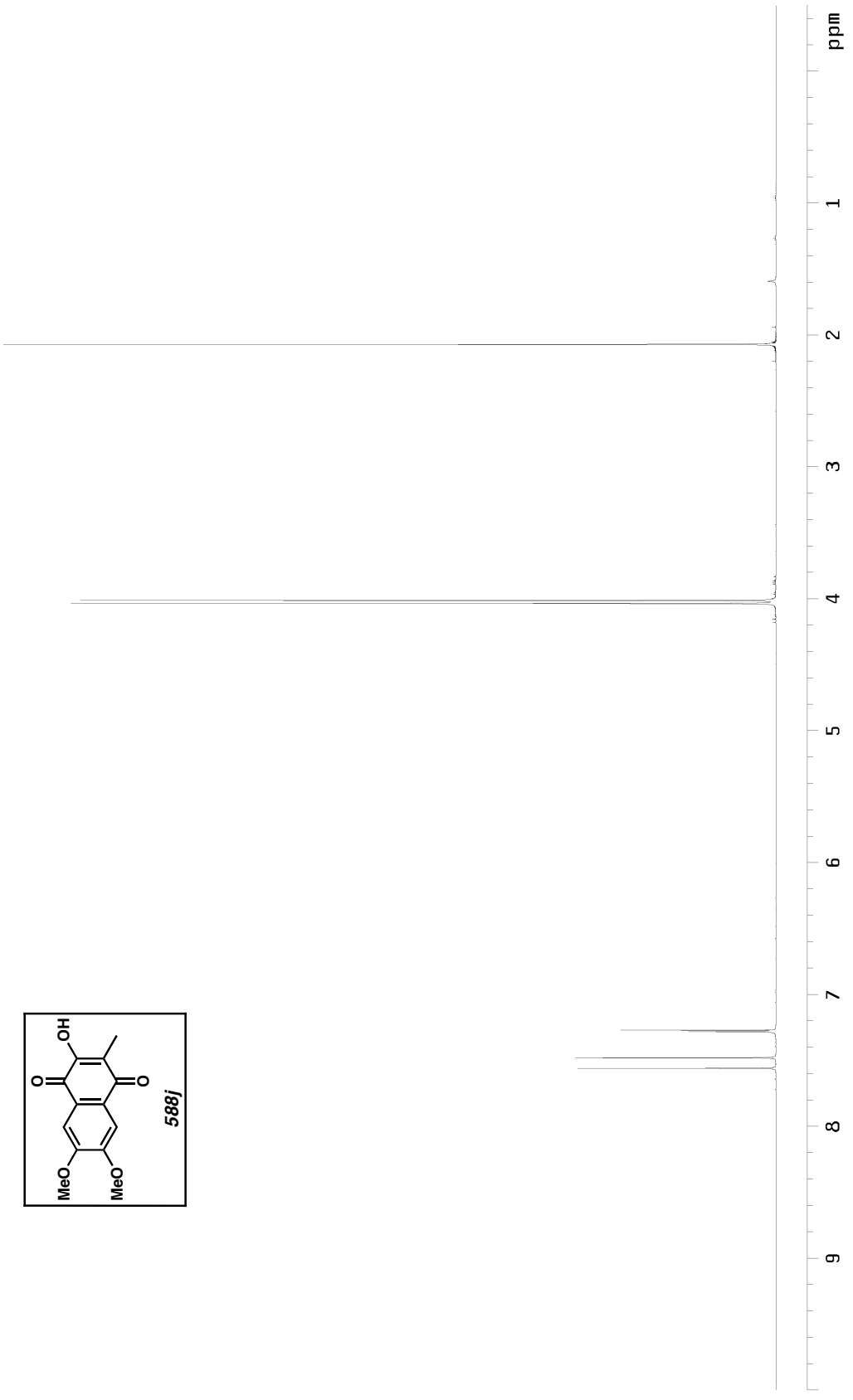


Figure A5.37.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588j** (Table 5.6, entry 10).

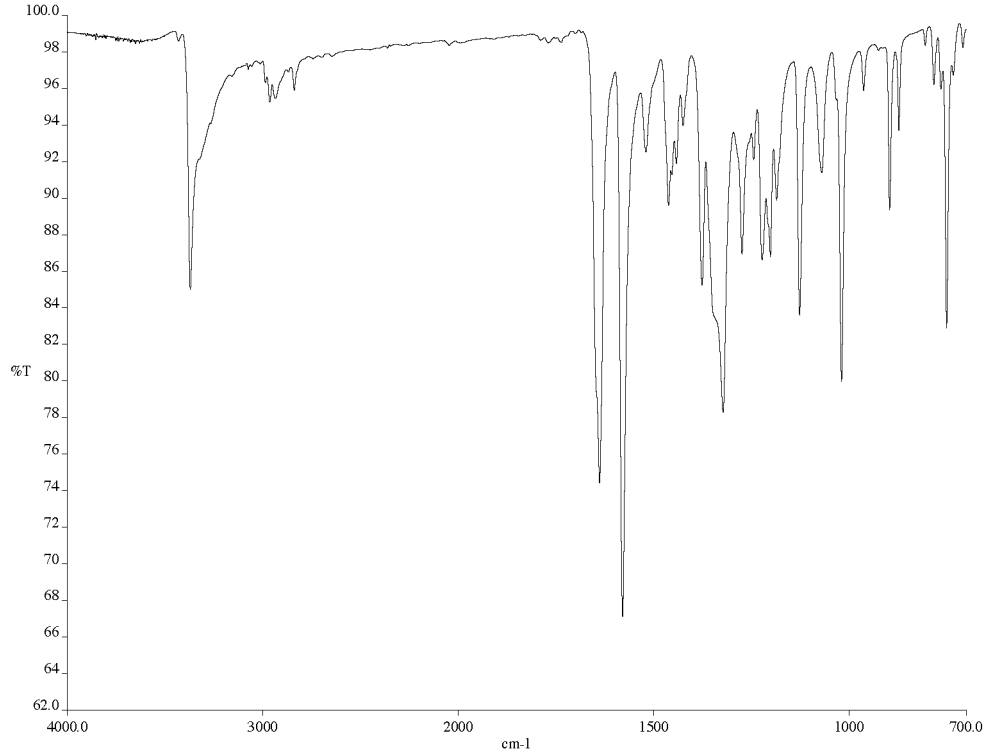


Figure A5.37.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588j** (Table 5.6, entry 10).

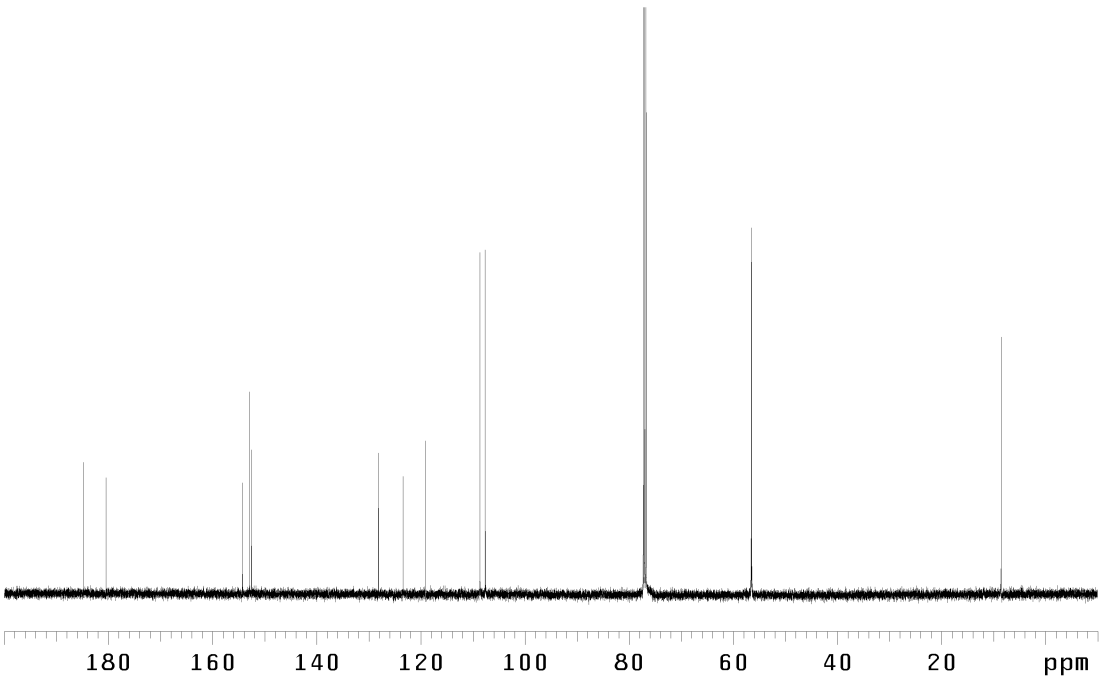


Figure A5.37.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588j** (Table 5.6, entry 10).

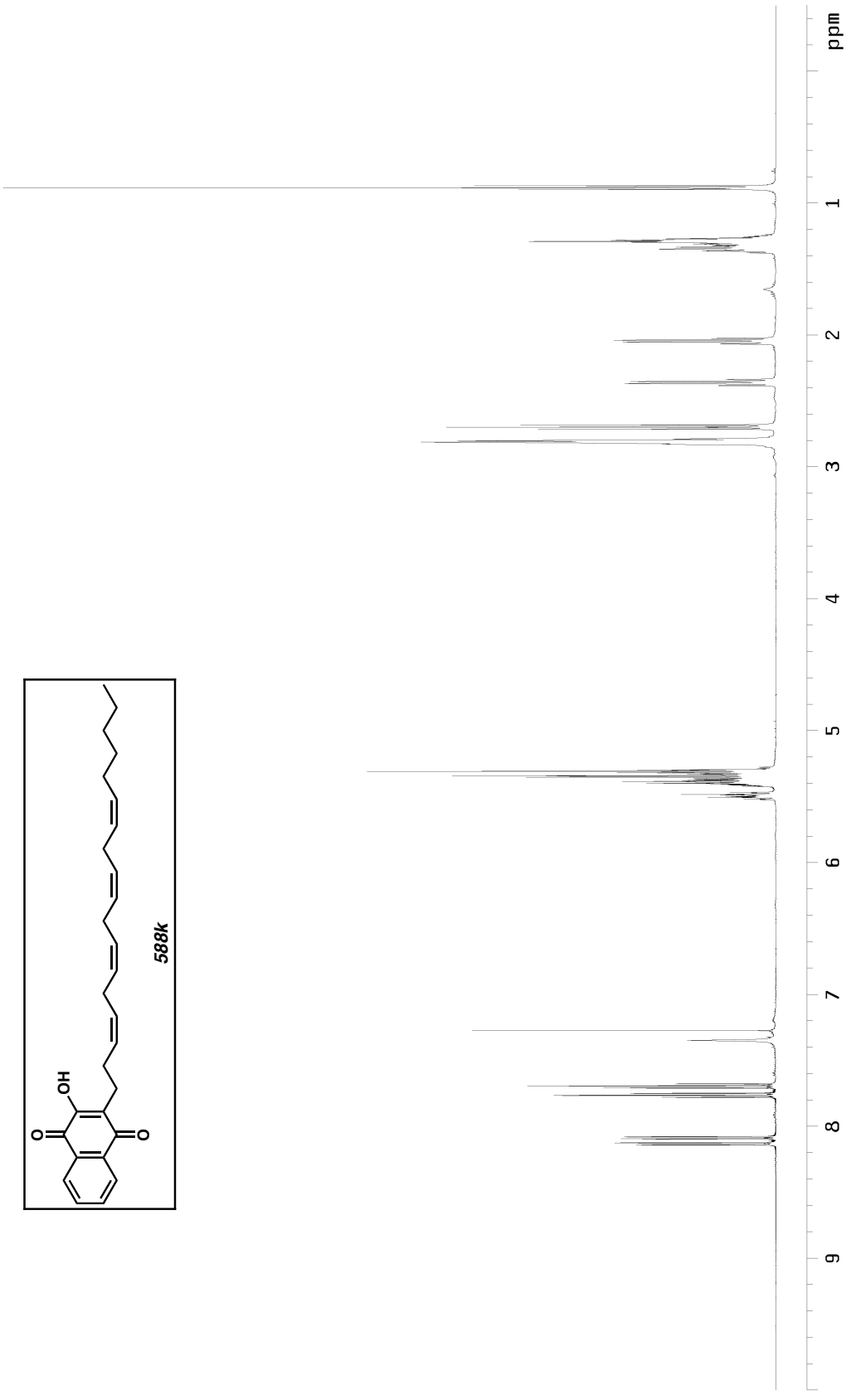


Figure A5.38.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588k** (Table 5.6, entry 11).

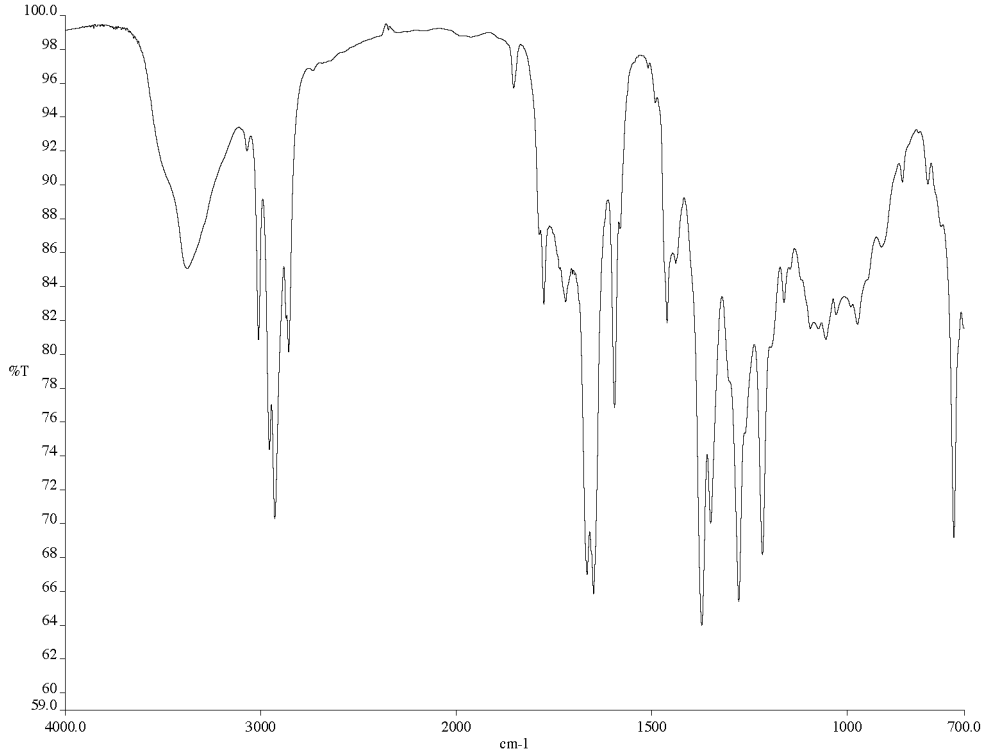


Figure A5.38.2 Infrared spectrum (thin film/NaCl) of 2-hydroxy-1,4-naphthaquinone **588k** (Table 5.6, entry 11).

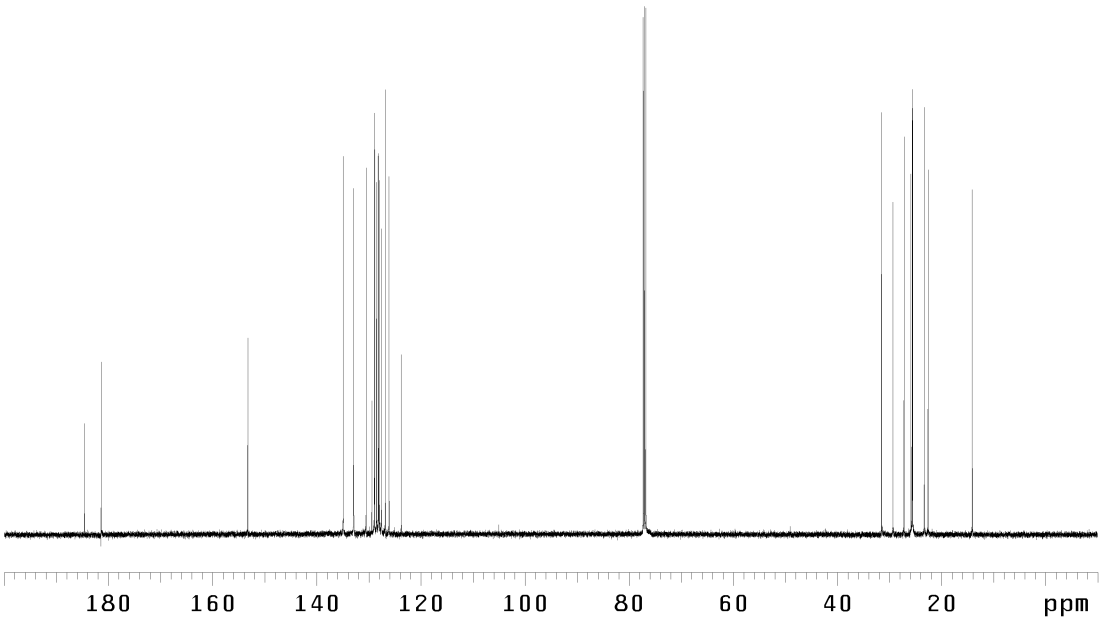


Figure A5.38.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2-hydroxy-1,4-naphthaquinone **588k** (Table 5.6, entry 11).

CHAPTER 6

Multicomponent Aryne Reactions

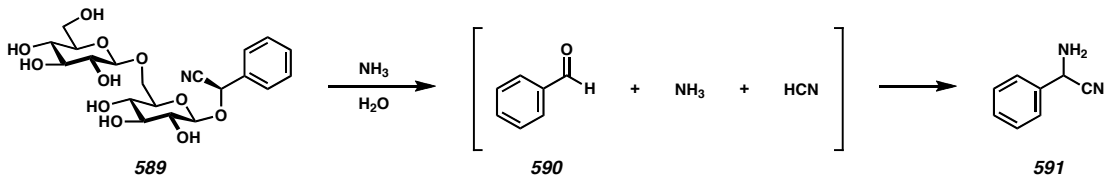
6.1 INTRODUCTION AND BACKGROUND

6.1.1 Introduction to Multicomponent Reactions

Multicomponent reactions are processes involving sequential reactions among three or more compounds that co-exist within the same reaction mixture.[1] While the products of these reactions comprise the whole or fragments of each of the constituent substrates, the mechanisms responsible for their formation involve a series of bimolecular processes. As such, each individual component must be compatible with all others, participating only along the desired mechanistic pathway and only in the proper order. The past 160 years have witnessed the discovery and development of a tremendous number of such reactions, the first example of which was reported by Laurent and Gerhardt in 1838. By treating bitter almond oil (containing amygdalin **589**) with ammonia, the authors were able to accomplish a three-component synthesis of α-aminobenzonitrile (**591**) by coupling benzaldehyde (**590**) with ammonia and hydrogen cyanide (Scheme 6.1).[2,3] Since then, the field of multicomponent organic synthesis has evolved to encompass a

wide variety of product structures originating from the combination of anywhere between three and seven distinct substrates.

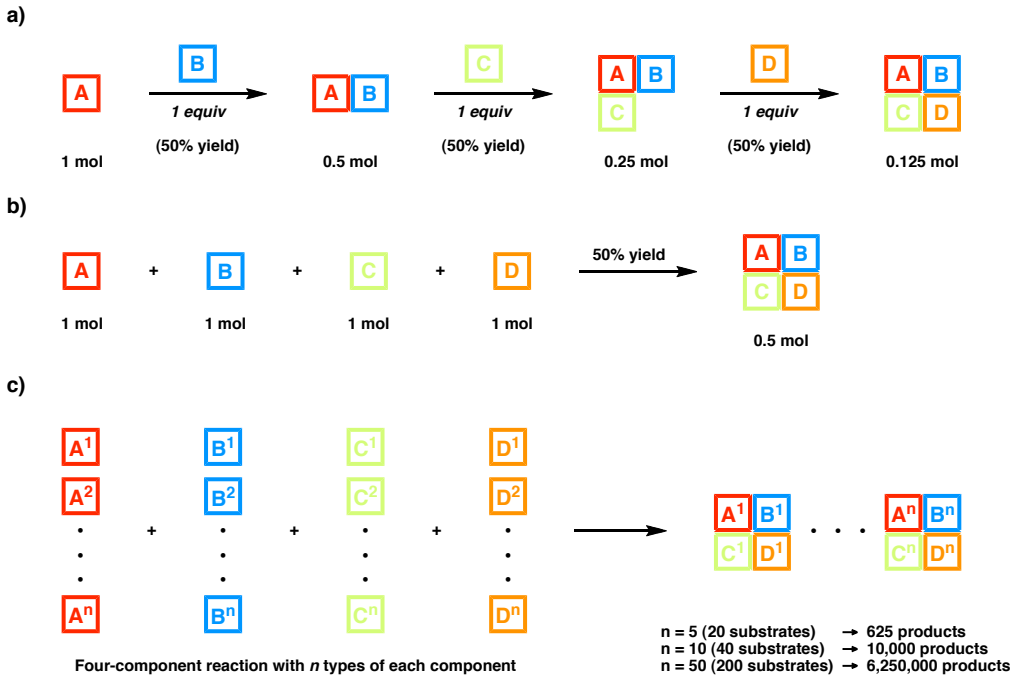
Scheme 6.1. Laurent & Gerhardt – Synthesis of α-aminobenzonitrile



589 ***590*** ***591***

Traditional approaches to multistep synthesis require a significant input of time and energy to advance starting materials to products along a linear path (Scheme 6.2a). In comparison, multicomponent reactions minimize the time spent and material lost by providing a convergent approach to the assembly of complex structures in a single step (Scheme 6.2b). Coupled with the fact that most of these reactions are performed at mild temperatures with few reagents other than the participating substrates, multicomponent strategies are becoming increasingly popular in the realm of natural product total synthesis.[4] Furthermore, the number of obtainable product structures increases exponentially with the addition of new substrates. For example, a four-component reaction comprising n individual substrates of each component type (A–D) would give rise to n^4 distinct product structures. The addition of a single substrate to any one of the four component types would then provide an additional n^3 products. Not surprisingly, this has led to an abundant use of multicomponent chemistry in the preparation of combinatorial libraries for bioactivity screening and pharmaceutical discovery (Scheme 6.2c).[5]

Scheme 6.2. a) Linear synthesis of a product containing four components. b) One-step synthesis via four-component reaction. c) Multicomponent reaction approach to library synthesis.

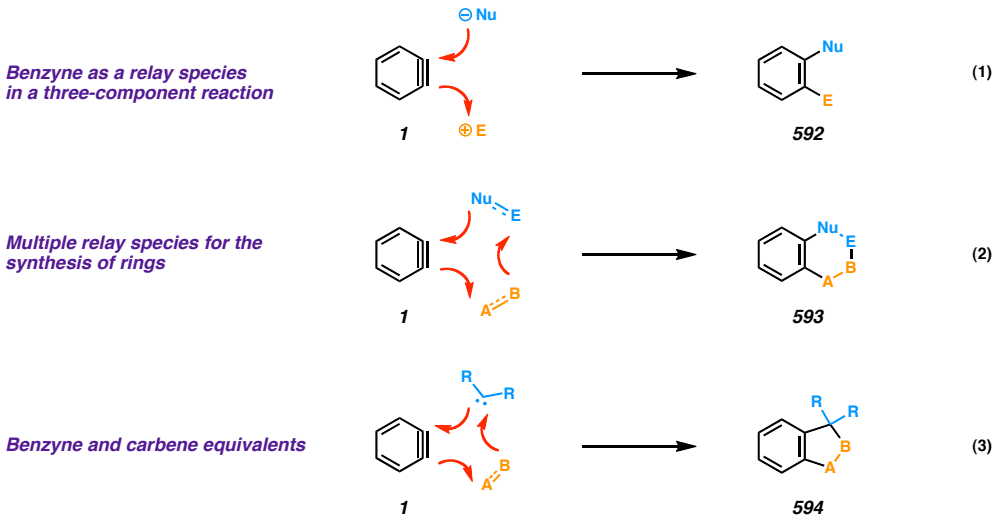


6.1.2 Multicomponent Aryne Reactions

Benzyne is ideally suited to multicomponent synthesis given its ability to function as an intermediary between nucleophiles and electrophiles. By effectively relaying electronic charge between the two species, this strategy provides ready access to 1,2-disubstituted arenes (**592**) (Scheme 6.3, eq 1). When the initiating nucleophile and terminating electrophile are contained within the same molecule, several relay species can be employed in concert to extend this method to the synthesis of polycycles (**593**) (eq 2). Along these lines, recent attention has been given to carbene equivalents—in particular, isocyanides—for the synthesis of benzannulated five-membered rings (**594**) (eq 3). The following sections of this chapter provide examples of recent advances in multicomponent aryne chemistry. The methods described are divided based on the

number of reactive components—either three or four—and further delineated by the number of aryne equivalents present in the final product. Separate consideration is given to those reactions that are catalyzed by transition metals, which thus far incorporate only three components. Finally, examples of multicomponent aryne reactions employed in total synthesis are discussed.

Scheme 6.3. Benzyne as a relay species in multicomponent reactions

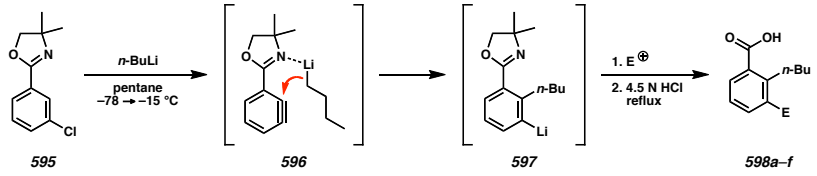


6.1.2.1 Three-Component Reactions

Only a handful of three-component aryne reactions were reported prior to Kobayashi's development of the *ortho*-silyl aryl triflate precursor to benzyne.[6] The earliest recorded observation was made by Bachmann and Clarke in 1927 and consisted of an unintentional cyclotrimerization of benzyne to form triphenylene.[7] However, it was not until 1940 that benzyne was deliberately used in a three-component reaction. In an attempt to probe the existence of a zwitterionic phenylene intermediate (prior to Roberts' studies), Wittig added phenyllithium to benzyne generated from fluorobenzene and

quenched the resulting biaryl anion with benzophenone.[8,9] Forty years later, Meyers *et al.* reported the preparation of *ortho*-oxazoline-substituted arynes (**596**) from aryl chlorides (**595**) under anionic conditions, followed by the addition of alkyl lithium species.[10–12] Nucleophilic attack at the ortho position was found to occur, counter to the regioselectivity predicted by inductive polarization of the aryne bond. This unexpected result was attributed to coordination of the incoming lithium species to the oxazoline nitrogen to favor a directed attack. Quenching the resulting aryl lithium intermediate (**597**) with one of a number of electrophiles and then hydrolyzing the oxazoline product provided a handful of 2,3-disubstituted benzoic acid derivatives (**598a–f**) in good yield.

Scheme 6.4. Meyers – Synthesis of 2,3-disubstituted benzoic acid derivatives



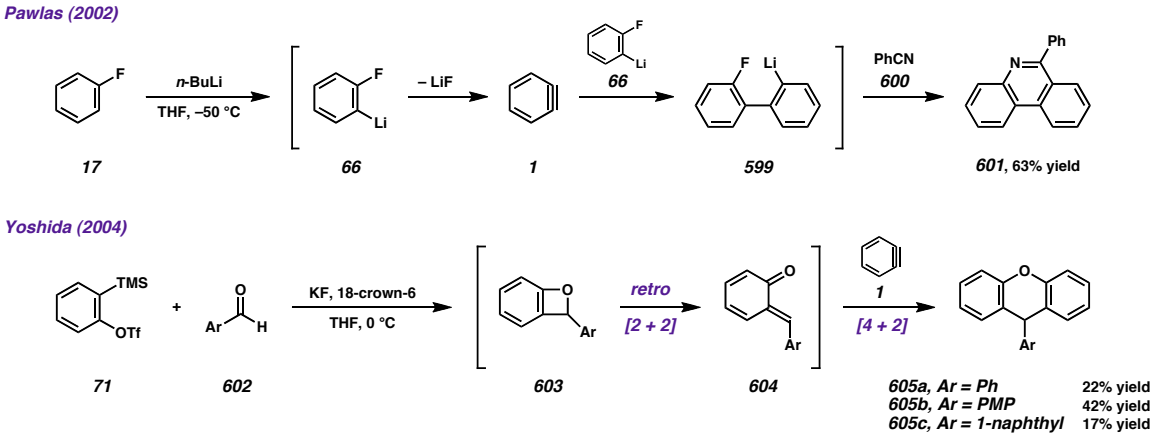
E^+	E	product	yield
EtOH	H	***598a***	70%
MeI	Me	***598b***	68%
HCHO	CH_2OH	***598c***	58%
DMF	CHO	***598d***	57%
PhCHO	PhC(H)OH	***598e***	57%
PhC(O)Cl	C(O)Ph	***598f***	53%

The vast majority of research directed toward the discovery of new multicomponent aryne reactions has taken place within the past decade. The simplest cases involve reactions between two equivalents of an aryne and a third reagent. One such example, reported in 2002 by Pawlas and Begtrup features a synthesis of functionalized phenanthridines (**601**) from aryl fluorides (**17**) and nitriles (**600**) (Scheme 6.5).[13] Upon treatment with *n*-butyllithium, the aryl fluoride undergoes *ortho*-deprotonation to form a transient *ortho*-fluoroaryllithium (**66**), which decomposes to benzyne (**1**). Reaction with a second equivalent of **66** then forms fluorobiaryllithium **599**. Nucleophilic addition to

the nitrile (**600**) is then followed by cyclization to close the central ring, yielding phenanthridine **601**.

The research group led by Yoshida and Kunai at Hiroshima University has been an active contributor to the body of knowledge concerning multicomponent aryne transformations over the past six years. This group first entered the field in 2004 by publishing a method to generate 9-arylxanthenes (**605a–c**) from aldehydes (**602**) and *ortho*-silyl aryl triflates (**71**).[14] In the presence of solubilized potassium fluoride, **71** forms benzyne in situ, which undergoes a formal [2 + 2] cycloaddition with the aldehyde to form benzoxetane **603**. A retro-[2 + 2] cycloaddition opens the four-membered ring to reveal *ortho*-quinone methide **604**, an intermediate capable of participating in a [4 + 2] cycloaddition with a second equivalent of benzyne to form the xanthene (**605**). The group went on to show that the reaction proceeds with most electron-rich, electron-deficient, and polycyclic aryl aldehydes to provide the corresponding 9-arylxanthenes in 17–70% yield.

*Scheme 6.5. Three-component synthesis of phenanthridines (**601**) and xanthenes (**605**) using two aryne equivalents*



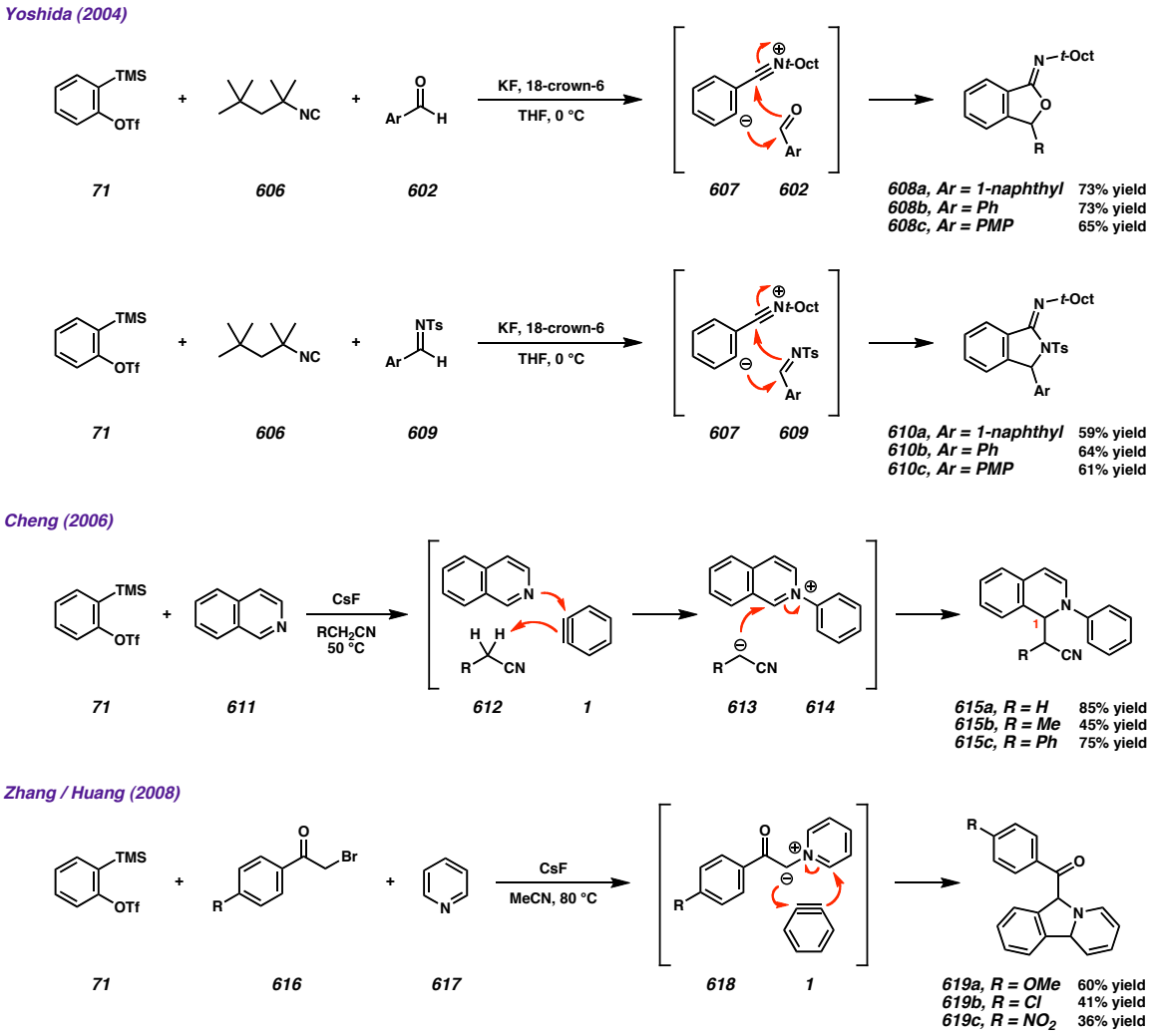
Following the first reports of the early 2000's, newer multicomponent aryne reactions began to feature three distinct reaction partners. Coincident with their previous communication, Yoshida *et al*. reported the synthesis of both iminoisobenzofurans[15] (**608a–c**) and iminoisoindoles[16] (**610a–c**) from *ortho*-silyl aryl triflates (**71**), isocyanides (**606**), and either aldehydes (**602**) or aldimines (**609**), respectively (Scheme 6.6).[17] As a carbene equivalent, the isocyanide functions as both a nucleophile and an electrophile. Addition to the aryne generates an intermediate zwitterion (**607**),[18] the anion of which adds to the carbonyl species to effectively relay the electron pair through these two additional atoms. Closure of the five-membered ring is then achieved through addition of the resulting oxygen-centered anion to the *N*-alkyl nitrilium ion to generate the product (**608** or **610**). While the majority of substrates were derivatives of benzaldehyde, both propionaldehyde and pivaldehyde were shown to participate in the three-component reaction to form alkyl-substituted iminoisobenzofurans.

In 2006, Jeganmohan and Cheng developed a three-component coupling of arynes, isoquinolines (**611**), and nitriles (**612**).[19] In this particular case, the aryne functions as an arylating agent, producing *N*-aryl isoquinolinium ion **614** after deprotonating the nitrile. Addition of the resulting anion (**613**) to the activated heteroaromatic system then yields an *N*-aryl dihydroisoquinoline (**615a–c**) bearing various substitution at C(1). The group also demonstrated that similar reactivity could be achieved using 2- and 4-substituted pyridines in place of the isoquinoline.[20]

More recently, the three-component synthesis of pyrido[2,1-*a*]isoindolines (**619**) was accomplished independently by the labs of Zhang[21] and Huang[22] by coupling arynes, α-bromoacetophenones (**616**), and pyridines (**617**). The groups each propose an initial

condensation between pyridine and the bromoketone, followed by deprotonation to form betaine **618**. A 1,3-dipolar cycloaddition between this intermediate and benzyne (**1**) then forms the nitrogen-containing tricycle (**619a–c**). While most examples featured substituted *para*-substituted acetophenones, Huang *et al.* also successfully employed bromoacetone and ethyl bromoacetate. Furthermore, each group was able to replace pyridine with isoquinoline in order to generate tetracyclic product scaffolds.

Scheme 6.6. Three-component synthesis of nitrogen-containing products using three distinct components



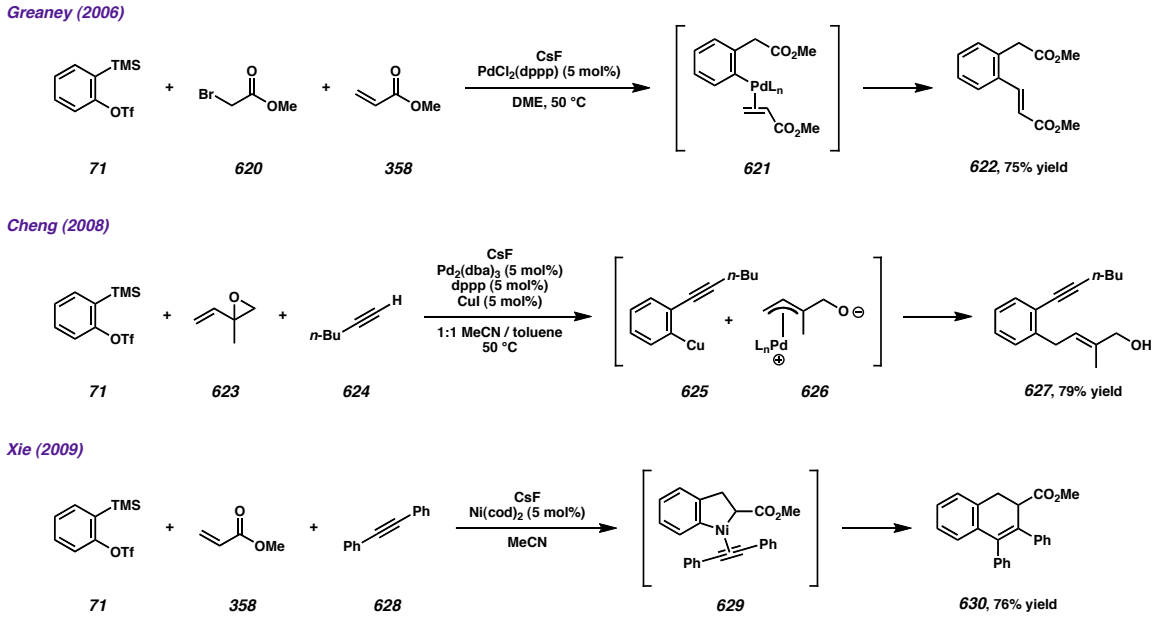
While the work performed by these four groups does not comprise the entirety of three-component aryne technology, it provides an accurate representation of the product structures attainable using this general strategy. Additional studies carried out between 2006 and 2008 accomplished the synthesis of benzoxazinones,[23] naphthalenes,[24] anthranilic acids,[25] and *ortho*-aminobenzyl alcohols[26] and amines.[27] Notably, each of these studies employed Kobayashi's *ortho*-silyl aryl triflate (**71**), further underscoring the versatility of this important aryne precursor.[6]

In addition to the metal-free multicomponent aryne reactions discussed above, there have been a number of transition metal-catalyzed transformations reported in recent years.[28–30] In comparison to non-catalytic variants, which typically require a heteroatom or carbanion nucleophile to initiate the reaction, these processes can be performed with simple alkyl and aryl halides, olefinic species, and terminal alkynes. Furthermore, metal-catalyzed aryne reactions often take place primarily, if not exclusively, at carbon centers. In 2006, Greaney *et al.* developed a catalytic approach to styrenyl diesters (**622**) by coupling arynes with α-bromoesters (**620**) and acrylates (**358**) (Scheme 6.7).[31] Beginning with oxidative insertion into the C–Br bond of **620**, the resulting alkylpalladium intermediate undergoes two sequential Heck-type migratory insertions, the first of which occurs across the aryne triple bond to form arylpalladium **621**. A second migratory insertion across the acrylate olefin followed by β-hydride elimination furnishes styrene **621**. Based on previous work by Yamamoto,[32] the authors also demonstrated that the bromoester could be replaced by allyl chloride, though purification of the resulting *ortho*-allylstyrene was complicated by the presence of phenanthrene side products derived from the combination of allyl chloride and two equivalents of the aryne.[33]

In a continuing effort to develop new transition metal-catalyzed multicomponent aryne reactions, the Cheng research group at Tsing Hua University has reported a number of methods for preparing 1,2-disubstituted arenes by coupling arylpalladium intermediates similar to **621** with alkynyl,[34] allenyl,[35] and aryl stannanes.[36] In 2008, the group devised a cooperative palladium- and copper-catalyzed process for the synthesis of *ortho*-allyl phenylacetylenes (**627**) from arynes, allylic epoxides (**623**), and terminal alkynes (**624**).[37] Having proven the efficacy of this strategy in previous coupling reactions utilizing allyl chlorides and acetates,[38,39] the authors were confident that allylic epoxides could be used to build products bearing terminal alcohols. In terms of the mechanism, copper(I) iodide is envisioned to form a copper acetylide, which undergoes addition to benzyne to form arylcopper intermediate **625**. Transmetallation to allylpalladium complex **626** and subsequent reductive elimination then forms the observed product and regenerates the catalyst.

Although less commonly used than palladium, nickel is beginning to appear in several multicomponent aryne reactions.[40] In 2009, Qiu and Xie reported a three-component coupling of arynes, acrylates (**358**), and alkynes (**628**) catalyzed by nickel(0) cyclooctadiene to form trisubstituted dihydronaphthalenes (**630**).[41] The proposed mechanism involves cyclometallation with the aryne and acrylate to form metalloindane **629**. Insertion of the alkyne and reductive elimination then forms the six-membered ring. The reaction is shown to proceed in good yield with a number of substituted arynes, though the two remaining substrates are limited to unsubstituted acrylates and internal alkynes.

Scheme 6.7. Transition metal-catalyzed three-component aryne reactions



6.1.2.2 Four-Component Reactions

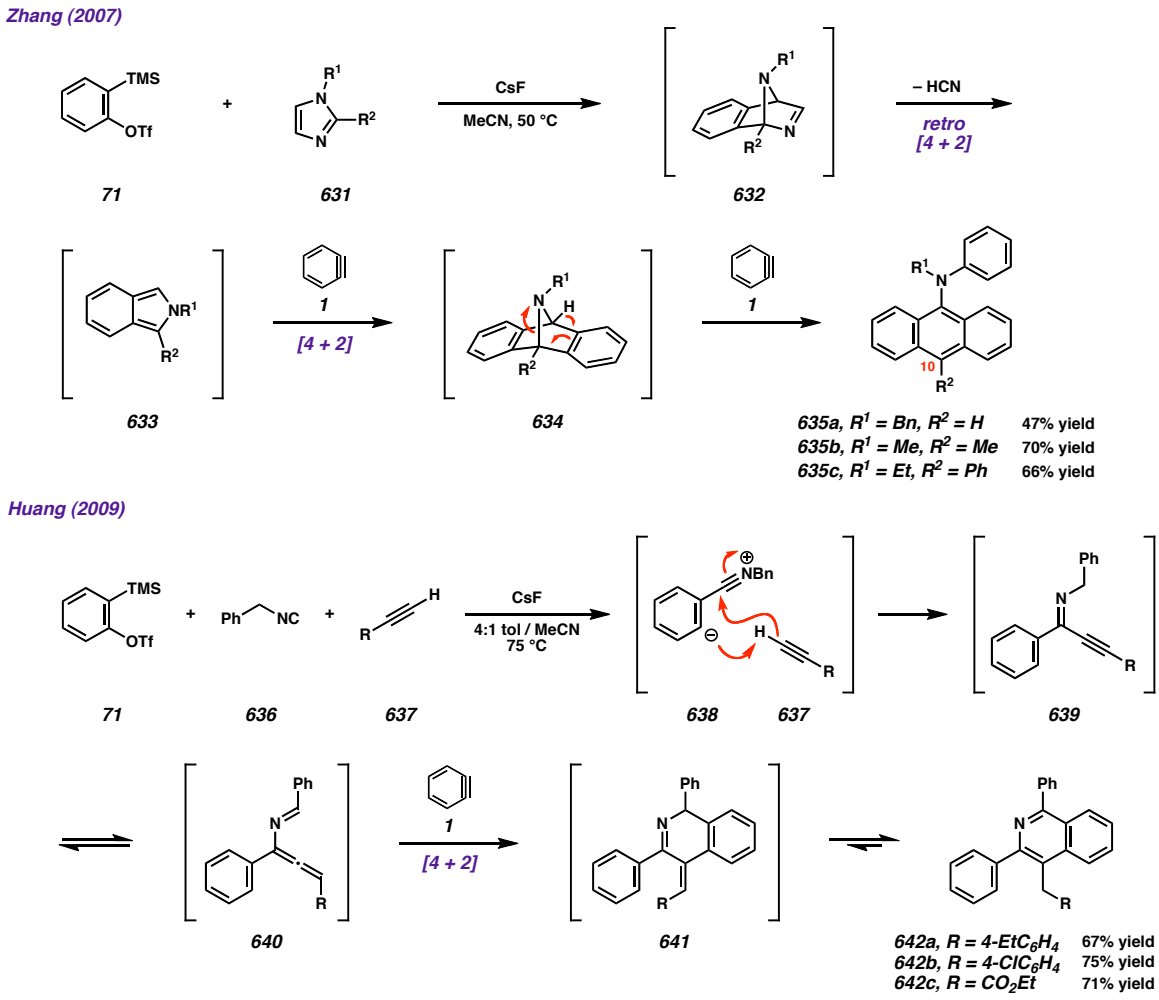
In comparison to the array of three-component aryne reactions described above, the field of four-component transformations is still very much in its infancy. To date, only three examples have been reported, two of which were developed as synthetic methods and the third as the key step in a total synthesis. The former are discussed below and the latter will be discussed in the following section.

Each of the four-component methodologies forms compounds derived from multiple equivalents of the aryne. The first involves a one-pot synthesis of *N*-aryl anthracenamines (**635**) reported in 2007 by Xie and Zhang (Scheme 6.8).[42] In the presence of excess quantities of benzyne, *N*-substituted imidazoles (**631**) will undergo a [4 + 2] cycloaddition to form a benzannulated diazabicyclo[2.2.1]heptene (**632**). Expulsion of hydrogen cyanide via retro-[4 + 2] cycloaddition then forms a reactive 2*H*-

isoindole (**633**), which undergoes another [4 + 2] cycloaddition with a second equivalent of benzyne to form a nitrogen-bridged tetracycle (**634**). Rearrangement to aromatize the central ring and subsequent addition of the amine to a third equivalent of benzyne then furnishes the polyaromatic product (**635a–c**). Based on the substitution pattern of imidazole **641**, products bearing various substitution at nitrogen and C(10) can be achieved in good yield.

The second four-component method was designed by Sha and Huang in 2009 as a novel approach to polyfunctionalized isoquinolines (**642**) using arynes, isocyanides, and terminal alkynes.[43] The mechanism of formation is proposed to begin with an addition of isocyanide **636** to benzyne to form zwitterion **638**. Deprotonation of the alkyne is then followed by addition to the nitrilium ion to generate propargylic imine **639**, which is envisioned to be in equilibrium with allene **640**. This intermediate undergoes a [4 + 2] cycloaddition with a second equivalent of benzyne to form dihydroisoquinoline **641**, which equilibrates to the isolated product (**642**). The authors also found that if the alkyne component was used in excess, the second [4 + 2] cycloaddition took place with this substrates to give rise to pyridine products.

*Scheme 6.8. Four-component synthesis of anthracenamines (**635**) and isoquinolines (**642**) using multiple aryne equivalents*



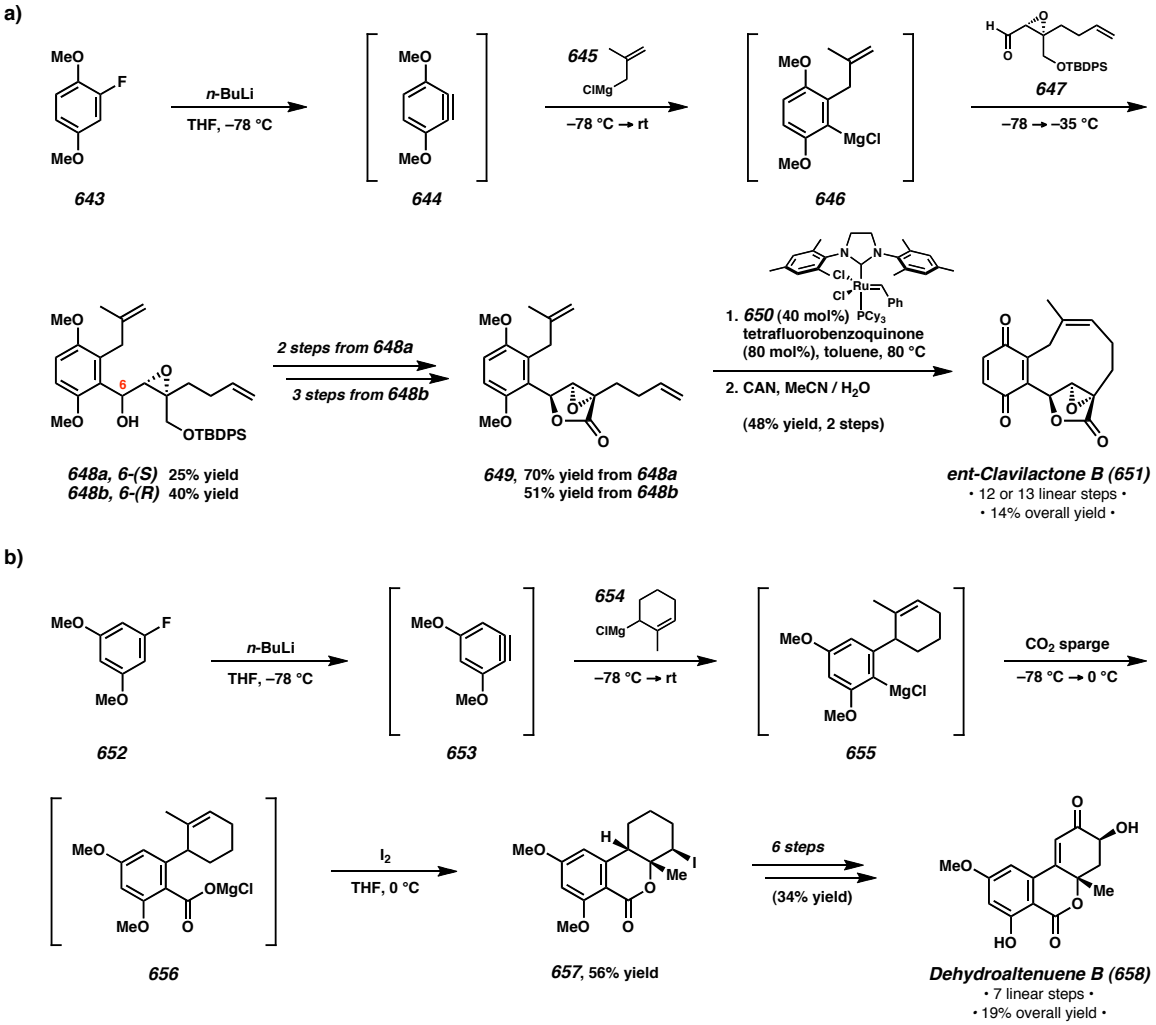
6.1.2.3 Multicomponent Aryne Reactions in Total Synthesis

Despite the advantages in speed and convergence afforded by multicomponent aryne reactions, approaches utilizing these transformations have only been applied to the total synthesis of two natural products—*ent*-clavilactone B[44] (**651**) and dehydroaltenuene B[45] (**658**)—both of which were completed by the Barrett group at Imperial College London (Scheme 6.9). The first synthesis featured a three-component relay addition of isobutenyl

Grignard **645** to aryne **644**, followed by an addition of the resulting aryl Grignard (**646**) to aldehyde **647** to form diastereomeric benzylic alcohols **648a** and **648b**. While the reaction proceeded with low diastereoselectivity to produce the alcohols in a ratio of only 1.6:1, the authors were able to quickly advance each of these products to a single diastereomer of epoxylactone **646**. In the last two steps, the macrocycle was then formed via ruthenium-catalyzed ring-closing metathesis and the hydroquinone was oxidized to furnish *ent*-clavilactone B (**652**) in 14% overall yield through a maximum of 13 steps.

With the success of this first synthesis, Barrett *et al*. turned to the development of a four-component reaction sequence for the synthesis of dehydroaltenuene B (**658**). The key step began in a manner similar to the previous, with the addition of cyclohexenyl Grignard **654** to aryne **653**. Aryl Grignard **655** was then exposed to carbon dioxide to carboxylate the aromatic ring, after which treatment with molecular iodine promoted iodolactonization of the magnesium carboxylate (**656**) to form tricycle **657**. Having thus assembled the core of the natural product in the first step, the authors then advanced this material through six additional steps to complete the first total synthesis of dehydroaltenuene B (**658**) in 19% overall yield.

Scheme 6.9. a) Three-component synthesis of alcohols ***648a*** *and* ***648b*** *en route to ent-clavilactone B. b) Four-component synthesis of tricycle* ***657*** *en route to dehydroaltenuene B.*

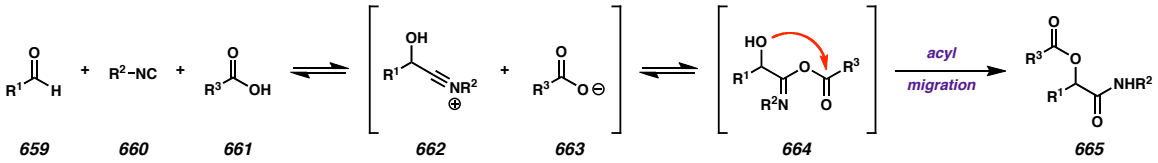


6.2 SYNTHESIS OF PHENOXY IMINOISOBENZOFURANS AND IMINOINDENONES VIA A THREE-COMPONENT COUPLING OF ARYNES, ISOCYANIDES, AND ESTERS OR ALKYNES[†]

6.2.1 Outline of Approach and Initial Studies

We decided to approach the task of designing a novel multicomponent aryne reaction by considering the mechanisms involved in more classical multicomponent transformations. In particular, we were interested in the Passerini reaction, a method used to prepare α-acyloxyamides (**665**) through the three-component coupling of aldehydes (**659**), isocyanides (**660**), and carboxylic acids (**661**) (Scheme 6.10).[46] The reaction proceeds through an initial combination of the aldehyde and isocyanide substrates to form a hydroxy nitrilium intermediate (**662**).[47] Nucleophilic addition of the carboxylate (**663**) then produces a neutral imidate (**664**), which undergoes acyl migration to the free alcohol to form the amide product (**665**).

Scheme 6.10. Passerini three-component synthesis of α-acyloxyamides

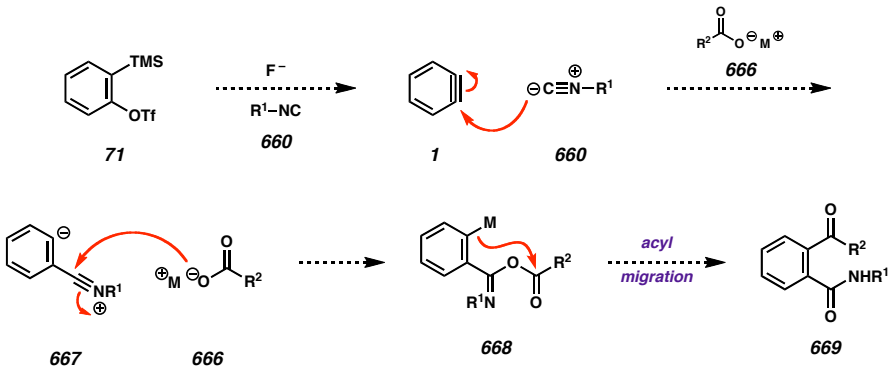


Upon closer examination of this mechanism, we recognized that the aldehyde component plays roles as both an electrophile and a nucleophile (in the form of an

[†] This work was performed in collaboration with Christopher D. Gilmore, a fellow graduate student in the Stoltz research group.

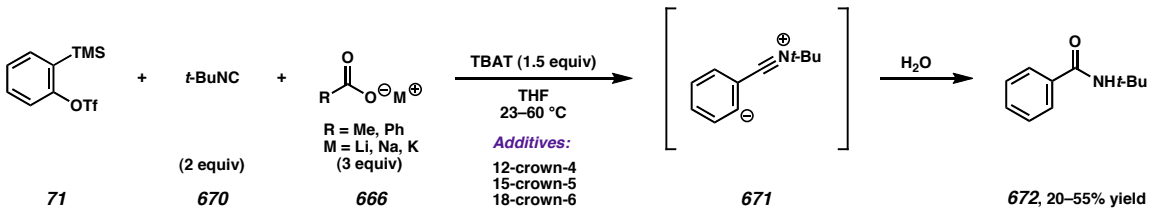
intermediate alcohol) during the course of the reaction. Based on the established tendency of benzyne to act in a similar capacity as a relay species in multicomponent transformations, we envisioned an analogue of the Passerini reaction in which benzyne would take the place of the aldehyde to generate *ortho*-ketobenzamides (**669**) (Scheme 6.11). Considering the mechanism in a stepwise sense, we anticipated an initial addition of the isocyanide (**660**) to benzyne (**1**) to form zwitterion **667**.[18] Then, nucleophilic addition of a carboxylate salt (**666**) to the nitrilium ion would produce *ortho*-metallated acyl imidate **668**. The specific use of the carboxylate salt was viewed as a necessity in light of the expectation that a carboxylic acid would simply protonate the aromatic ring. In the final step, acyl migration from oxygen to carbon in a manner analogous to the anionic *ortho*-Fries rearrangement[48] would produce *ortho*-ketobenzamide **669**. In line with our previous development of the aryne acyl-alkylation reaction,[49] we expected this method would provide a useful new addition to the arsenal of aryne 1,2-disubstitution reactions.

Scheme 6.11. Proposed benzyne analogue of the Passerini three-component coupling



Our first attempts to accomplish an aryne analogue of the Passerini three-component coupling reaction featured *ortho*-silyl aryl triflate **71**, *tert*-butyl isocyanide (**670**), and various alkali salts of acetic and benzoic acid (**666**) (Scheme 6.12). We combined these reagents in tetrahydrofuran using tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) as the fluoride source and performed the reaction at temperatures between 23 °C and 60 °C. However, in all cases, the only product isolated from the reaction mixture was *N*-*tert*-butyl benzamide (**672**), presumably resulting from addition of the isocyanide to benzyne followed by quenching of the nitrilium (**671**) with adventitious water. Suspecting that the lack of carboxylate addition was due to the insolubility of the salt, we added the appropriate crown ethers. Unfortunately, these additives had little effect upon the outcome, often resulting only in a lower yield of **672**.

Scheme 6.12. Attempted three-component coupling of benzyne, tert-butyl isocyanide, and carboxylate salts

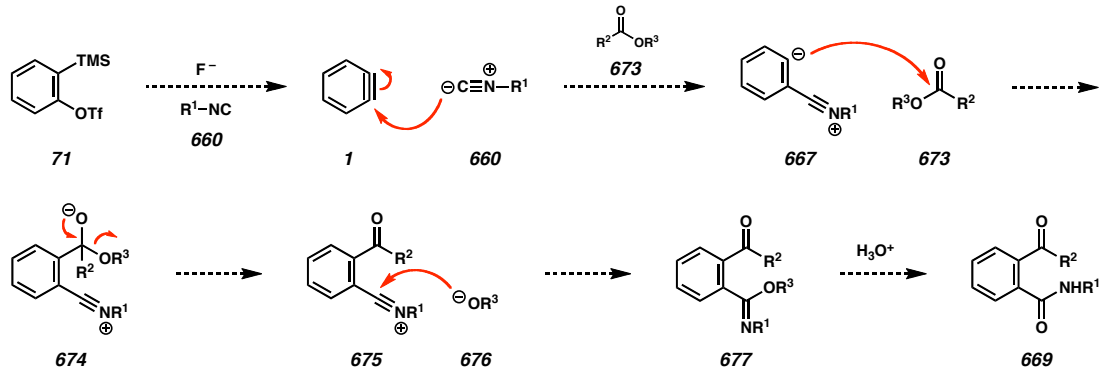


6.2.2 Synthesis of Phenoxy Iminoisobenzofurans

Given our lack of success in utilizing carboxylate salts, we chose to modify our initial mechanistic proposal to employ the aryl anion nucleophile (**667**) prior to attack at the nitrilium ion (Scheme 6.13). Replacing the salt with a carboxylic ester (**673**), we envisioned nucleophilic addition of the anion to the carbonyl to generate a tetrahedral

intermediate (**674**). Expulsion of the alkoxide (**676**) followed by recombination with the nitrilium ion (**675**) would then furnish a neutral imidate (**677**). Finally, this compound could be hydrolyzed upon work-up or in a subsequent step in order to intercept the originally targeted *ortho*-ketobenzamide (**669**).

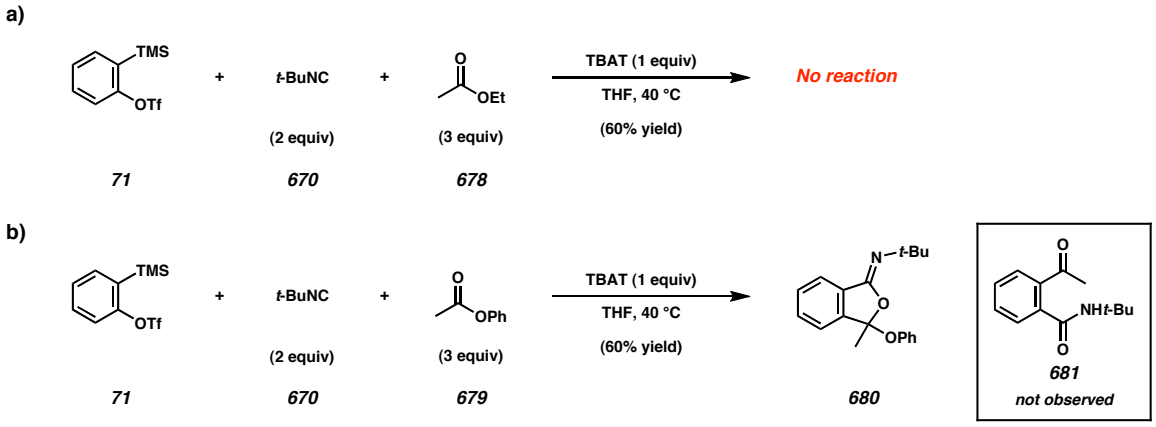
Scheme 6.13. Revised approach to the synthesis of ortho-ketobenzamides via three-component coupling of arynes, isocyanides, and esters



Adapting the reaction conditions to this new proposal proved straightforward. Ethyl acetate (**678**) was chosen for the first trial due to its availability as an organic solvent (Scheme 6.14a). Unfortunately, when the reaction was performed according to the previous conditions at 40 °C, none of the desired ketobenzamide was observed. Given that similar additions had been established with aldehydes[15,26] and aldimines,[16,27] we endeavored to employ a more electrophilic ester. Based on the knowledge that phenyl esters possess lower pK_a values than the corresponding ethyl and *tert*-butyl esters[50]—presumably due to electron withdrawal from the aryl ring—we reasoned that phenyl acetate (**679**) would display greater electrophilicity than ethyl acetate (Scheme 6.14b). When the reaction was performed under identical conditions, however, we were

surprised to find that instead of generating the expected ketobenzamide (**681**) or its related imidate, phenoxy iminoisobenzofuran **680** was isolated in 60% yield. The formation of this product most likely occurs through intramolecular attack of alkoxide **674** upon the nitrilium ion, suggesting that closure of the five-membered ring occurs faster than expulsion of the alkoxide. To our knowledge, this method represents the first preparation of a stable ether-substituted iminoisobenzofuran.[51]

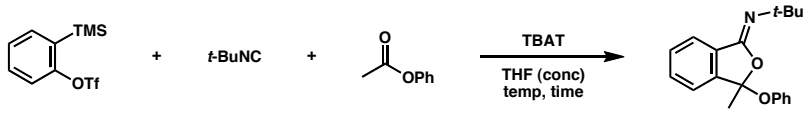
Scheme 6.14. a) Attempted three-component coupling of benzyne, tert-butyl isocyanide, and ethyl acetate. b) Three-component coupling of benzyne, tert-butyl isocyanide, and phenyl acetate.



Having discovered this unexpected new reaction, we decided to ascertain the optimal conditions for the formation of phenoxy iminoisobenzofuran **680** (Table 6.1). In the first experiment, we had established the aryne as the limiting reagent. A greater excess of the phenyl ester was employed relative to the isocyanide in light of the previous difficulties we had encountered while attempting to stimulate the reactivity of the carbonyl component. Subsequent trials were performed using the original stoichiometric ratios at room temperature (entry 2) and 60 °C (entry 3), though neither provided **680** in greater

than 60% yield. We then evaluated conditions in which the isocyanide (entry 4) and the phenyl ester (entry 5) were each used in limiting quantities. Although neither trial proved more effective than the first, we were intrigued to find that using the phenyl ester as the limiting reagent had nearly the same effect on the yield as did the aryne (entry 1). Considering this method from the standpoint of multistep synthesis, we anticipated that the ester would likely represent the most valuable component. As such, we decided to pursue conditions in which this substrate would be used in limiting quantities. In accordance with the previous optimization of our aryne annulation technology,[52] we diluted the reaction solution to 0.1 M (entry 6). While this had a modest retarding effect on the reaction, it was accompanied by an appreciable increase in yield. Further attempts to decrease the reaction temperature (entry 7) and the amount of excess material used (entry 8) met only with lesser yields.

Table 6.1. Optimization of reaction conditions for the three-component coupling of benzyne, tert-butyl isocyanide, and phenyl acetate

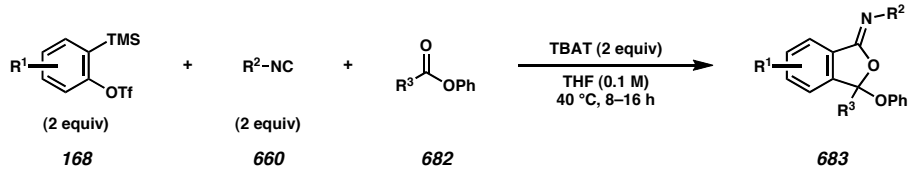


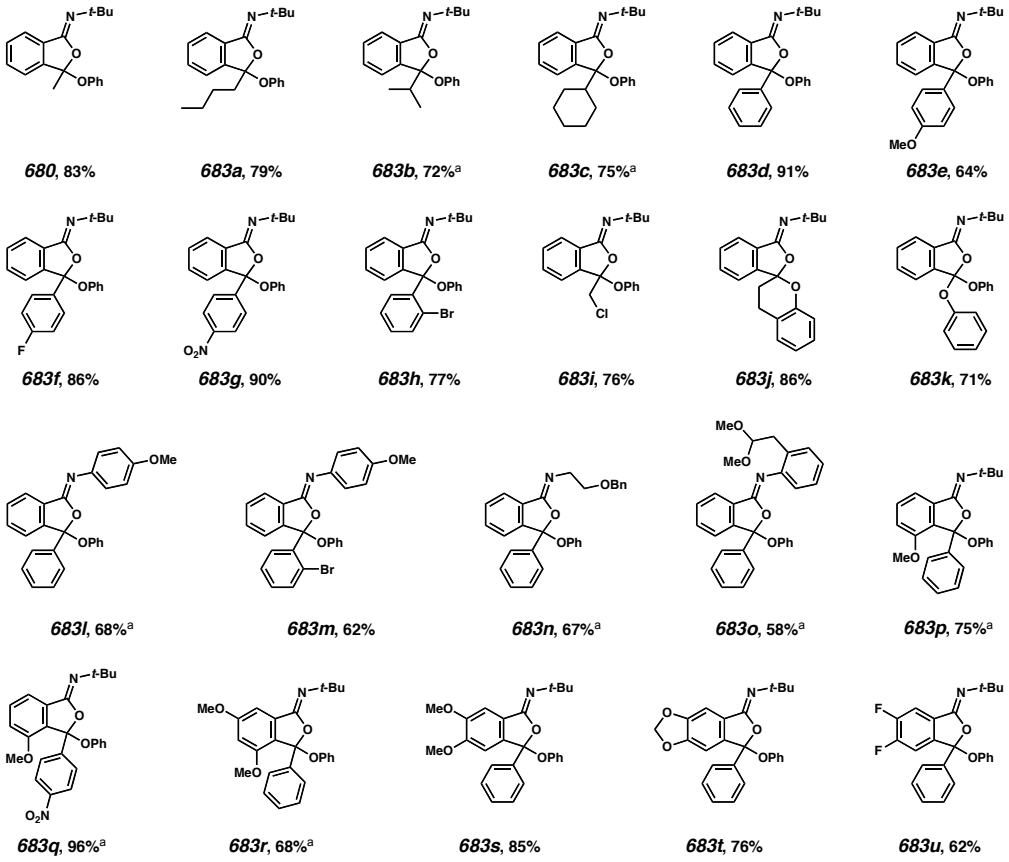
71 ***670*** ***679*** ***680***

entry	aryne equivalents	TBAT equivalents	*t*-BuNC equivalents	PhOAc equivalents	conc. (M)	temp. (°C)	time (h)	yield
1	1	1	2	3	0.2	40	8	60%
2	1	1	2	3	0.2	23	24	35%
3	1	1	2	3	0.2	60	6	44%
4	2	2	1	3	0.2	40	8	49%
5	2	2	2	1	0.2	40	8	57%
6	**2**	**2**	**2**	**1**	**0.1**	**40**	**12**	**83%**
7	2	2	2	1	0.1	23	24	69%
8	1	1	1	1	0.1	40	12	40%

Having devised an optimal set of conditions to prepare the phenoxy iminoisobenzofuran (**683**), we were determined to gain a better understanding of the synthetic capabilities of this reaction. We began by examining a number of differentially substituted phenyl esters prepared from the corresponding carboxylic acids in a single step (Table 6.2). Esters bearing linear (**680** and **683a**), branched (**683b**), and cyclic (**683c**) aliphatic substituents performed well under the established reaction conditions. Benzoic esters faired equally well, though we found that electron-withdrawing substituents (**683f–h**) promoted greater reactivity than electron-donating substituents (**683e**). Despite concerns that an α-haloester would react with *tert*-butyl isocyanide (**670**), phenyl chloroacetate produced the expected three-component adduct (**683i**) in comparable yield. Even dihydrocoumarin and phenyl carbonate gave rise to interesting spirocyclic (**683j)** and masked orthoester products (**683k**), respectively. Next, we evaluated the isocyanide component, replacing *tert*-butyl isocyanide (**670**) with 4-methoxyphenyl isocyanide (**683l** and **683m**) and 2-benzyloxyethyl isocyanide (**683n**) to form novel *N*-functionalized imidate structures. We also prepared and tested the *ortho*-(dimethoxyethyl)phenyl isocyanide designed by Kobayashi as a convertible functional handle for Ugi reactions,[53] which produced iminoisobenzofuran **683o** in a reasonable yield given the increased steric bulk of the nucleophile. Finally, we performed the three-component coupling with a series of heteroatom-functionalized aryne precursors to generate aryl-substituted adducts **683p–u**. Importantly, when unsymmetrical arynes were employed, the products (**683p–r**) were isolated as single isomers derived from the expected addition of *tert*-butyl isocyanide to the inductively activated position meta to the heteroatom.[54,55]

Table 6.2. Synthesis of phenoxy iminoisobenzofurans via three-component coupling of arynes, isocyanides, and phenyl esters



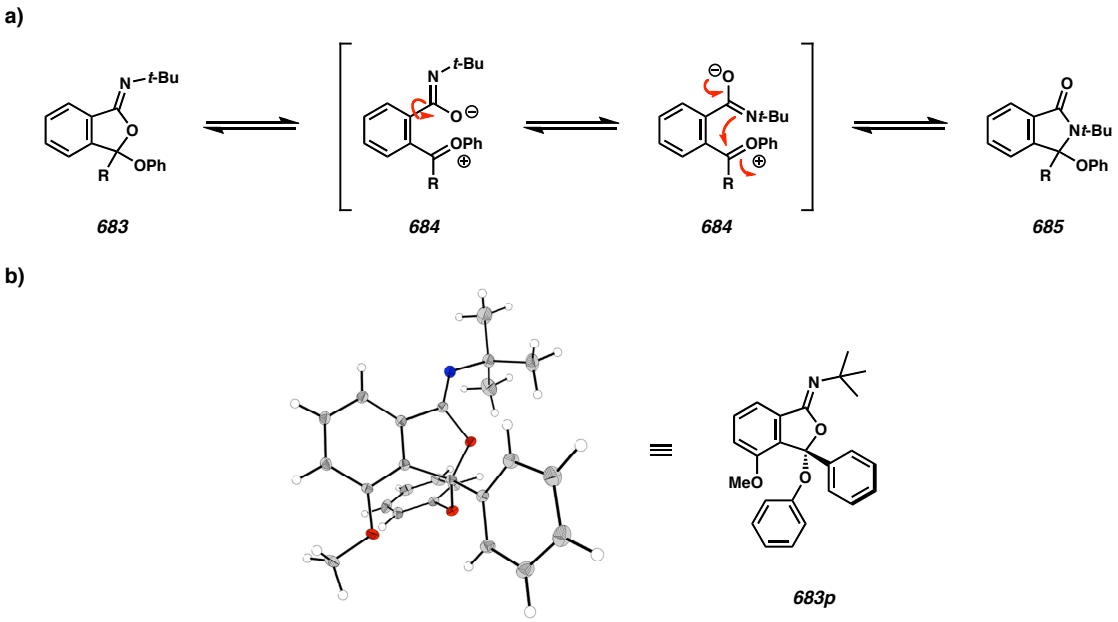


[a] Reaction performed at 60 °C

Our original structural assignment of the phenoxy iminoisobenzofurans was based primarily on analogy to Yoshida's earlier work with iminoisobenzofurans[15] and iminoisoindoles.[16] However, we recognized the potential for a structural rearrangement pathway uniquely available to our products based on the presence of the phenyl ether.

Donation of an electron pair from the oxygen of the phenoxy substituent would result in ring opening to generate an intermediate oxocarbenium species (**684**) (Scheme 6.15a). Bond rotation and addition of the imidate nitrogen to the activated carbonyl would then lead to the isomeric isoindolinone (**685**). Given the close structural similarity between iminoisobenzofuran **683** and lactam **685**, we were hesitant to make a definitive assignment based solely on NMR and IR data. We therefore obtained a crystal of adduct **683p** suitable for X-ray diffraction (Scheme 6.15b). The structure obtained unambiguously confirmed our original assignment as the phenoxy iminoisobenzofuran.

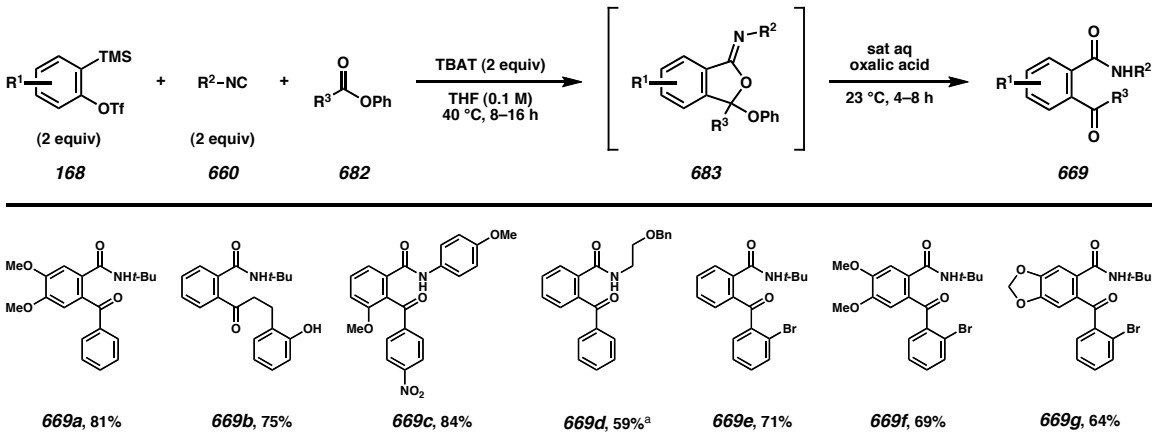
*Scheme 6.15. a) Potential equilibration between iminoisobenzofuran and isoindolinone isomers. b) X-ray crystal structure of phenoxy iminoisobenzofuran **683p**.*



While considering the possibility of structural rearrangement, we realized that the phenoxy iminoisobenzofurans could potentially be converted to our original

targets—*ortho*-ketobenzamides (e.g., **669**)—by intercepting a ring-opened intermediate such as **684** with an equivalent of water. We therefore began examining conditions under which the three-component adducts might be hydrolyzed in situ to generate *ortho*-ketobenzamides (Table 6.3). A thorough screen of protic acids (e.g., HCl, HF, H_2SO_4, AcOH, TFA) eventually yielded oxalic acid as the optimal additive. Upon completion of the three-component coupling, a saturated aqueous solution of oxalic acid is added to the crude reaction and the biphasic mixture is allowed to stir a room temperature until the phenoxy iminoisobenzofuran is fully consumed. In this way, we are able to generate di- (**669b**, **d**, and **e**), tri- (**669c**), and tetrasubstituted (**669a**, **f**, and **g**) *ortho*-ketobenzamides in good yield in a single step from readily available *ortho*-silyl aryl triflate (**168**), isocyanide (**660**), and phenyl ester (**682**) starting materials.[56]

Table 6.3. Synthesis of ortho-ketobenzamides via one-pot three-component coupling and hydrolysis

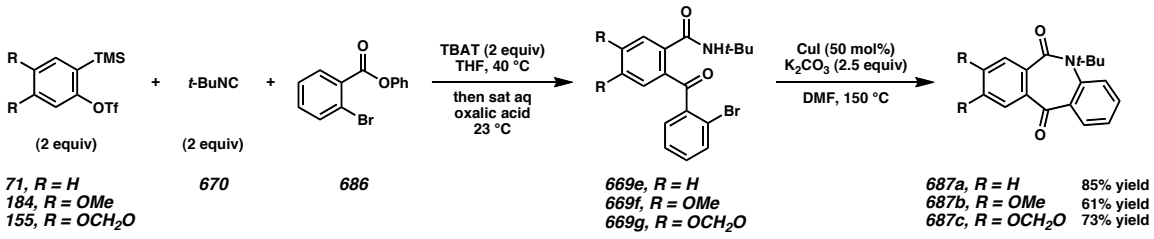


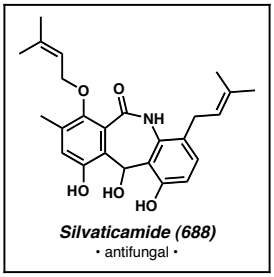
[a] Reaction performed at 60 °C.

In an effort to demonstrate the utility of the *ortho*-ketobenzamides, we sought to achieve an intramolecular coupling between the amide nitrogen and the aryl bromide of

2-(*ortho*-bromobenzoyl)benzamides **669e–g** to generate caprolactams (Scheme 6.16). Unfortunately, preliminary attempts employing **669e** in the presence of several different palladium[57] and copper[58] complexes failed to produce the desired seven-membered ring, most likely due to the steric bulk of the *tert*-butyl amide. We eventually discovered that copper(I) iodide in the absence of an added ligand effectively catalyzed the reaction in *N*,*N*-dimethylformamide at 150 °C, providing dibenzoketocaprolactams **669a–c** in 61–85% yield The structural similarity that these products share with natural isolates such as silvaticamide[59] (**688**) suggests that this method may prove useful in the realm of total synthesis.

Scheme 6.16. Two-step synthesis of dibenzoketocaprolactams

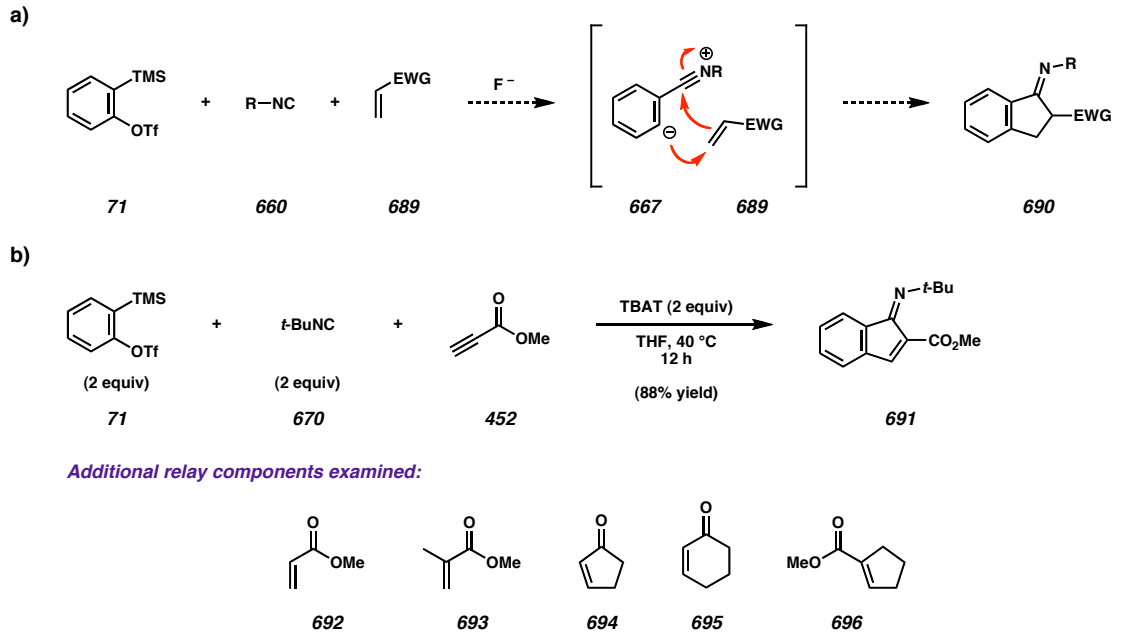




6.2.3 Synthesis of Iminoindenones

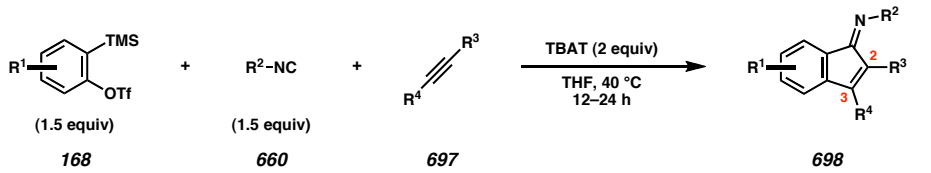
During the course of our efforts to develop an aryne analogue of the Passerini reaction, we had uncovered a novel three-component synthesis of unusual phenoxy iminoisobenzofuran structural motifs. Further investigations demonstrated the broad scope of this reaction, both alone and in tandem with a hydrolysis step en route to *ortho*-ketobenzamides. Seeking to harness this general mode of reactivity, we began to examine substrates other than phenyl esters capable of fulfilling the role as a relay species. Based on our results, as well as those of Rigby,[18] Yoshida,[14,15] and Huang,[43] we were confident that the first step of the reaction mechanism involved addition of the isocyanide (**660**) to benzyne to form zwitterion **667** (Scheme 6.17a). The aryl anion then added to the relay component, through which the negative charge was conveyed back to the nitrilium ion. It occurred to us that a conjugate acceptor (**689**) should fill this role adequately, acting as both an β-electrophile and an α-nucleophile. Thus, we tested a series of α,β-unsaturated carbonyl compounds under the optimized coupling conditions in the hope of generating carbocyclic adducts (**690**). Eventually, we found that methyl propiolate (**452**) furnished iminoindenone **691** in 88% yield after 12 h, a result that was all the more significant in light of the fact that compounds **692**–**696** failed to react (Scheme 6.17b).

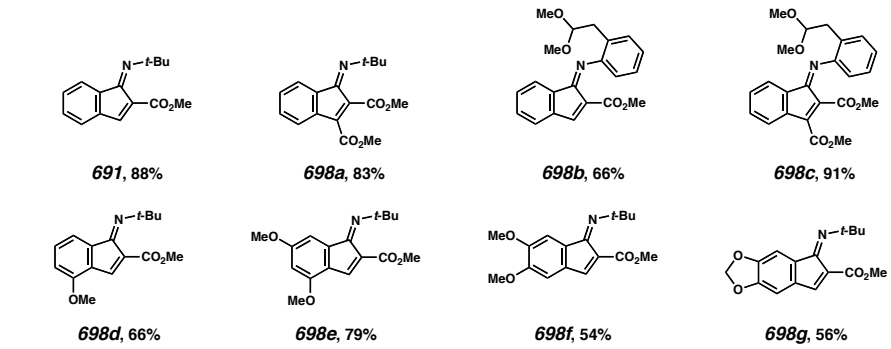
Scheme 6.17. a) Proposed three-component coupling of arynes, isocyanides, and a two-carbon relay species. b) Three-component coupling of benzyne, tert-butyl isocyanide, and methyl propiolate.



With our initial result in hand, we performed a more in-depth analysis of the substrate tolerances of our newly discovered three-component coupling reaction (Table 6.4). Introducing substitution at the β-position of the propiolate framework provided access to 2,3-disubstituted iminoindenone **698a** without significantly impacting the yield. The reaction also proved amenable to the replacement of *tert*-butyl isocyanide with Kobayashi's *ortho*-(dimethoxyethyl)phenyl isocyanide,[53] generating compounds **698b** and **698c** in 66% and 91% yield, respectively. Finally, we examined the effects of aryne substitution upon product distribution. As in the previous synthesis of phenoxy iminoisobenzofurans, we found that both symmetrical and unsymmetrical heteroatom-functionalized arynes formed the expected three-component adducts (**698d–g**) in good yield as single isomers.

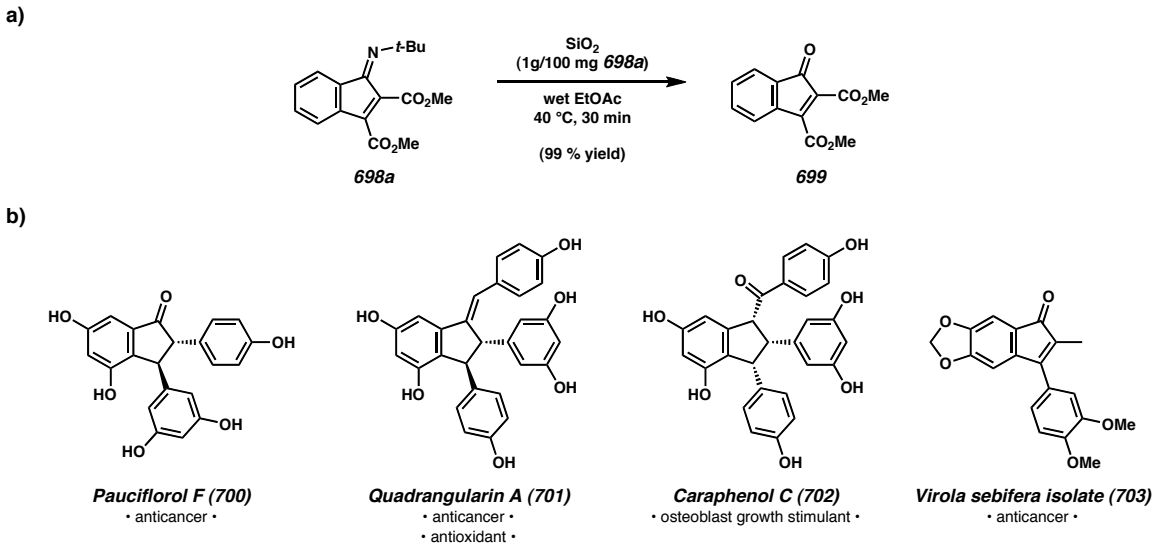
Table 6.4. Three-component coupling of arynes, isocyanides, and alkynes





Once again, we endeavored to hydrolyze the product of our three-component reaction (**698a**), this time to reveal an indenone (**699**) (Scheme 6.18a). The ubiquity of this bicyclic framework in bioactive natural products such as pauciflorol F (**700**),[60] quadrangularin A (**701**),[61] caraphenol C (**702**),[62] and the *Virola sebifera* isolate **703**[63] suggested that the development of a facile method for hydrolysis of our products could provide a novel approach to the construction of medicinally relevant small molecules (Scheme 6.18b). Gratifyingly, conversion of iminoindenone **698a** to indenone **699** proved exceedingly straightforward, as this transformation could be achieved simply by stirring the substrate in wet ethyl acetate at 40 °C in the presence of silica gel. In this way, we were able to generate the desired indenone (**699**) in nearly quantitative yield in as little as 30 min.

Scheme 6.18. a) Hydrolysis of iminoindenone ***698a****. b) Natural products containing indenone-derived core structures*

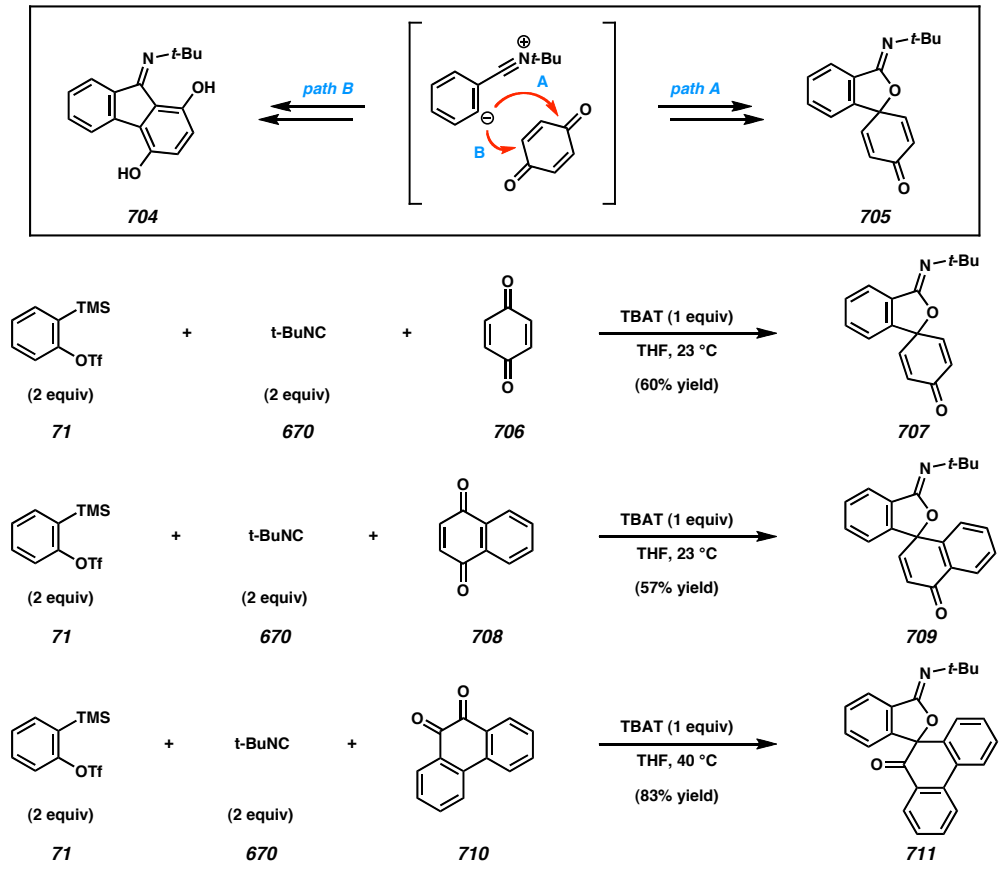


6.2.4 Quinones as Relay Components

At present, our efforts are focused upon the discovery of new relay species for the synthesis of additional three-component products. We were particularly interested in quinones, given that they represent electrophiles capable of undergoing either 1,2- (path A) or 1,4-addition (path B) of the aryl anion to generate either fused (**704**) or spirocyclic (**705**) tricycles (Scheme 6.19). In a preliminary experiment, 1,4-benzoquinone (**706**) was employed as the relay species in combination with *ortho*-silyl aryl triflate **71** and *tert*-butyl isocyanide (**670**). Under standard conditions, spirocyclic hemiquinone **707** was isolated in 60% yield, thereby confirming the 1,2-addition pathway.[64] Additional experiments with 1,4-naphthoquinone (**708**) and 9,10-phenanthrenequinone (**710**) yielded similar products (**709** and **711**, respectively) resulting from addition directly to the quinone carbonyl. Further research within this class of substrates is ongoing and we

anticipate that the results of these studies will provide greater insight into the synthetic capabilities of the three-component aryne coupling reactions.

Scheme 6.19. Three-component coupling of benzyne, tert-butyl isocyanide, and quinones



6.3 CONCLUSION

We entered the forum of multicomponent synthesis with the intention of applying classical mechanistic understanding to the development of new aryne methodologies. However, in the course of our efforts to employ arynes in a modern analogue of the Passerini reaction, we discovered a novel three-component coupling of arynes, isocyanides, and phenyl esters that forms unusual phenoxy iminoisobenzofuran products.

Given that stable versions of these products had not been prepared prior to our work, we were eager to demonstrate their synthetic utility. By adding a saturated aqueous solution of oxalic acid to the reaction mixture, we are able to hydrolyze the three-component adducts to accomplish a one-pot synthesis of *ortho*-ketobenzamides and thus generate the original targets of our work toward the modified Passerini reaction. Furthermore, we have been able to advance certain of these compounds through a copper-catalyzed intramolecular coupling reaction to construct interesting dibenzoketocaprolactams. In an attempt to translate the general mechanism of the three-component coupling reaction to the formation of additional adducts, we examined a number of α,β-unsaturated carbonyl compounds. These studies led to the discovery that activated alkynes participated in a similar transformation to yield iminoindenones. As before, a method for the hydrolysis of these products was uncovered, and with it, a route to indenone frameworks relevant to the assembly of resveratrol-derived natural products. Ongoing efforts are directed toward the investigation of additional relay species for the synthesis of novel spirocyclic compounds.

6.4 EXPERIMENTAL SECTION

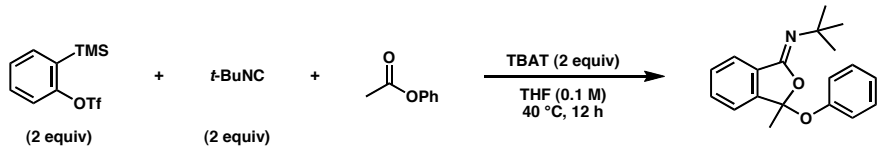
6.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) was azeotropically dried from acetonitrile prior to use. 3-Methoxy-2-(trimethylsilyl)phenyl triflate (**108**),[65] 3,5-dimethoxy-2-(trimethylsilyl)phenyl triflate (**572**),[66] 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate (**184**),[67] 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl triflate (**155**),[68] and 4,5-difluoro-2-(trimethylsilyl)phenyl triflate (**185**)[69] were prepared according to literature procedures. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or ceric ammonium molybdate staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical

ionization (APCI) or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility (EI+ or FAB+).

6.4.2 Preparative Procedures and Spectroscopic Data

6.4.2.1 Representative Procedure for the Three-Component Synthesis of Phenoxy Iminoisobenzofurans from Arynes, Isocyanides, and Phenyl Esters

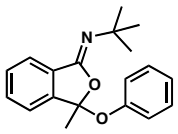


(2 equiv) (2 equiv)

71 *670* *679* *680*

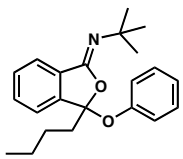
A flame-dried 50 mL round bottomed flask with a magnetic stir bar was charged with TBAT (1.70 g, 3.15 mmol, 2.0 equiv) and THF (16 mL). To this solution was added phenyl acetate (**679**) (0.20 mL, 1.57 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**71**) (0.765 mL, 3.15 mmol, 2.0 equiv), and *tert*-butylisocyanide (**670**) (0.356 mL, 3.15 mmol, 2.0 equiv), each via syringe. The reaction was heated to 40 °C under argon for 12 h, at which point TLC analysis showed complete consumption of phenyl acetate. The reaction was cooled to room temperature and passed over a plug of silica (3 cm diam. x 5 cm length) eluting with 15:85 EtOAc/hexanes in order to remove excess TBAT from solution. The solvents were removed under reduced pressure and the crude residue was purified by flash chromatography over silica gel.

6.4.2.2 Spectroscopic Data for Phenoxy Iminoisobenzofurans



Phenoxy iminoisobenzofuran 680

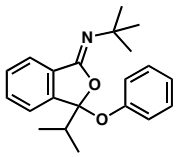
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (83% yield). R_f = 0.46 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{19}H_{21}NO_2$ $[M+H]^+$: 296.1651, found 296.1650.



Phenoxy iminoisobenzofuran 683a

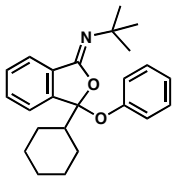
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (79% yield). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 1H), 7.50–7.42 (comp m, 2H), 7.37 (dt, J = 7.8, 2.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 7.6 Hz, 2H), 2.42 (ddd, J = 13.9, 12.0, 4.6 Hz, 1H), 2.20 (ddd, J = 13.9, 12.0, 4.6 Hz, 1H), 1.51–1.40 (m, 1H), 1.44 (s, 9H), 1.39–1.26 (m, 2H), 1.22–1.11 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 153.7, 153.0, 142.5, 136.6, 130.0, 129.0, 128.3, 124.3, 123.4, 122.9, 122.6, 112.8, 54.0, 39.2, 30.4, 25.7, 22.8, 14.2; IR (Neat Film, NaCl) 2963, 2871, 1706, 1592, 1491, 1214 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{22}H_{27}NO_2$ $[M+H]^+$: 338.2120, found 338.2125.



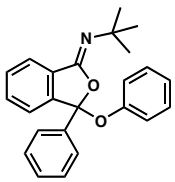
Phenoxy iminoisobenzofuran 683b

Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (72% yield). R_f = 0.54 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dt, J = 7.6, 1.0 Hz, 1H), 7.43 (dd, J = 4.4, 1.2 Hz, 1H), 7.41 (d, J = 5.1 Hz, 1H), 7.34 (ddd, J = 7.8, 6.1, 2.4 Hz, 1H), 7.03 (dd, J = 8.3, 7.3 Hz, 2H), 6.90 (tt, J = 7.3, 1.2 Hz, 1H), 6.78 (dd, J = 8.8, 1.2 Hz, 2H), 2.62 (septet, J = 6.8 Hz, 1H), 1.42 (s, 9H), 1.22 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.4, 141.6, 134.1, 131.2, 130.0, 129.0, 124.2, 123.3, 123.0, 122.9, 114.9, 54.0, 37.4, 30.4, 17.3, 16.8; IR (Neat Film, NaCl) 2968, 1706, 1592, 1491, 1214, 1070 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{21}H_{25}NO_2$ $[M+H]^+$: 324.1964, found 324.1959.



Phenoxy iminoisobenzofuran 683c

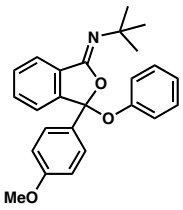
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (75% yield). R_f = 0.46 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.6 Hz, 1H), 7.43–7.40 (comp m, 2H), 7.34 (dd, J = 7.8, 2.4 Hz, 1H), 7.03 (t, J = 7.6 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 7.6 Hz, 2H), 2.29 (td, J = 12.0, 3.2 Hz, 2H), 1.86 (br d, J = 12.9 Hz, 1H), 1.71 (br s, 1H), 1.50–1.41 (m, 1H), 1.43 (s, 9H), 1.38–1.14 (comp m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 153.3, 141.7, 136.6, 134.1, 131.1, 129.9, 129.0, 128.3, 124.2, 123.3, 123.0, 122.9, 114.3, 54.0, 47.0, 30.4, 27.2, 26.8, 26.6, 26.3, 26.2; IR (Neat Film, NaCl) 2931, 1706, 1593, 1491, 1213 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{29}NO_2$ $[M+H]^+$: 364.2271, found 364.2273.



Phenoxy iminoisobenzofuran 683d

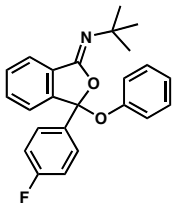
Purified by flash chromatography (SiO_2, 3:97 EtOAc/hexanes) to yield a white solid (91% yield). R_f = 0.40 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dt, J = 7.6, 1.0 Hz, 1H), 7.64 (dd, J = 7.1, 1.5 Hz, 2H), 7.45-7.33 (comp m, 6H), 7.13 (dd, J = 8.5, 7.3 Hz, 2H), 6.99 (dd, J = 7.6, 1.2 Hz, 2H), 6.95 (t, J = 7.3 Hz, 1H), 1.47 (s, 9H););

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 152.8, 144.5, 139.8, 131.8, 131.7, 130.1, 129.2, 129.0, 128.9, 126.0, 123.6, 123.5, 123.3, 121.5, 110.4, 54.3, 30.5; IR (Neat Film, NaCl) 2968, 1709, 1590, 1491, 1213 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{24}NO_2$ $[M+H]^+$: 358.1807, found 358.1798.



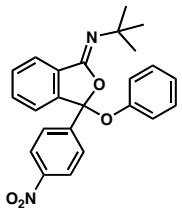
Phenoxy iminoisobenzofuran 683e

Purified by flash chromatography (SiO_2, 4:96 EtOAc/hexanes) to yield a colorless oil (64% yield). R_f = 0.30 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.44 (dd, J = 7.3, 6.6 Hz, 1H), 7.41–7.36 (comp m, 2H), 7.13 (dd, J = 8.5, 7.3 Hz, 2H), 6.99 (d, J = 7.8 Hz, 2H), 6.95 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 154.1, 152.9, 144.7, 131.9, 131.7, 131.3, 130.0, 129.1, 128.7, 127.4, 126.9, 123.6, 123.2, 121.6, 114.2, 55.5, 54.3, 30.5; IR (Neat Film, NaCl) 2967, 1708, 1661, 1513, 1490, 1254, 1213, 1173 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{25}H_{25}NO_3$ $[M+H]^+$: 388.1913, found 388.1923.



Phenoxy iminoisobenzofuran 683f

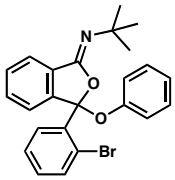
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (86% yield). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dt, J = 7.3, 1.0 Hz, 1H), 7.61 (dd, J = 9.0, 5.1 Hz, 2H), 7.45 (td, J = 7.3, 1.2 Hz, 1H), 7.40 (dd, J = 7.3, 1.2 Hz, 1H), 7.38 (tt, J = 7.3, 1.0 Hz, 1H), 7.13 (dd, J = 8.8, 7.1 Hz, 2H), 7.07 (t, J = 8.8 Hz, 2H), 6.97 (d, J = 7.1 Hz, 2H), 6.96 (tt, J = 7.1, 1.2 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 161.9, 153.6, 152.1, 143.9, 136.4, 131.7, 131.5, 130.1, 129.9, 129.0, 128.1, 127.8 (d, $J_{C–F}$ = 8.6 Hz), 123.6 (d, $J_{C–F}$ = 21.9 Hz), 123.0, 121.5, 115.6 (d, $J_{C–F}$ = 21.5 Hz), 109.9, 54.1, 30.2; ^{19}F NMR (282 MHz, $CDCl_3$) d –113.0 (app septet, J = 5.1 Hz); IR (Neat Film, NaCl) 2968, 1710, 1590, 1509, 1491, 1211, 1158 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{22}FNO_2$ $[M+H]^+$: 376.1713, found 376.1747.



Phenoxy iminoisobenzofuran 683g

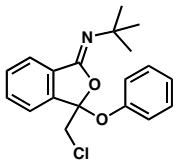
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a white solid (90% yield). R_f = 0.37 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 7.76 (dt, J = 7.6, 1.0 Hz, 1H), 7.47 (td, J = 7.3, 1.2 Hz, 1H), 7.42 (td, J = 7.6, 1.2 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.15 (dd, J = 8.5, 7.3

Hz, 2H), 7.00 (tt, J = 7.3, 1.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 151.6, 148.2, 146.6, 142.9, 135.1, 131.8, 130.5, 129.2, 127.9, 127.0, 124.1, 124.0, 123.8, 123.0, 121.6, 109.3, 54.4, 30.3; IR (Neat Film, NaCl) 2969, 1712, 1590, 1525, 1490, 1350, 1210 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{22}N_2O_4$ $[M+H]^+$: 403.1658, found 403.1670.



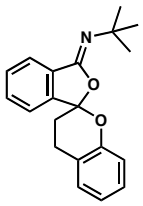
Phenoxy iminoisobenzofuran 683h

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (77% yield). R_f = 0.40 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.1, 1.7 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.62 (td, J = 7.9, 1.2 Hz, 2H), 7.46 (td, J = 7.9, 1.2 Hz, 1H), 7.45–7.38 (comp m, 2H), 7.25 (td, J = 7.6, 1.7 Hz, 1H), 7.11 (t, J = 7.3 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.6 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 152.4, 142.5, 137.2, 136.4, 135.4, 135.0, 131.2, 130.5, 130.1, 129.7, 128.8, 128.1, 127.9, 127.2, 123.9, 123.1, 123.0, 122.5, 109.5, 54.2, 30.3; IR (Neat Film, NaCl) 2968, 1711, 1589, 1490, 1429, 1289, 1209 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{24}H_{22}BrNO_2$ $[M+H]^+$: 438.0889, found 438.0881.



Phenoxy iminoisobenzofuran 683i

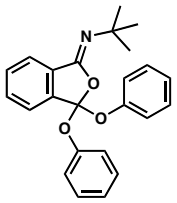
Purified by flash chromatography (SiO_2, 3:97 EtOAc/hexanes) to yield a pale yellow oil (76% yield). R_f = 0.55 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 7.6 Hz, 1H), 7.56 (dt, J = 7.6, 1.0 Hz, 1H), 7.48 (dt, J = 7.6, 1.0 Hz, 1H), 7.42 (dt, J = 7.6, 1.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 2H), 6.98 (tt, J = 7.3, 1.0 Hz, 1H), 6.90 (dd, J = 7.6, 1.0 Hz, 2H), 4.14 (d, J = 11.7 Hz, 1H), 4.07 (d, J = 11.7 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 151.7, 139.7, 134.1, 131.5, 130.8, 129.3, 124.9, 123.6, 123.2, 122.7, 109.6, 54.4, 47.9, 30.3; IR (Neat Film, NaCl) 2968, 1788, 1709, 1591, 1490, 1210 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{19}H_{20}ClNO_2$ $[M+H]^+$: 330.1255, found 330.1271.



Phenoxy iminoisobenzofuran 683j

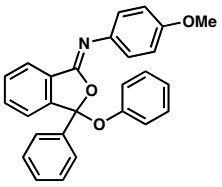
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a white solid (86% yield). R_f = 0.37 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.55 (dd, J = 7.3, 1.5 Hz, 1H), 7.51 (ddd, J = 7.3, 1.5, 1.2 Hz, 1H), 7.39 (td, J = 7.3, 1.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 7.00 (td, J = 7.3, 1.2 Hz, 1H), 6.87 (dd, J = 8.1, 1.2 Hz, 1H), 3.29 (ddd, J = 13.7, 13.4, 5.6 Hz, 1H),

2.95 (ddd, J = 16.4, 5.6, 1.7 Hz, 1H), 2.43 (td, J = 13.7, 5.9 Hz, 1H), 2.19 (ddd, J = 13.4, 5.9, 2.0 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 152.7, 143.7, 136.1, 135.0, 131.4, 130.3, 129.2, 127.7, 123.6, 121.7, 121.5, 117.0, 105.9, 54.1, 30.0, 28.0, 22.0; IR (Neat Film, NaCl) 2967, 1706, 1586, 1489, 1362, 1228, 1044 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{20}H_{21}NO_2$ $[M+H]^+$: 308.1651, found 308.1661.



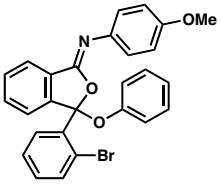
Phenoxy iminoisobenzofuran 683k

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (71% yield). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.6, 1.0 Hz, 1H), 7.62 (d, J = 8.1, 1.5 Hz, 2H), 7.48 (tt, J = 7.3, 1.5 Hz, 1H), 7.43 (dd, J = 6.8, 1.2 Hz, 1H), 7.38 (td, J = 7.6, 1.0 Hz, 1H), 7.20 (dd, J = 8.5, 7.6 Hz, 2H), 7.12 (td, J = 7.6, 1.2 Hz, 1H), 7.05 (ddd, J = 7.3, 1.2, 1.0 Hz, 2H), 6.94 (dd, J = 8.5, 1.0 Hz, 2H), 6.36 (dt, J = 7.6, 1.0 Hz, 1H), 1.77 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 153.6, 139.1, 138.2, 136.4, 134.2, 132.4, 132.3, 131.6, 131.1, 130.3, 130.1, 129.1, 128.1, 124.1, 123.2, 123.0, 121.9, 121.3, 113.4, 57.1, 28.4; IR (Neat Film, NaCl) 2966, 1713, 1589, 1489, 1357, 1323, 1202, 1128, 1016 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{23}NO_3$ $[M+H]^+$: 374.1756, found 374.1763.



Phenoxy iminoisobenzofuran 683l

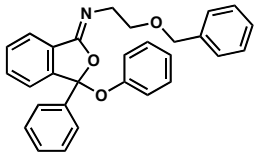
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 4:96 EtOAc/hexanes) to yield a white solid (68% yield). R_f = 0.35 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (ddd, J = 7.6, 1.2, 1.0 Hz, 1H), 7.65 (ddd, J = 8.1, 1.2 Hz, 2H), 7.50–7.45 (comp m, 3H), 7.49 (d, J = 9.0 Hz, 2H), 7.42–7.35 (comp m, 3H), 7.12 (dd, J = 8.8, 7.3 Hz, 2H), 6.98 (dd, J = 8.8, 1.2 Hz, 2H), 6.97 (dd, J = 6.1, 1.0 Hz, 1H), 6.92 (d, J = 9.3 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 153.9, 153.6, 144.4, 138.9, 138.6, 135.0, 131.9, 131.2, 130.2, 130.1, 129.0, 129.0, 128.7, 127.9, 125.9, 125.9, 123.8, 123.5, 123.3, 121.8, 113.9, 55.4; IR (Neat Film, NaCl) 3062, 2928, 2833, 1685, 1591, 1506, 1488, 1292, 1245, 1208, 1030 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{27}H_{21}NO_3$ $[M+H]^+$: 408.1594, found 408.1608.



Phenoxy iminoisobenzofuran 683m

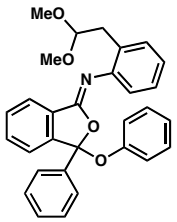
Purified by flash chromatography (SiO_2, 2:98→ 4:96 EtOAc/hexanes) to yield a white solid (62% yield). R_f = 0.37 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.8, 1.5 Hz, 1H), 7.77 (dd, J = 7.3, 1.0 Hz, 1H), 7.62 (dd, J = 7.8, 1.2 Hz, 1H), 7.51 (td, J = 7.3, 1.2 Hz, 1H), 7.47 (dd, J = 7.3, 1.2 Hz, 1H), 7.44–7.41 (comp m, 2H),

7.43 (d, J = 9.0 Hz, 2H), 7.26 (ddd, J = 0.5, 1.7, 8.1 Hz, 1H), 7.09 (dd, J = 8.6, 7.3 Hz, 2H), 6.99 (ddd, J = 7.3, 1.2, 1.0 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.87 (dd, J = 8.6, 1.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 154.3, 152.4, 142.7, 138.7, 136.4, 135.4, 135.0, 133.3, 131.7, 130.7, 130.4, 130.1, 129.6, 128.9, 127.9, 127.3, 125.6, 124.4, 123.2, 123.1, 123.0, 121.4, 113.9, 55.4; IR (Neat Film, NaCl) 3062, 2928, 2833, 1692, 1590, 1506, 1490, 1466, 1293, 1244, 1202, 1034 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{27}H_{20}BrNO_3$ $[M+H]^+$: 488.0684, found 488.0714.



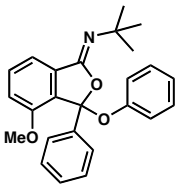
Phenoxy iminoisobenzofuran 683n

Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98→ 8:92 EtOAc/hexanes) to yield a pale yellow solid (67% yield). R_f = 0.30 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dt, J = 7.8, 1.0 Hz, 1H), 7.65–7.62 (comp m, 2H), 7.46 (dd, J = 6.8, 1.0 Hz, 1H), 7.44 (dd, J = 7.6, 0.7 Hz, 1H), 7.41 (ddd, J = 7.6, 1.7, 1.0 Hz, 1H), 7.40–7.37 (comp m, 2H), 7.36–7.33 (comp m, 5H), 7.28 (tt, J = 7.3, 1.0, 1H), 7.10 (dd, J = 8.8, 7.3 Hz, 2H), 6.99 (dd, J = 7.6, 1.2 Hz, 2H), 6.94 (tt, J = 7.3, 1.2 Hz, 1H), 4.64 (s, 2H), 3.98 (dt, J = 13.7, 6.3 Hz, 1H), 3.88 (ddd, J = 13.7, 6.3, 5.4 Hz, 1H), 3.80 (ddd, J = 6.6, 6.3, 1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 153.5, 144.9, 138.9, 138.5, 135.3, 131.6, 130.3, 129.9, 128.9, 128.8, 128.5, 128.3, 127.7, 127.4, 125.8, 123.7, 123.2, 123.1, 121.8, 73.0, 70.1, 47.8; IR (Neat Film, NaCl) 3057, 2858, 1707, 1589, 1490, 1449, 1293, 1208, 1100 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{29}H_{25}NO_3$ $[M+H]^+$: 436.1907, found 436.1893.



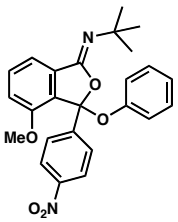
Phenoxy iminoisobenzofuran 683o

Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 5:95 EtOAc/hexanes) to yield a yellow oil (58% yield). R_f = 0.40 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (dd, J = 7.3, 1.0 Hz, 1H), 7.74 (ddd, J = 7.3, 1.2, 1.0 Hz, 1H), 7.65 (dd, J = 8.1, 1.5 Hz, 2H), 7.57 (ddd, J = 7.6, 1.5, 1.0 Hz, 1H), 7.45 (dd, J = 7.3, 1.5 Hz, 2H), 7.40 (ddd, J = 7.57, 1.5, 1.2 Hz, 2H), 7.27 (m, 1H), 7.26 (tt, J = 7.3, 1.5 Hz, 1H), 7.22 (dd, J = 7.8, 7.3 Hz, 2H), 7.12 (dd, J = 7.8, 1.2 Hz, 2H), 6.99 (dd, J = 7.8, 1.0 Hz, 1H), 6.82 (td, J = 7.6, 1.2 Hz, 1H), 6.62 (td, J = 8.1, 1.5 Hz, 1H), 5.23 (dd, J = 7.8, 1.2 Hz, 1H), 3.66 (t, J = 5.4 Hz, 1H), 3.01 (s, 6H), 2.98 (t, J = 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 144.7, 142.9, 138.1, 138.0, 135.8, 135.6, 134.7, 133.5, 133.2, 131.2, 130.2, 130.1, 129.8, 128.8, 128.6, 128.5, 127.9, 127.6, 127.4, 127.3, 125.0, 124.2, 121.4, 102.9, 51.7, 31.3; IR (Neat Film, NaCl) 3067, 2935, 1617, 1597, 1429, 1303, 1121, 1068, 1048 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{30}H_{27}NO_4$ $[M+H]^+$: 466.2013, found 466.2008.



Phenoxy iminoisobenzofuran 683p

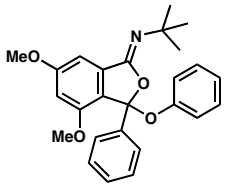
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 4:96 EtOAc/hexanes) to yield a white solid (75% yield). X-ray diffraction crystals were grown via slow evaporation of a solution of the white solid (20 mg) in $CDCl_3$ (0.6 mL) on the bench top at 23 °C over 3 days; mp 101–104 °C. R_f = 0.30 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 6.6 Hz, 2H), 7.40–7.34 (comp m, 3H), 7.32 (t, J = 7.8 Hz, 2H), 7.11 (dd, J = 8.6, 7.1 Hz, 2H), 7.06 (dd, J = 7.6, 1.2 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 3.78 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 154.0, 153.1, 139.2, 135.1, 134.6, 132.3, 130.6, 129.0, 128.7, 128.1, 126.9, 124.4, 122.4, 115.5, 113.6, 55.7, 54.3, 30.4; IR (Neat Film, NaCl) 2967, 1699, 1612, 1489, 1271, 1213, 1049 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{25}H_{25}NO_3$ $[M+H]^+$: 388.1907, found 388.1925.



Phenoxy iminoisobenzofuran 683q

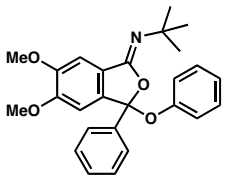
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 6:94 EtOAc/hexanes) to yield a pale yellow solid (96% yield). R_f = 0.10 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 9.0

Hz, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.8, 0.7 Hz, 1H), 7.13 (dd, J = 8.5, 7.3 Hz, 2H), 7.02 (dd, J = 8.8, 1.2 Hz, 2H), 6.99 (ddd, J = 7.3, 1.2, 1.0 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 3.79 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 153.2, 151.6, 147.9, 146.1, 134.4, 132.7, 129.2, 128.9, 127.8, 124.7, 123.2, 122.2, 115.4, 113.4, 109.8, 55.5, 54.2, 30.2; IR (Neat Film, NaCl) 2968, 1700, 1613, 1524, 1490, 1349, 1271, 1211, 1044 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{25}H_{24}N_2O_5$ $[M–H]^-$: 431.1612, found 431.1621.



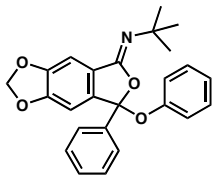
Phenoxy iminoisobenzofuran 683r

Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 4:96 EtOAc/hexanes) to yield a white solid (68% yield). R_f = 0.27 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.8, 1.7 Hz, 2H), 7.36 (dd, J = 7.8, 1.7 Hz, 2H), 7.35 (tt, J = 7.8, 1.7 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 7.04 (dd, J = 8.3, 1.2 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 155.1, 153.8, 152.9, 139.4, 135.5, 128.7, 128.4, 128.1, 127.8, 126.5, 124.1, 123.8, 122.4, 102.7, 97.0, 55.8, 55.4, 54.0, 30.2; IR (Neat Film, NaCl) 2964, 1695, 1619, 1599, 1355, 1204, 1146, 1037 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{26}H_{27}NO_4$ $[M+H]^+$: 418.2013, found 418.2020.



Phenoxy iminoisobenzofuran 683s

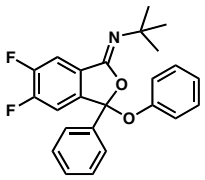
Purified by flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield a white solid (85% yield). R_f = 0.23 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 6.8 Hz, 2H), 7.40 (dd, J = 7.1, 6.8 Hz, 2H), 7.35 (tt, J = 7.1, 1.5 Hz, 1H), 7.14 (dd, J = 8.5, 7.1, 2H), 7.12 (s, 1H), 7.00–6.95 (comp m, 3H), 6.77 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 153.0, 152.6, 151.0, 139.8, 137.4, 129.8, 128.9, 128.7, 128.6, 128.2, 125.7, 123.5, 121.5, 104.5, 104.4, 56.3, 56.2, 54.0, 30.3; IR (Neat Film, NaCl) 2966, 1701, 1595, 1501, 1491, 1317, 1214 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{26}H_{27}NO_4$ $[M+H]^+$: 418.2013, found 418.2016.



Phenoxy iminoisobenzofuran 683t

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (76% yield). R_f = 0.30 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.1 Hz, 2H), 7.39 (dd, J = 7.6, 6.8 Hz, 2H), 7.34 (tt, J = 7.1, 1.0 Hz, 1H), 7.16 (dd, J = 8.5, 7.6 Hz, 2H), 7.06 (s, 1H), 7.00 (dd, J = 8.5, 1.0 Hz, 2H), 6.98 (t, J= 7.3 Hz, 1H), 6.74 (s, 1H), 6.02 (d, J = 1.2 Hz, 1H), 5.97 (d, J = 1.2 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.2, 151.2, 149.7, 139.7, 139.3, 136.0, 135.0, 129.0, 128.8,

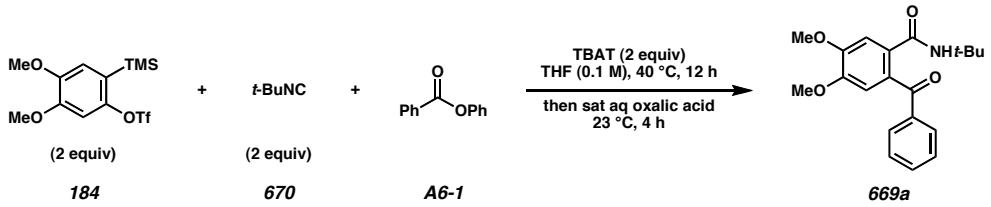
128.7, 125.7, 123.4, 121.4, 102.8, 102.6, 102.2, 53.9, 30.3;IR (Neat Film, NaCl) 2967, 1707, 1473, 1307, 1213, 1059, 1037 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{25}H_{23}NO_4$ $[M+H]^+$: 402.1700, found 402.1684.



Phenoxy iminoisobenzofuran 683u

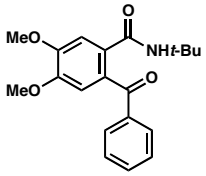
Purified by flash chromatography (SiO_2, 0:100 → 2:98 EtOAc/hexanes) to yield a pale yellow oil (62% yield). R_f = 0.50 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 6.6, 1.5 Hz, 2H), 7.48 (dd, J = 8.8, 7.1 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.39 (dd, J = 8.3, 6.8 Hz, 1H), 7.17 (tt, J = 7.6, 1.5 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 6.99 (t, J = 7.6 Hz, 1H), 6.98 (dd, J = 7.6, 7.1 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0 (d, $J_{C–F}$ = 14.7 Hz), 153.5, 153.1 (d, $J_{C–F}$ = 14.3 Hz), 151.9 (d, $J_{C–F}$ = 14.3 Hz), 151.1 (d, $J_{C–F}$ = 14.3 Hz), 150.3, 140.3, 138.8, 129.2, 129.1, 128.9, 125.6, 123.8, 121.3, 111.0 (dd, $J_{C–F}$ = 19.8, 4.1 Hz), 109.4, 54.3, 30.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ –130.3 (ddd, J = 18.9, 7.9, 7.6 Hz), –133.7 (ddd, J = 18.9, 7.1, 6.8 Hz); IR (Neat Film, NaCl) 2968, 1711, 1498, 1451, 1343, 1211 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{24}H_{21}F_2NO_2$ $[M–H]^–$: 392.1468, found 392.1479.

6.4.2.3 Representative Procedure for the One-Pot Synthesis of Ortho-Ketobenzamides via Three-Component Synthesis and Hydrolysis of Phenoxy Iminoisobenzofurans



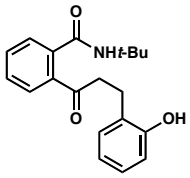
A flame-dried 15 mL long reaction tube with a magnetic stir bar was charged with TBAT (0.545 g, 1.01 mmol, 2 equiv), phenyl benzoate (**A6-1**) (0.100 g, 0.504 mmol), and THF (5 mL). To this solution was added silyl aryl triflate **184** (0.362 g, 1.01 mmol, 2 equiv) and *tert*-butylisocyanide (**670**) (0.114 mL, 1.01 mmol, 2 equiv), each via syringe. The reaction was heated to 40 °C under argon for 12 h, at which point TLC analysis showed complete consumption of phenyl benzoate (**A6-1**) (NOTE: at this point, the major component of the reaction is phenoxy iminoisobenzofuran **683s**). The reaction was cooled to room temperature and a saturated aqueous solution of oxalic acid (5 mL) was added via syringe. The mixture was vigorously stirred at room temperature for 4 h, at which point TLC analysis showed complete comsumption of the intermediate iminoisobenzofuran. The reaction was quenched by the slow addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was stirred until bubbling ceased and then extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

6.4.2.4 Spectroscopic Data for Ortho-Ketobenzamides



ortho-Ketobenzamide 669a

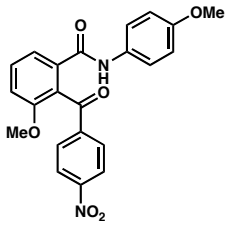
Purified by flash chromatography (SiO_2, 15:85 → 40:60 EtOAc/hexanes) to yield a white solid (81% yield). R_f = 0.37 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.3, 1.2 Hz, 2H), 7.57 (tt, J = 7.6, 1.2 Hz, 1H), 7.45 (dd, J = 8.1, 7.6 Hz, 2H), 7.24 (s, 1H), 6.95 (s, 1H), 5.59 (br s, 1H), 4.00 (s, 3H), 3.92 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 166.7, 150.4, 150.3, 137.5, 133.5, 130.7, 129.8, 128.6, 127.8, 111.1, 110.7, 56.3, 56.2, 51.8, 28.0; IR (Neat Film, NaCl) 3318, 2965, 1654, 1648, 1596, 1502, 1449, 1348, 1293, 1273, 1215 1084 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{20}H_{23}NO_4$ $[M–H]^-$: 340.1554, found 340.1556.



ortho-Ketobenzamide 669b

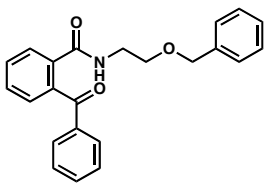
Purified by flash chromatography (SiO_2, 10:90 → 25:75 EtOAc/hexanes) to yield a white solid (75% yield). R_f = 0.10 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.42 (comp m, 4H), 7.12–7.08 (comp m, 2H), 6.88 (dd, J = 8.5, 1.2 Hz, 1H), 6.84 (td, J = 7.3, 1.2 Hz, 1H), 5.72 (br s, 1H), 3.26 (t, J = 6.4 Hz, 2H), 3.02 (t, J = 6.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0,168.4, 154.5, 138.5, 136.8, 131.1,

130.4, 130.2, 129.9, 127.6, 127.5, 127.3, 120.5, 117.2, 52.2, 43.2, 28.6, 24.2;IR (Neat Film, NaCl) 3315, 2970, 1681, 1644, 1593, 1532, 1456, 1366, 1230 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{20}H_{23}NO_3$ $[M–H]^-$: 324.1605, found 324.1620.



***ortho*-Ketobenzamide 669c**

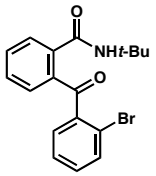
Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes) to yield a yellow solid (84% yield). R_f = 0.10 (25:75 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 11.7 Hz, 1H), 8.33 (d, *J* = 1.7 Hz, 1H), 7.88 (m, 1H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.28 (br s, 1H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 158.8, 157.7, 156.7, 129.9, 129.5, 121.8, 121.7, 114.9, 114.2, 55.6, 55.5; IR (Neat Film, NaCl) 3270, 3127, 3062, 1684, 1603, 1512, 1412, 1301, 1247, 1032 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{22}H_{18}N_2O_6$ $[M+H]^+$: 407.1238, found 407.1233.



***ortho*-Ketobenzamide 669d**

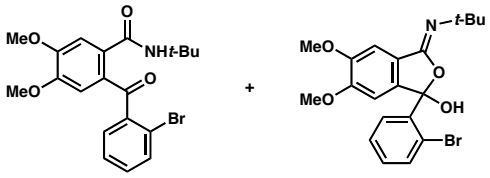
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 5:95 → 15:85 EtOAc/hexanes) to yield a white solid (59% yield). R_f = 0.27 (25:75 EtOAc/hexanes); ^1H

NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.48 (td, *J* = 7.3, 1.5 Hz, 1H), 7.45 (ddd, *J* = 7.3, 1.5, 0.5 Hz, 1H), 7.39 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.38–7.31 (comp m, 7H), 7.29 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.09 (t, *J* = 5.4 Hz, 1H), 4.38 (s, 2H), 3.15 (t, *J* = 5.1 Hz, 2H), 2.97 (dt, *J* = 5.4, 5.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 169.4, 143.2, 139.2, 138.0, 136.1, 135.7, 134.0, 129.8, 129.7, 129.0, 128.5, 127.8, 127.7, 127.6, 126.6, 72.9, 68.4, 39.4; IR (Neat Film, NaCl) 3284, 3067, 2860, 1634, 1631, 1536, 1427, 1300, 1107 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{23}H_{21}NO_3$ $[M+H]^+$: 360.1594, found 360.1588.



***ortho*-Ketobenzamide 669e**

Purified by flash chromatography (SiO_2, 20:80 → 30:70 EtOAc/hexanes) to yield a colorless oil (77% yield). R_f = 0.20 (25:75 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.56–7.54 (comp m, 2H), 7.49 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.46–7.44 (comp m, 2H), 7.38 (td, *J* = 7.6, 1.5 Hz, 1H), 7.34 (td, *J* = 7.8, 2.0 Hz, 1H), 5.74 (br s, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.1, 167.9, 139.4, 138.7, 137.3, 133.8, 132.3, 131.8, 131.7, 130.3, 129.6, 127.9, 127.3, 120.8, 51.9, 28.5; IR (Neat Film, NaCl) 3320, 2969, 1663, 1534, 1452, 1297, 1248, 1220 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{18}H_{18}BrNO_2$ $[M+H]^+$: 360.0594, found 360.0594.



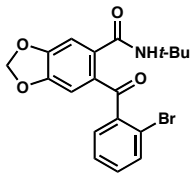
***ortho*-Ketobenzamide 669f**

Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes) to yield a colorless oil (69% yield). $R_f = 0.10$ (25:75 EtOAc/hexanes). Product was isolated as a 2:1 mixture of inseparable ketobenzamide and cyclic imidate isomers. ^{1}H and ^{13}C NMR data are reported for individual isomers; IR and HRMS data are reported for the mixture.

***ortho*-Ketobenzamide**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.8, 1.2 Hz, 1H), 7.46 (dd, J = 7.3, 2.0 Hz, 1H), 7.40 (td, J = 7.6, 1.5 Hz, 1H), 7.34 (td, J = 7.8, 2.0 Hz, 1H), 7.08 (s, 1H), 6.96 (s, 1H), 5.70 (br s, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 167.6, 151.9, 149.4, 139.7, 135.2, 133.8, 133.1, 132.2, 131.5, 127.4, 120.7, 113.1, 111.2, 56.3, 56.2, 51.9, 28.3.

Cyclic imidate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, J = 8.1, 1.7 Hz, 1H), 7.50 (dd, J = 7.8, 1.2 Hz, 1H), 7.43 (ddd, J = 8.1, 7.3, 1.2 Hz, 1H), 7.23 (s, 1H), 7.19 (ddd, J = 7.8, 7.3, 1.7 Hz, 1H), 6.37 (s, 1H), 3.94 (s, 3H), 3.77 (s, 3H), 2.87 (br s, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 153.0, 150.7, 140.4, 139.0, 129.9, 129.7, 129.0, 127.3, 126.0, 121.0, 104.3, 103.6, 91.8, 57.0, 56.3, 56.2, 28.8.

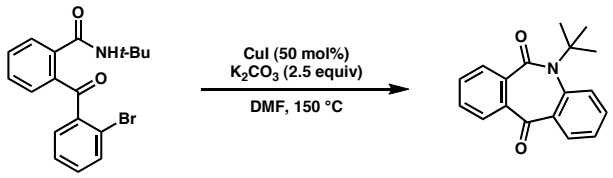
IR (Neat Film, NaCl) 3357, 2966, 2936, 1664, 1593, 1507, 1502, 1463, 1349, 1289, 1272, 1212, 1089 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{20}H_{22}BrNO_4$ $[M+H]^+$: 420.0805, found 420.0817.



***ortho*-Ketobenzamide 669g**

Purified by flash chromatography (SiO_2, 5:95 → 20:80 EtOAc/hexanes) to yield a white solid (64% yield). $R_f = 0.10$ (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.8, 1.2 Hz, 1H), 7.47 (dd, J = 7.6, 2.0 Hz, 1H), 7.39 (td, J = 7.6, 1.2 Hz, 1H), 7.33 (td, J = 7.8, 2.0 Hz, 1H), 7.01 (s, 1H), 6.86 (s, 1H), 6.07 (s, 2H), 5.63 (br s, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 167.4, 150.5, 148.3, 139.7, 135.1, 133.6, 132.1, 131.3, 127.4, 121.4, 120.5, 110.4, 108.7, 102.3, 51.9, 28.4; IR (Neat Film, NaCl) 3317, 2969, 2907, 1654, 1650, 1607, 1503, 1482, 1453, 1367, 1285, 1259, 1226, 1035 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{19}H_{18}BrNO_4$ $[M+H]^+$: 404.0492, found 404.0505.

6.4.2.5 Representative Procedure for the Copper-Catalyzed Intramolecular Coupling of 2-(Ortho-bromobenzoyl)benzamides

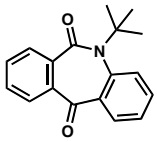


669e ***687a***

A flame-dried 1.5 dram vial containing a magnetic stir bar and sealed with a PTFE/silicone septum and screw cap was charged with copper(I) iodide (0.005 g, 0.028 mmol, 0.5 equiv) and potassium carbonate (0.019 g, 0.137 mmol, 2.5 equiv). The vial was evacuated and backfilled with argon twice. Then ketobenzamide **669e** (0.020 g,

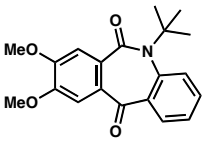
0.056 mmol) in DMF (0.6 mL) was added and the mixture was heated to 150 °C. The solution started as a pale yellow and became progressively brighter yellow over the course of the reaction. After stirring for 24 h, the reaction was cooled to room temperature and filtered through a pad of silica under EtOAc elution. The solvents were removed under reduced pressure and the resulting yellow residue was purified via flash chromatography over silica gel.

6.4.2.6 Spectroscopic Data for Dibenzoketocaprolactams



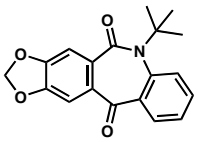
Dibenzoketocaprolactam 687a

Purified by flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield a white solid (85% yield). R_f = 0.50 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (ddd, J = 7.8, 1.2, 0.7 Hz, 1H), 7.57 (ddd, J = 7.8, 6.4, 2.5 Hz, 1H), 7.53 (d, J = 1.7 Hz, 1H), 7.52 (dd, J = 7.6, 1.2 Hz, 1H), 7.42–7.37 (comp m, 2H), 7.40 (dd, J = 6.1, 1.5 Hz, 1H), 7.31–7.27 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 166.9, 142.1, 141.1, 137.3, 133.5, 132.2, 131.9, 131.8, 130.1, 127.9, 127.3, 126.0, 125.8, 60.9, 30.0; IR (Neat Film, NaCl) 2974, 1689, 1647, 1592, 1483, 1446, 1340, 1280, 1188 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{18}H_{17}NO_2$ $[M+H]^+$: 280.1332, found 280.1340.



Dibenzoketocaprolactam 687b

Purified by flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield a pale yellow oil (61% yield). R_f = 0.30 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.44 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 7.42 (ddd, *J* = 7.6, 1.7, 1.5 Hz, 1H), 7.39 (app td, *J* = 6.8, 1.7 Hz, 1H), 7.29 (ddd, *J* = 7.6, 6.8, 1.7 Hz, 1H), 7.08 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 166.7, 151.8, 151.5, 141.6, 137.2, 134.6, 130.0, 127.6, 127.4, 127.0, 126.3, 113.9, 108.4, 60.9, 56.3, 56.2, 30.1; IR (Neat Film, NaCl) 2969, 2935, 1674, 1645, 1589, 1514, 1447, 1360, 1331, 1286, 1219, 1185, 1077 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{21}NO_4$ $[M^{\bullet}]^+$: 339.1471, found 339.1484.

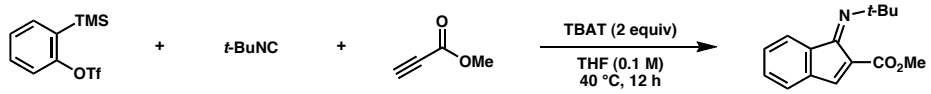


Dibenzoketocaprolactam 687c

Purified by flash chromatography (SiO_2, 5:95 EtOAc/hexanes) to yield a yellow oil (73% yield). R_f = 0.40 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.39 (app dd, *J* = 2.7, 1.0 Hz, 2H), 7.38 (dd, *J* = 5.9, 1.5 Hz, 1H), 7.29 (t, *J* = 3.7 Hz, 1H), 7.00 (s, 1H), 6.05 (d, *J* = 9.5 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 166.1, 150.8, 150.4, 141.7, 137.1, 136.8, 129.9, 127.7, 127.1, 126.1, 111.6, 105.9, 102.4, 60.9, 30.0; IR (Neat Film, NaCl) 2973, 2909, 1679, 1645, 1608, 1593, 1483, 1448, 1373,

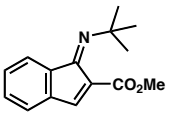
1332, 1282, 1187, 1037 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{17}NO_4$ $[M+H]^+$: 324.1230, found 324.1241.

6.4.2.7 Representative Procedure for the Three-Component Synthesis of Iminoindenones from Arynes, Isocyanides, and Alkynes



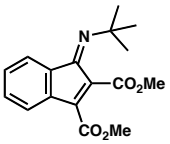
A flame-dried 15 mL round bottomed flask with a magnetic stir bar was charged with TBAT (0.607 g, 1.124 mmol, 2.0 equiv) and THF (3 mL). To this solution was added methyl propiolate (**452**) (0.05 mL, 0.562 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**71**) (0.204 mL, 0.843 mmol, 1.5 equiv), and *tert*-butylisocyanide (**670**) (0.095 mL, 0.843 mmol, 1.5 equiv), each via syringe. The reaction was heated to 40 °C under argon for 12 h, at which point TLC analysis showed complete consumption of aryne precursor. The reaction was cooled to room temperature, and then concentrated on celite. The crude suspension was purified by flash chromatography over silica gel.

6.4.2.8 Spectroscopic Data for Iminoindenones



Iminoindenone 691

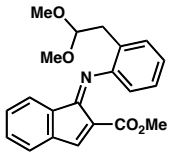
Purified by flash chromatography (SiO_2, 5:95 EtOAc/hexanes) to yield a yellow solid (88% yield). R_f = 0.66 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{15}H_{17}NO_2$ [M+]: 243.1259, found 243.1260.



Iminoindenone 698a

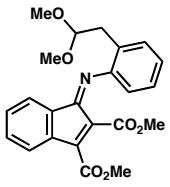
Purified by flash chromatography (SiO_2, 10:90 EtOAc/hexanes) to yield a white solid (83% yield). R_f = 0.38 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6,

54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{17}H_{19}NO_4$ $[M]^+$: 301.1314, found 301.1315.



Iminoindenone 698b

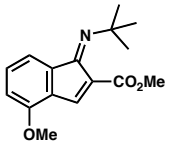
Purified by flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a yellow oil (66% yield). R_f = 0.39 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.75 Hz, 2H), 7.56-7.50 (m, 3H), 7.35 (d, J = 7.24 Hz, 1H), 7.28 (t, J = 7.83 Hz, 1H), 7.19 (t, J = 7.24 Hz, 1H), 7.02 (d, J = 7.24 Hz, 1H) 4.53 (t, J = 5.85 Hz, 1H), 3.79 (s, 3H), 3.29 (s, 6H), 2.97 (d, J = 5.85); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.00, 149.04, 147.04, 135.96, 131.79, 130.88, 129.21, 128.64, 127.99, 126.96, 126.02, 118.65, 104.82, 85.55, 77.74, 53.74, 53.11, 35.85; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{21}H_{21}NO_4$ $[M]^+$: 351.1471, found 351.1457.



Iminoindenone 698c

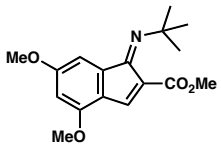
Purified by flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a yellow solid (91% yield). R_f = 0.57 (20:80 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 6.51 Hz, 1H), 7.68-7.61 (m, 3H), 7.31 (d, J = 7.50 Hz, 1H), 7.26 (t, J = 6.51 Hz, 2H) 7.11 (t, J = 6.93 Hz, 1H), 4.62 (t, J = 4.98, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.31 (s, 3H),

3.30 (s, 3H), 3.04 (t, J = 7.07 Hz, 2H; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2939, 2832, 1722, 1598, 1489, 1435, 1337, 1281, 1258, 1088, 1060, 982, 1060, 758 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{23}H_{23}NO_6$ $[M+H]^+$: 409.1525, found 410.1524.



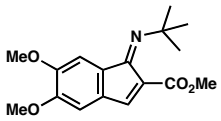
Iminoindenone 698d

Purified by flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a yellow oil (66% yield). R_f = 0.41 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.97 Hz, 1H), 7.54 (s, 1H), 7.37 (t, J = 7.97 Hz, 1H), 6.98 (d, J = 7.97 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.63, 153.55, 144.13, 139.43, 129.31, 119.96, 116.74, 111.76, 87.92, 78.63, 57.75, 55.35, 53.14, 29.61; IR (Neat Film, NaCl) 2969, 215, 1720, 1602, 1576, 1486, 1466, 1433, 1362, 1275, 1252, 1206, 1175, 1043, 983, 914, 879, 790, 748 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{16}H_{19}NO_3$ $[M+H]^+$: 274.1365, found 274.1454



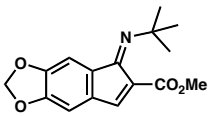
Iminoindenone 698e

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (79% yield). R_f = 0.41 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{17}H_{21}NO_4$ $[M+H]^+$: 304.1471, found 304.1560.



Iminoindenone 698f

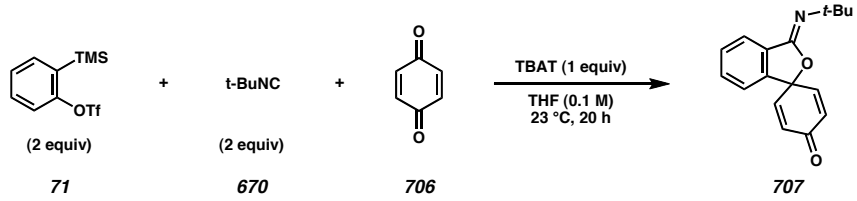
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (54% yield). R_f = 0.22 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{17}H_{21}NO_4$ $[M+H]^+$: 304.1471, found 304.1552.



Iminoindenone 698g

Purified by flash chromatography (SiO_2, 10:90 EtOAc/hexanes) to yield a white solid (56% yield). R_f = 0.46 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.51 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.00 (s, 2H), 3.88 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 148.0, 143.3, 132.9, 122.6, 110.0, 107.7, 106.7, 101.5, 87.7, 78.3, 57.4, 53.1, 29.7; IR (Neat Film, NaCl) 2697, 2217, 1718, 1576, 1504, 1488, 1444, 1362, 1275, 1257, 1207, 1117, 1039, 980, 937, 918, 812, 748 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{16}H_{17}NO_4$ $[M+H]^+$: 288.1158, found 288.1227.

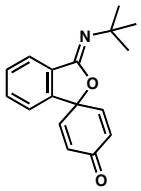
6.4.2.9 Representative Procedure for the Three-Component Synthesis of Spirocycles from Arynes, Isocyanides, and Quinones



A flame-dried 1.5 dram vial with a magnetic stir bar was charged with TBAT (0.162 g, 0.300 mmol, 2.0 equiv), 1,4-benzoquinone (**706**) (0.0165g, 0.153 mmol) and THF (1.5 mL). To this solution was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**71**) (0.073 mL, 0.301 mmol, 2.0 equiv) and *tert*-butylisocyanide (**670**) (0.034 mL, 0.301 mmol, 2.0 equiv), each via syringe. The reaction was stirred at 23 °C under argon for 20 h, at which point TLC analysis showed complete consumption of benzoquinone. The reaction was then passed over a plug of silica (3 cm diam. x 3 cm length) eluting with

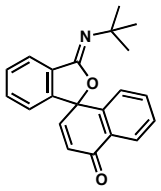
25:75 EtOAc/hexanes in order to remove excess TBAT from solution. The solvents were removed under reduced pressure and the crude residue was purified by flash chromatography over silica gel.

6.4.2.10 Spectroscopic Data for Spirocycles



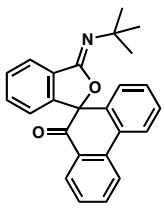
Spirocycle 707

Reaction performed at 23 °C. Purified by flash chromatography (SiO_2, 5:95 → 15:85 EtOAc/hexanes) to yield a pale yellow solid (60% yield). R_f = 0.13 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (ddd, J = 6.1, 2.7, 0.7 Hz, 1H), 7.52–7.46 (comp m, 2H), 7,13 (ddd, J = 6.1, 2.7, 0.7 Hz, 1H), 6.69 (dd, J = 8.1, 2.0 Hz, 2H), 6.35 (dd, J = 8.1, 2.0 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 153.4, 146.2, 142.1, 132.3, 131.8, 129.9, 128.7, 124.7, 121.7, 82.2, 54.3, 30.0; IR (Neat Film, NaCl) 2967, 1696, 1672, 1635, 1463, 1285, 1214, 1062 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{17}H_{17}NO_2$ $[M–H]^-$: 266.1187, found 266.1183.



Spirocycle 709

Reaction performed at 23 °C. Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a yellow solid (57% yield). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.89 (dd, *J* = 6.6, 1.0 Hz, 1H), 7.49 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.48 (dd, *J* = 6.1, 1.7 Hz, 1H), 7.45 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.39 (td, *J* = 7.57, 1.2 Hz, 1H), 7.06 (dd, *J* = 7.1, 2.0 Hz, 1H), 6.91 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.82 (d, *J* = 10.0 Hz, 1H), 6.53 (d, *J* = 10.3 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 154.4, 146.6, 145.8, 141.8, 133.4, 131.9, 131.5, 129.9, 129.4, 128.8, 128.6, 126.8, 126.7, 124.4, 121.9, 83.4, 54.2, 30.0; IR (Neat Film, NaCl) 2966, 1701, 1672, 1601, 1457, 1298, 1286, 1214, 1076 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{21}H_{19}NO_2$ [M+H]: 318.1489, found 318.1481.



Spirocycle 711

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a yellow solid (83% yield). R_f = 0.20 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 7.3 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.78 (ddd, *J* = 8.1, 7.3, 1.5 Hz, 1H), 7.46 (ddd, *J* = 7.6, 1.7, 1.0 Hz, 1H), 7.45

(ddd, J = 7.3, 1.7, 1.2 Hz, 1H), 7.37 (dd, J = 7.8, 1.5 Hz, 1H), 7.34 (dd, J = 7.3, 1.2 Hz, 1H), 7.32 (dd, J = 7.6, 1.5 Hz, 1H), 7.16 (app td, J = 7.6, 1.2 Hz, 1H), 6.75 (dd, J = 7.8, 1.0 Hz, 1H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.8, 155.2, 144.6, 137.6, 137.2, 135.5, 131.2, 130.4, 129.8, 129.6, 129.3, 129.2, 128.9, 128.7, 128.6, 126.0, 124.8, 124.6, 123.4, 120.9, 91.3, 54.4, 30.0; IR (Neat Film, NaCl) 2966, 1708, 1601, 1451, 1360, 1270, 1214, 1065 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{25}H_{21}NO_2$ [M+H]: 368.1645, found 368.1639.

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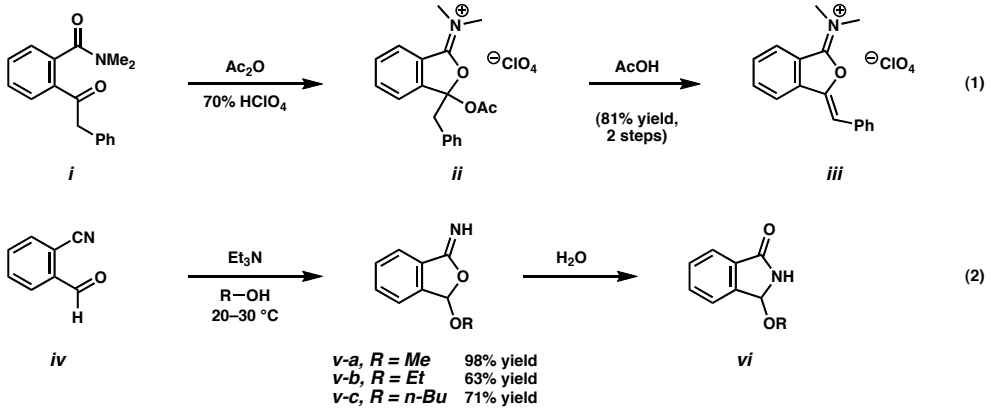

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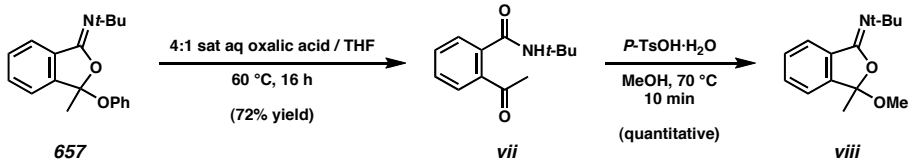

657 ***vii*** ***viii***

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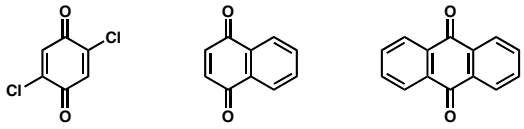
However, the authors noted that quinones **ix–xi** failed to react under their conditions. See ref. 17.



ix ***x*** ***xi***

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APPENDIX 6

Spectra Relevant to Chapter 6:

Multicomponent Aryne Reactions

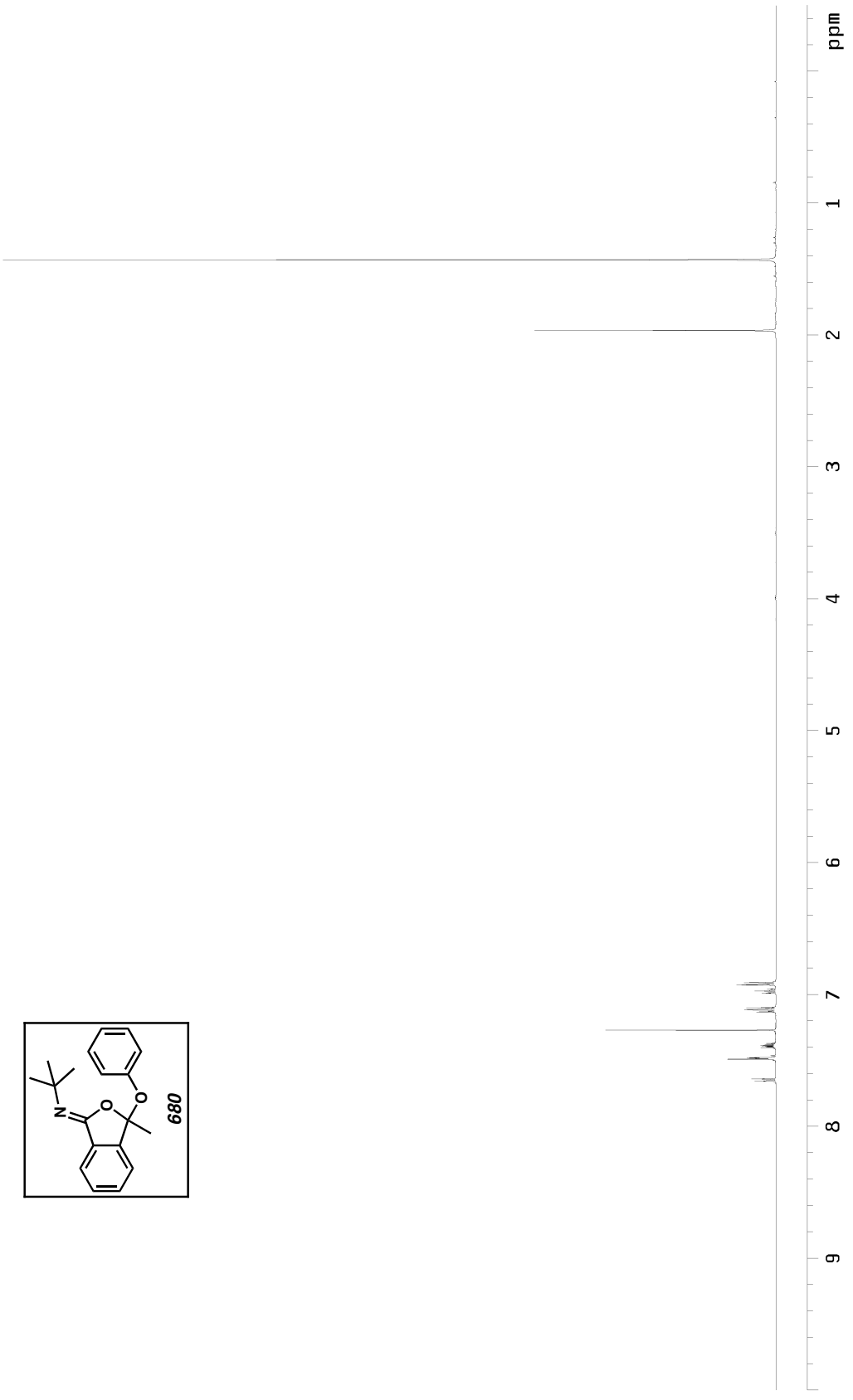


Figure A6.1.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **680**.

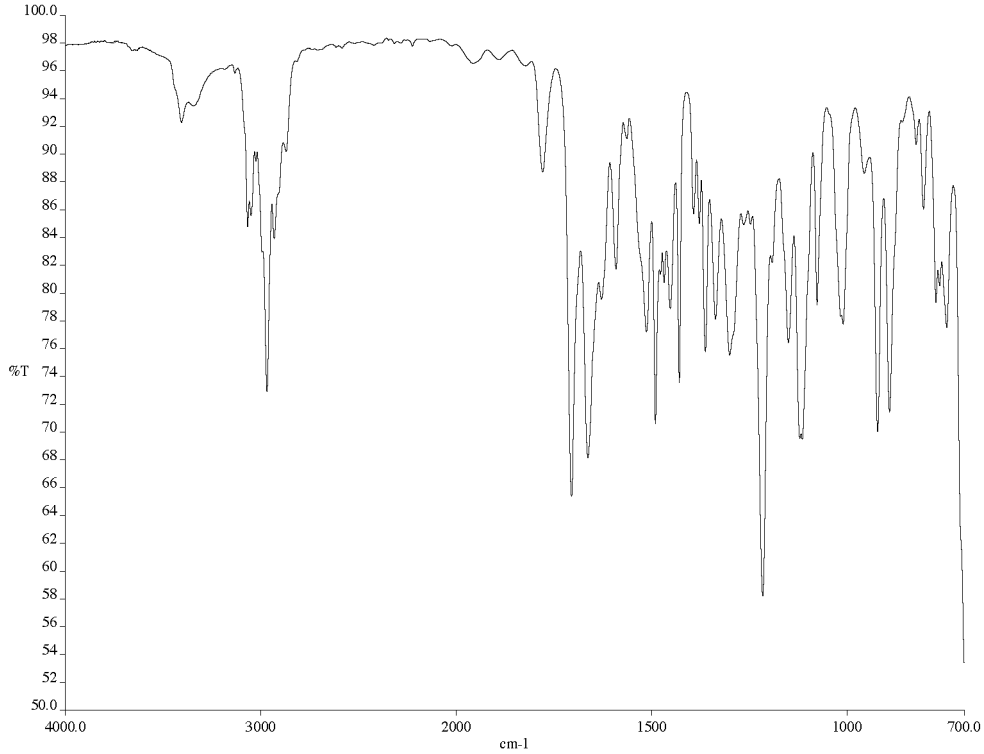


Figure A6.1.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **680**.

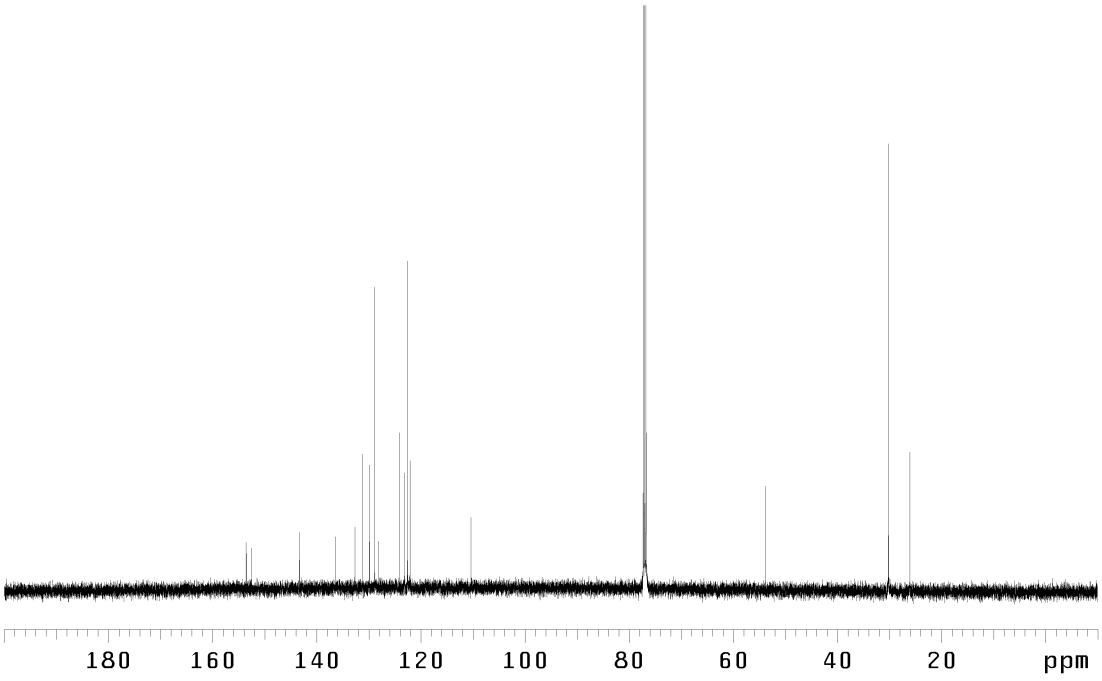


Figure A6.1.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **680**.

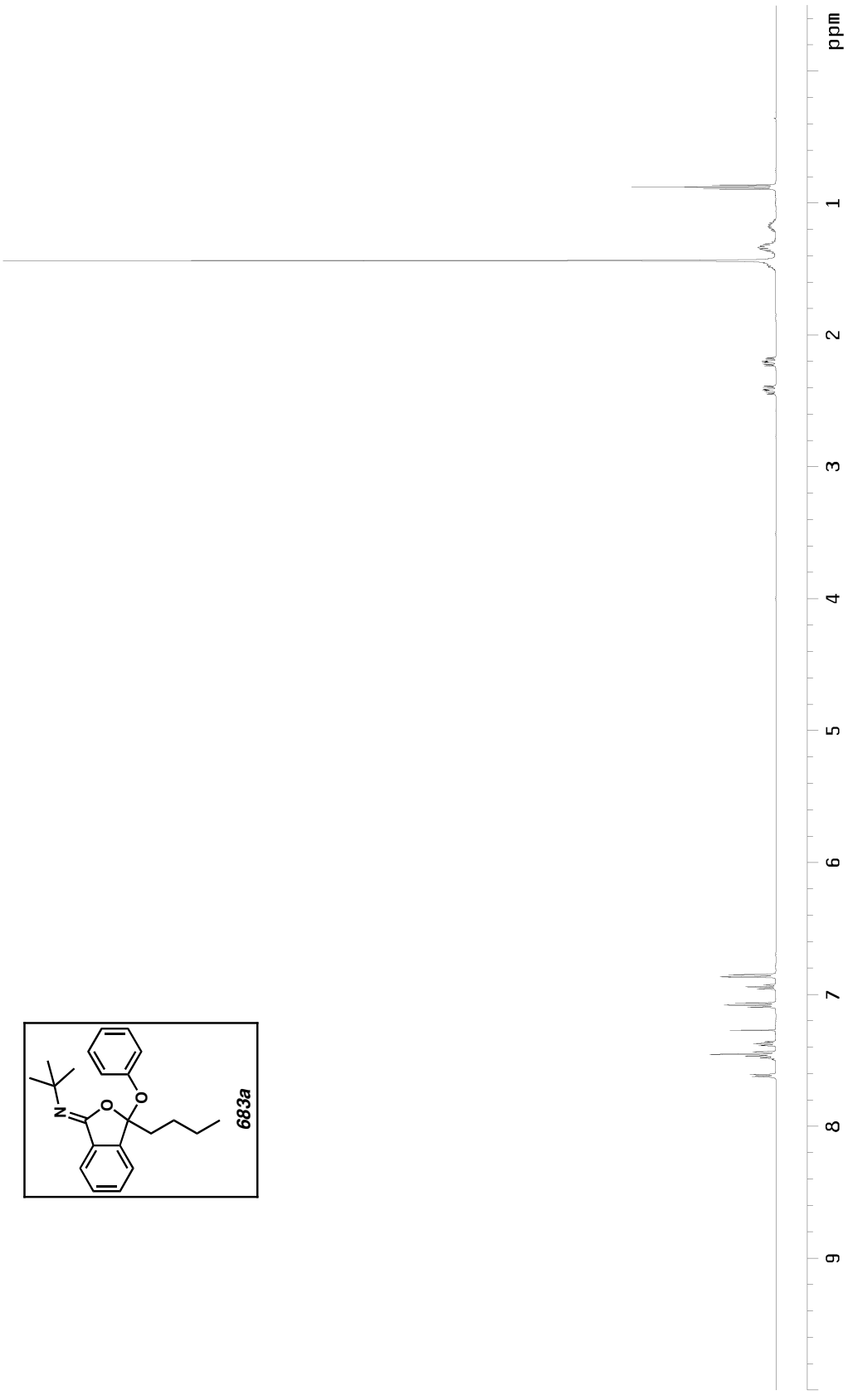


Figure A6.2.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683a**.

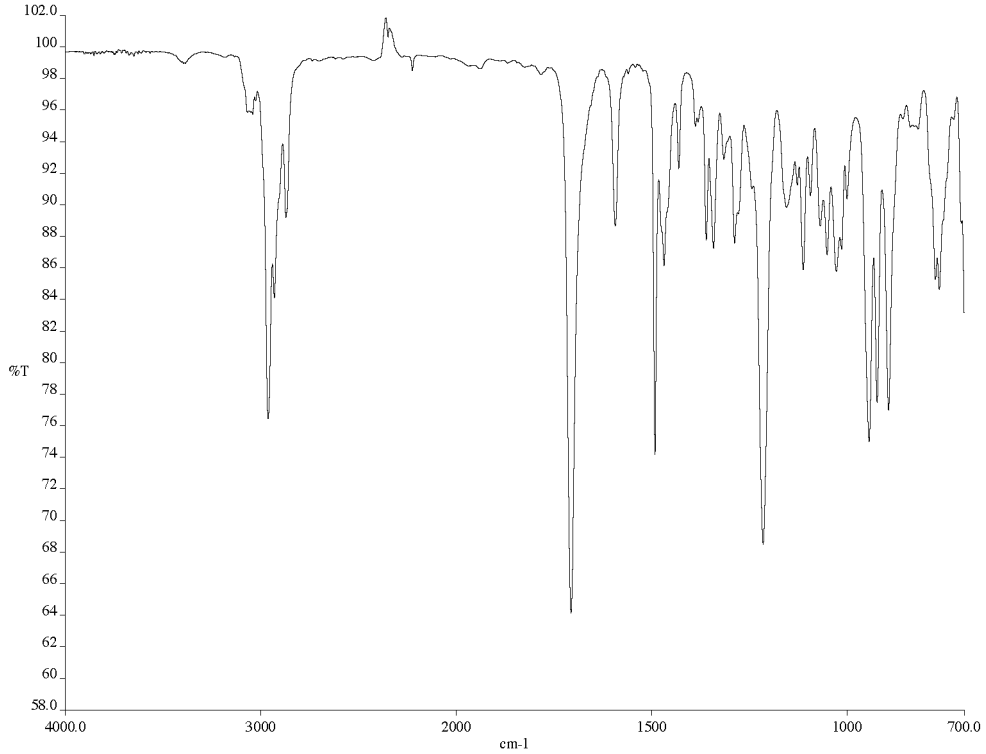


Figure A6.2.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683a**.

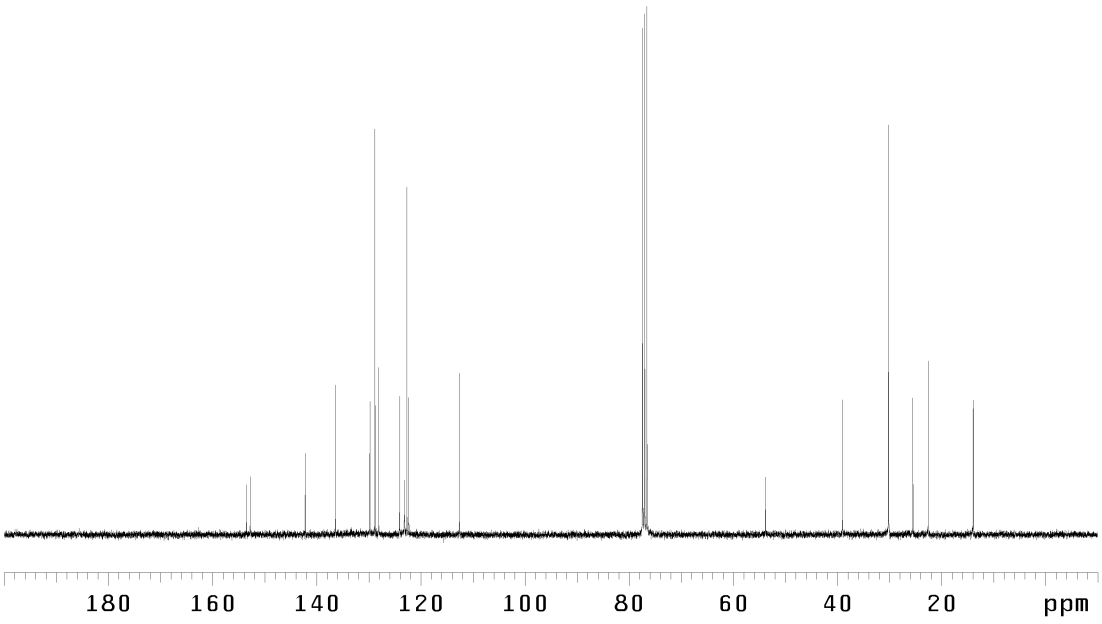


Figure A6.2.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683a**.

Figure A6.3.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683b**.

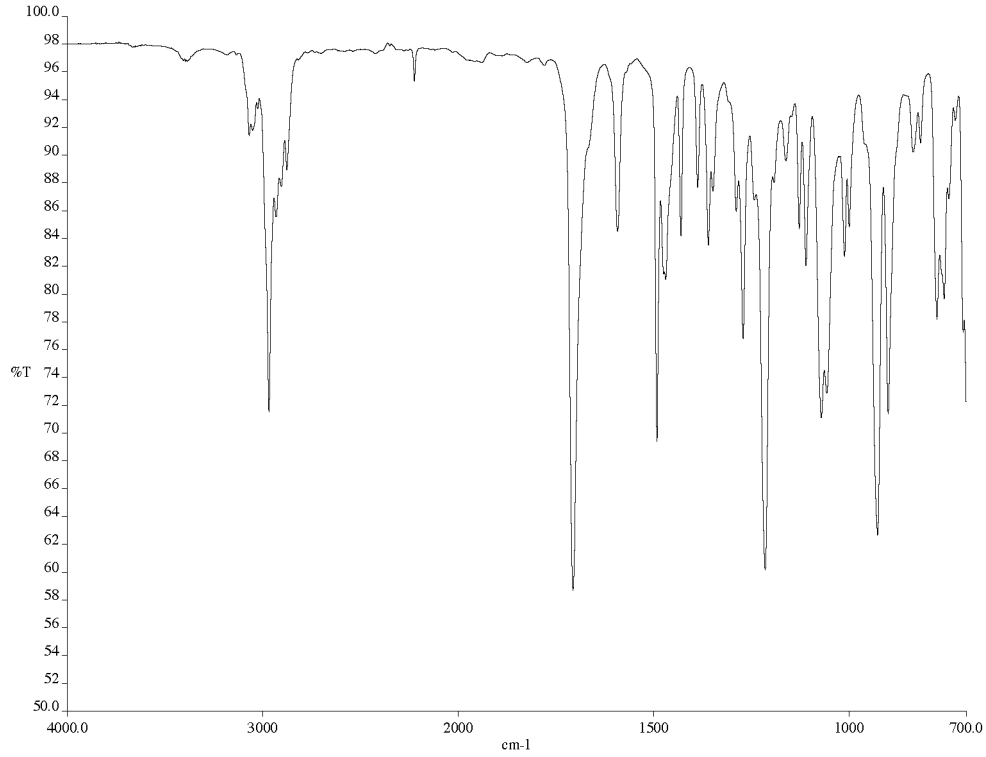


Figure A6.3.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683b**.

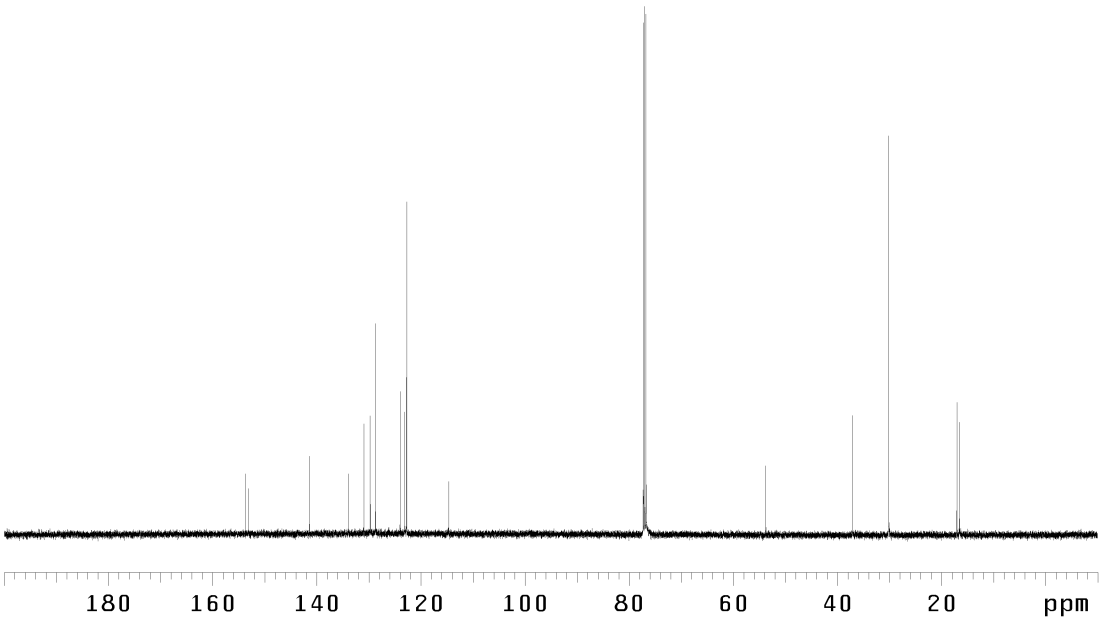


Figure A6.3.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683b**.

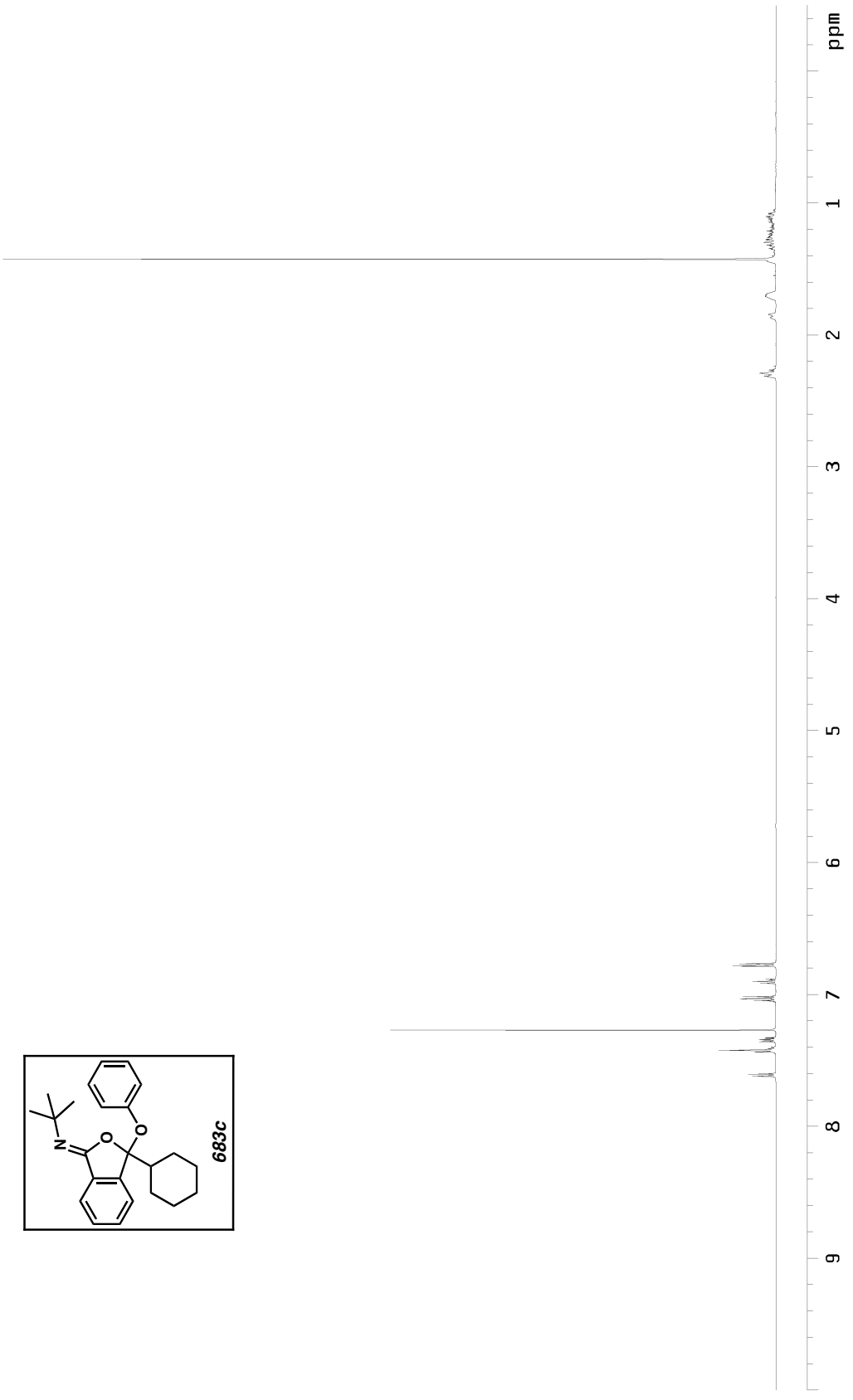


Figure A6.4.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683c**.

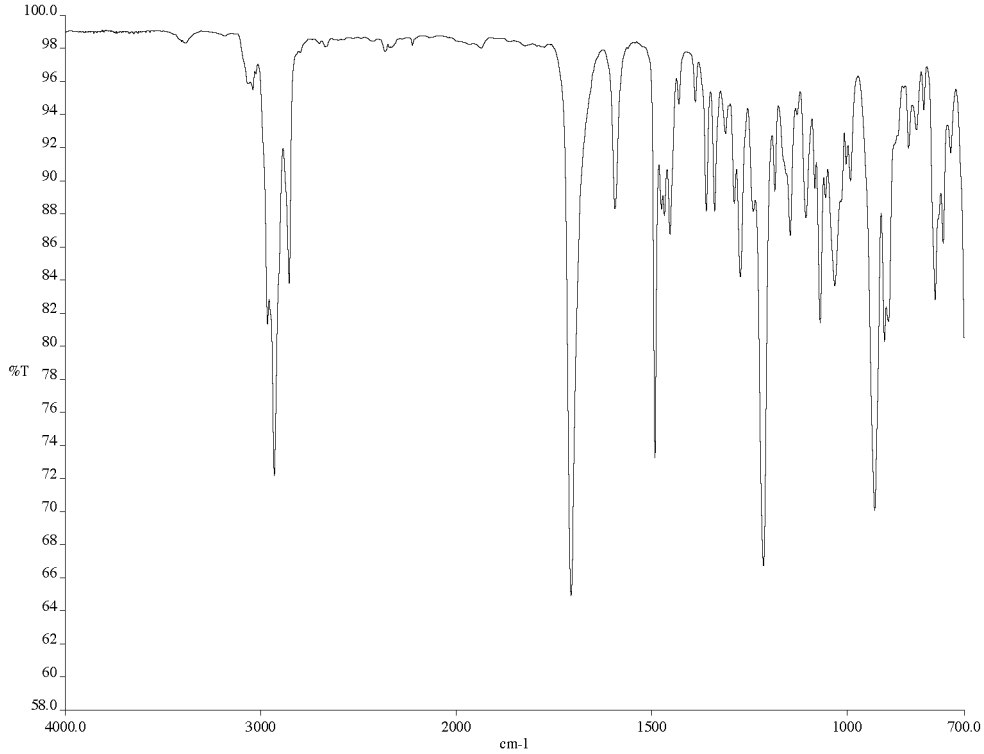


Figure A6.4.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683c**.

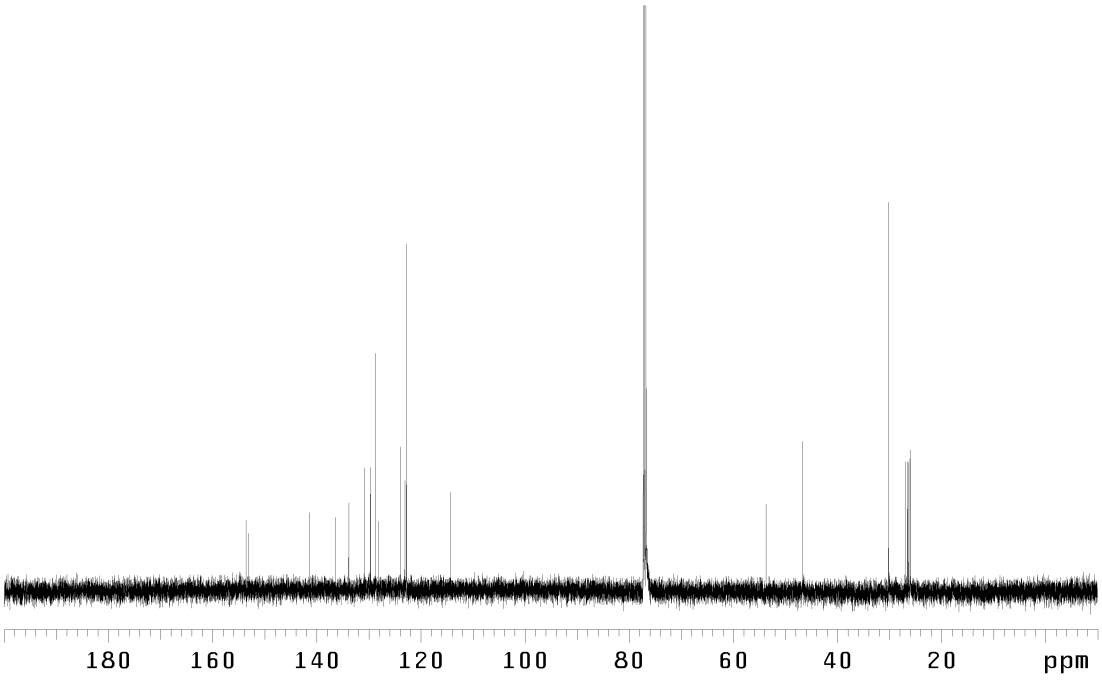


Figure A6.4.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683c**.

Figure A6.5.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683d**.

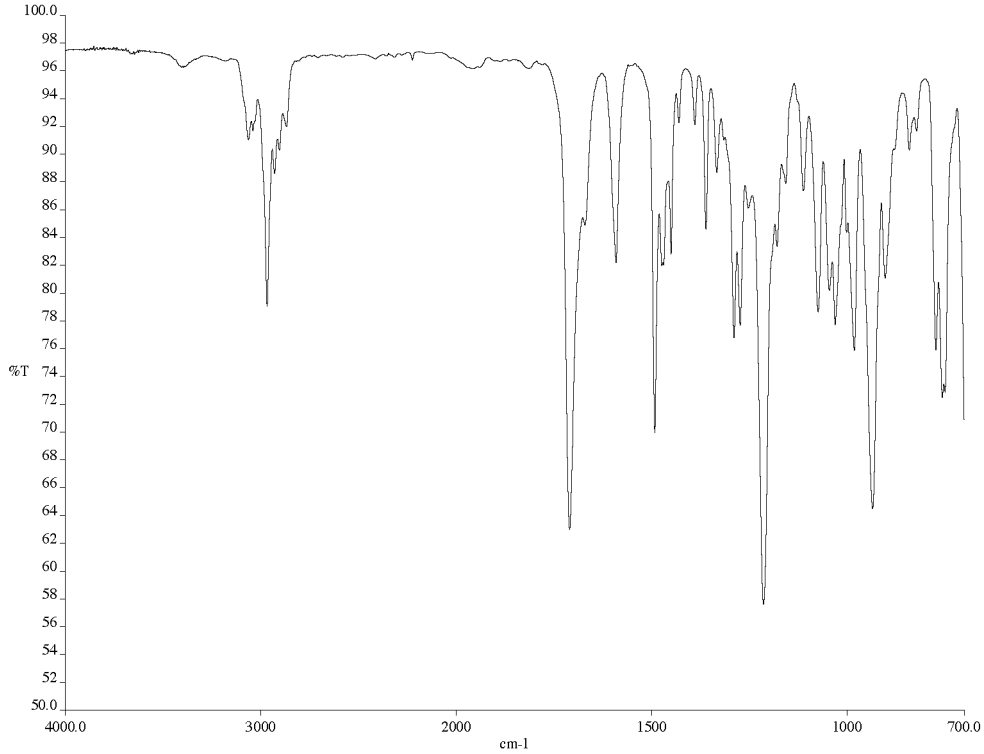


Figure A6.5.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683d**.

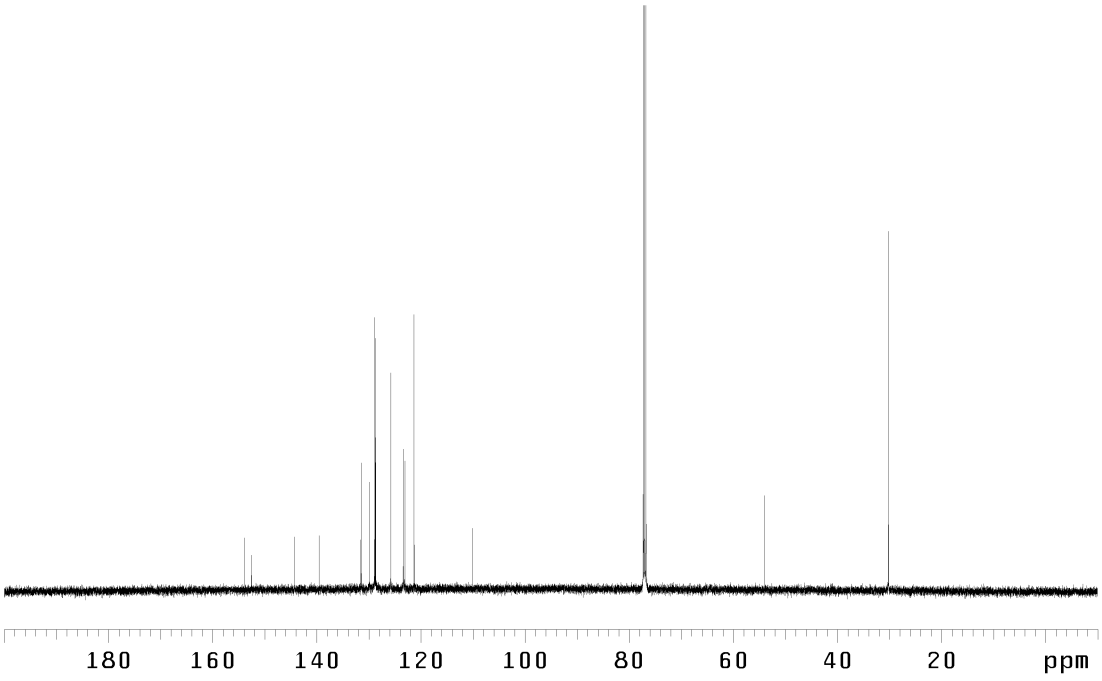


Figure A6.5.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683d**.

Figure A6.6.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683e**.

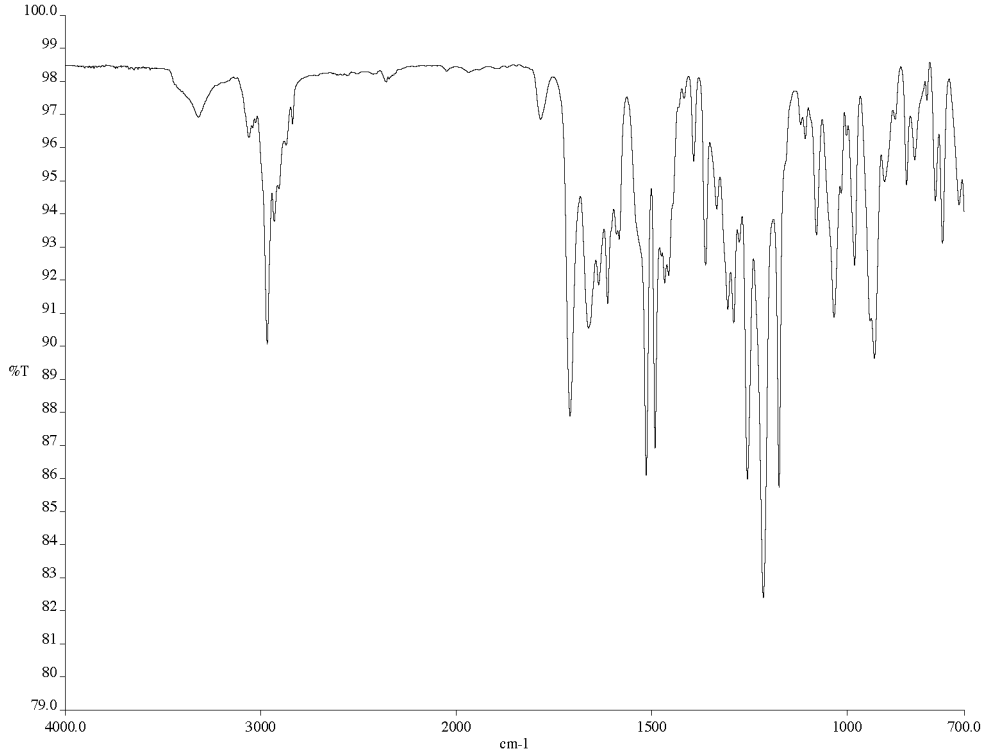


Figure A6.6.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683e**.

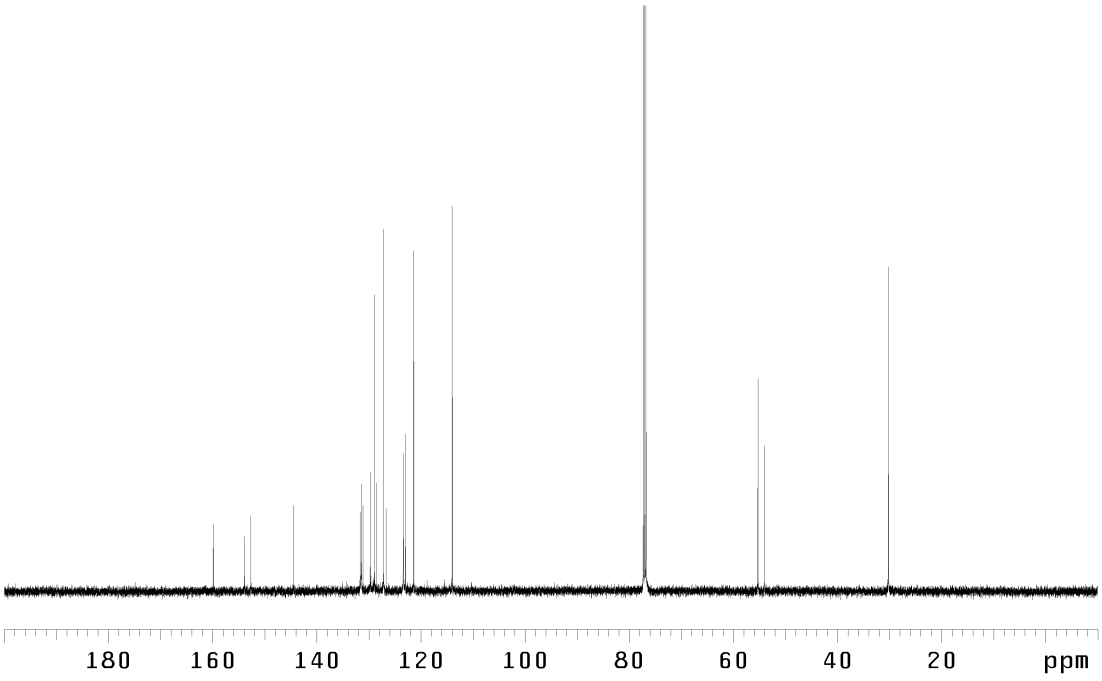


Figure A6.6.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683e**.

Figure A6.7.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683f**.

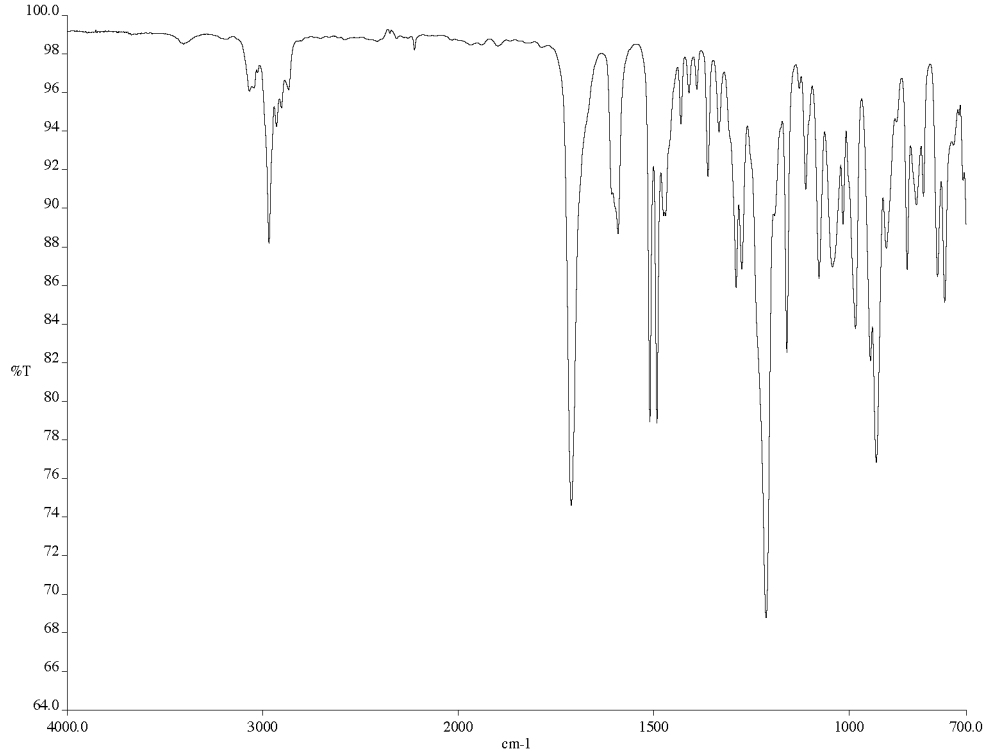


Figure A6.7.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683f**.

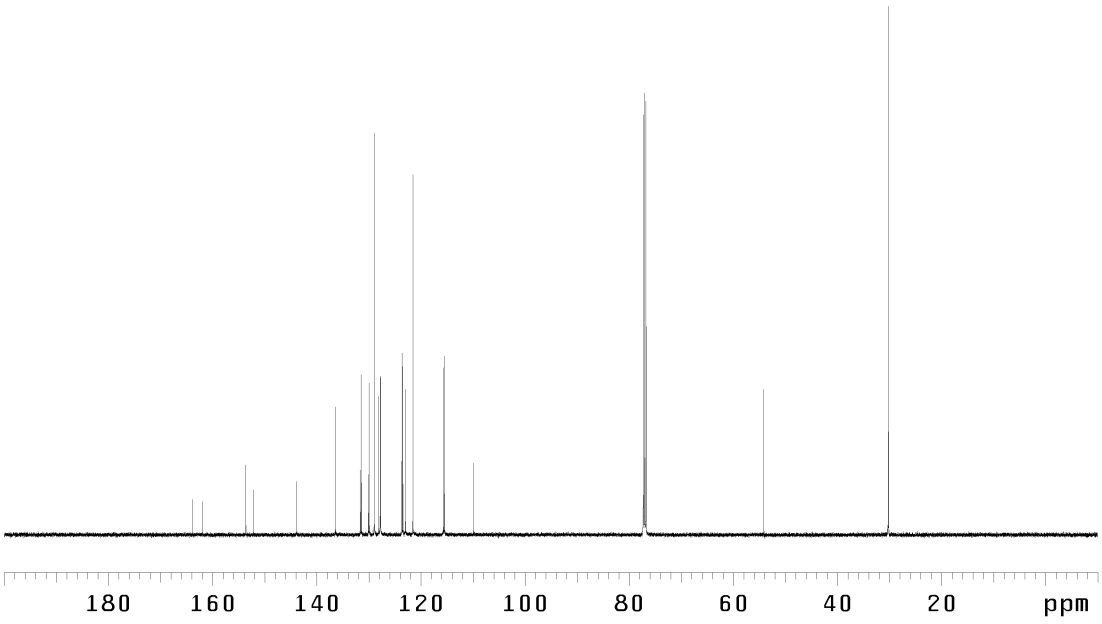


Figure A6.7.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683f**.

Figure A6.8.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683g**.

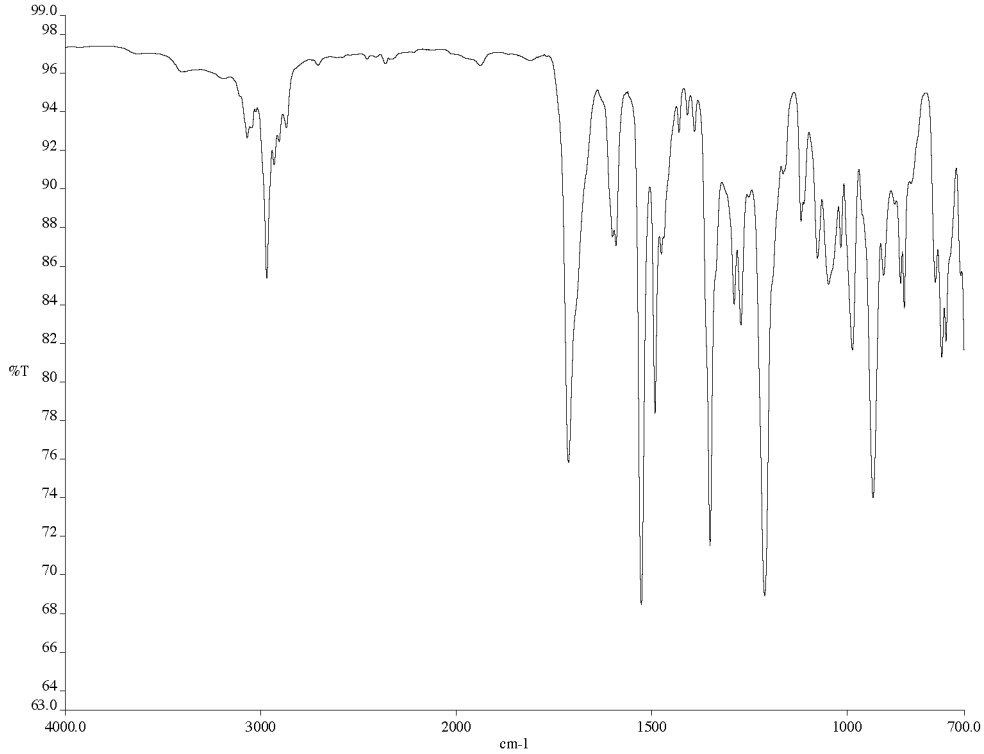


Figure A6.8.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683g**.

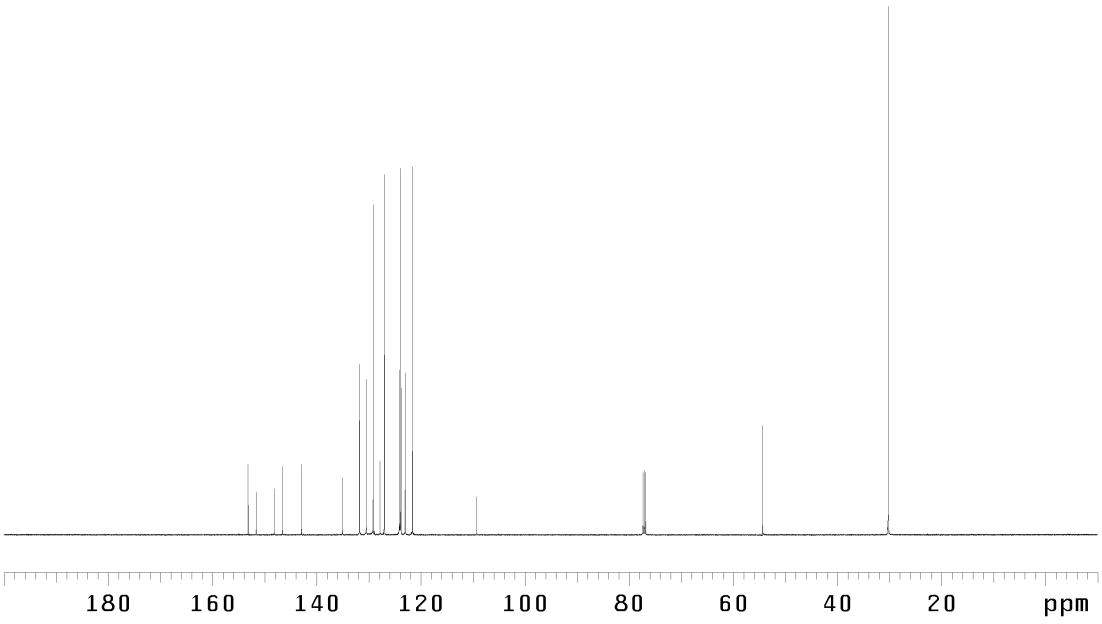


Figure A6.8.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683g**.

Figure A6.9.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683h**.

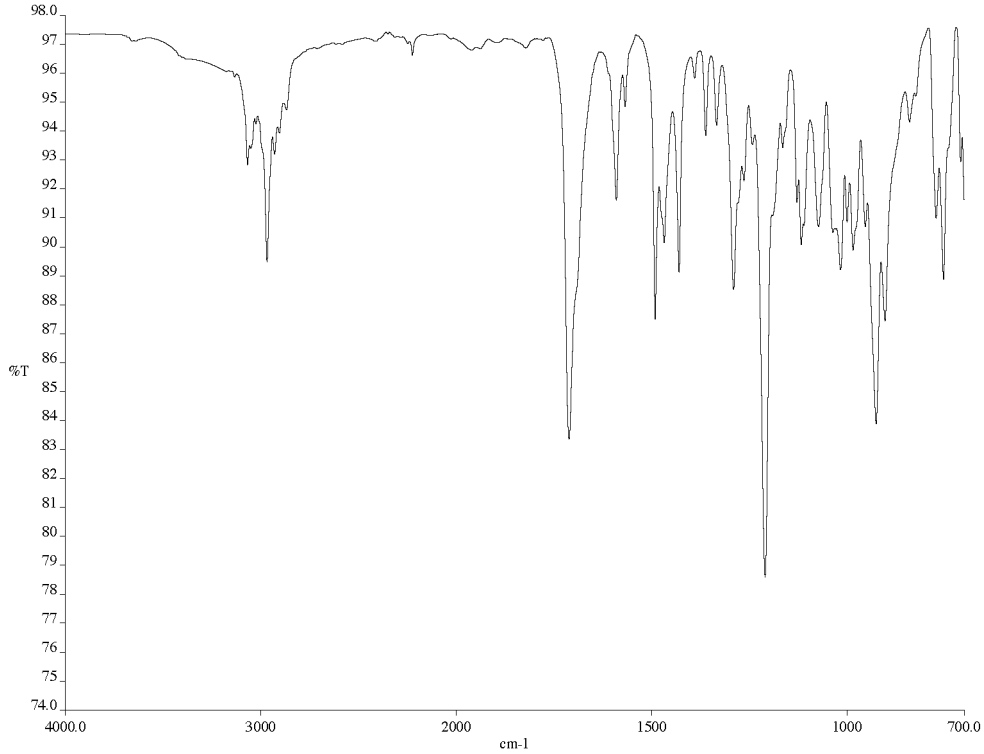


Figure A6.9.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683h**.

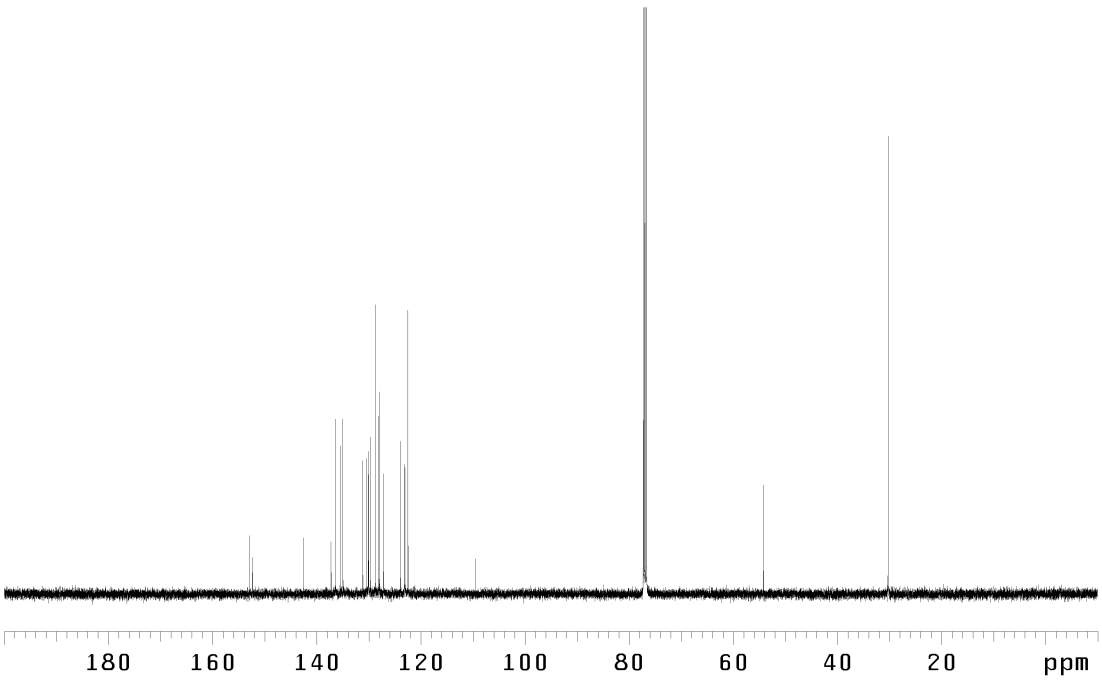


Figure A6.9.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683h**.

Figure A6.10.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683i**.

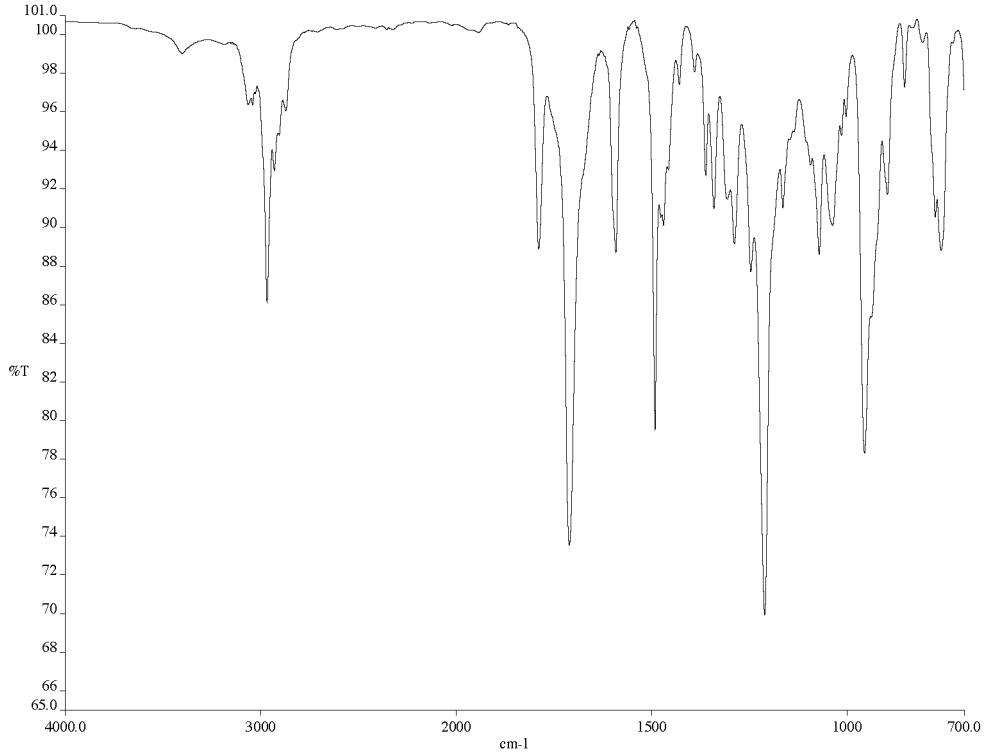


Figure A6.10.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683i**.

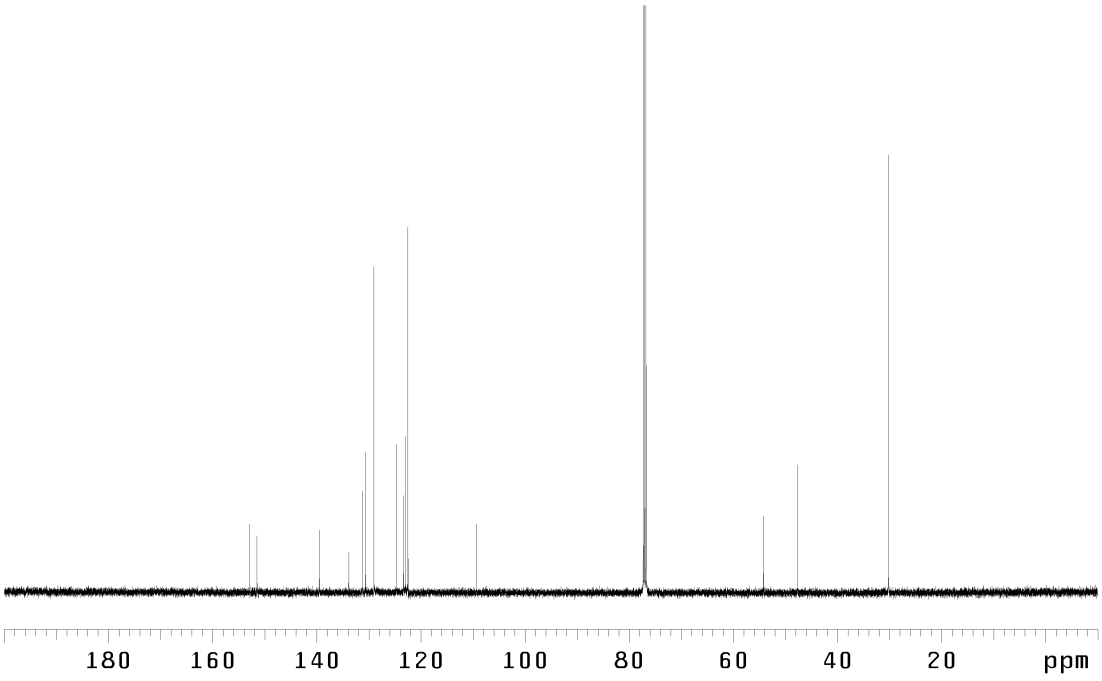


Figure A6.10.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683i**.

Figure A6.11.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683j**.

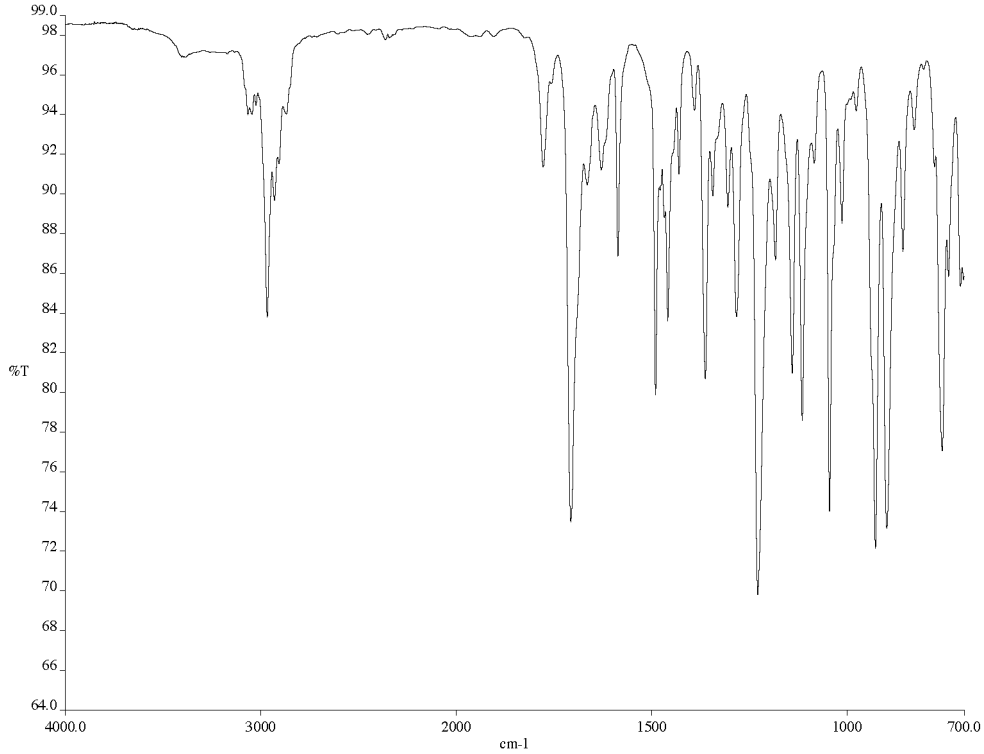


Figure A6.11.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683j**.

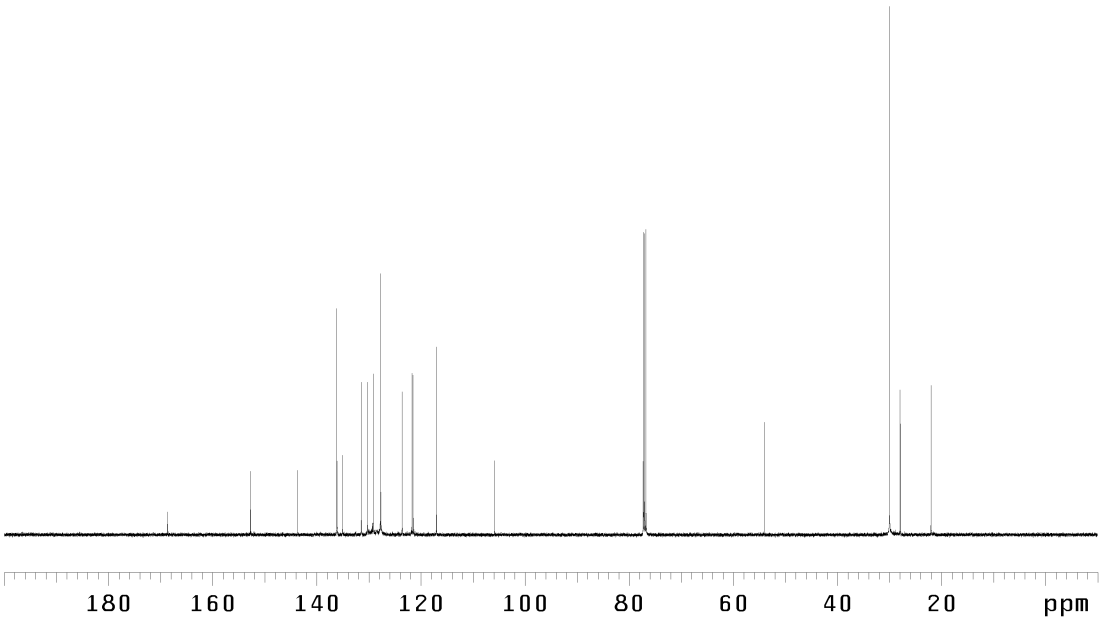


Figure A6.11.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683j**.

Figure A6.12.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683k**.

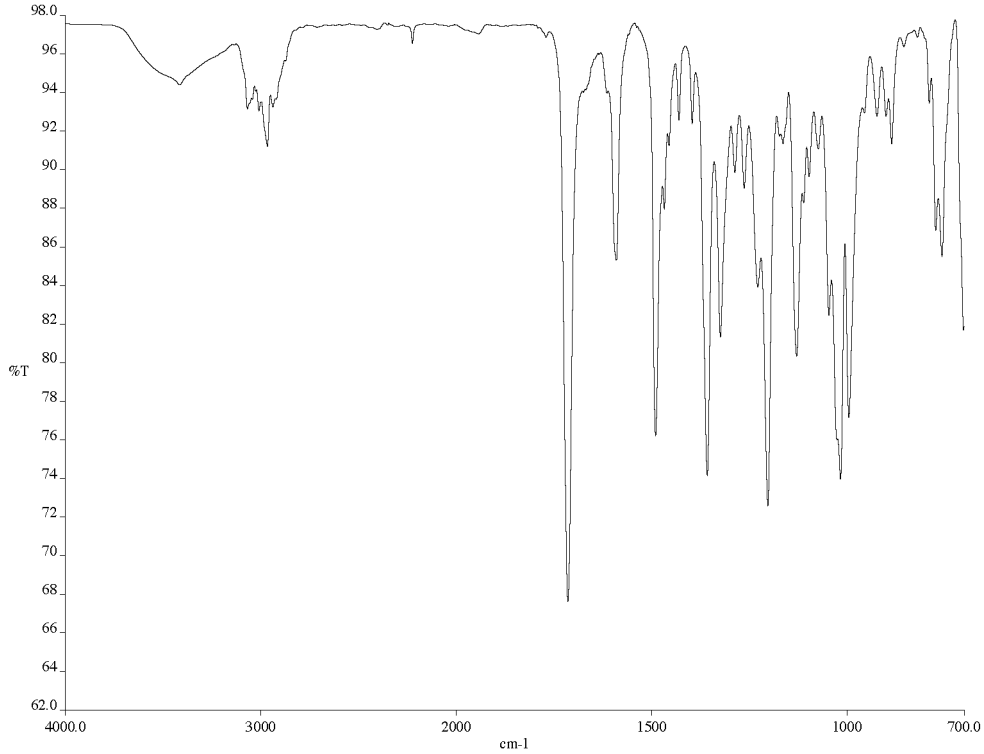


Figure A6.12.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683k**.

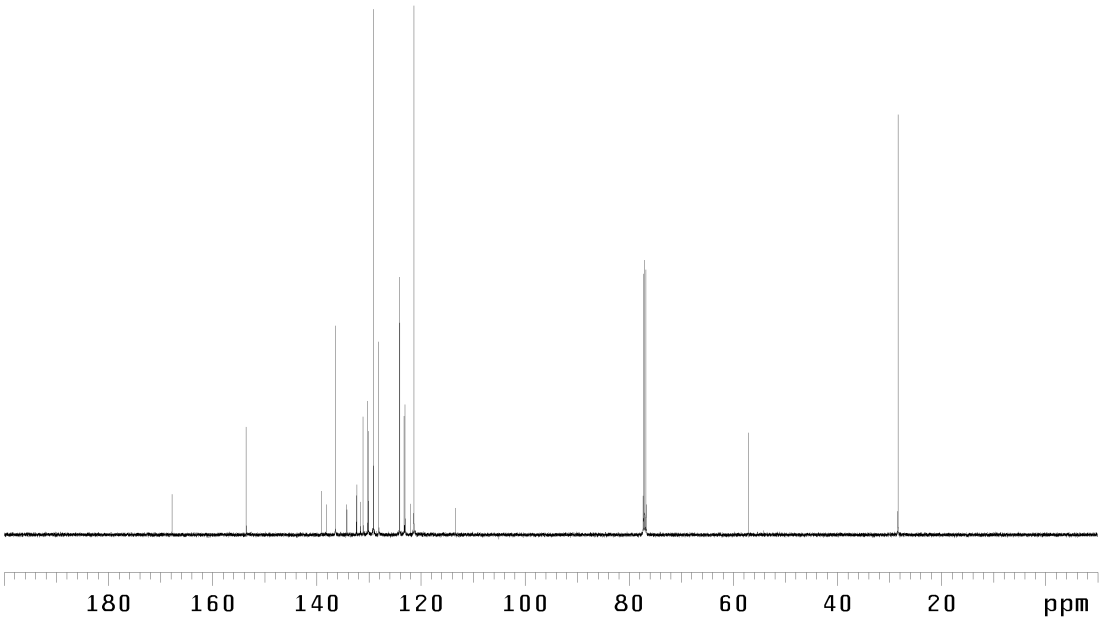


Figure A6.12.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683k**.

Figure A6.13.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **6831**.

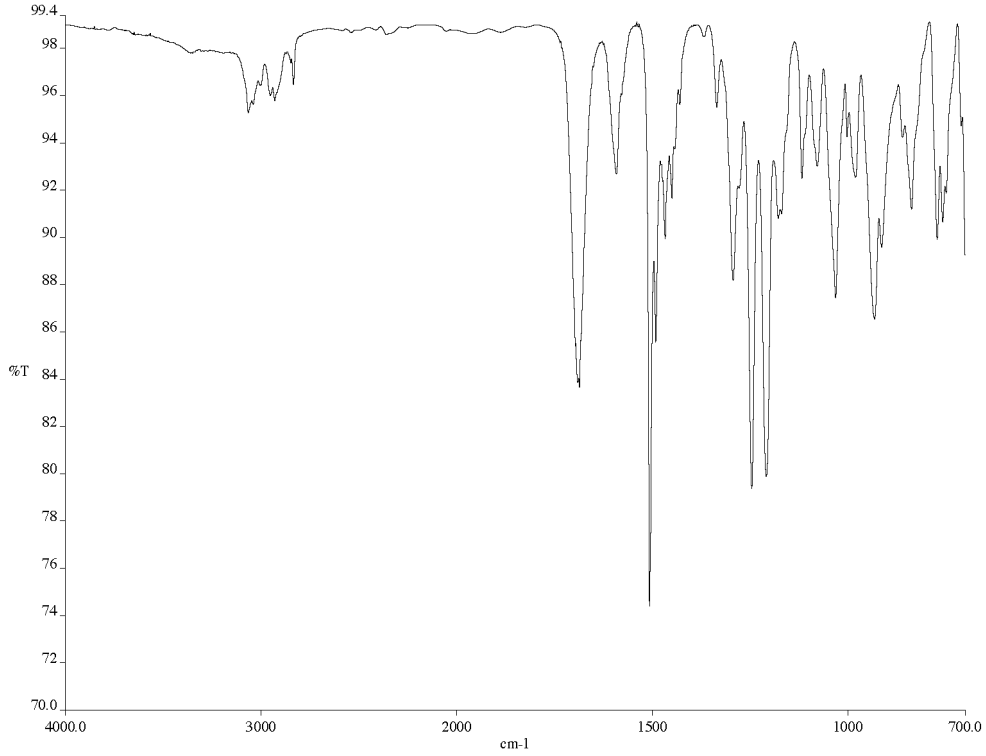


Figure A6.13.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683l**.

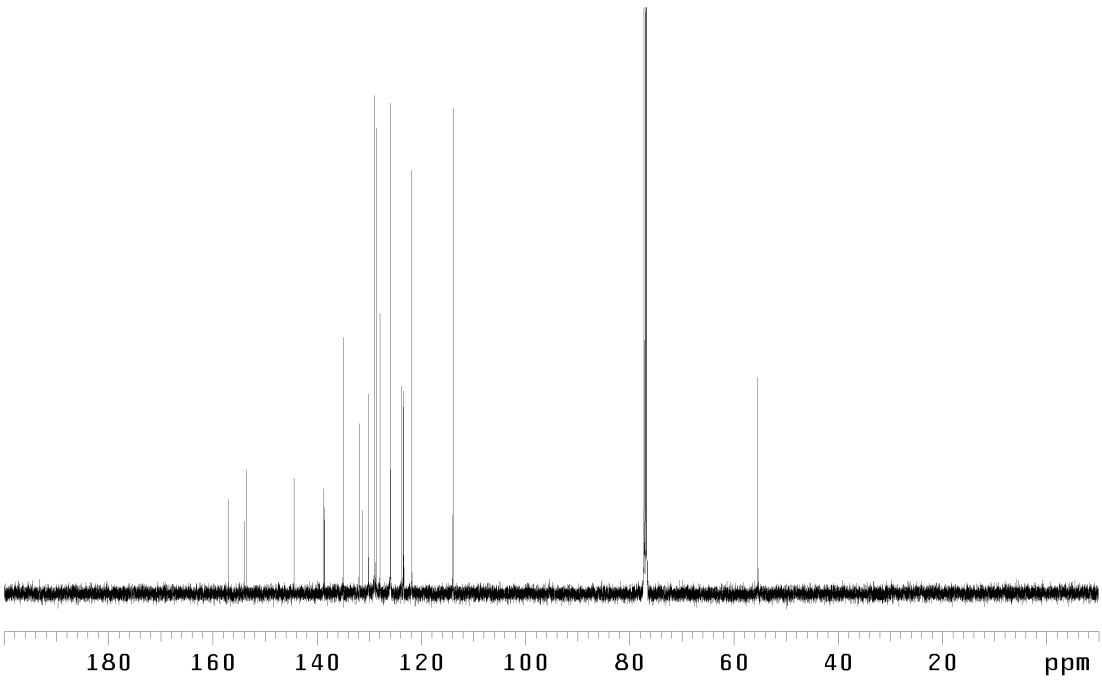


Figure A6.13.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683l**.

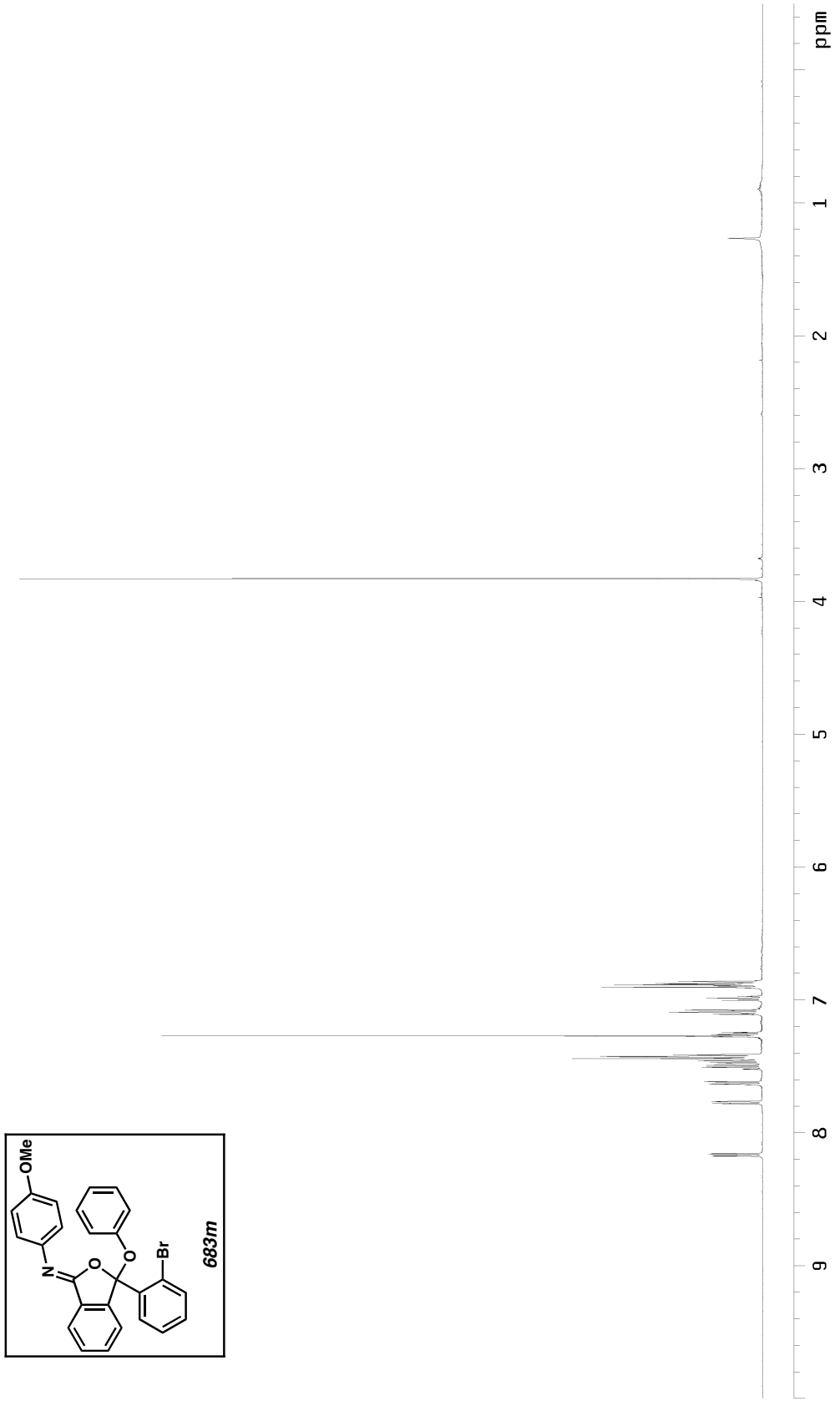


Figure A6.14.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683m**.

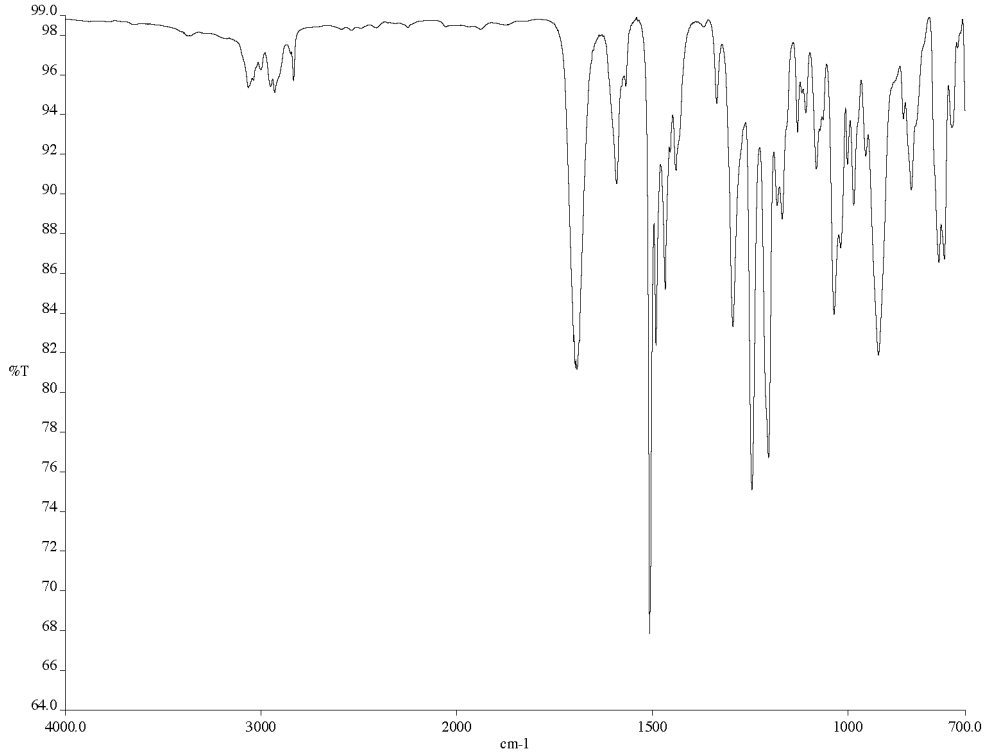


Figure A6.14.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683m**.

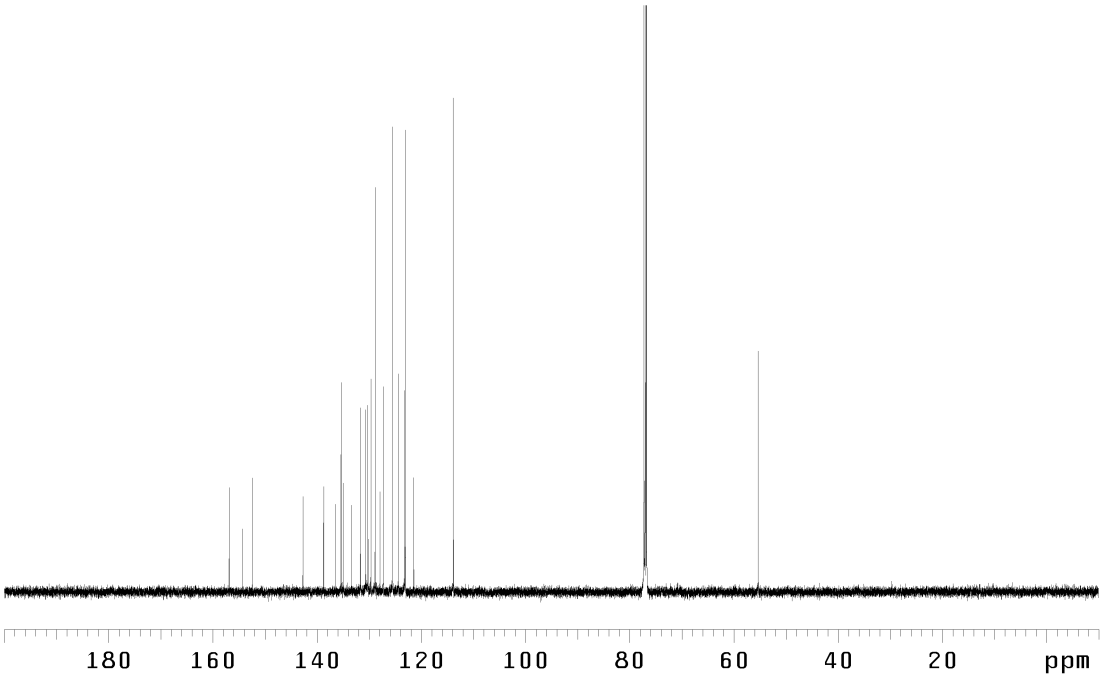


Figure A6.14.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683m**.

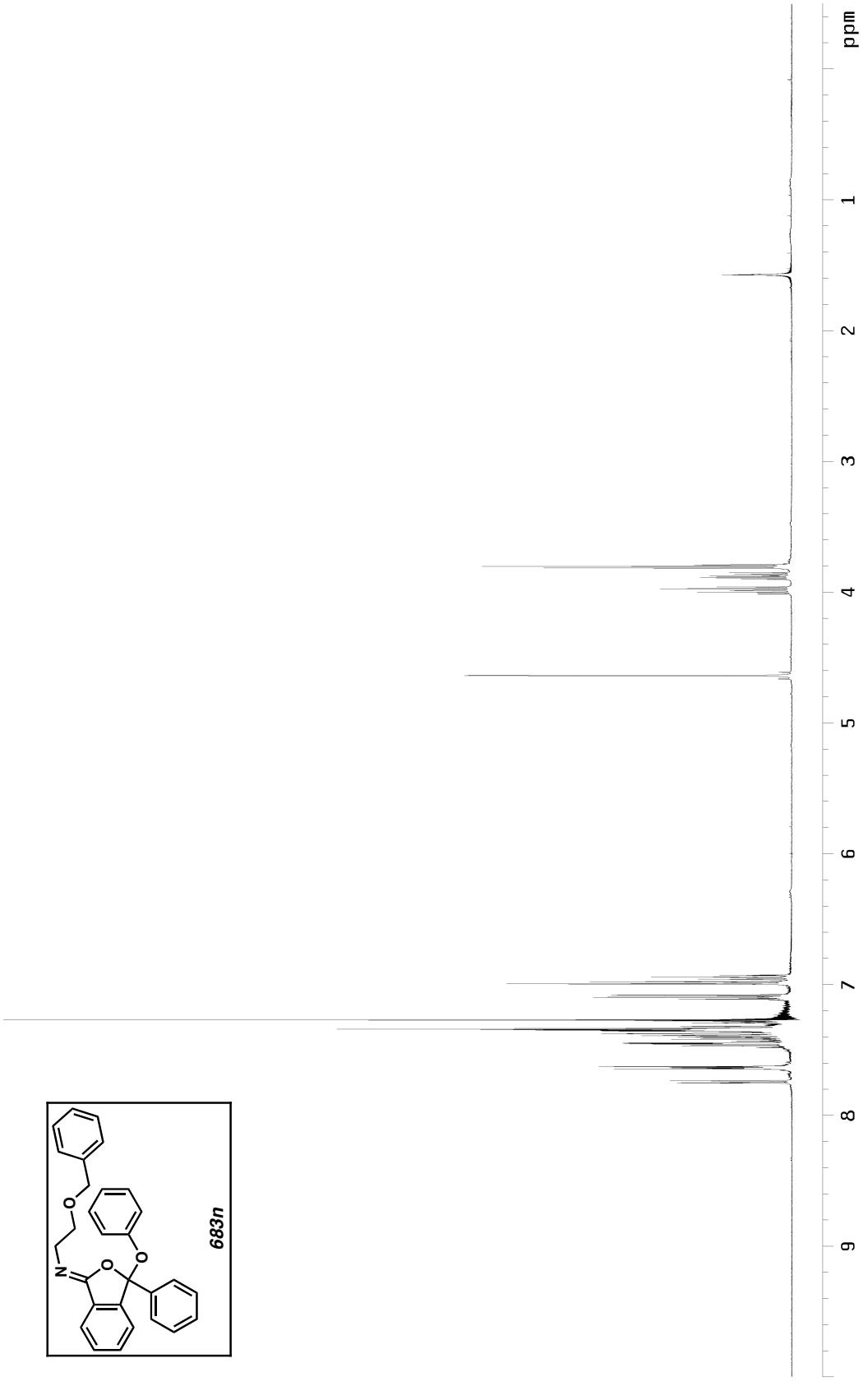


Figure A6.15.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683n**.

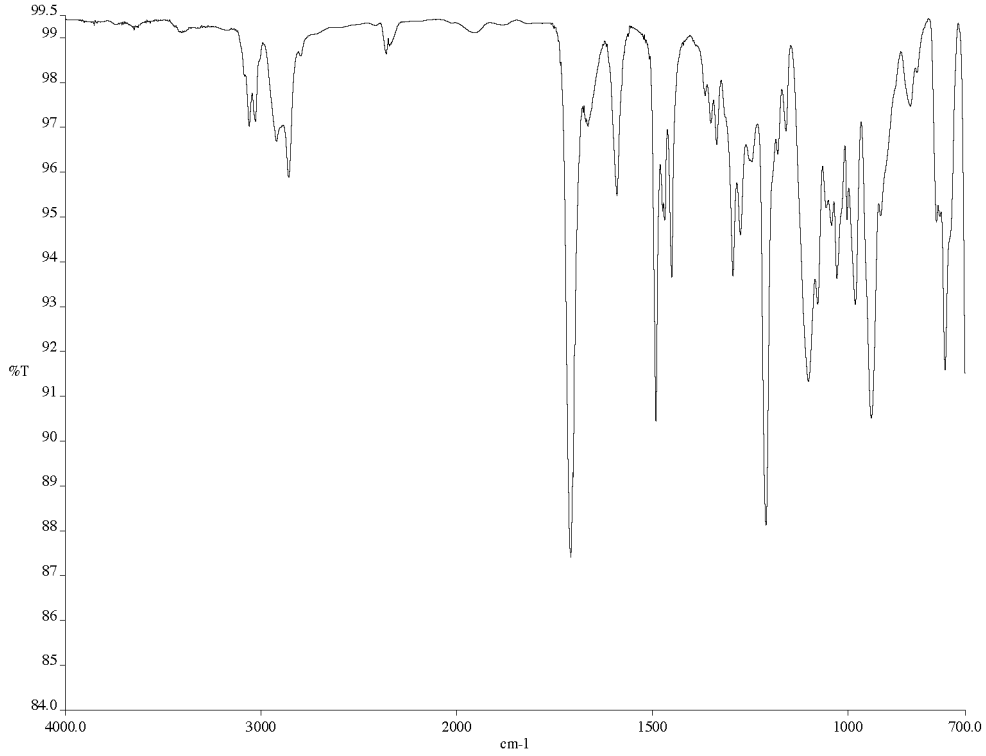


Figure A6.15.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683n**.

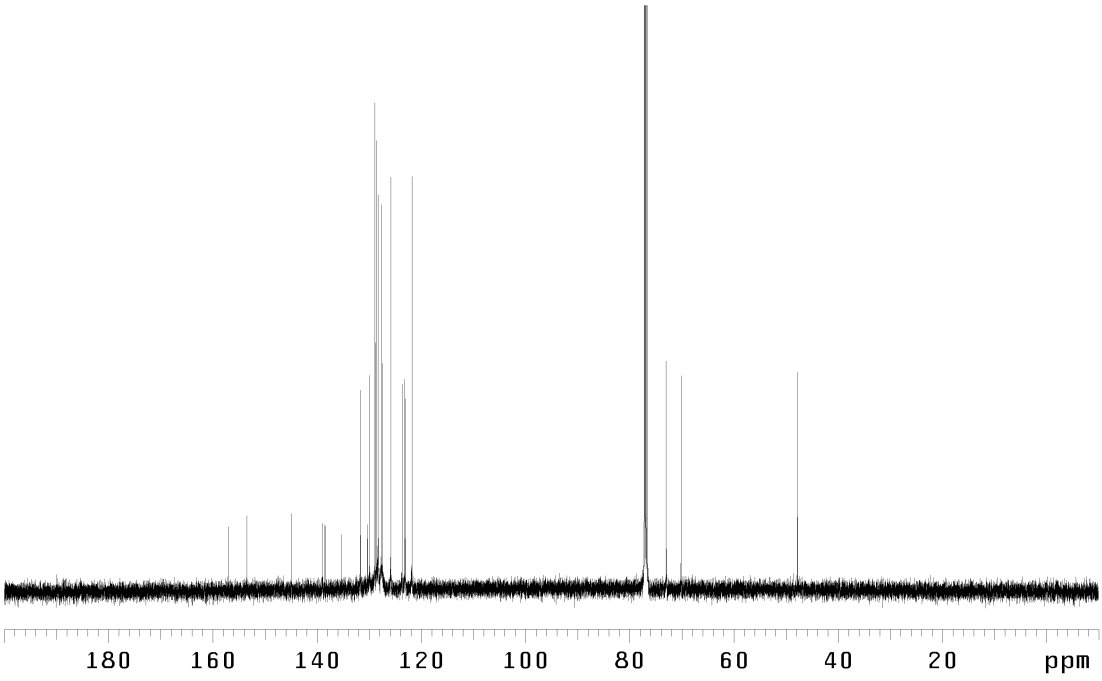


Figure A6.15.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683n**.

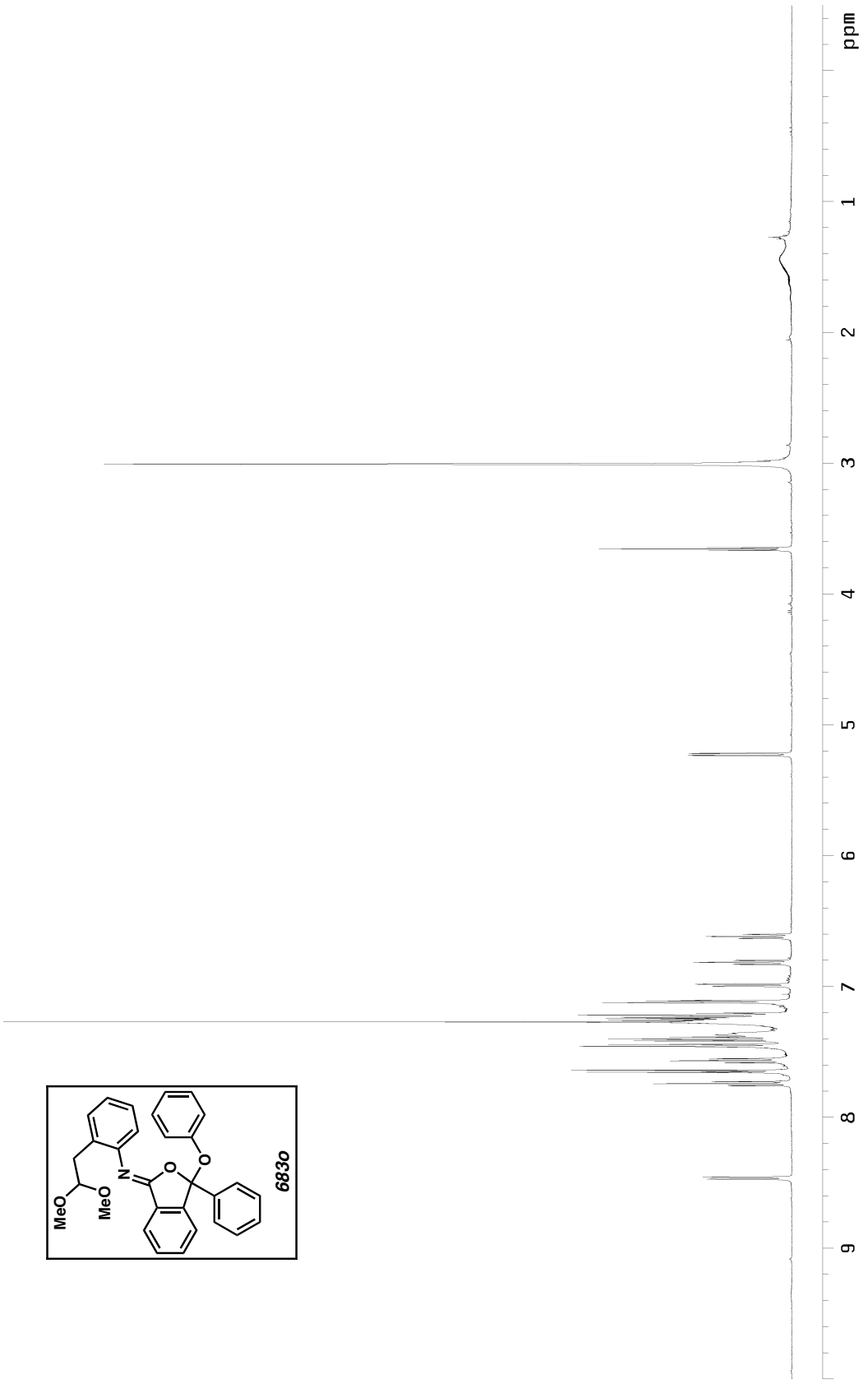


Figure A6.16.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683o**.

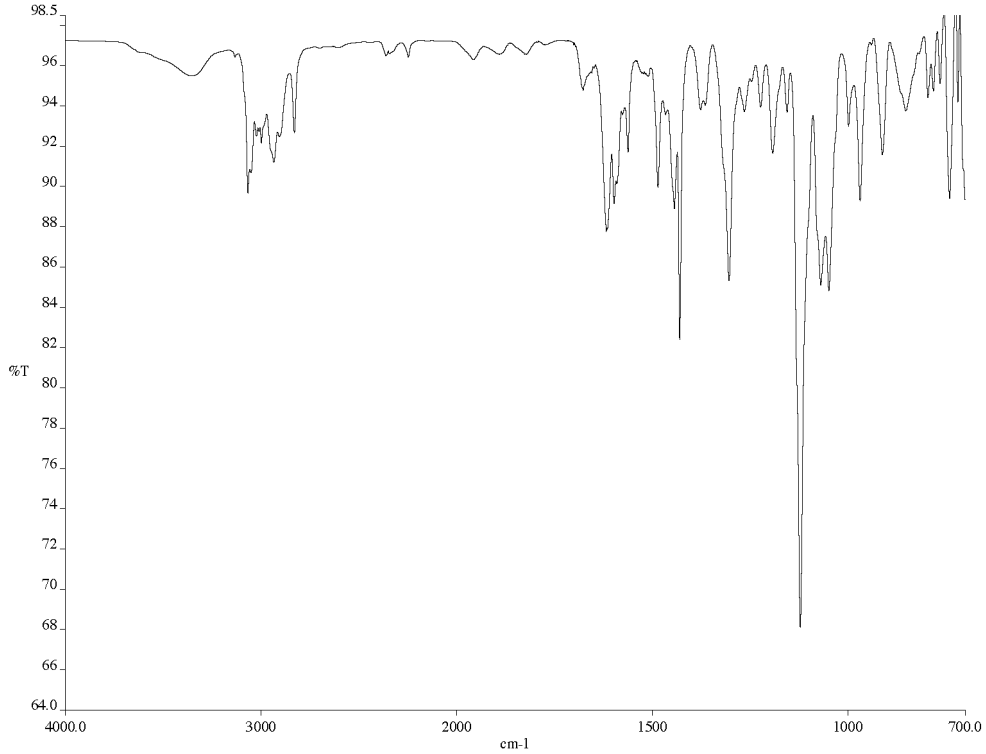


Figure A6.16.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683o**.

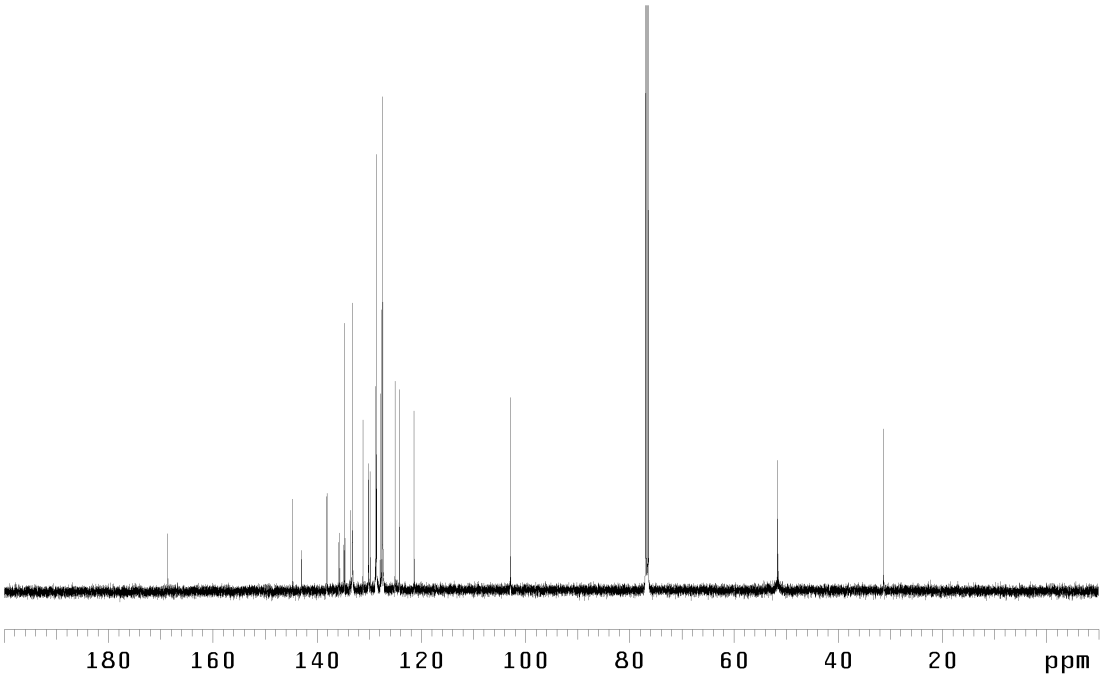


Figure A6.16.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683o**.

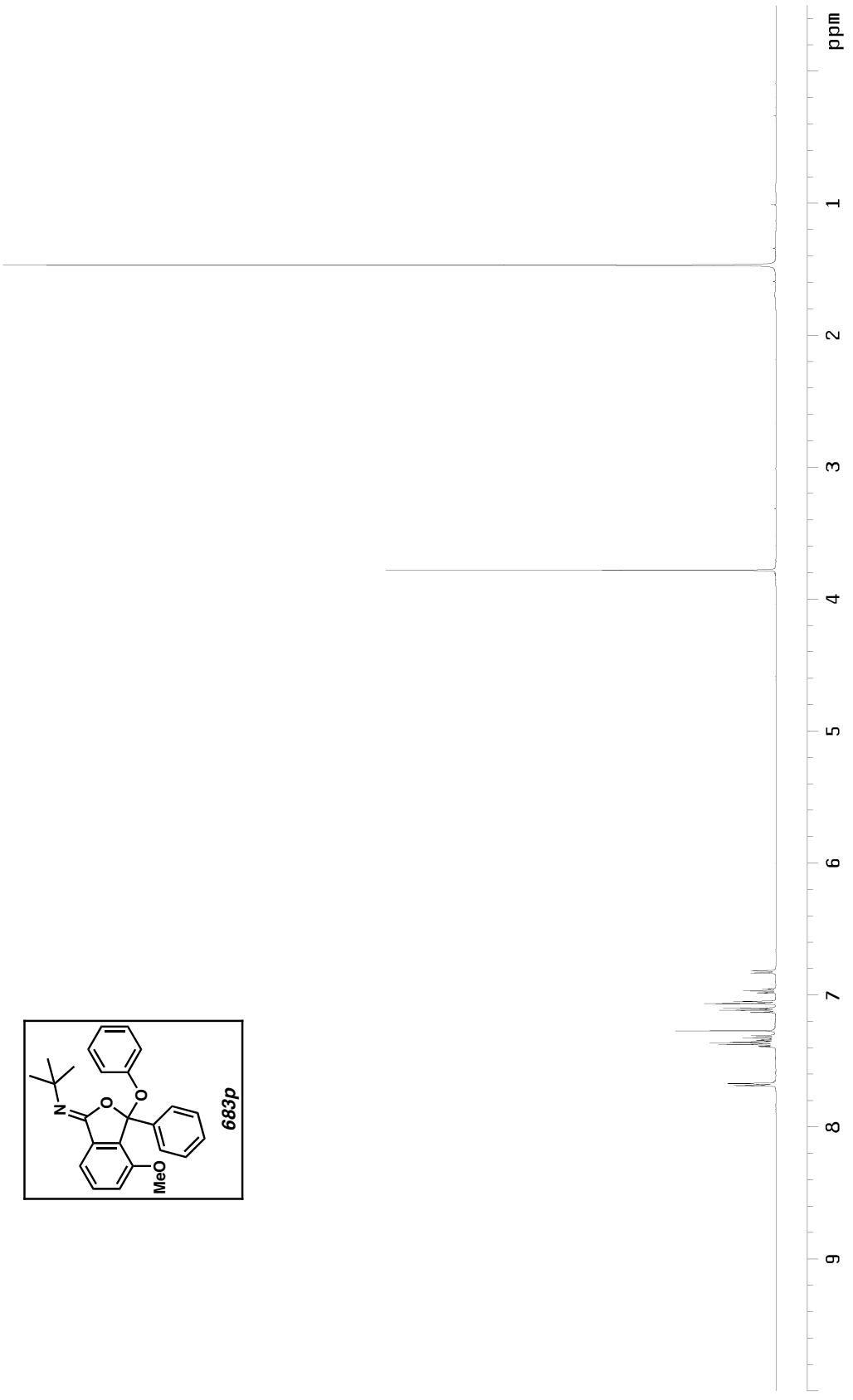


Figure A6.17.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683p**.

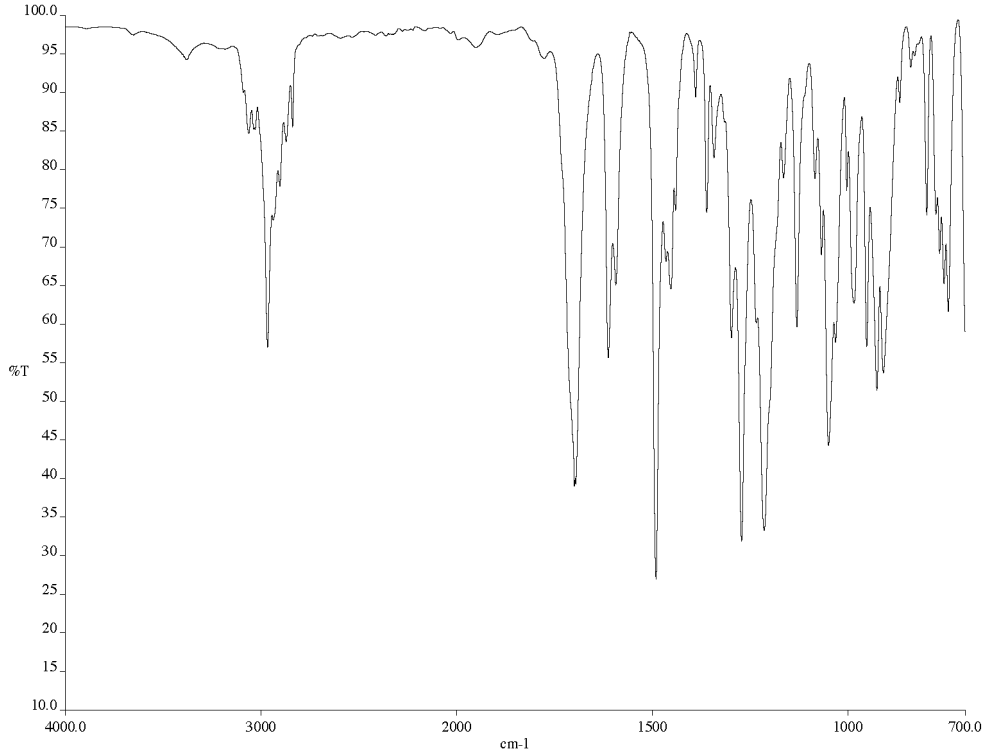


Figure A6.17.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683p**.

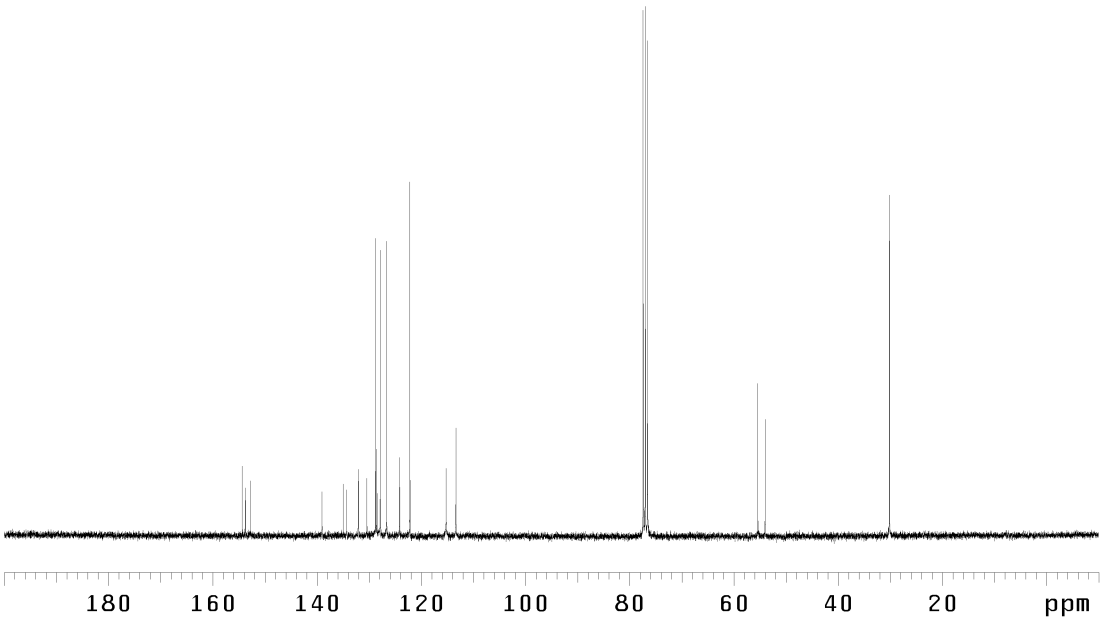


Figure A6.17.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683p**.

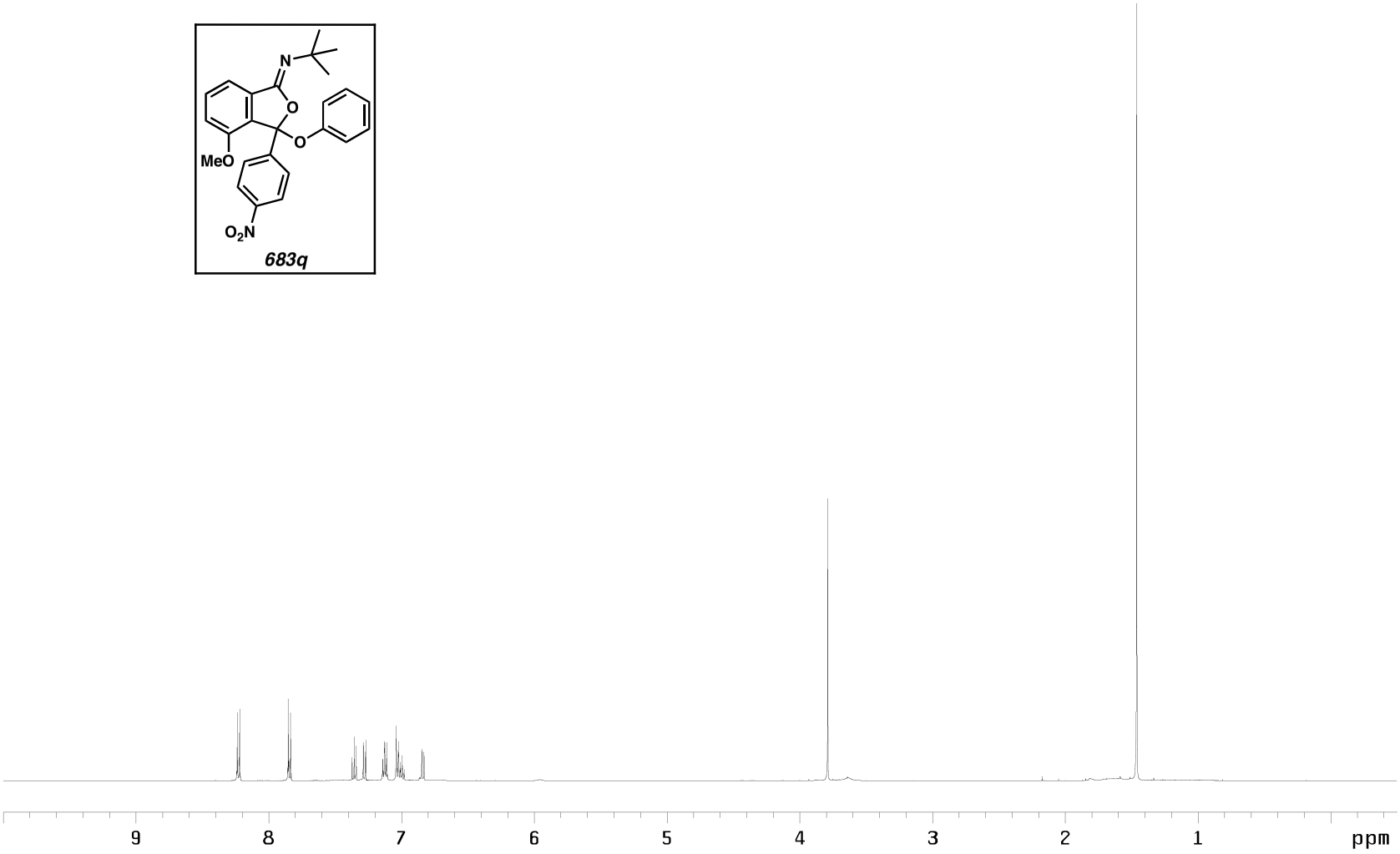


Figure A6.18.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683q**.

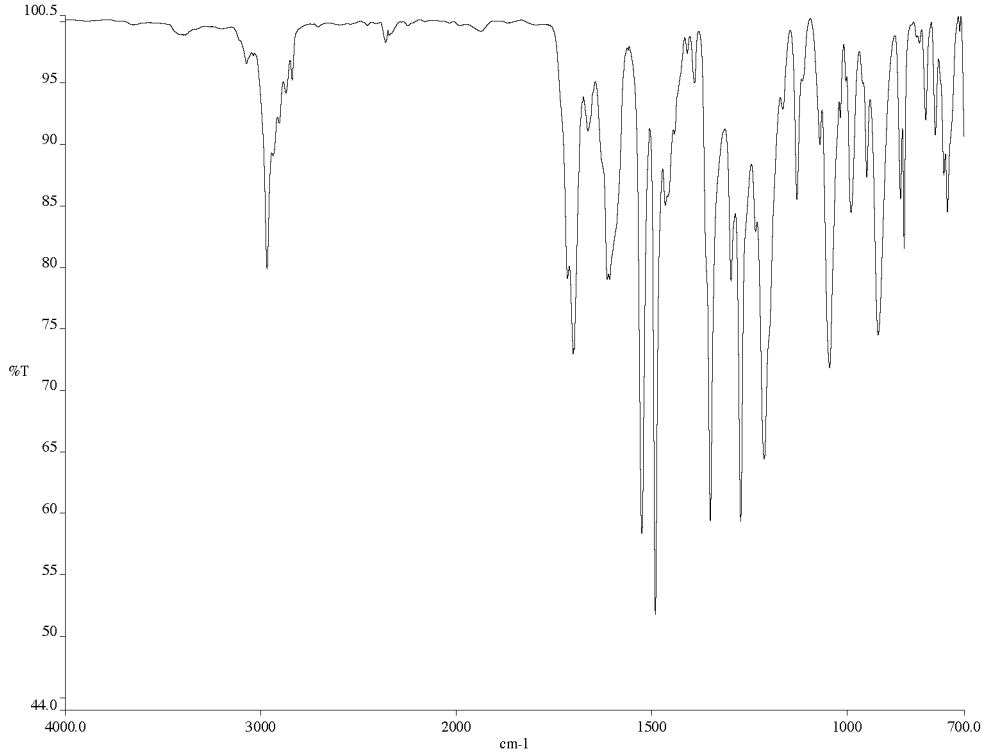


Figure A6.18.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683q**.

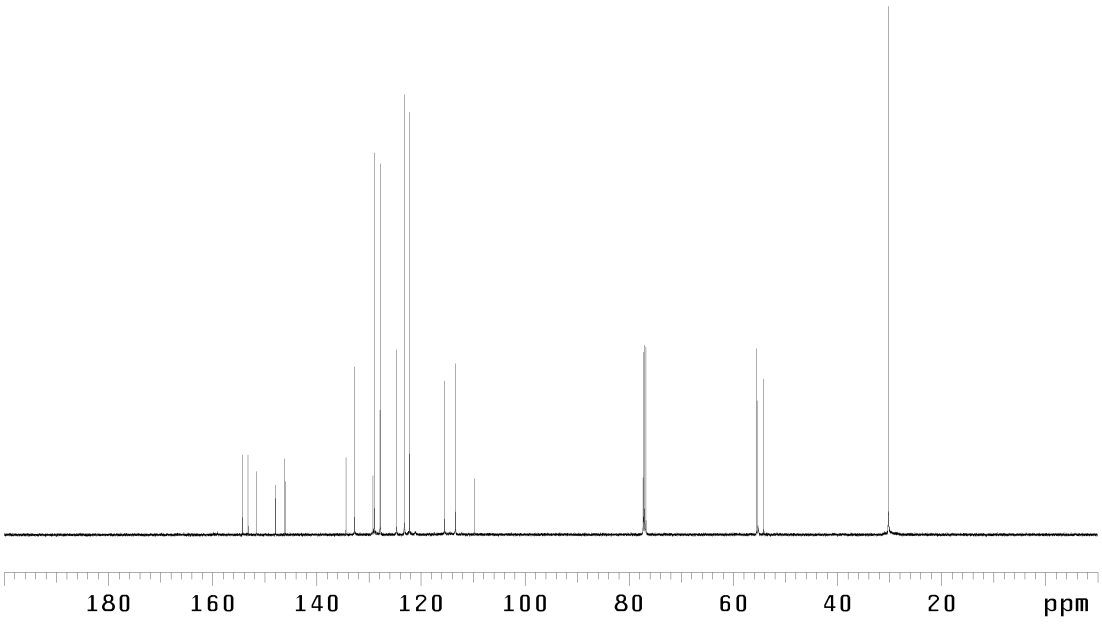


Figure A6.18.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683q**.

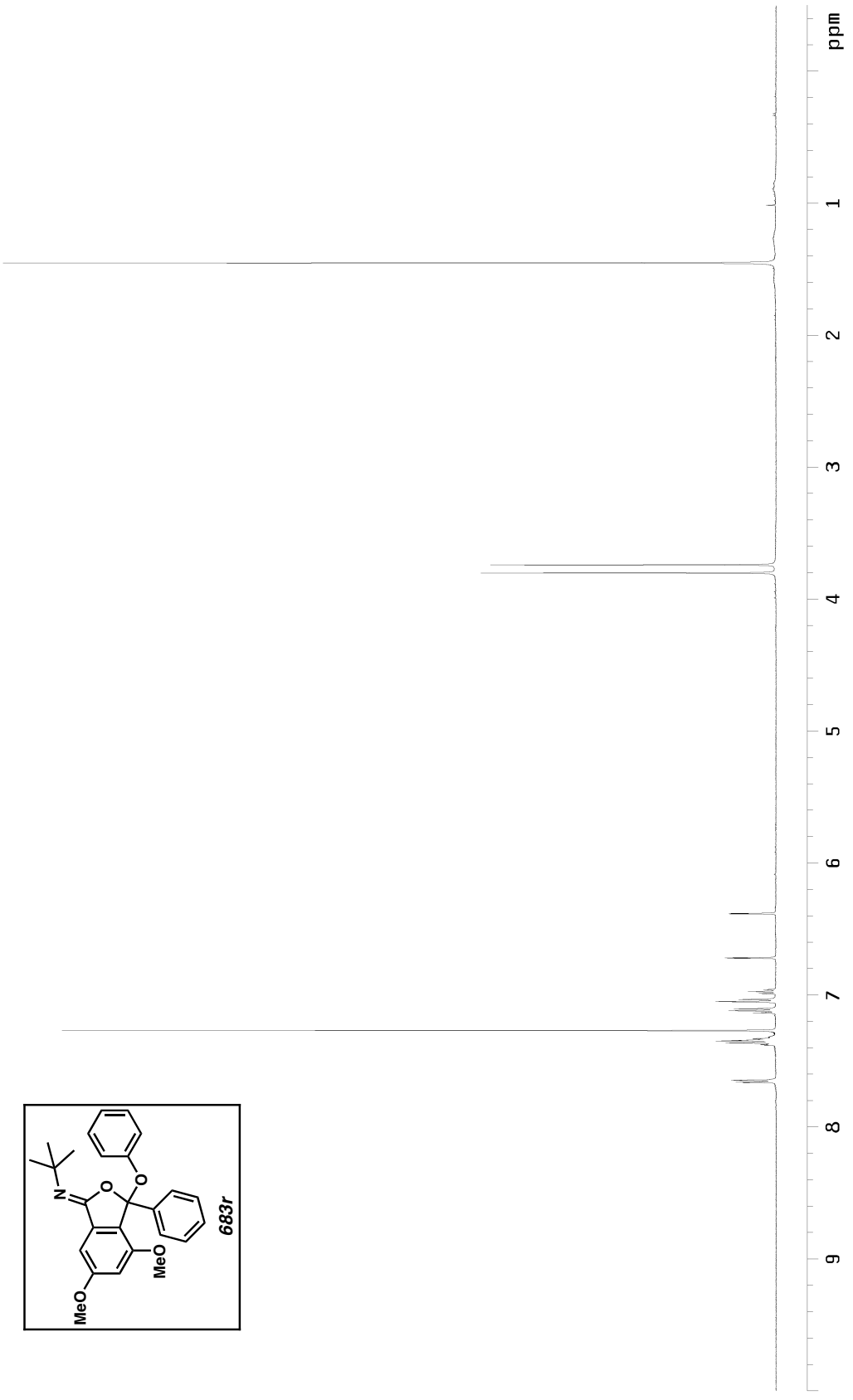


Figure A6.19.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683r**.

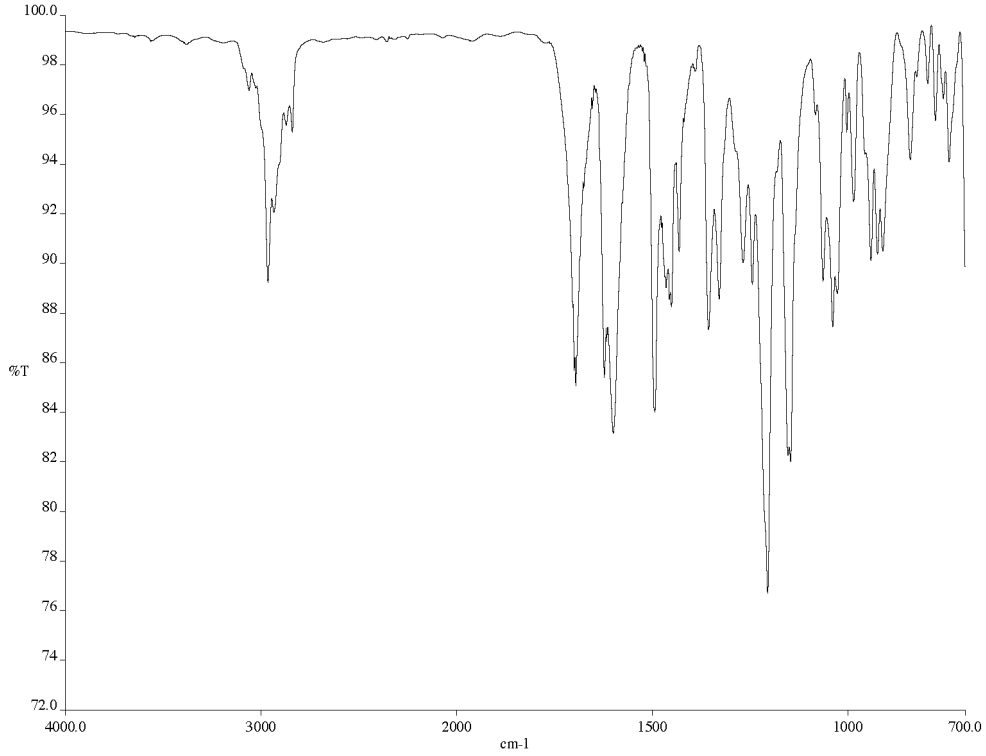


Figure A6.19.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683r**.

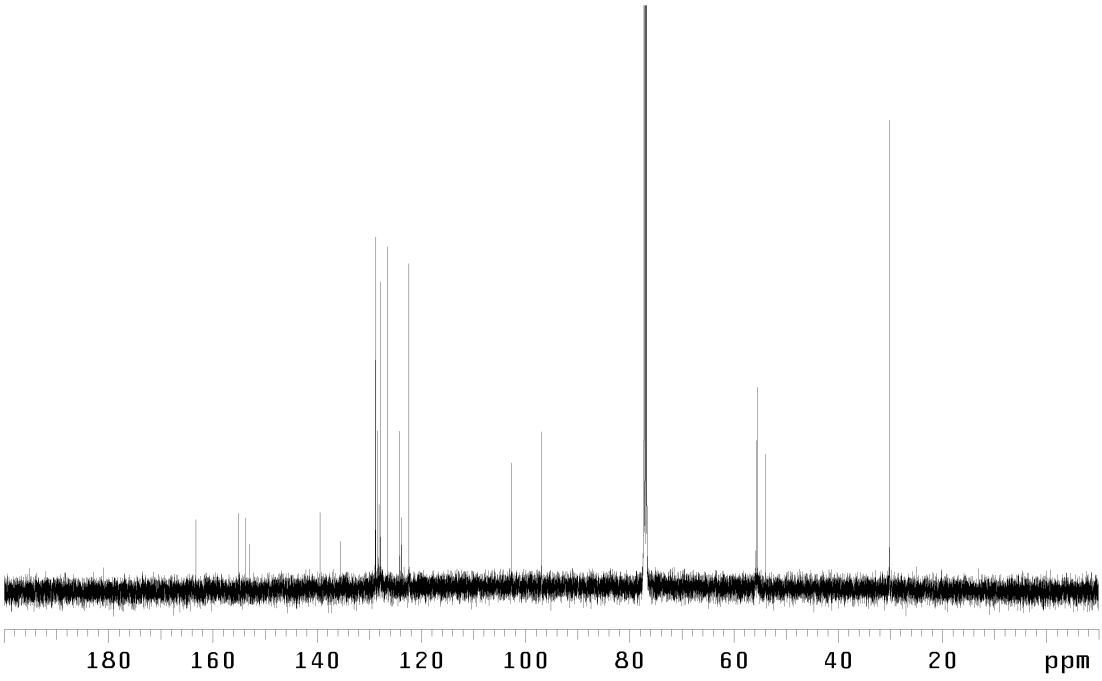


Figure A6.19.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683r**.

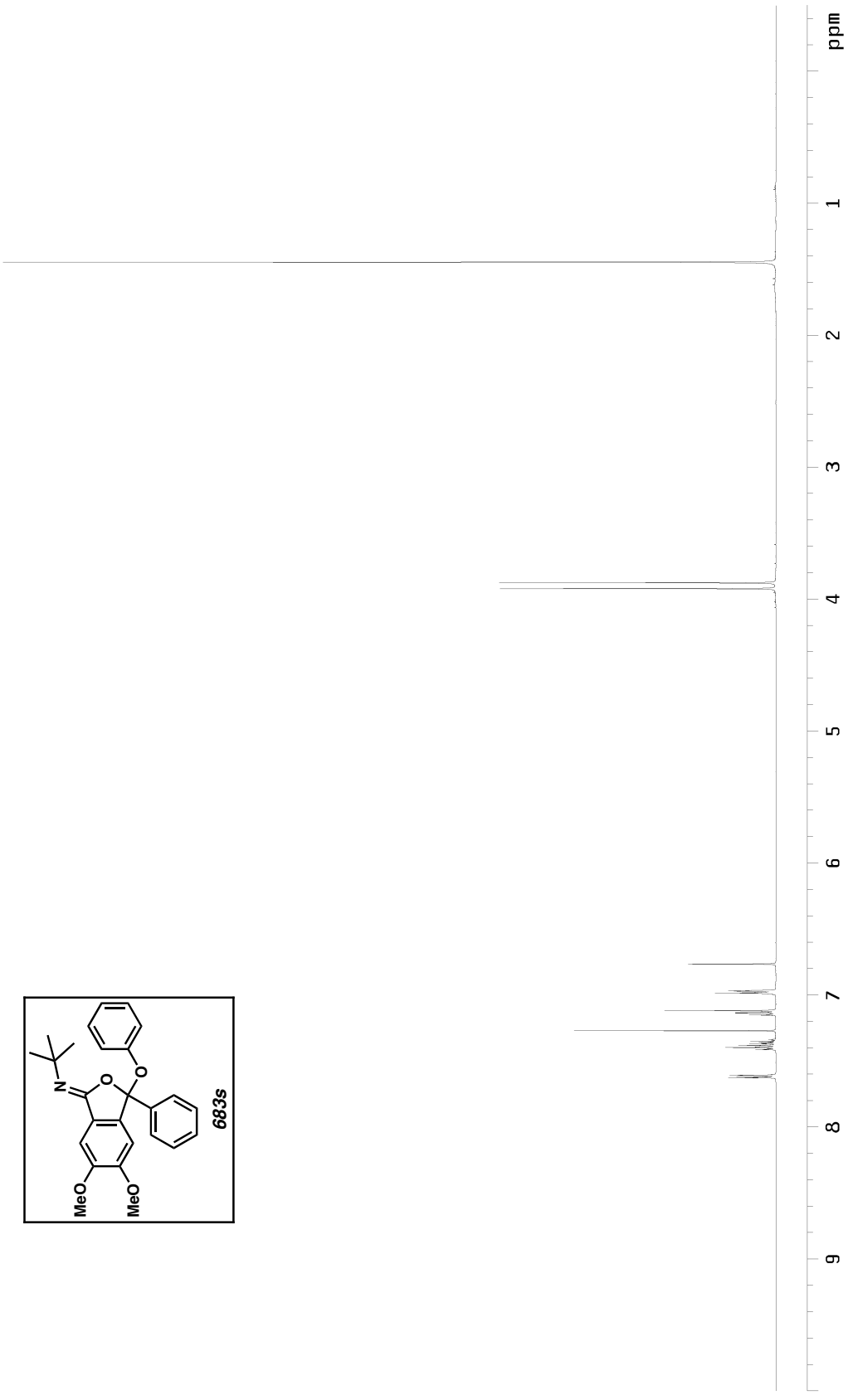


Figure A6.20.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683s**.

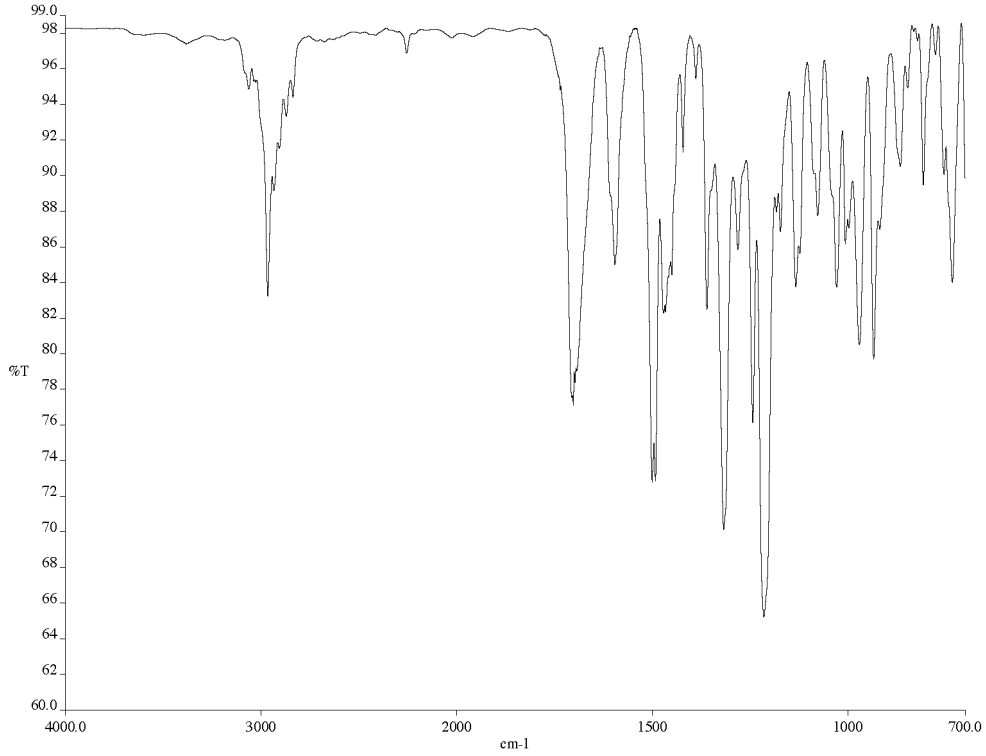


Figure A6.20.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683s**.

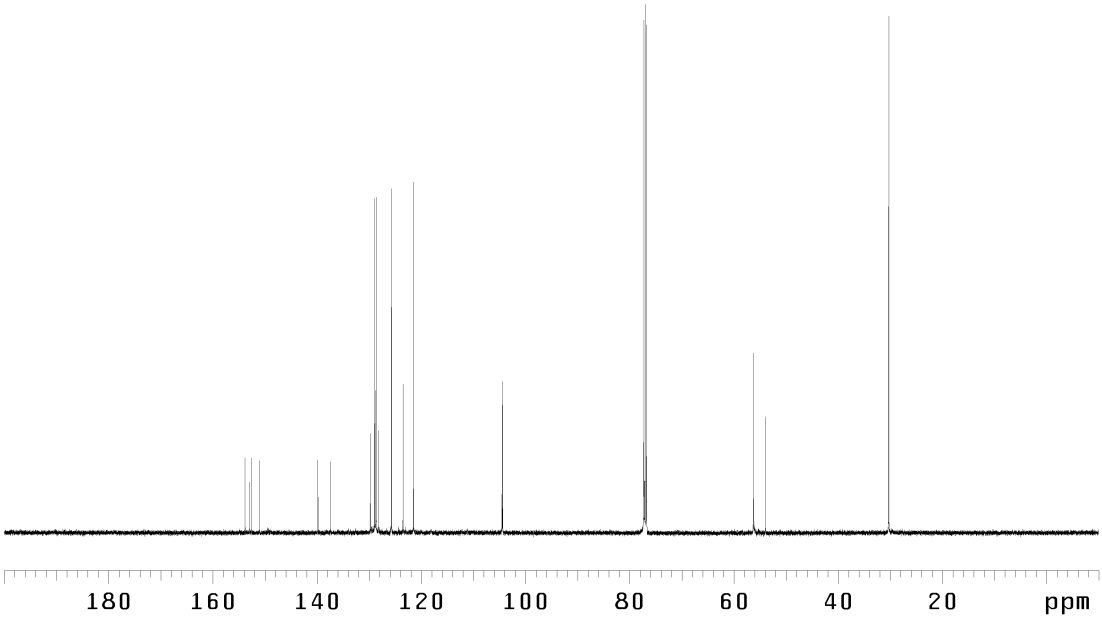


Figure A6.20.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683s**.

Figure A6.21.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683t**.

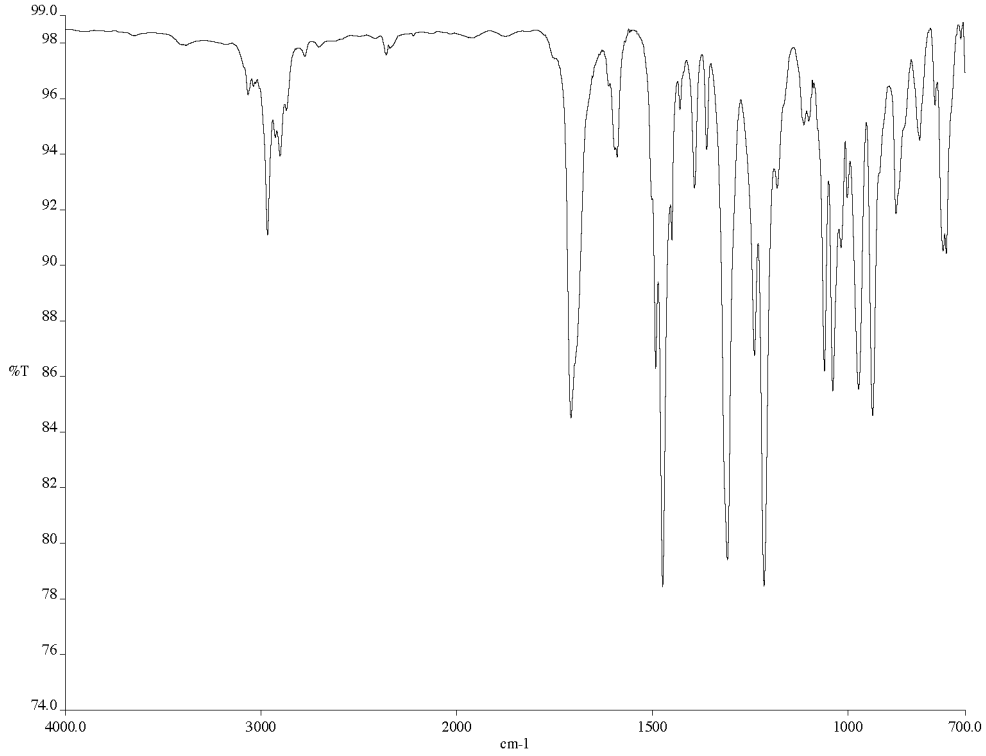


Figure A6.21.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683t**.

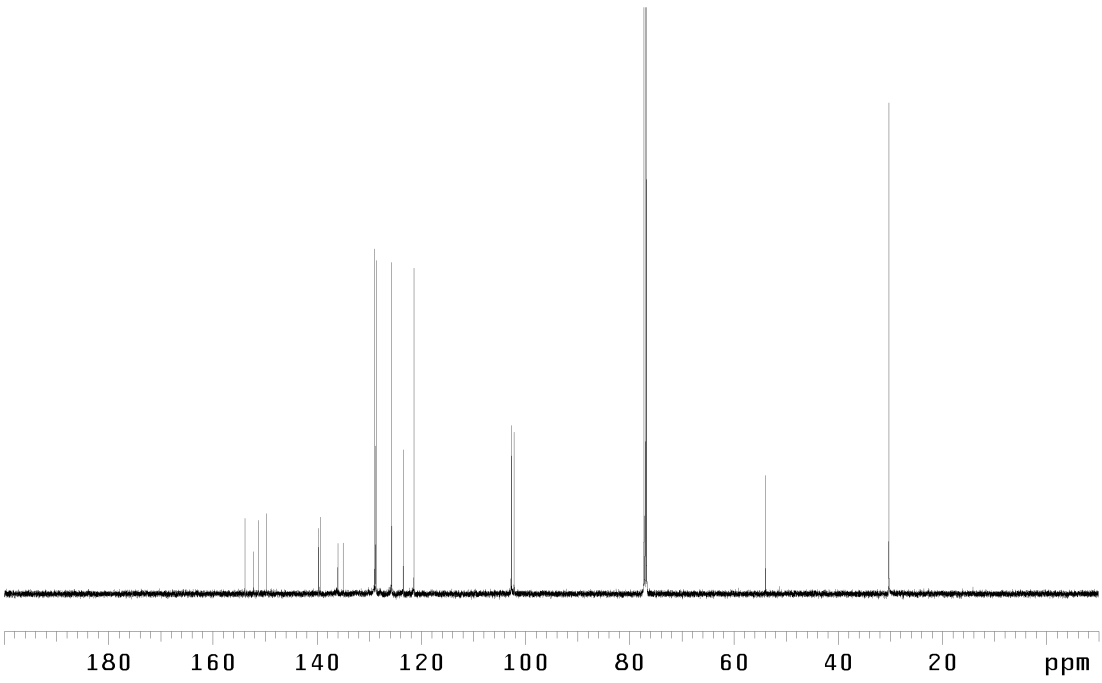


Figure A6.21.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683t**.

Figure A6.22.1 ^{1}H NMR (500 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683u**.

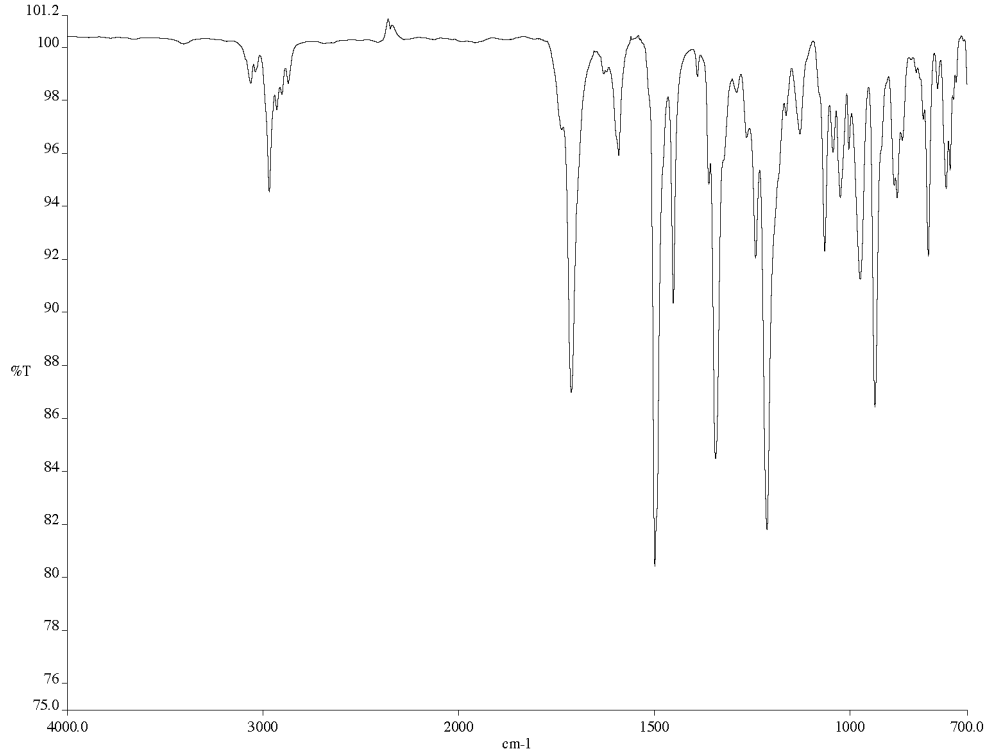


Figure A6.22.2 Infrared spectrum (thin film/NaCl) of phenoxy iminoisobenzofuran **683u**.

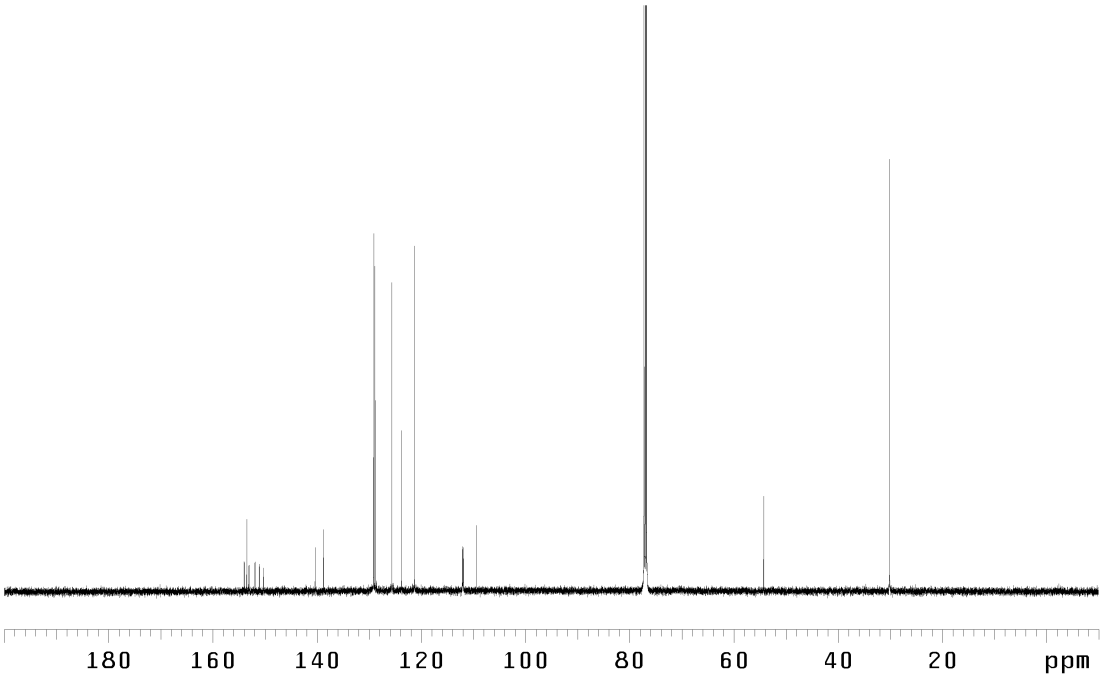


Figure A6.22.3 ^{13}C NMR (125 MHz, $CDCl_3$) of phenoxy iminoisobenzofuran **683u**.

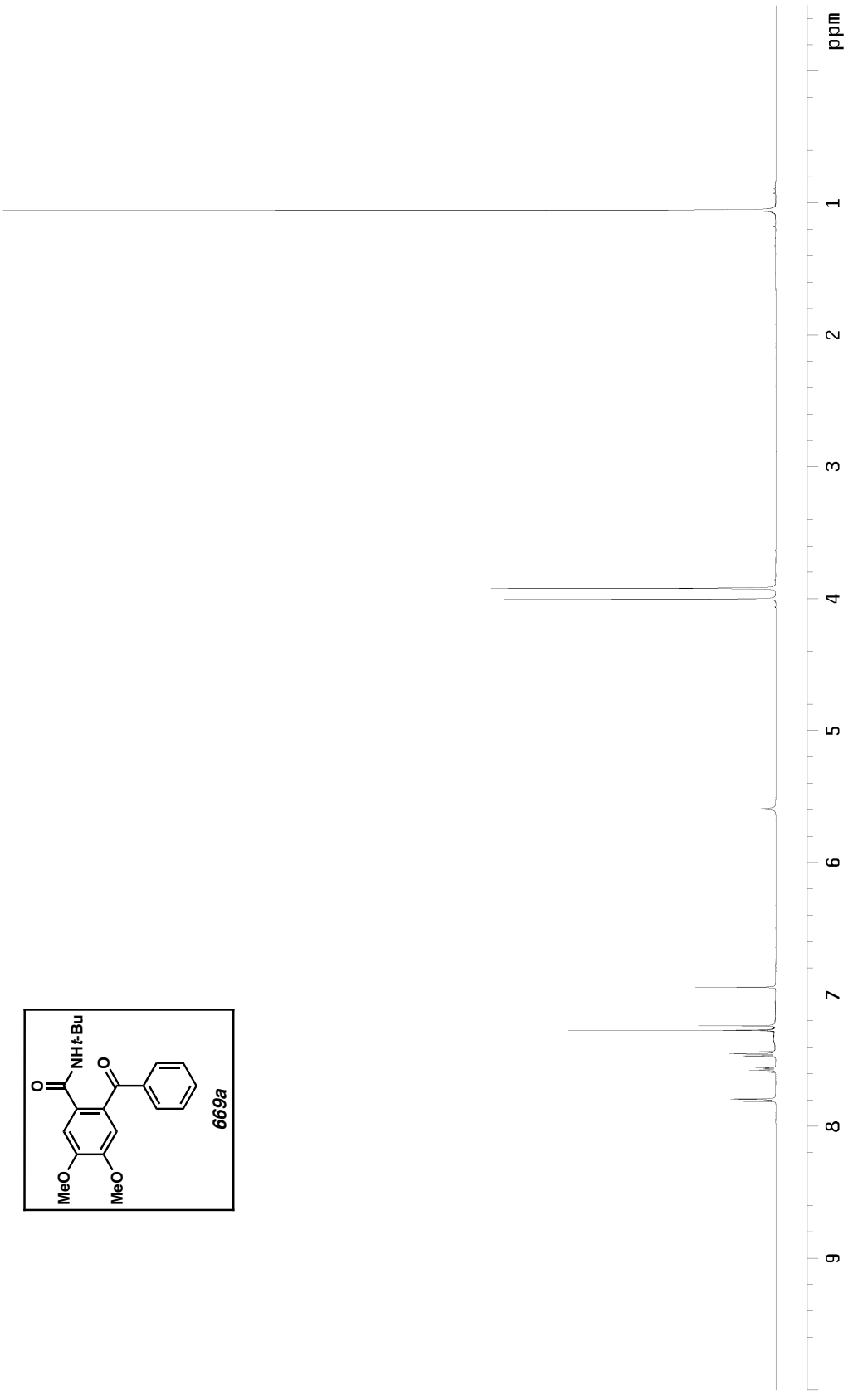


Figure A6.23.1 ^{1}H NMR (500 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669a**.

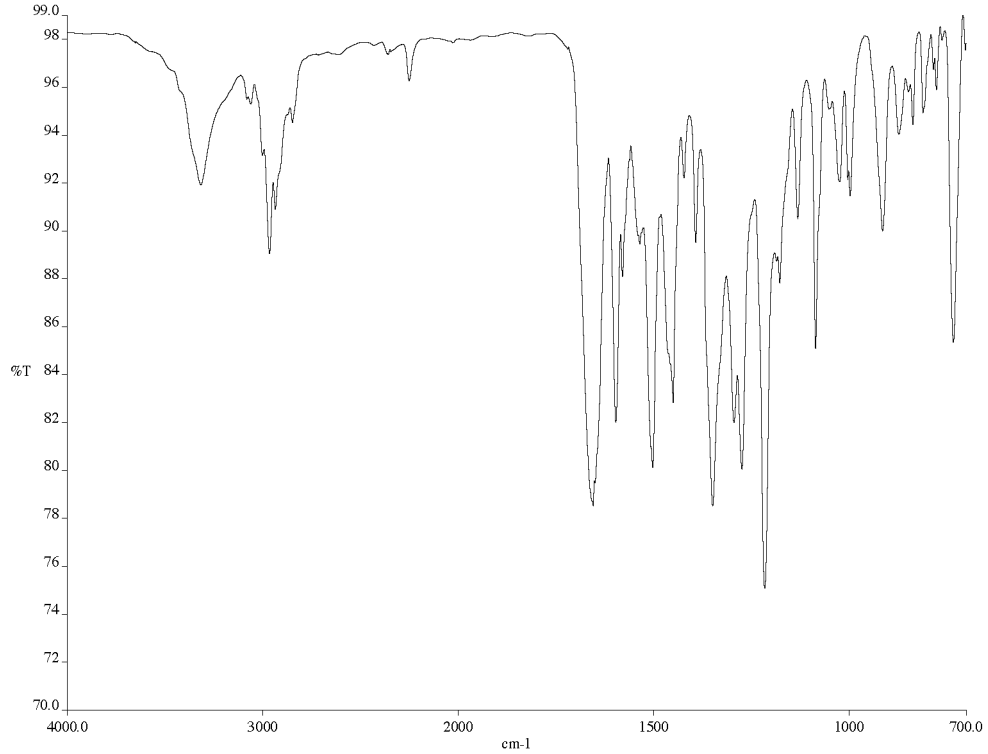


Figure A6.23.2 Infrared spectrum (thin film/NaCl) of *ortho*-ketobenzamide **669a**.

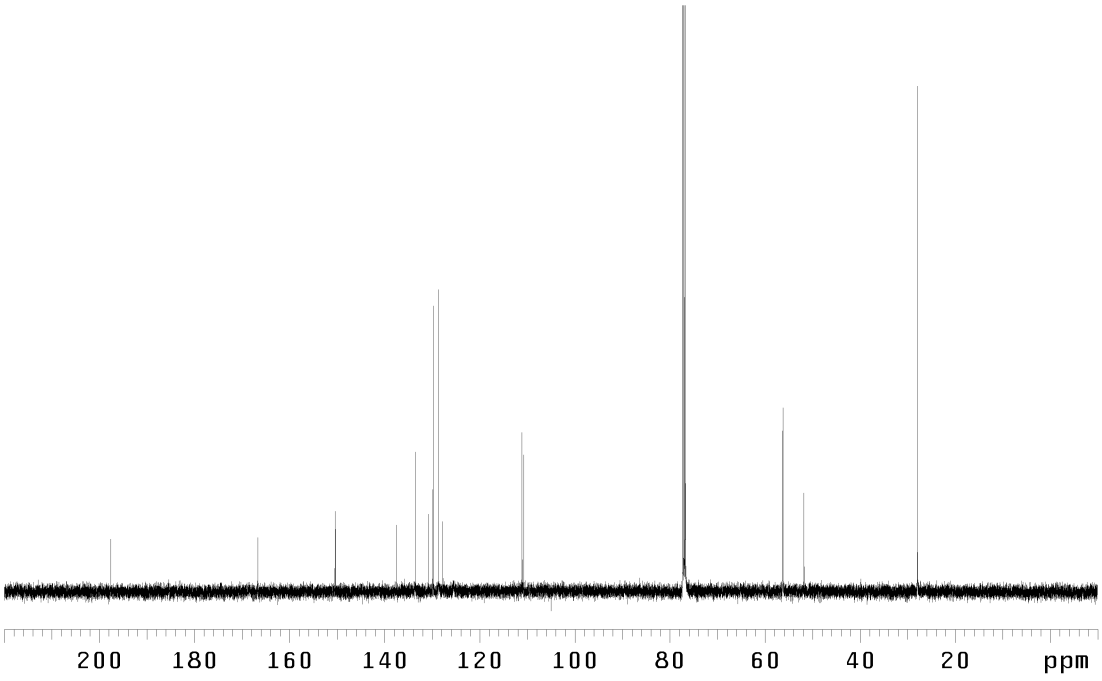


Figure A6.23.3 ^{13}C NMR (125 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669a**.

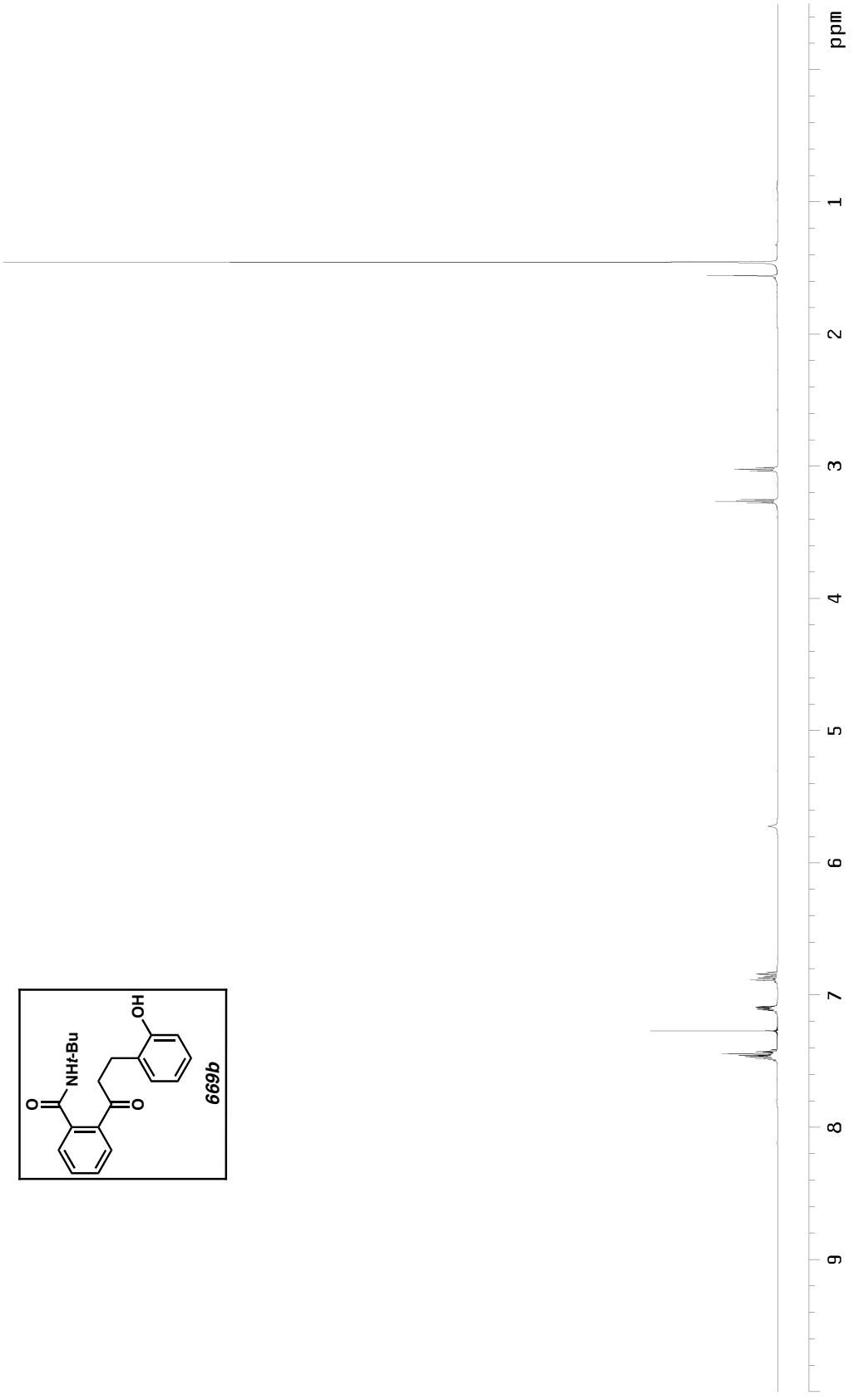


Figure A6.24.1 ^{1}H NMR (500 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669b**.

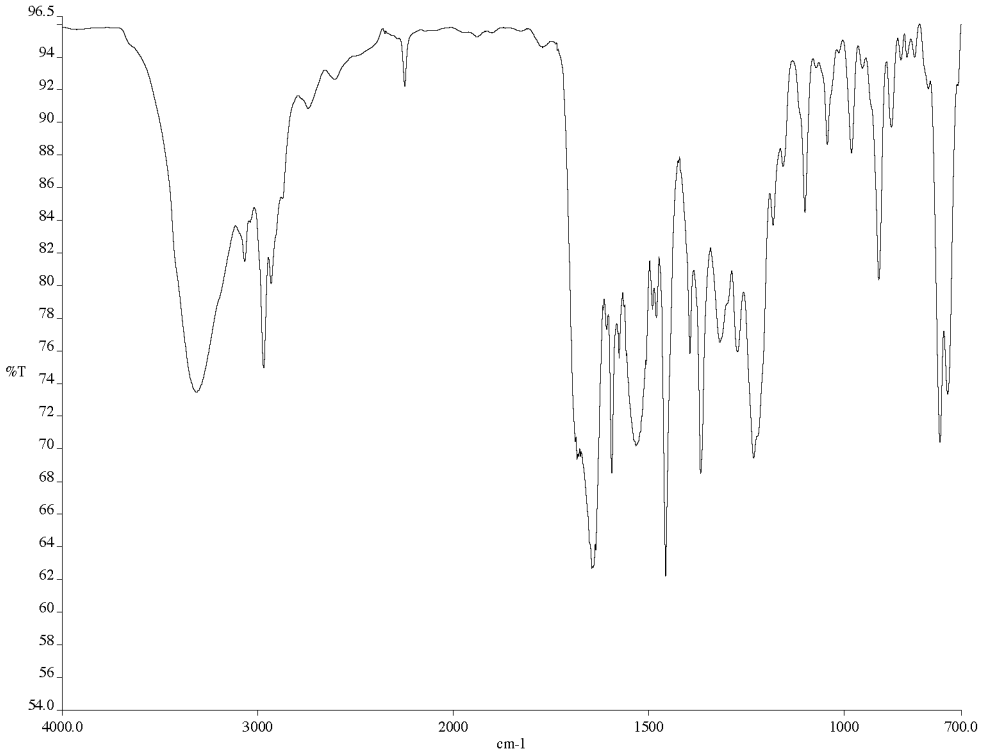


Figure A6.24.2 Infrared spectrum (thin film/NaCl) of *ortho*-ketobenzamide **669b**.

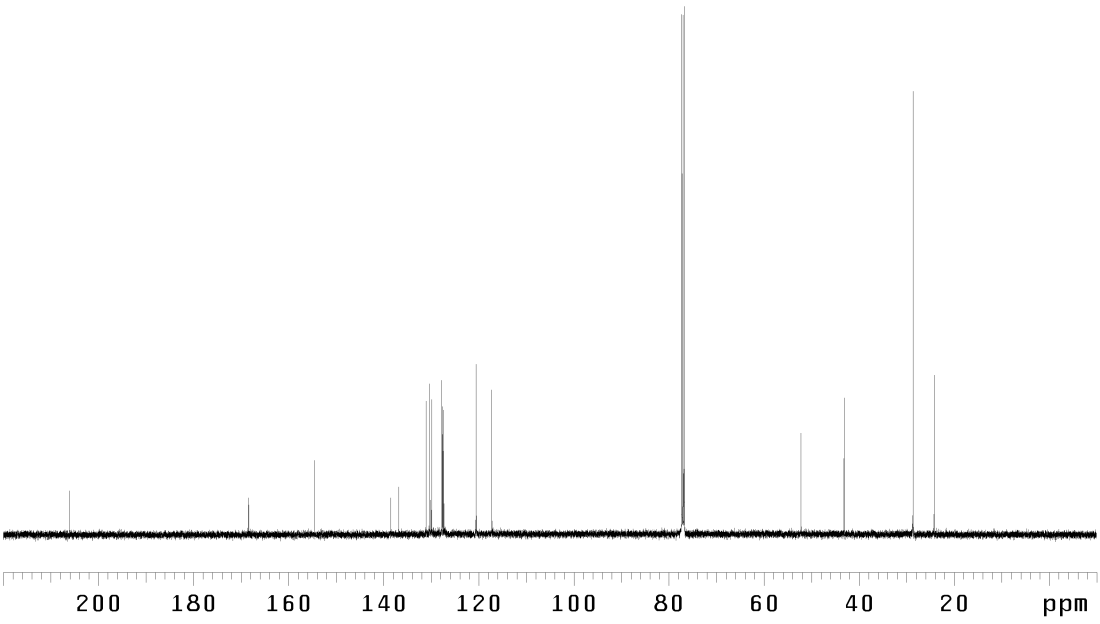


Figure A6.24.3 ^{13}C NMR (125 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669b**.

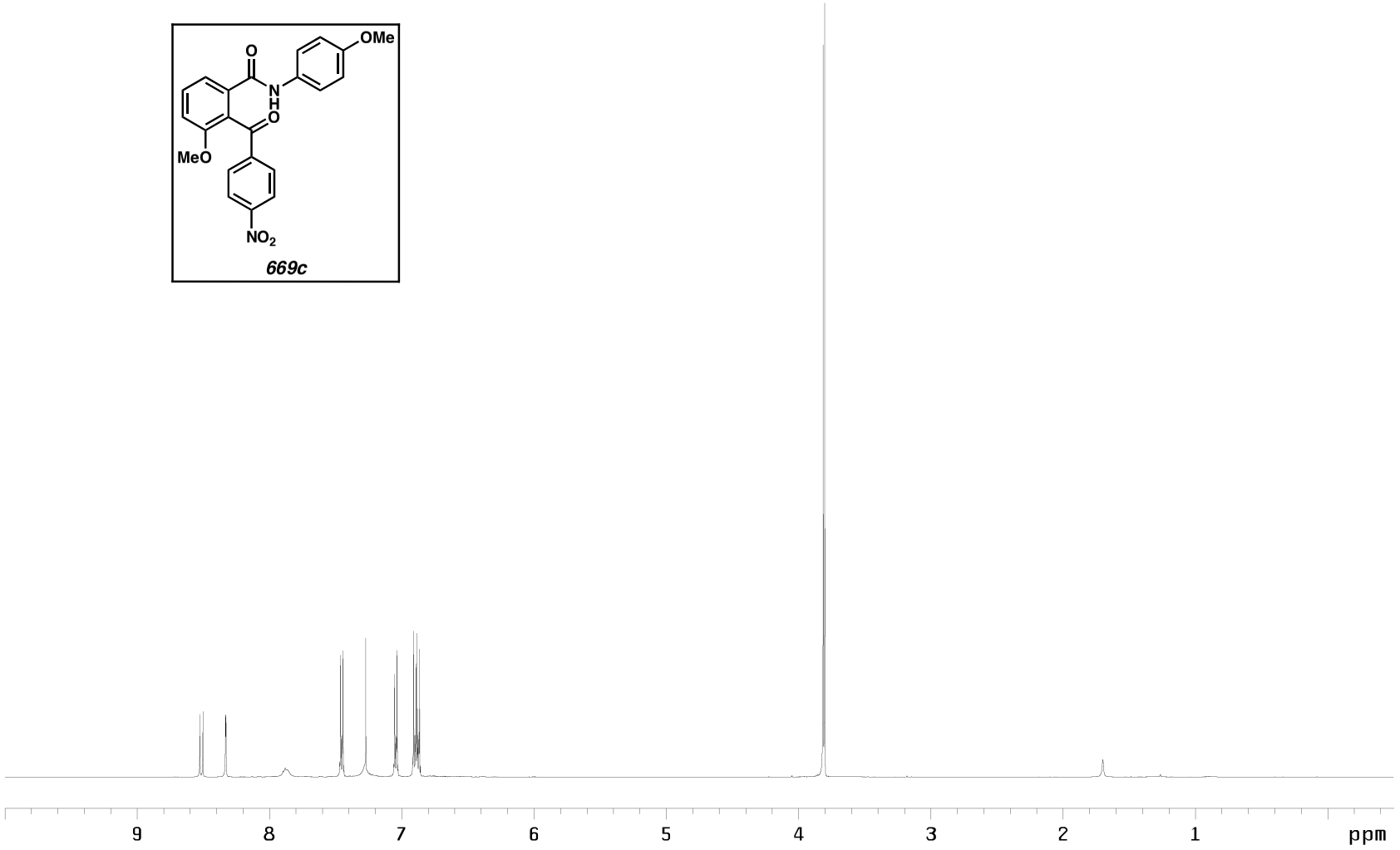


Figure A6.25.1 ^{1}H NMR (500 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669c**.

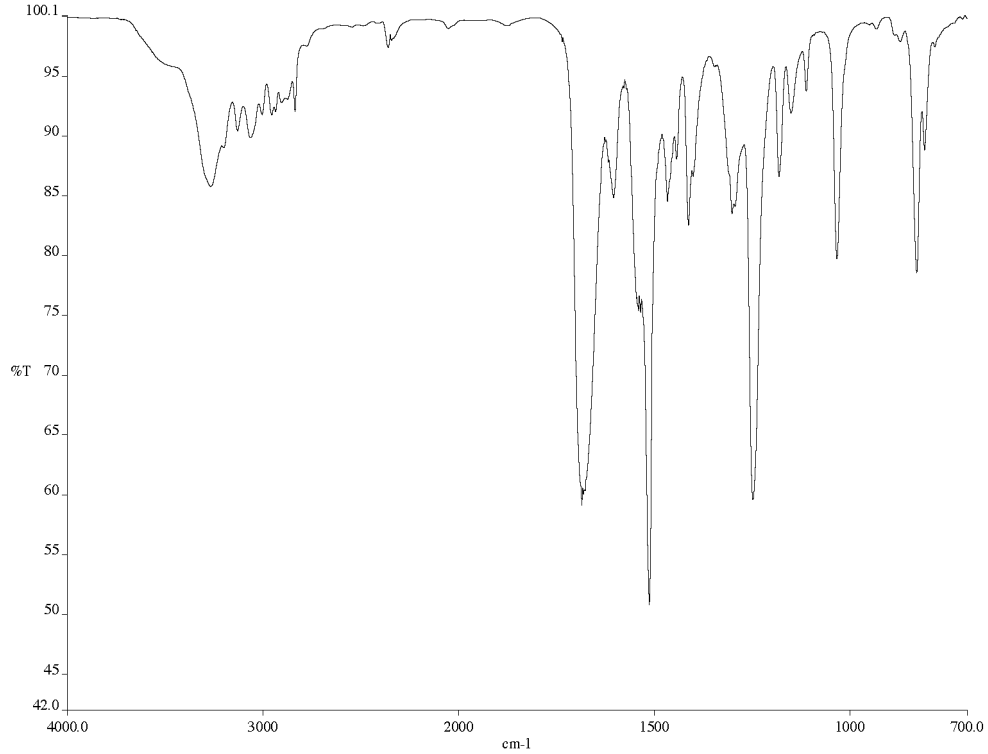


Figure A6.25.2 Infrared spectrum (thin film/NaCl) of *ortho*-ketobenzamide **669c**.

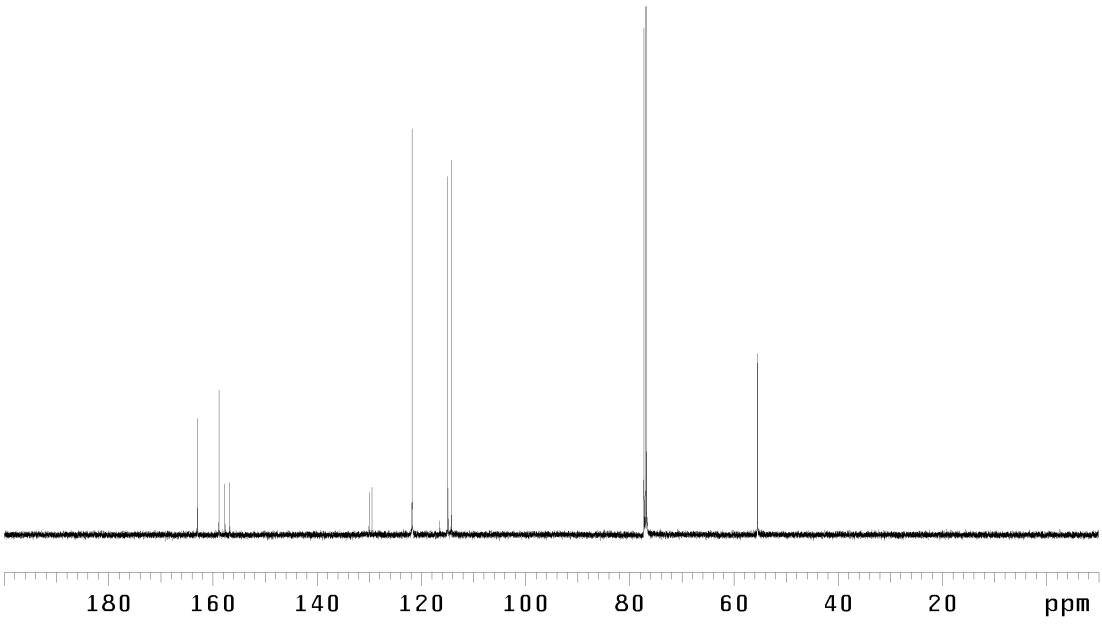


Figure A6.25.3 ^{13}C NMR (125 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669c**.

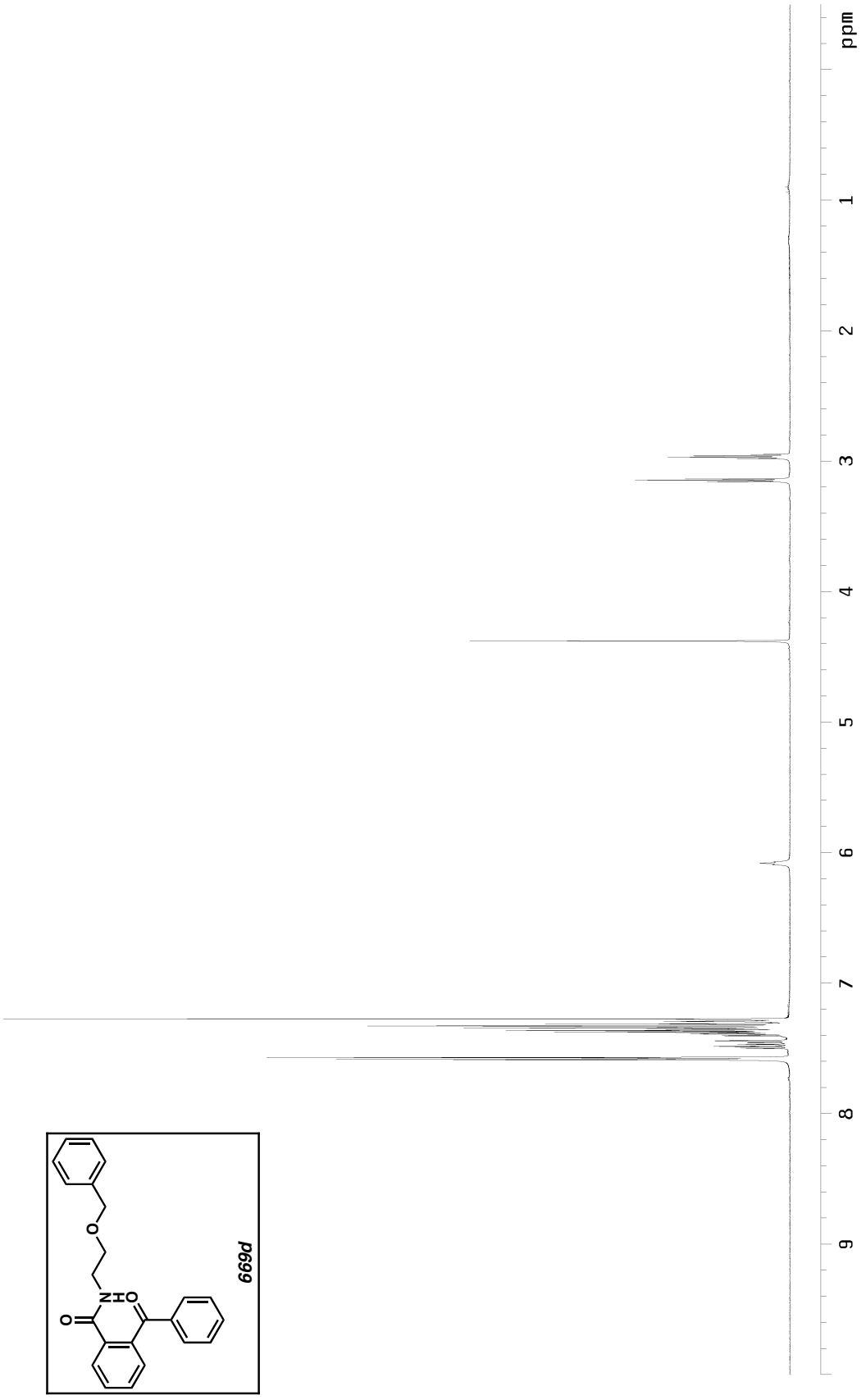


Figure A6.26.1 ^{1}H NMR (500 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669d**.

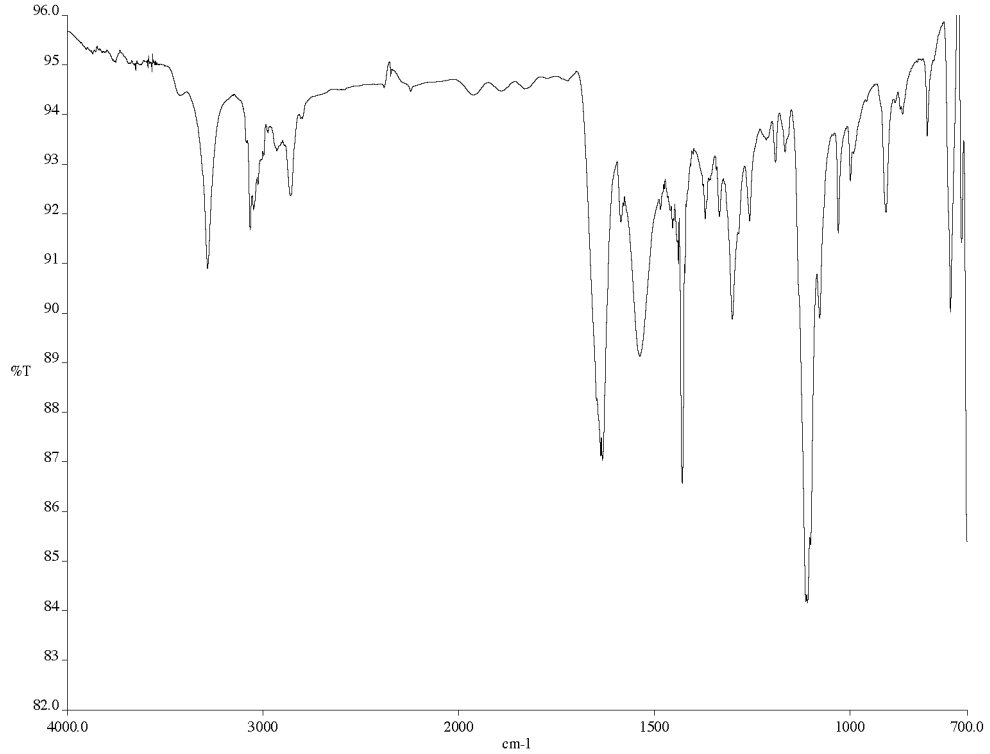


Figure A6.26.2 Infrared spectrum (thin film/NaCl) of *ortho*-ketobenzamide **669d**.

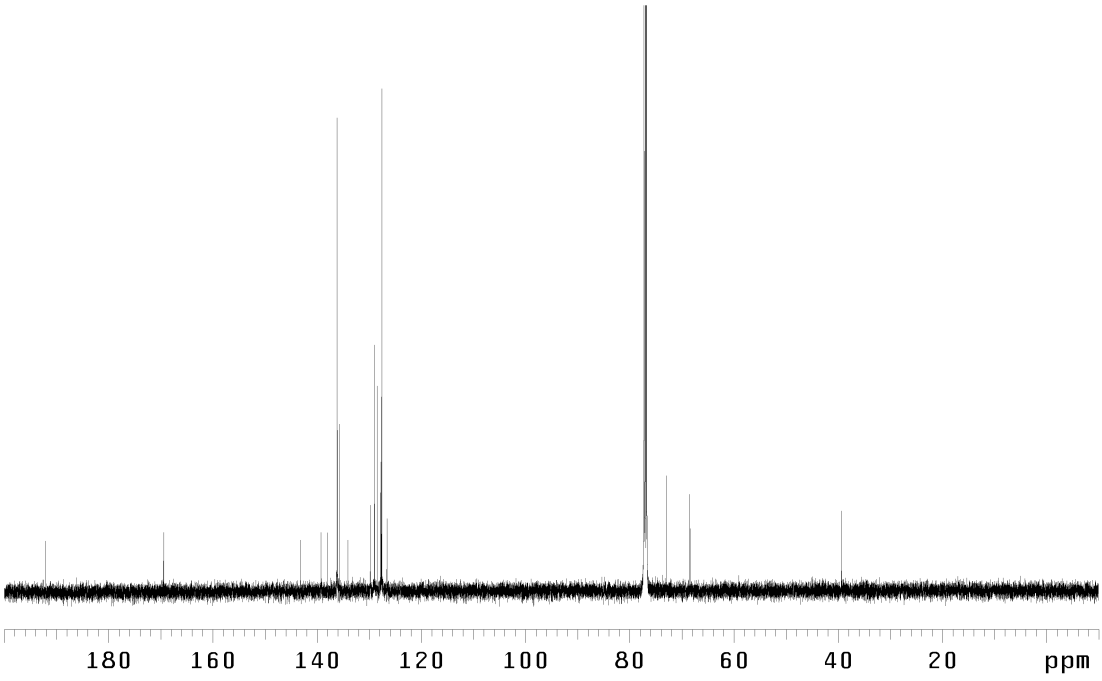


Figure A6.26.3 ^{13}C NMR (125 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669d**.

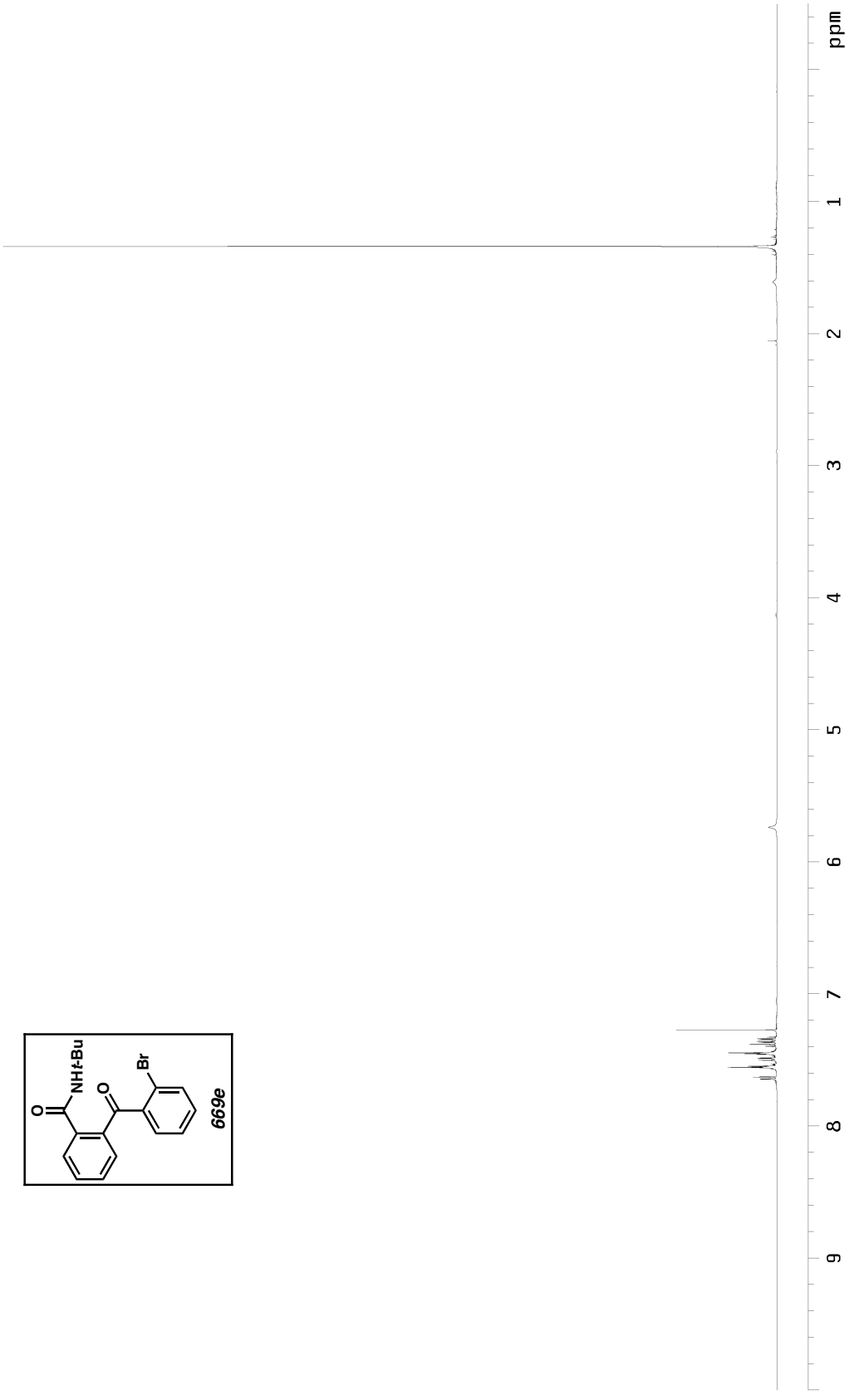


Figure A6.27.1 ^{1}H NMR (500 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669e**.

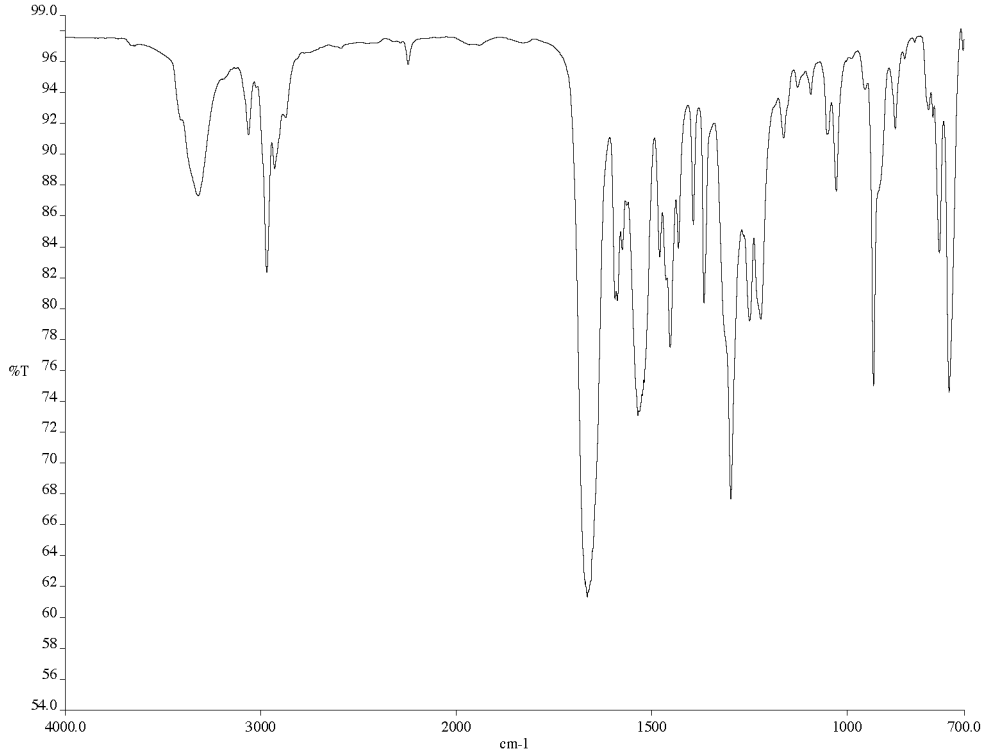


Figure A6.27.2 Infrared spectrum (thin film/NaCl) of *ortho*-ketobenzamide **669e**.

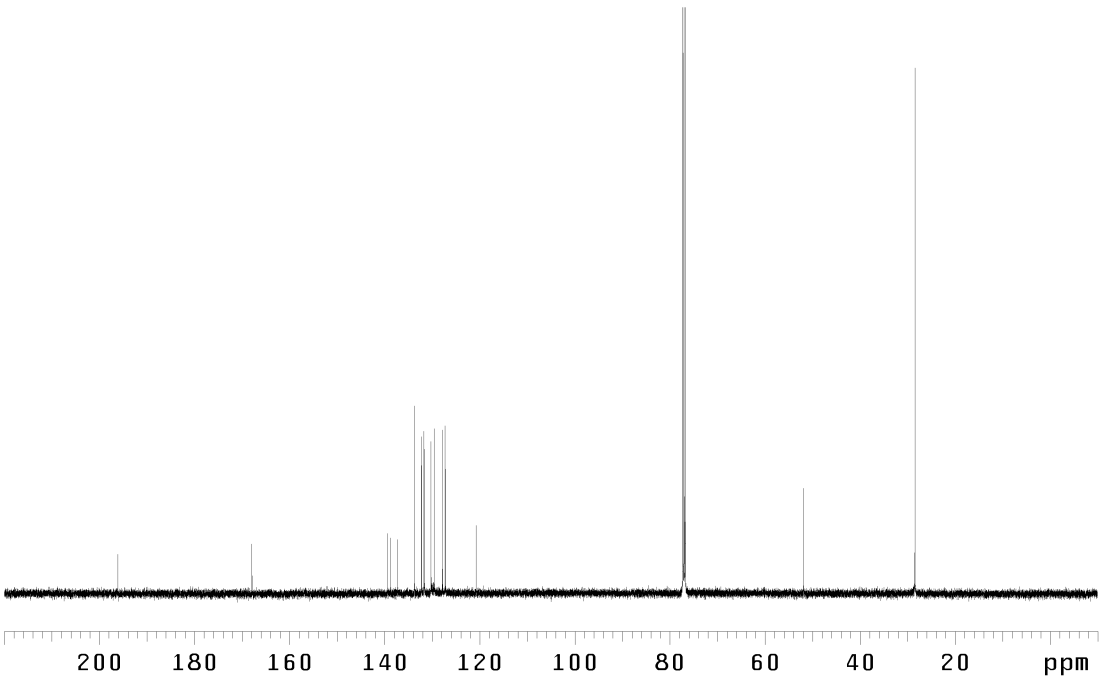


Figure A6.27.3 ^{13}C NMR (125 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669e**.

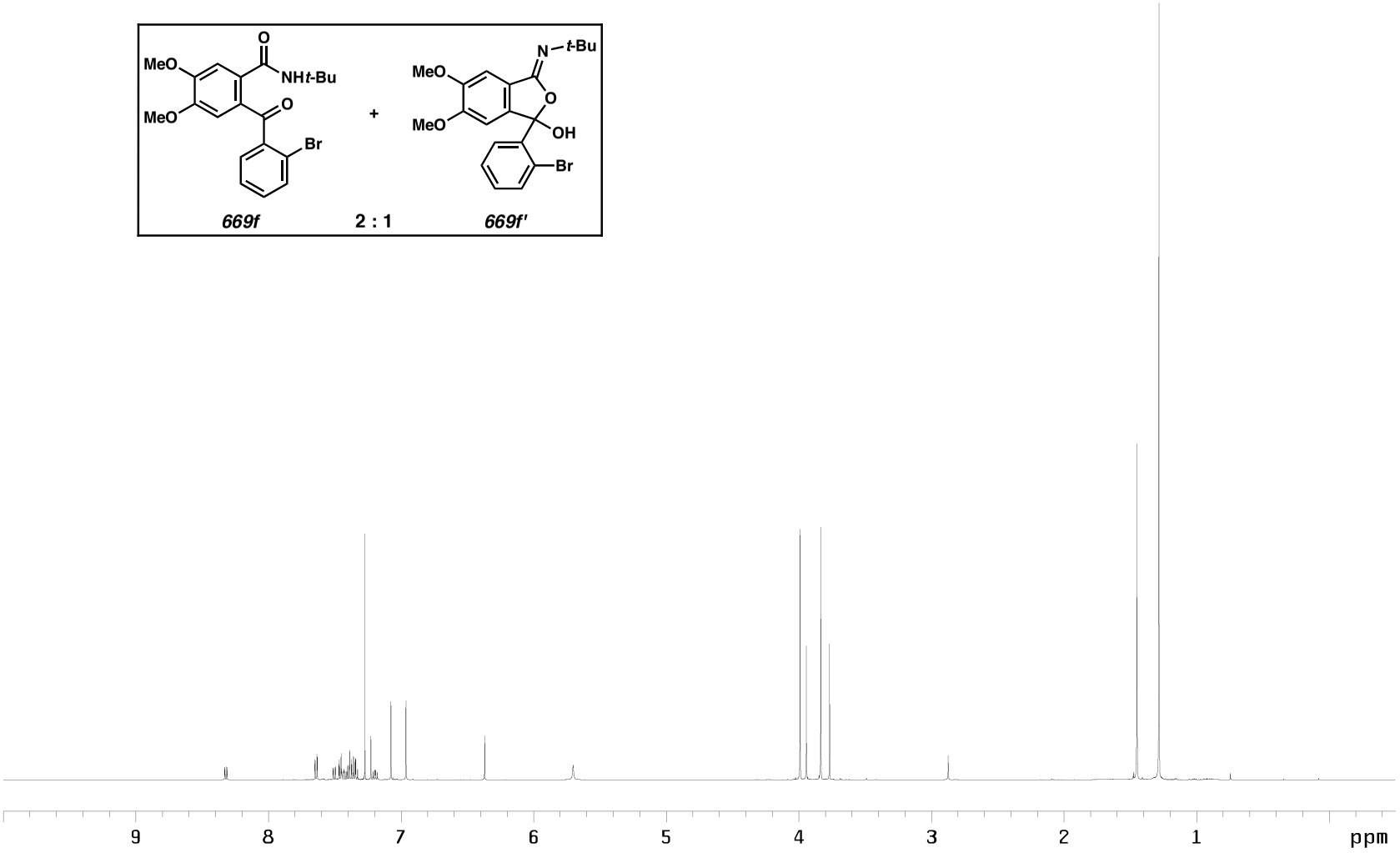


Figure A6.28.1 ^{1}H NMR (500 MHz, $CDCl_3$) of 2:1 mixture of *ortho*-ketobenzamide **669f** and cyclic imidate **669f'**.

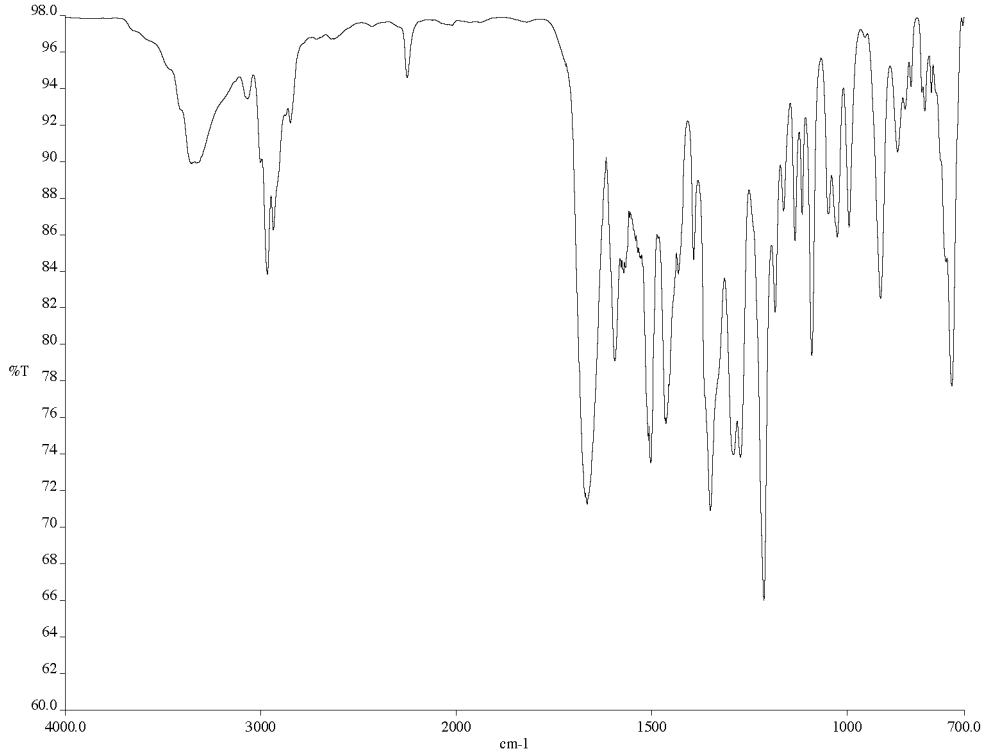


Figure A6.28.2 Infrared spectrum (thin film/NaCl) of 2:1 mixture of *ortho*-ketobenzamide **669f** and cyclic imidate **669f'**.

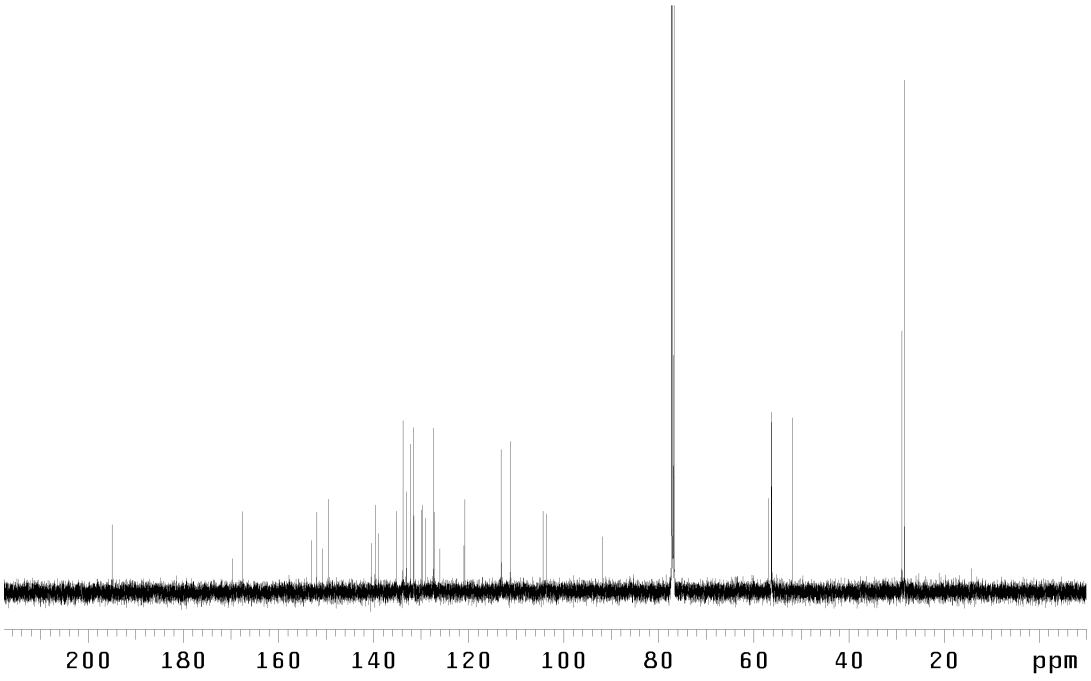


Figure A6.28.3 ^{13}C NMR (125 MHz, $CDCl_3$) of 2:1 mixture of *ortho*-ketobenzamide **669f** and cyclic imidate **669f'**.

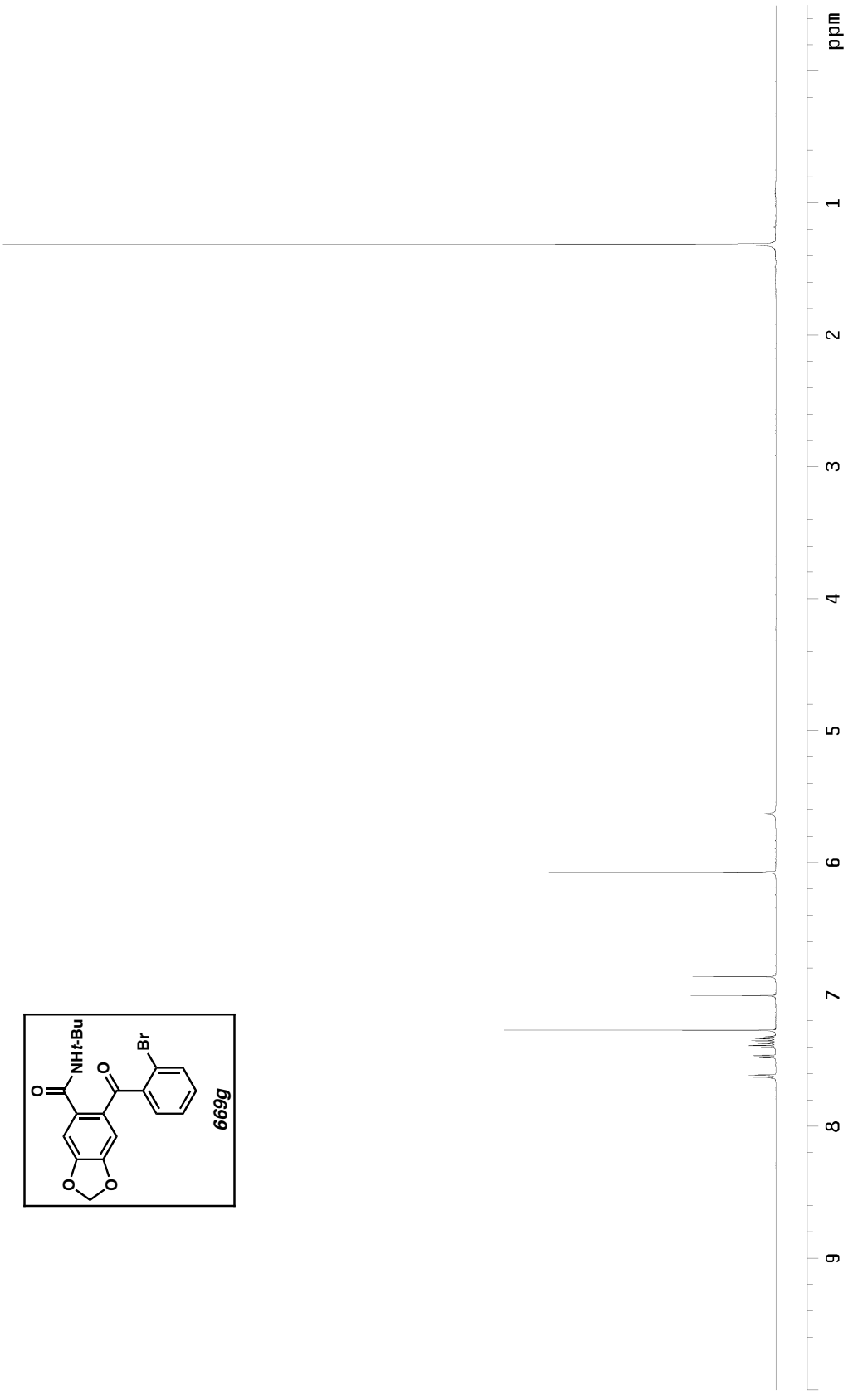


Figure A6.29.1 ^{1}H NMR (500 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669g**.

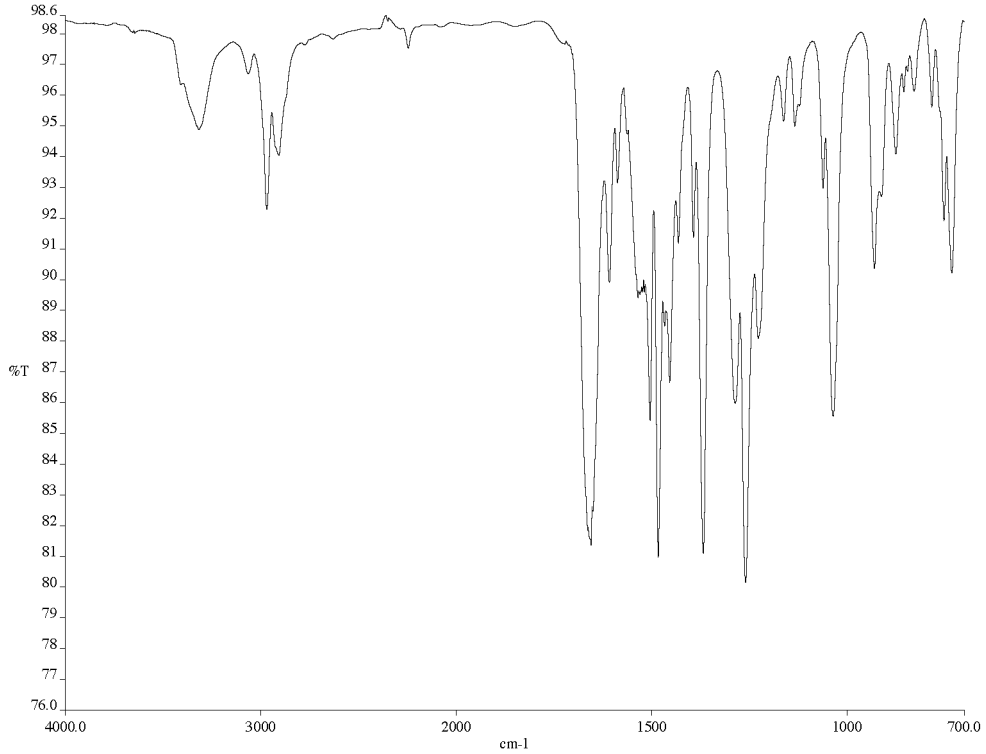


Figure A6.29.2 Infrared spectrum (thin film/NaCl) of *ortho*-ketobenzamide **669g**.

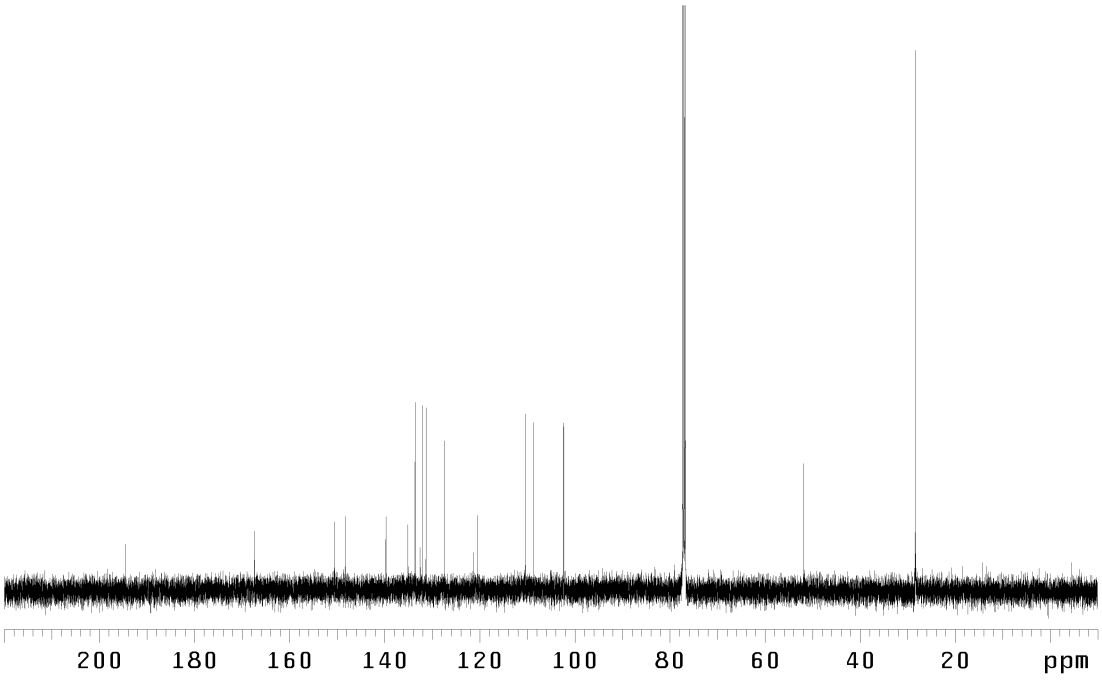


Figure A6.29.3 ^{13}C NMR (125 MHz, $CDCl_3$) of *ortho*-ketobenzamide **669g**.

Figure A6.30.1 ^{1}H NMR (500 MHz, $CDCl_3$) of dibenzoketocaprolactam **687a**.

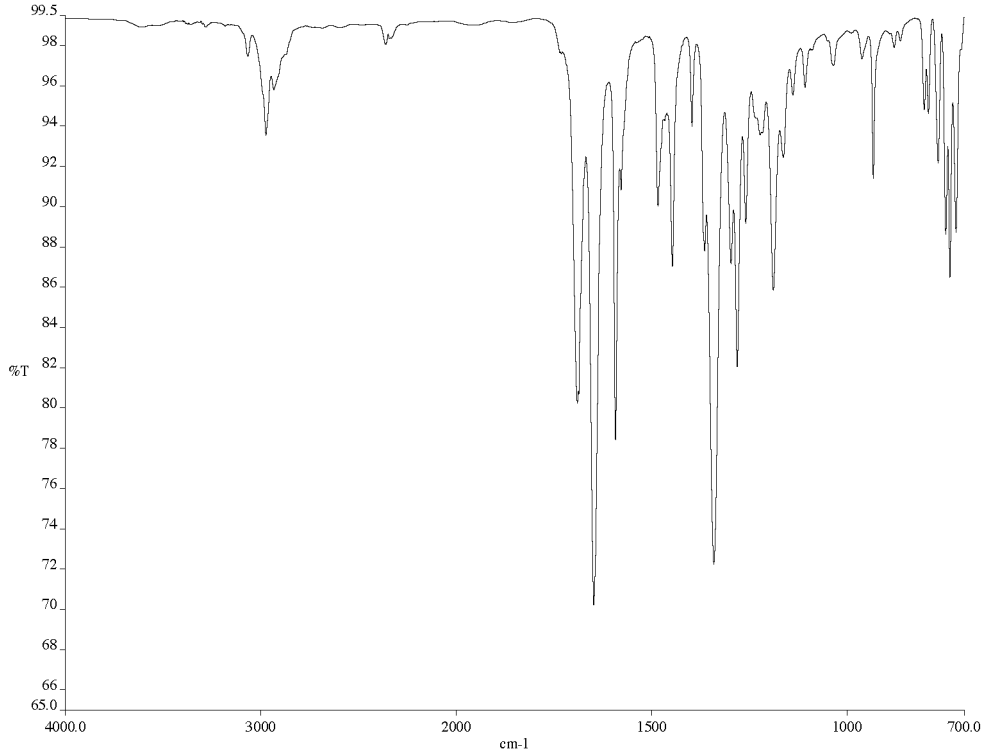


Figure A6.30.2 Infrared spectrum (thin film/NaCl) of dibenzoketocaprolactam **687a**

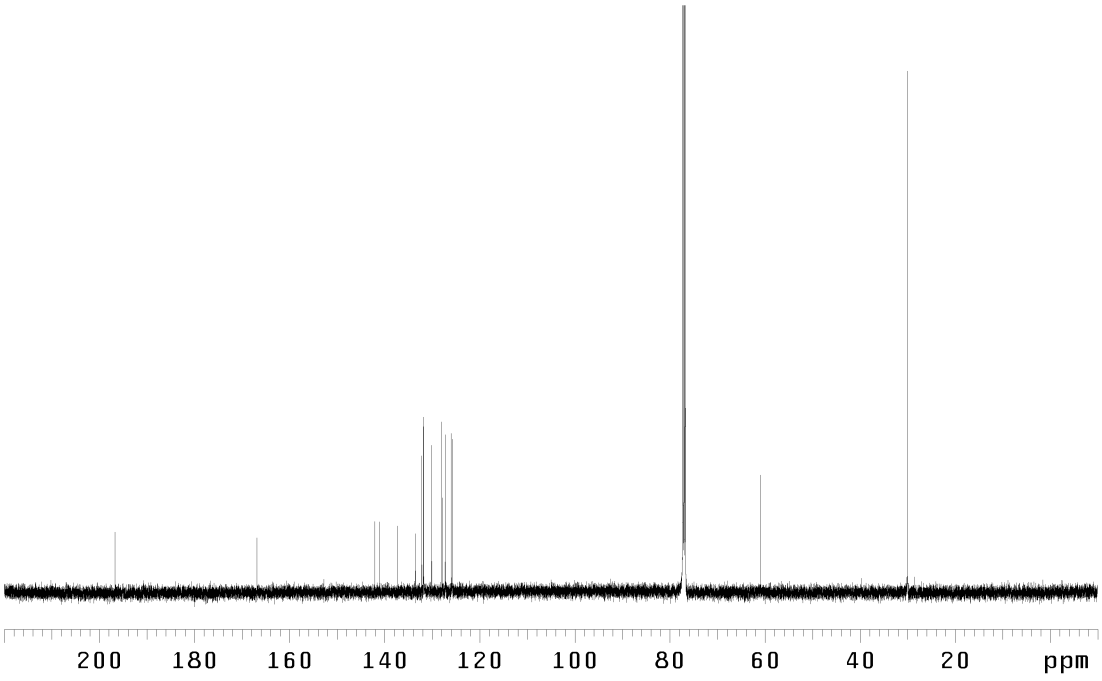


Figure A6.30.3 ^{13}C NMR (125 MHz, $CDCl_3$) of dibenzoketocaprolactam **687a**.

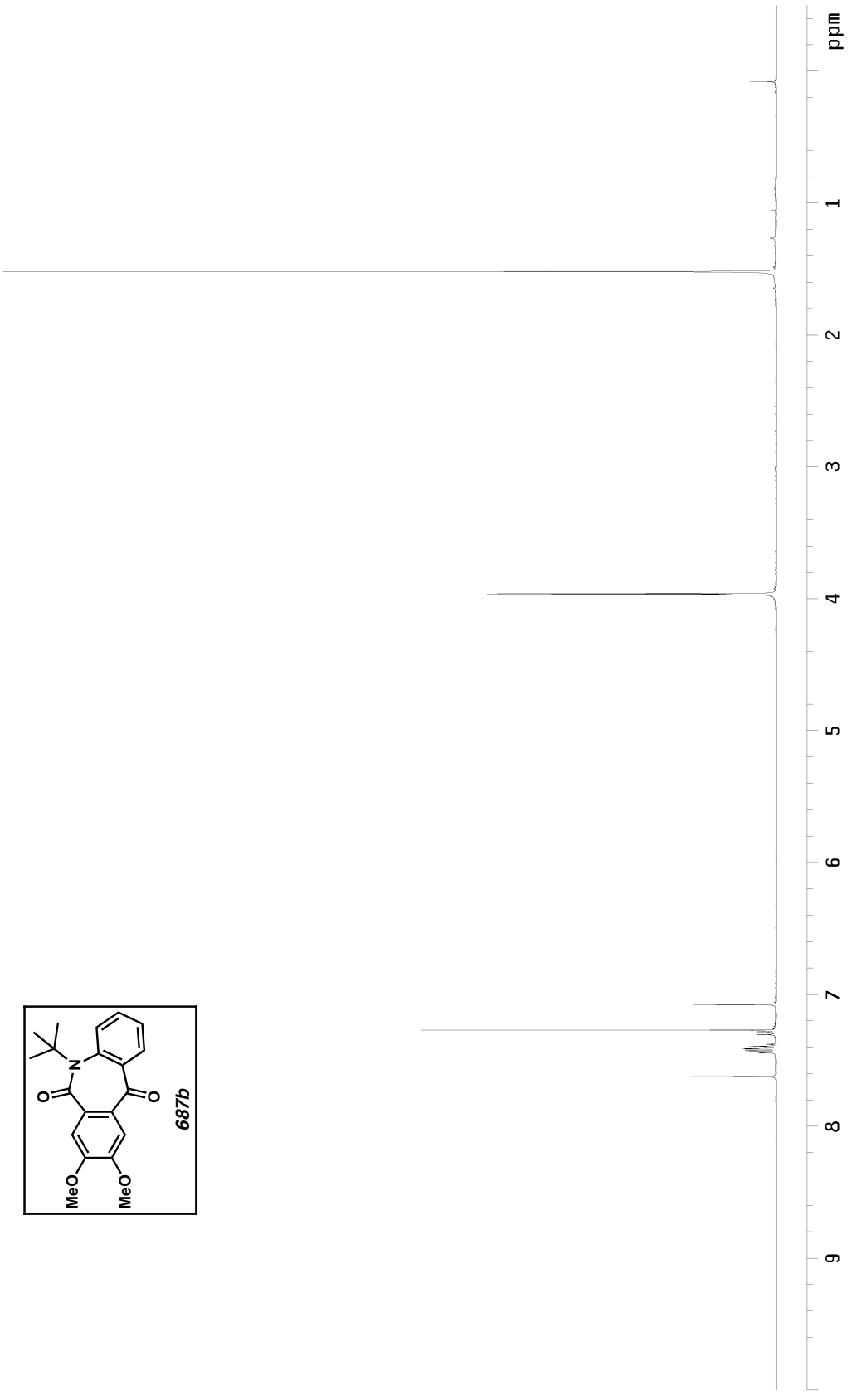


Figure A6.31.1 ^{1}H NMR (500 MHz, $CDCl_3$) of dibenzoketocaprolactam **687b**.

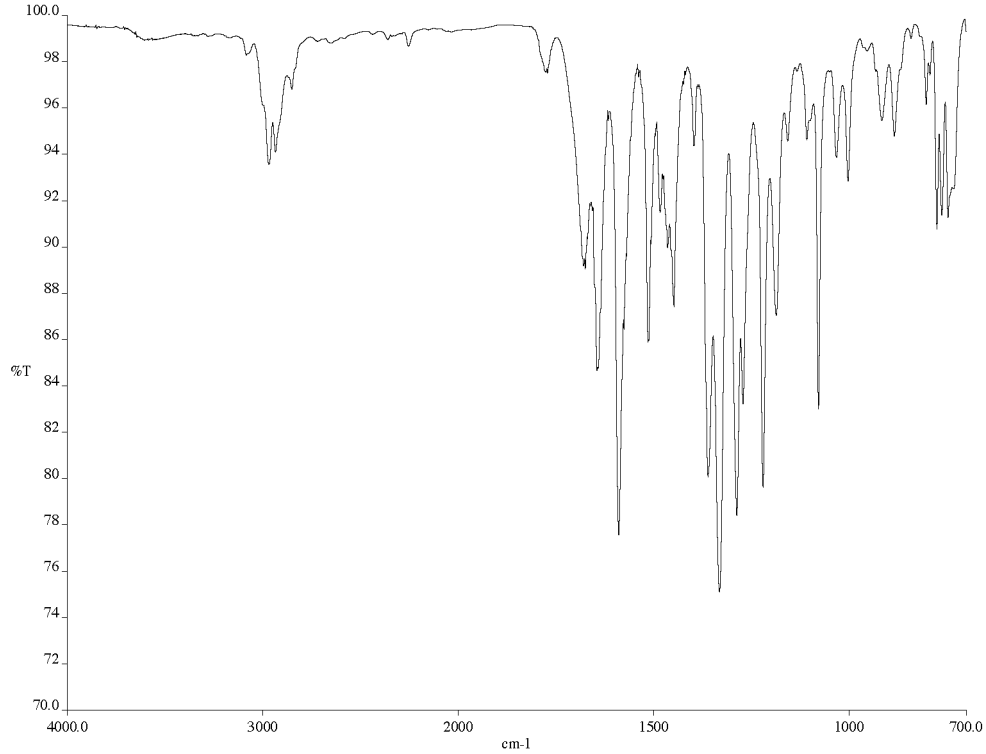


Figure A6.31.2 Infrared spectrum (thin film/NaCl) of dibenzoketocaprolactam **687b**.

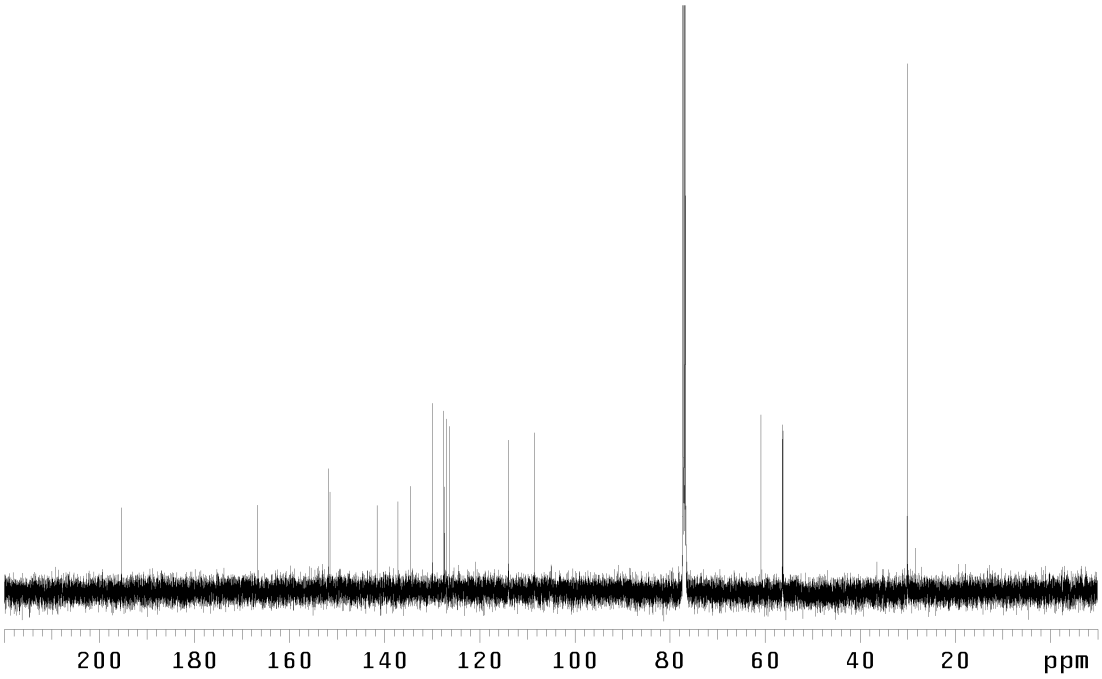


Figure A6.31.3 ^{13}C NMR (125 MHz, $CDCl_3$) of dibenzoketocaprolactam **687b**.

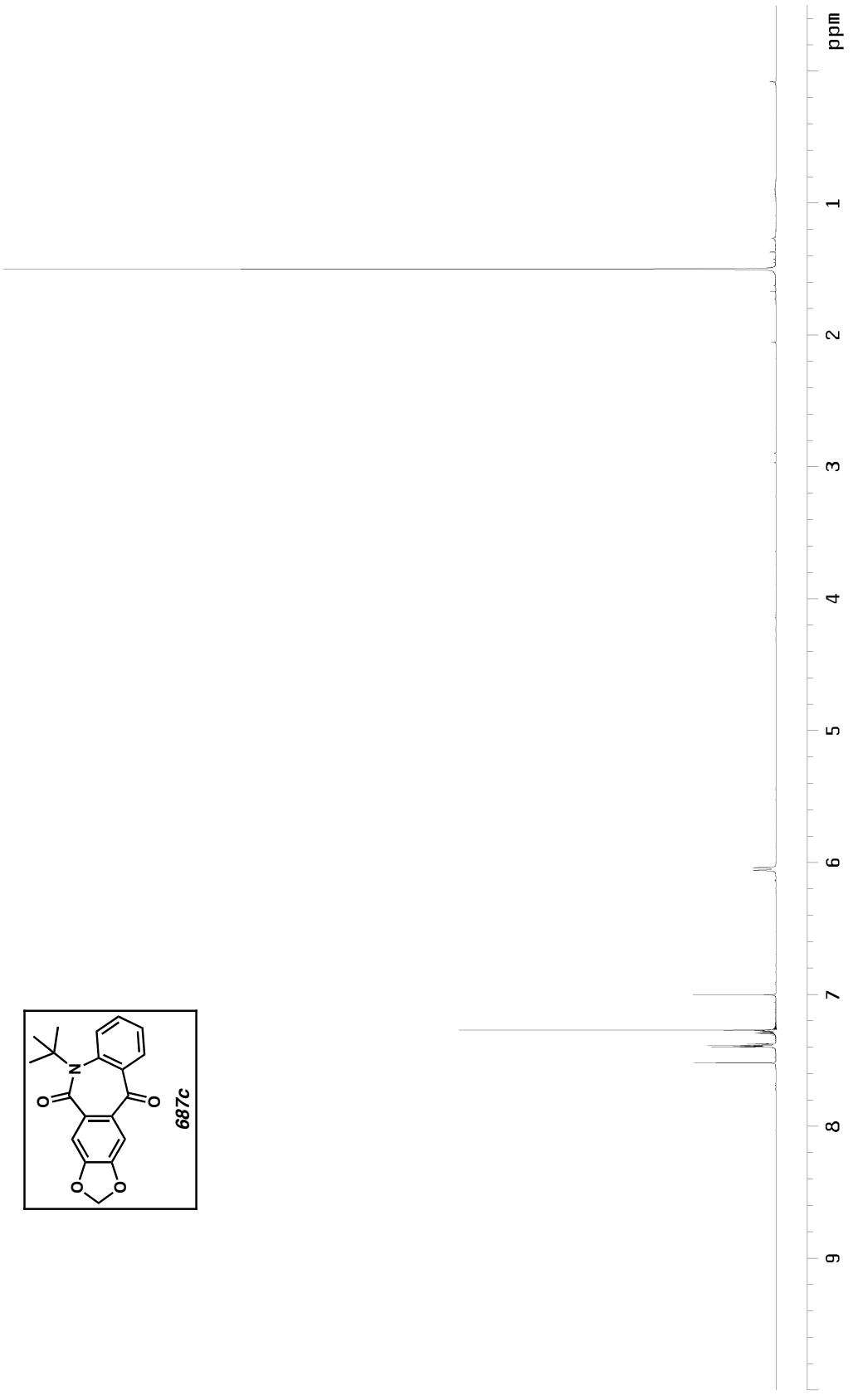


Figure A6.32.1 ^{1}H NMR (500 MHz, $CDCl_3$) of dibenzoketocaprolactam **687c**.

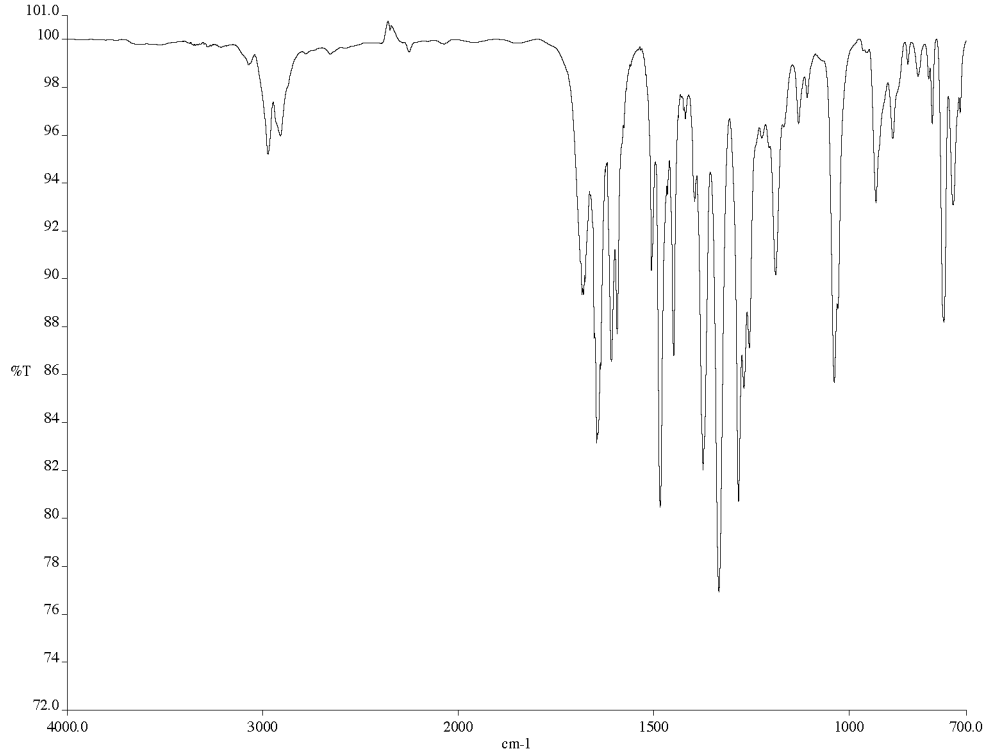


Figure A6.32.2 Infrared spectrum (thin film/NaCl) of dibenzoketocaprolactam **687c**.

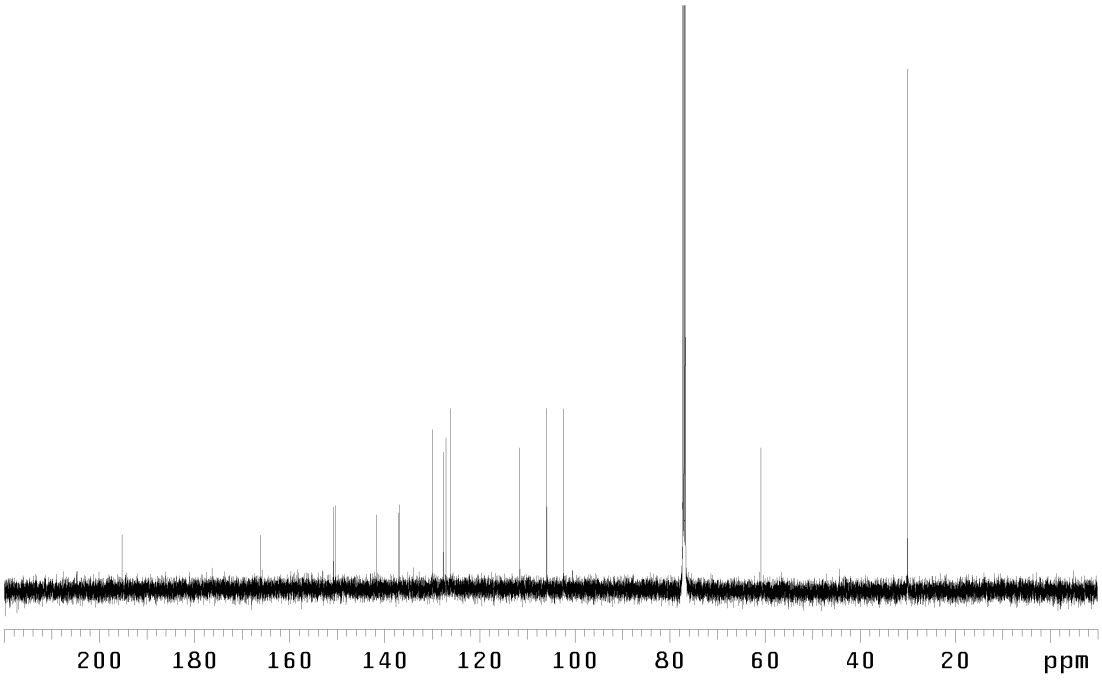


Figure A6.32.3 ^{13}C NMR (125 MHz, $CDCl_3$) of dibenzoketocaprolactam **687c**.

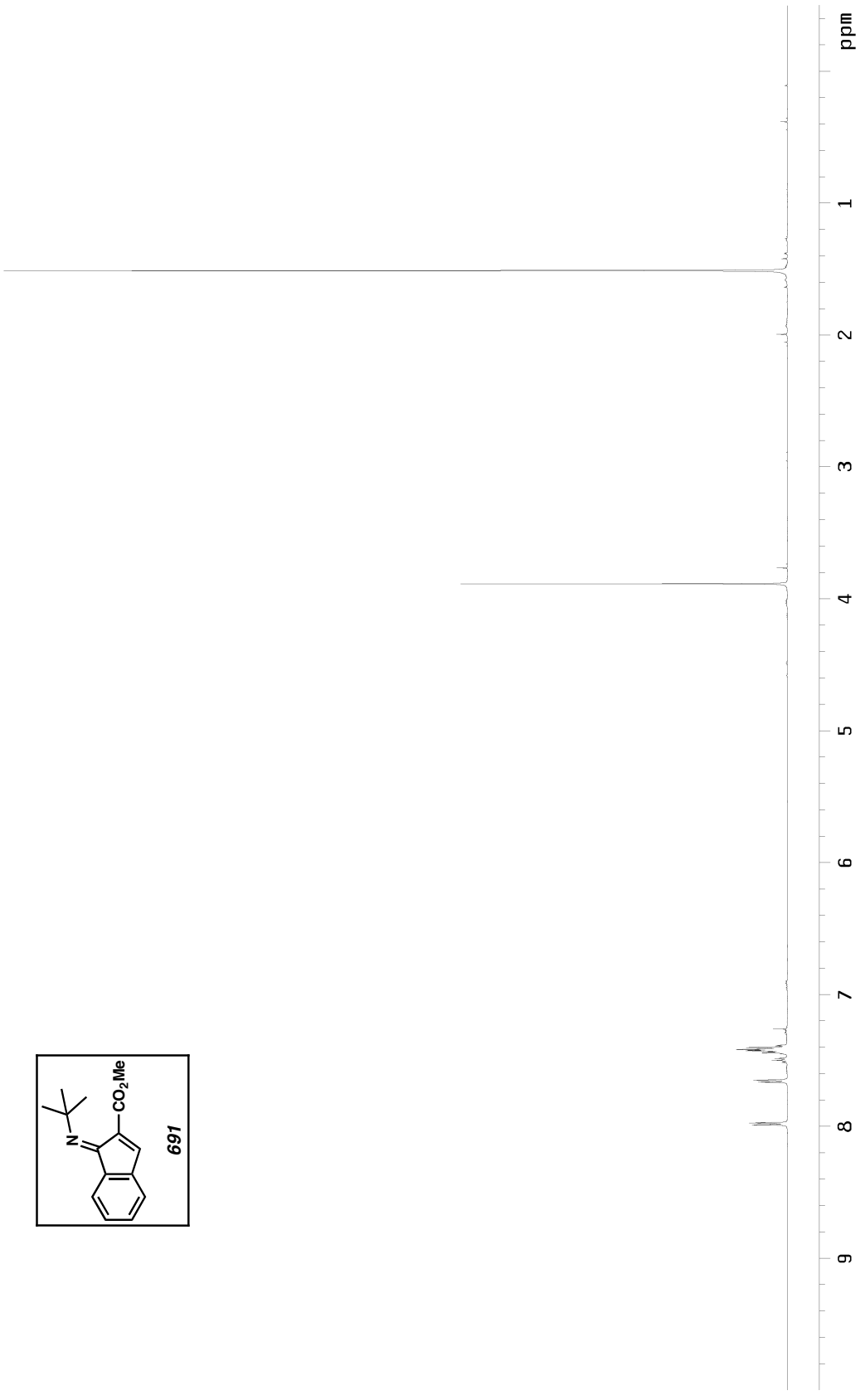


Figure A6.33.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **691**.

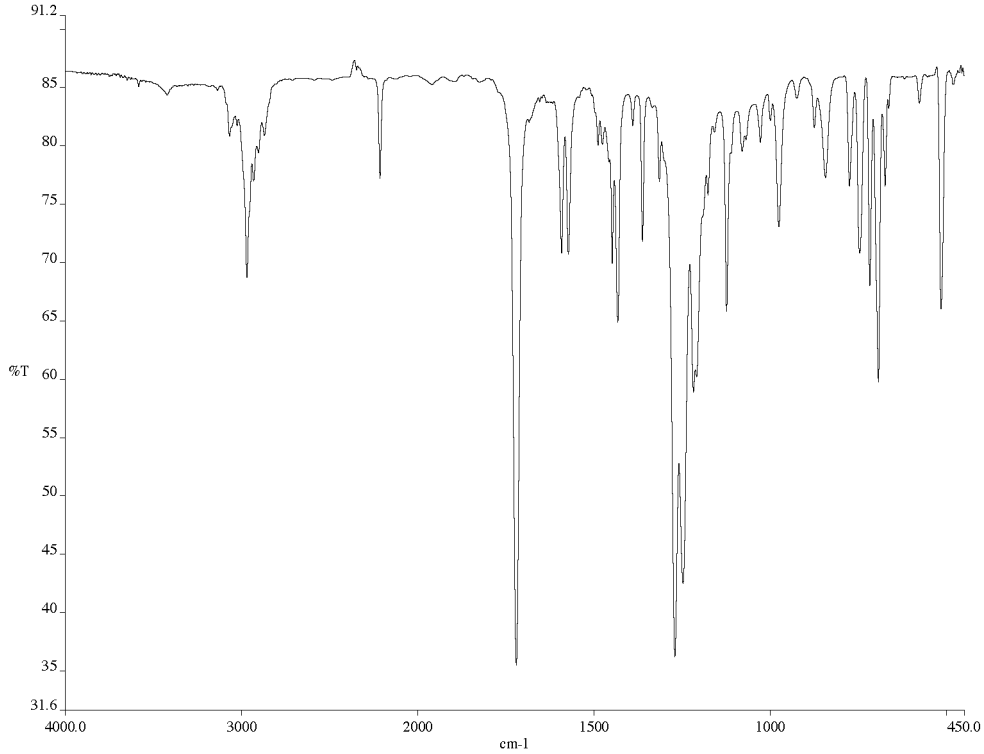


Figure A6.33.2 Infrared spectrum (thin film/NaCl) of iminoindenone **691**.

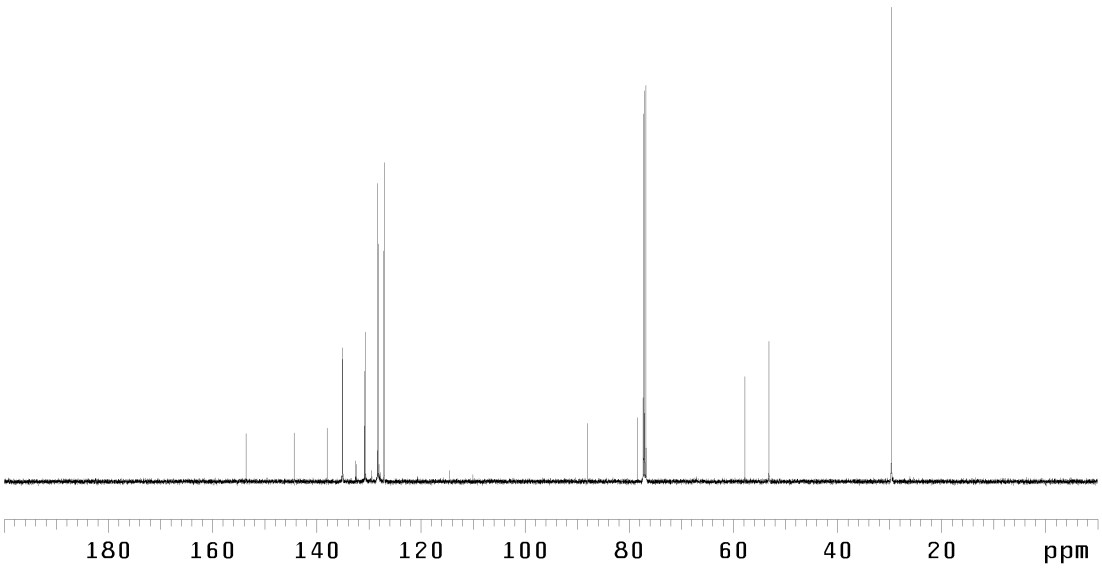


Figure A6.33.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **691**.

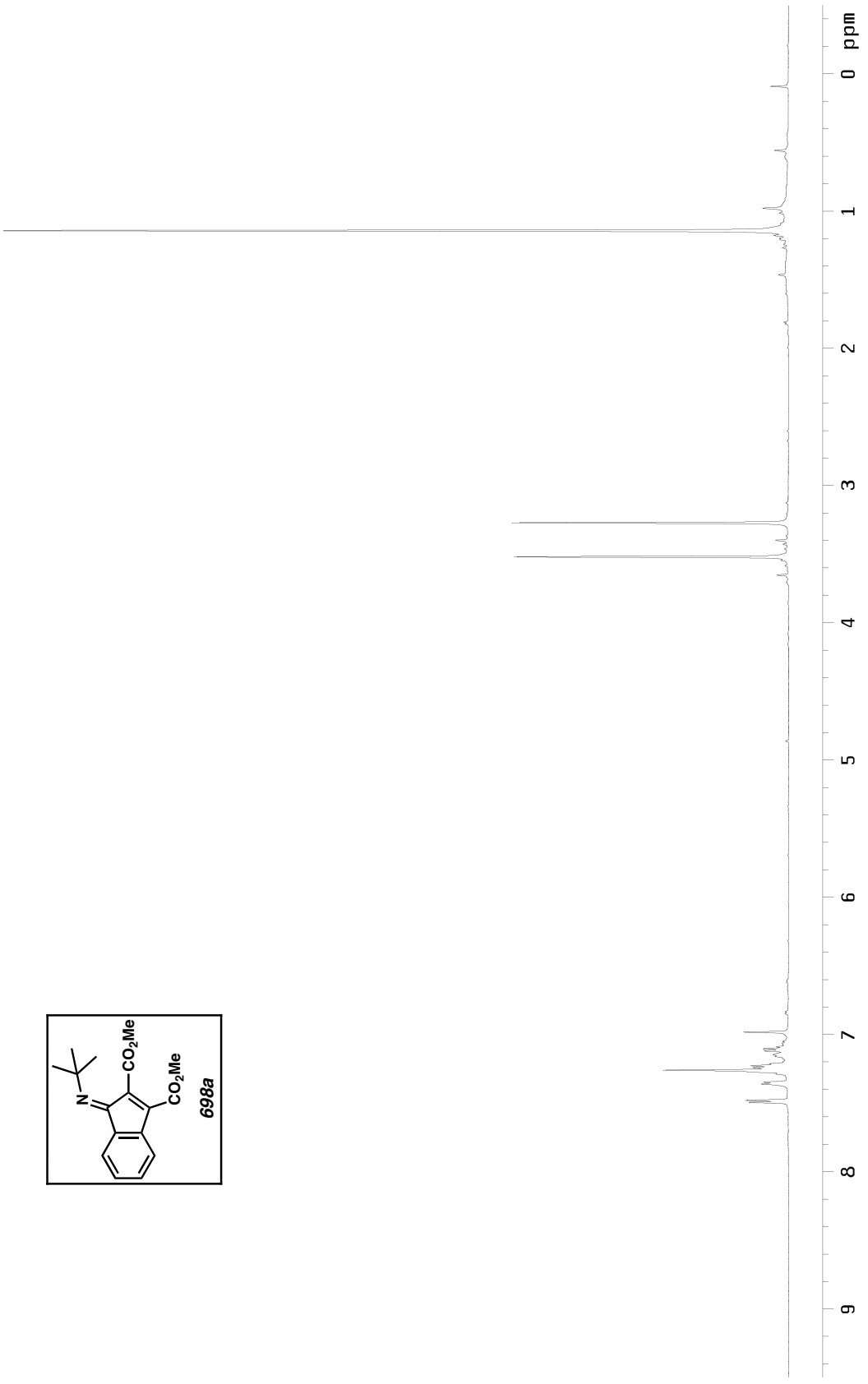


Figure A6.34.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **698a**.

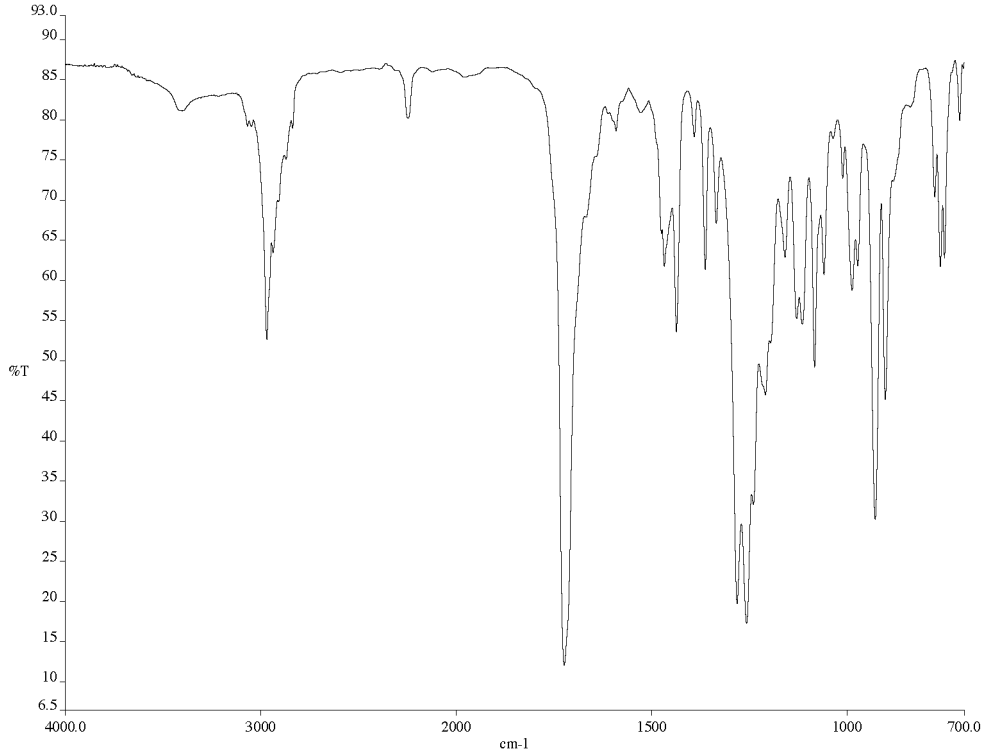


Figure A6.34.2 Infrared spectrum (thin film/NaCl) of iminoindenone **698a**.

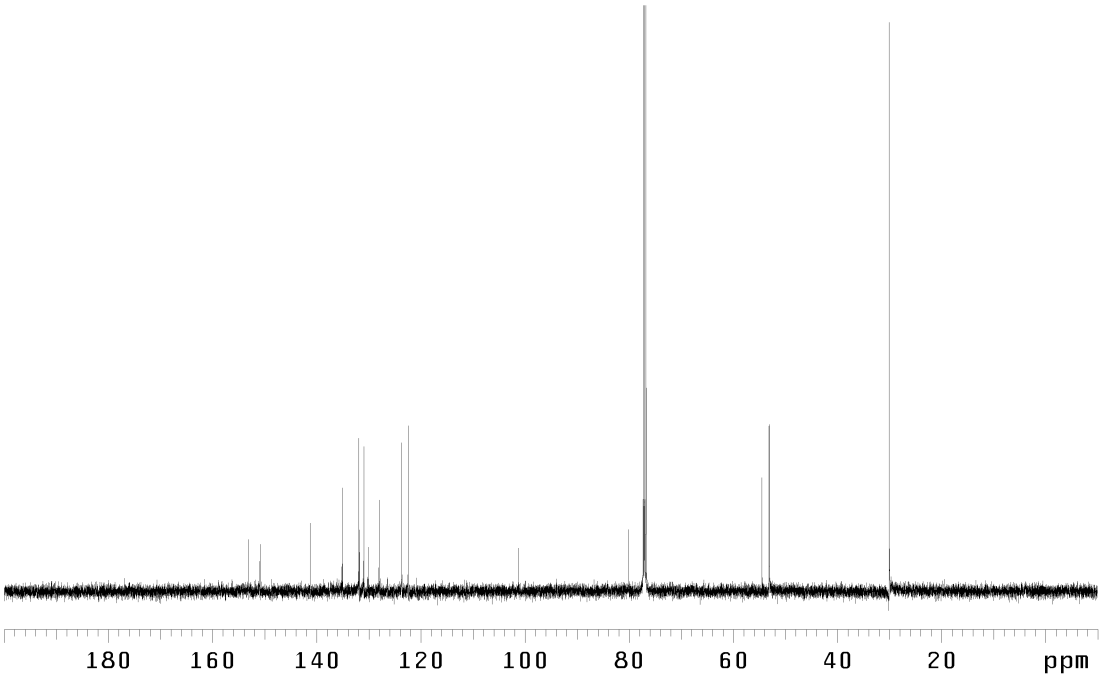


Figure A6.34.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **698a**.

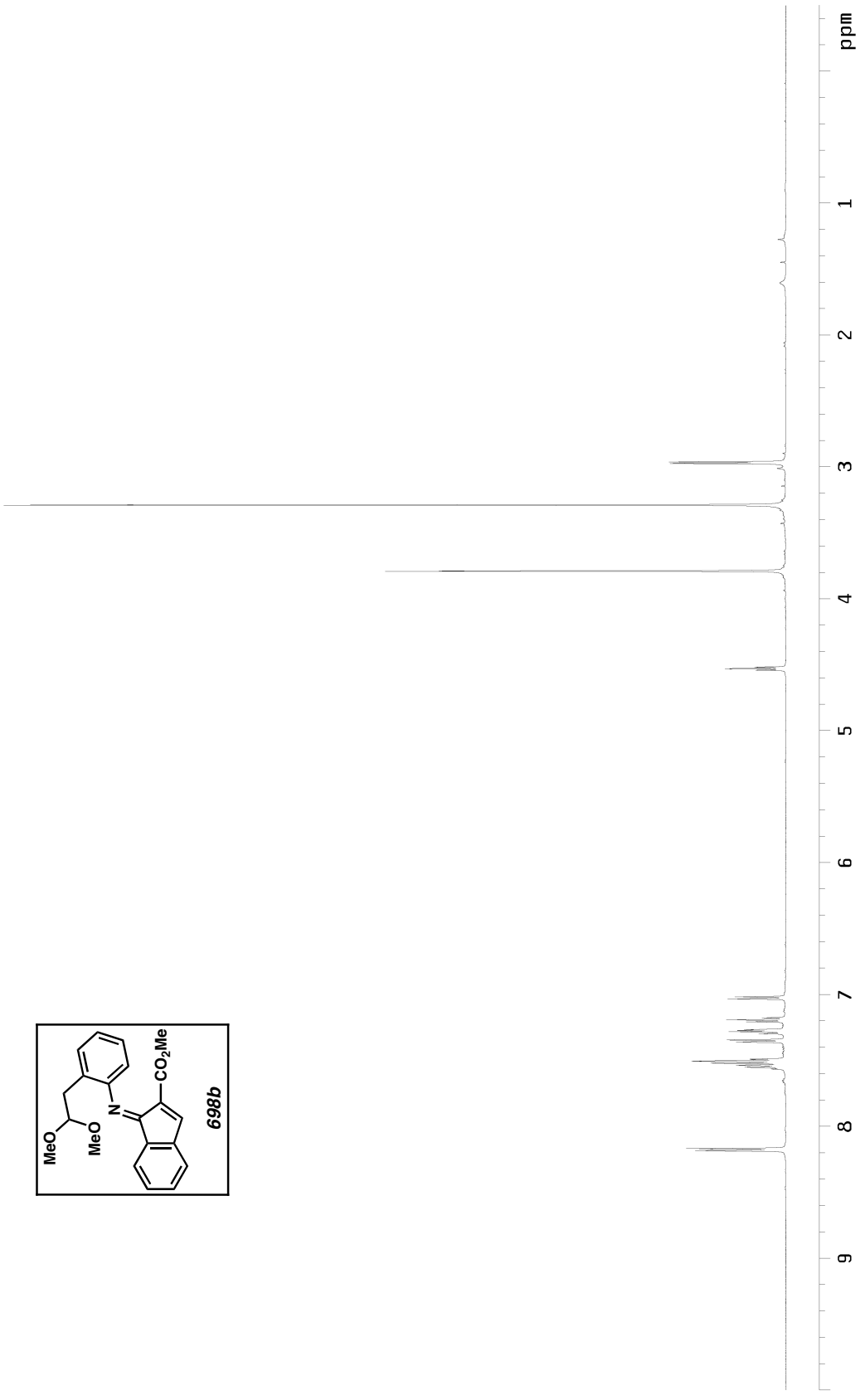


Figure A6.35.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **698b**.

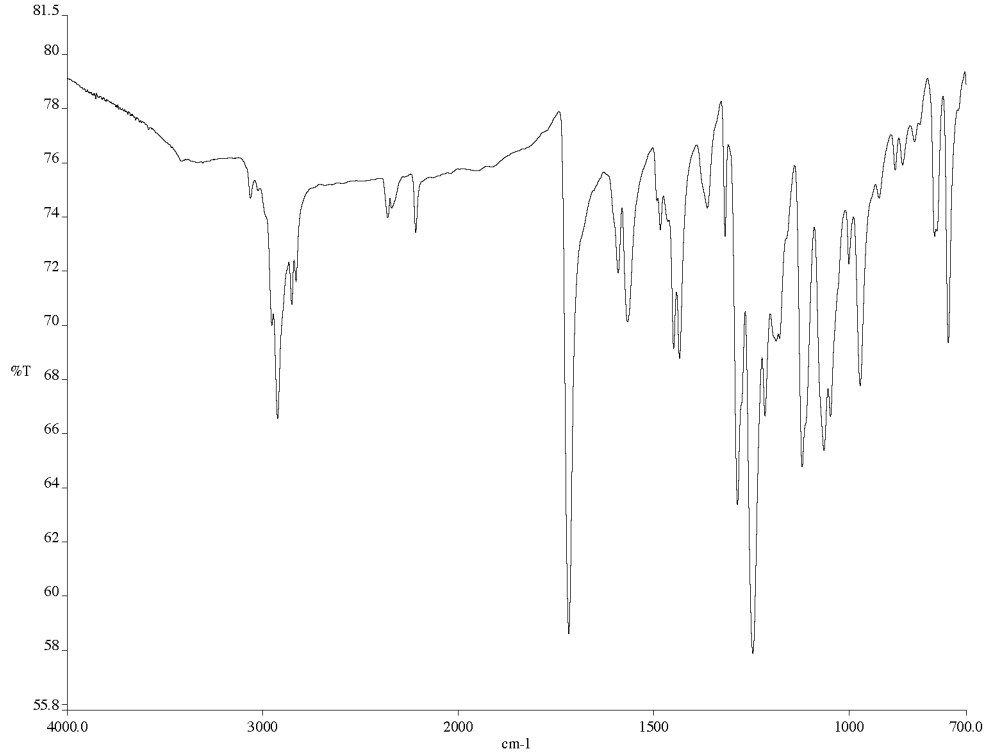


Figure A6.35.2 Infrared spectrum (thin film/NaCl) of iminoindenone **698b**.

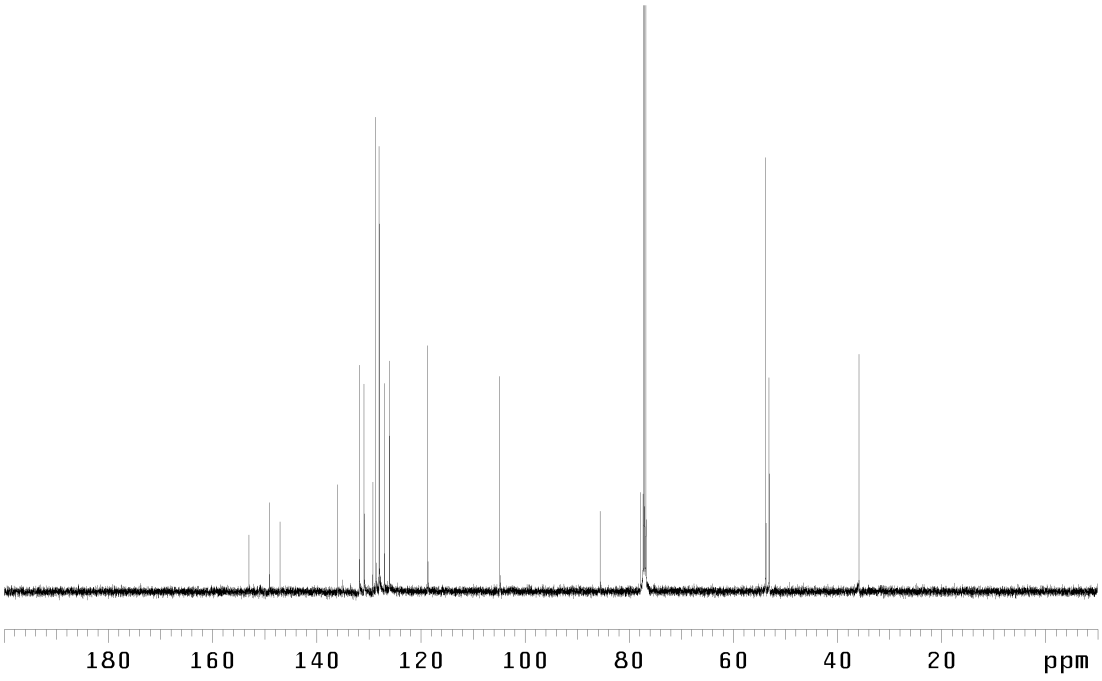


Figure A6.35.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **698b**.

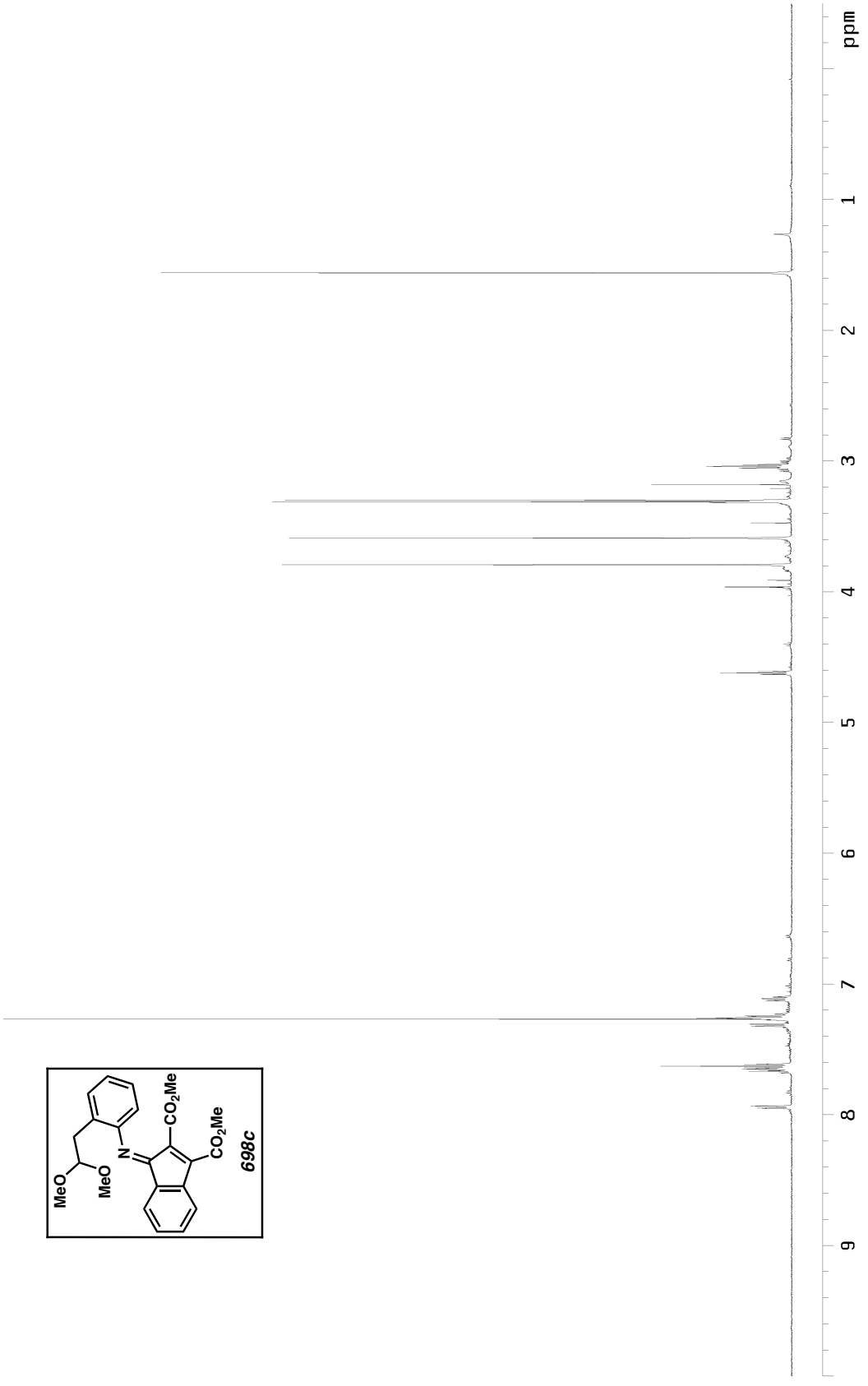


Figure A6.36.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **698c**.

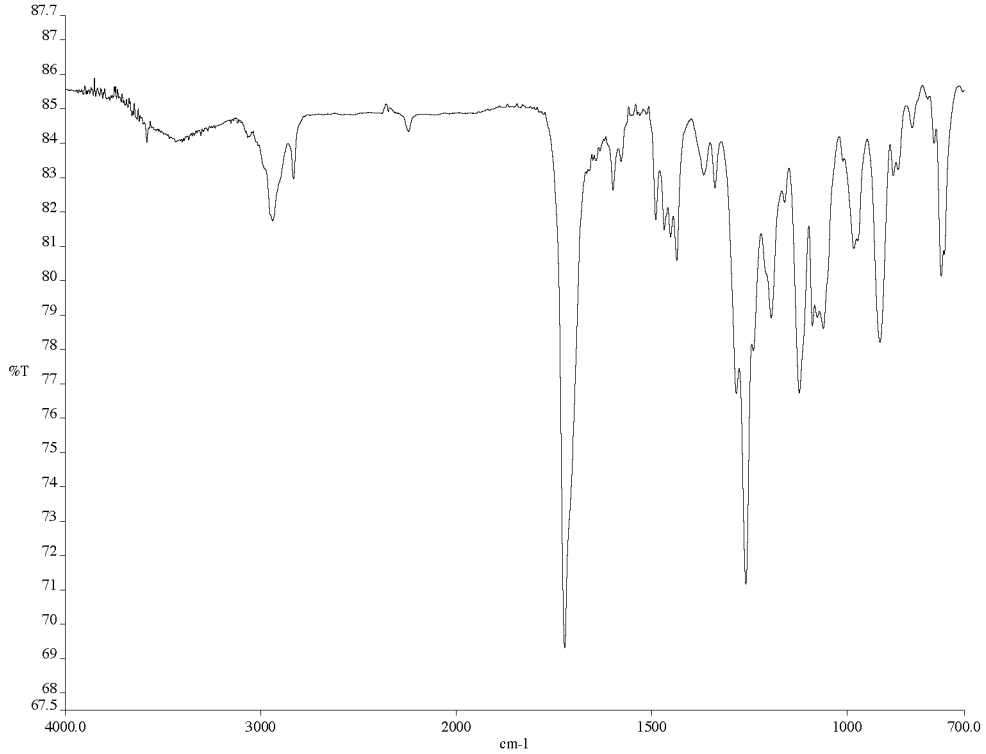


Figure A6.36.2 Infrared spectrum (thin film/NaCl) of iminoindenone **698c**.

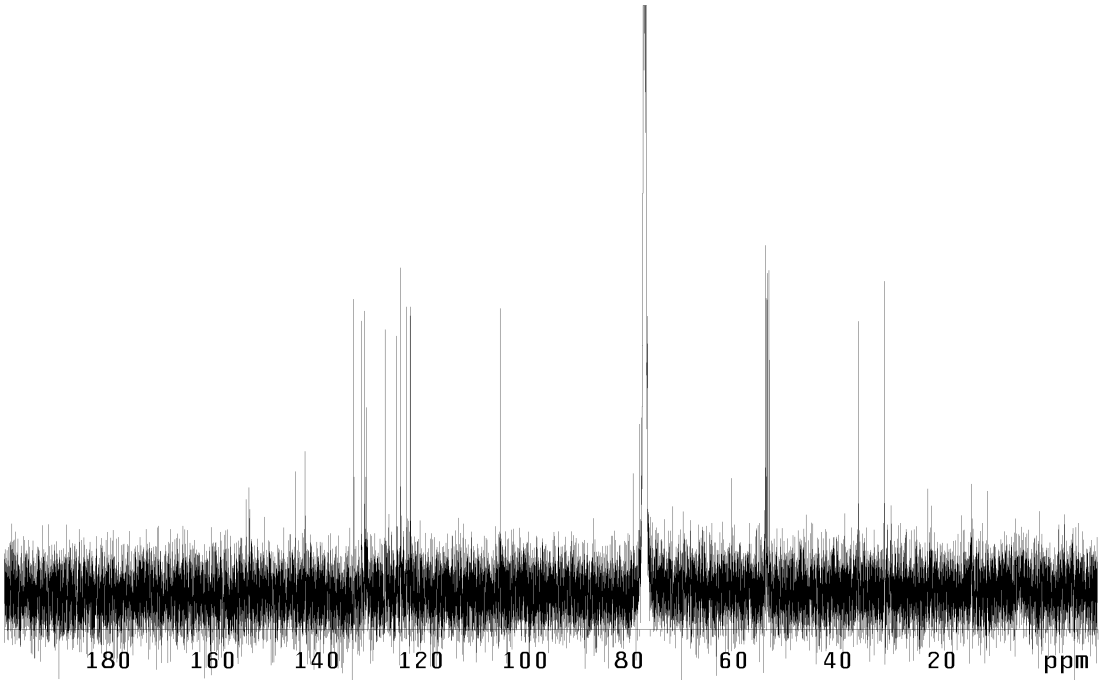


Figure A6.36.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **698c**.

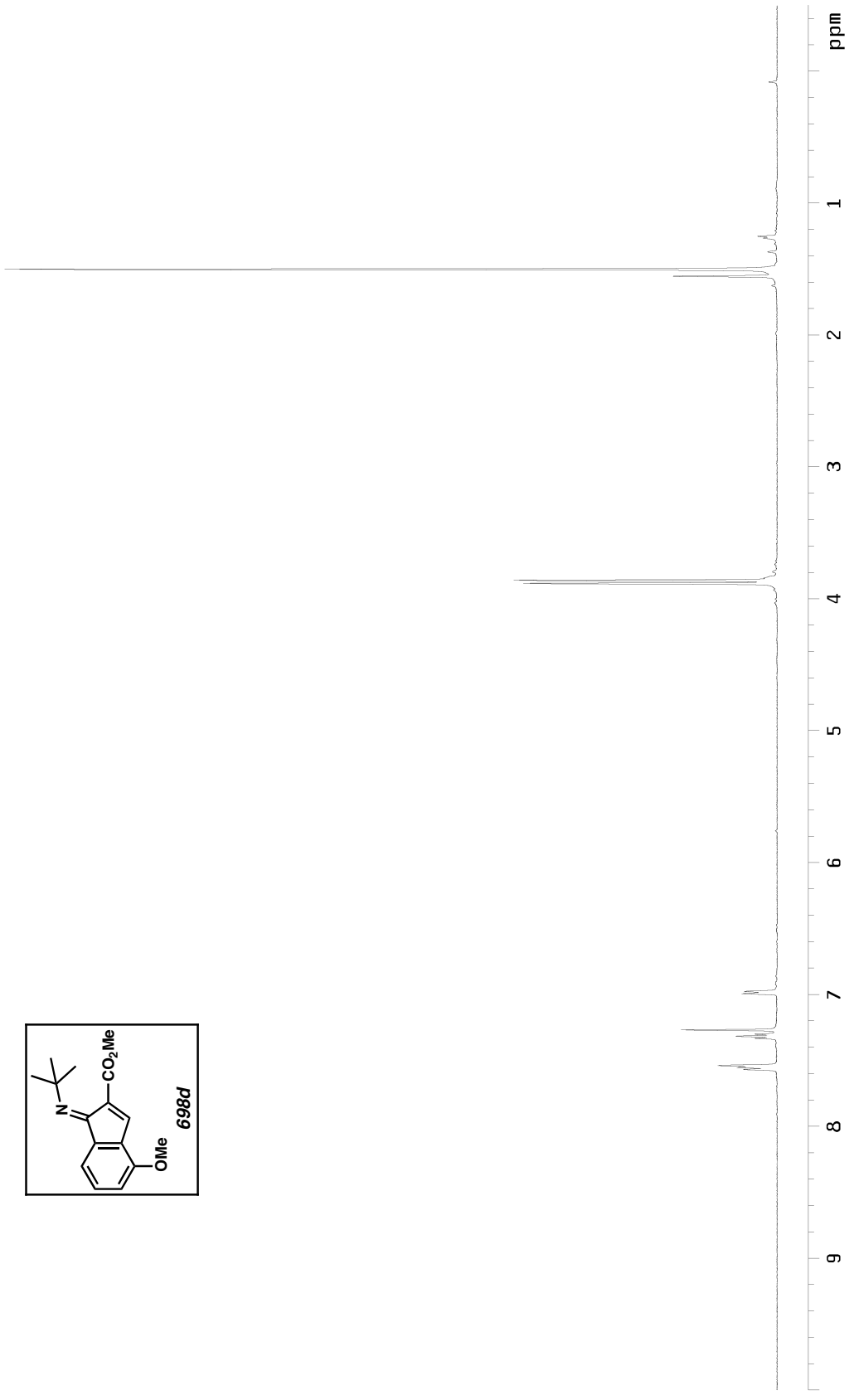


Figure A6.37.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **698d**.

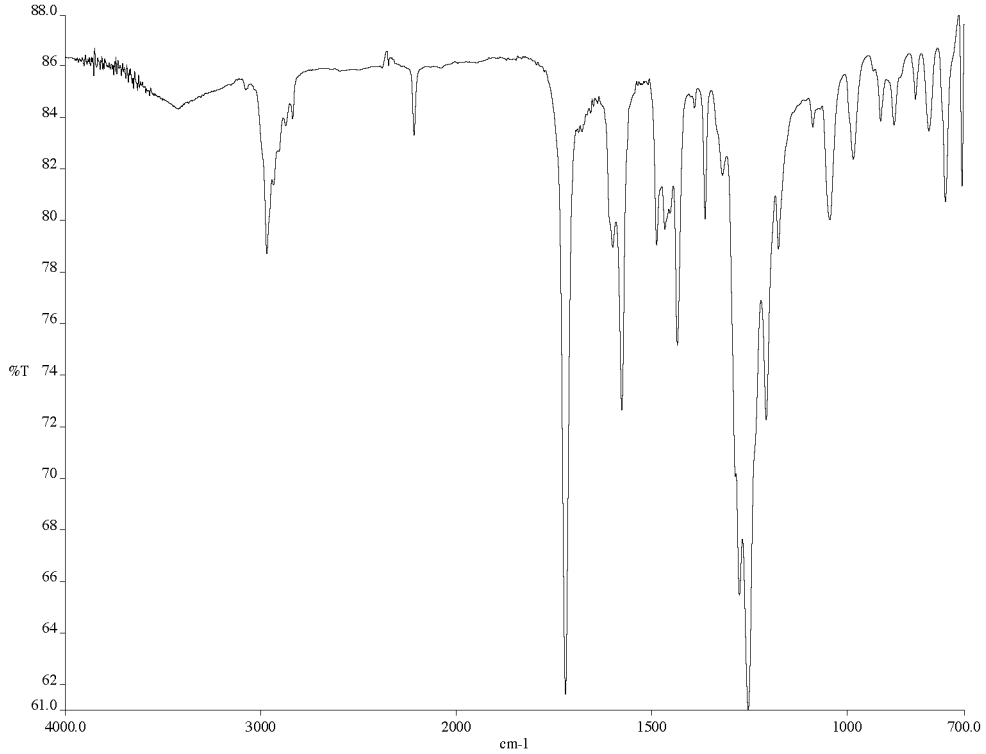


Figure A6.37.2 Infrared spectrum (thin film/NaCl) of iminoindenone **698d**.

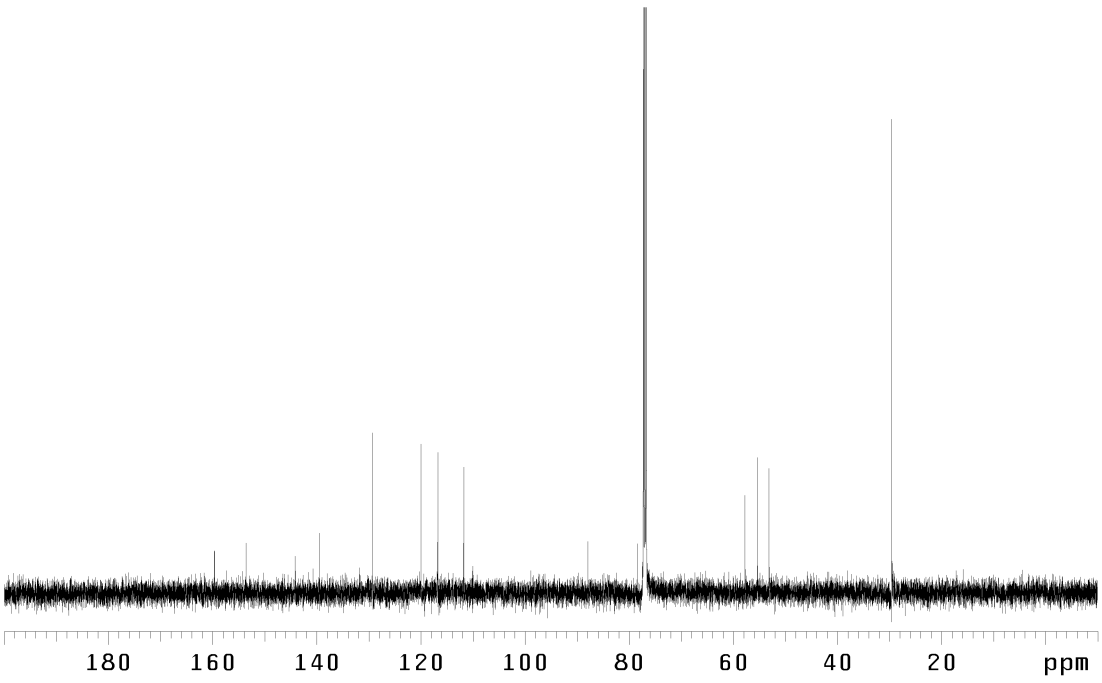


Figure A6.37.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **698d**.

Figure A6.38.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **698e**.

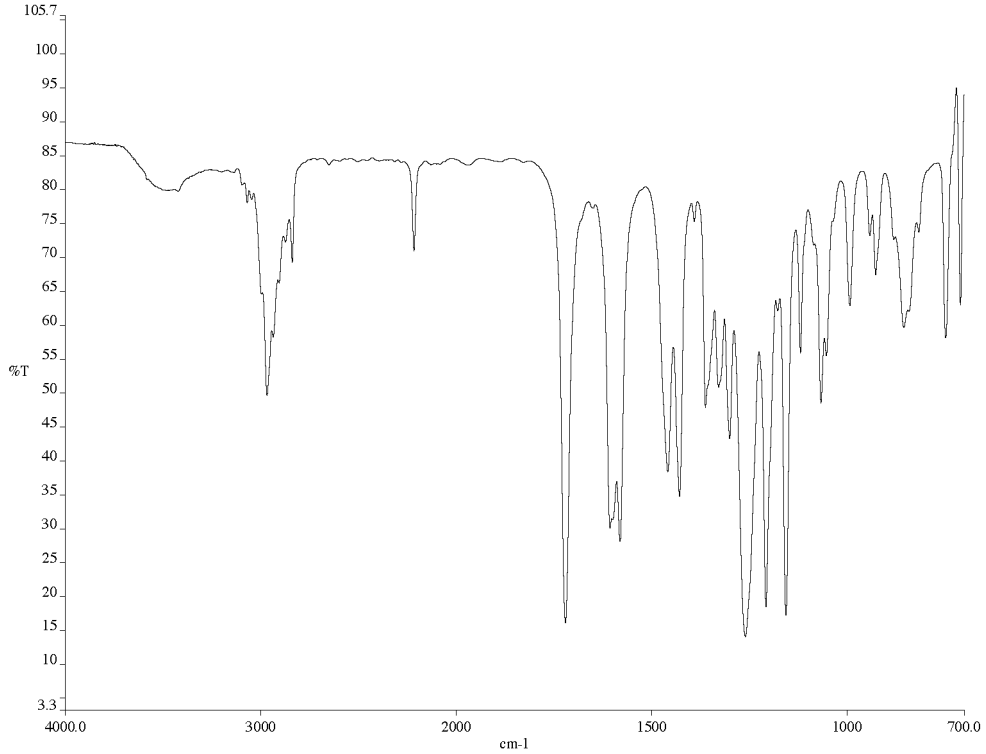


Figure A6.38.2 Infrared spectrum (thin film/NaCl) of iminoindenone **698e**.

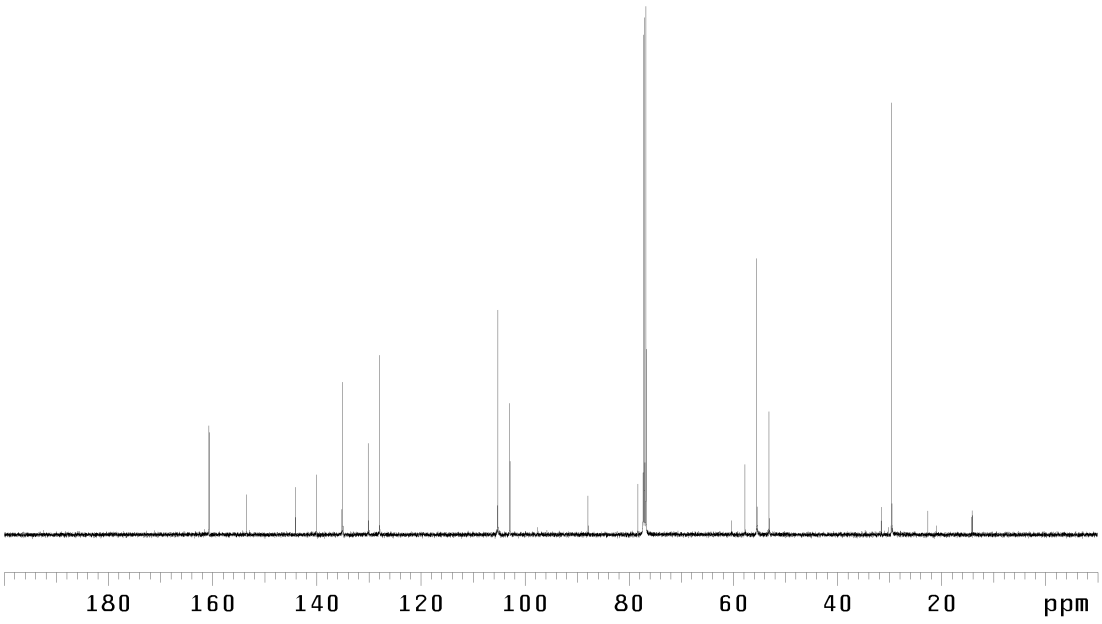


Figure A6.38.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **698e**.

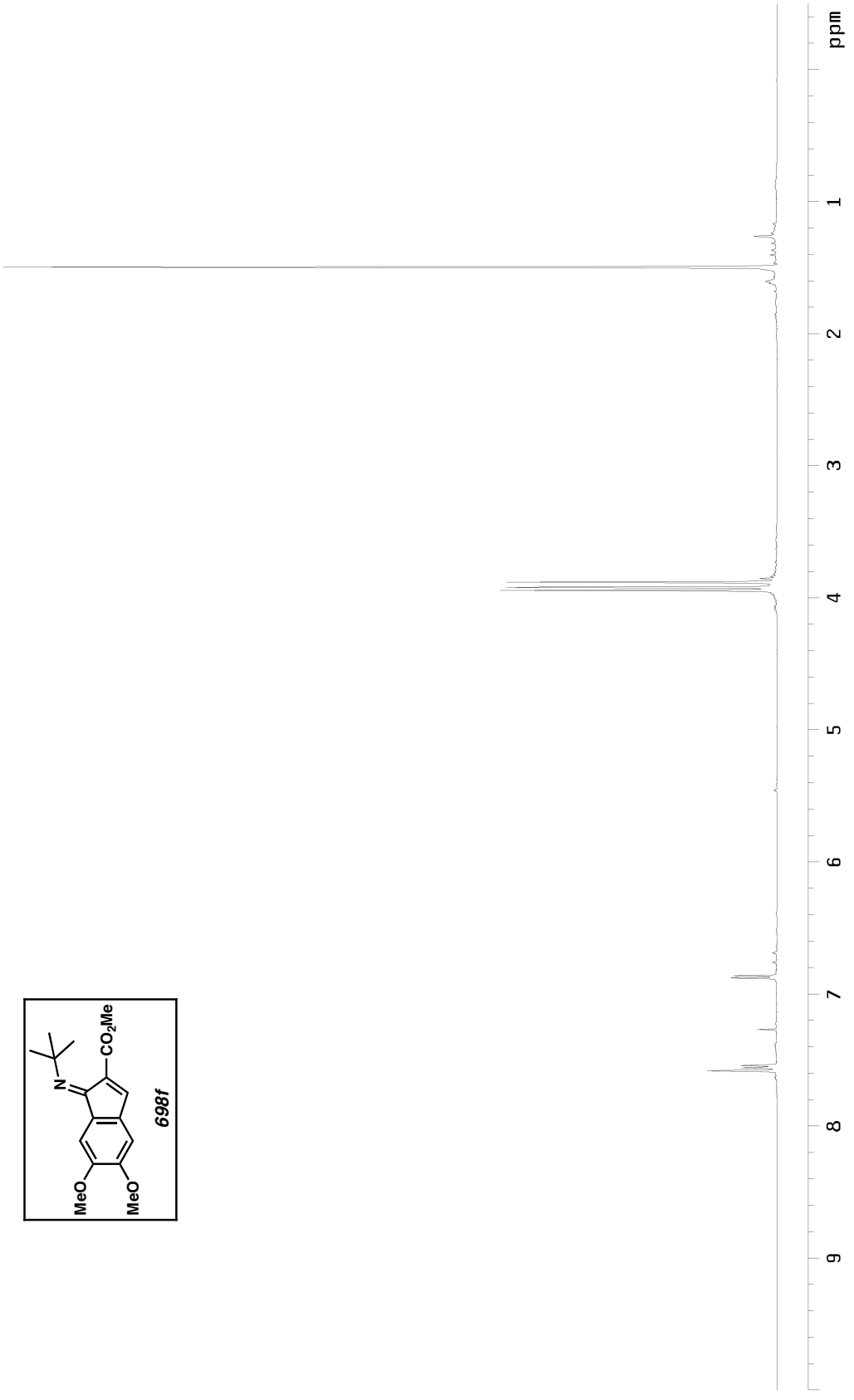


Figure A6.39.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **698f**.

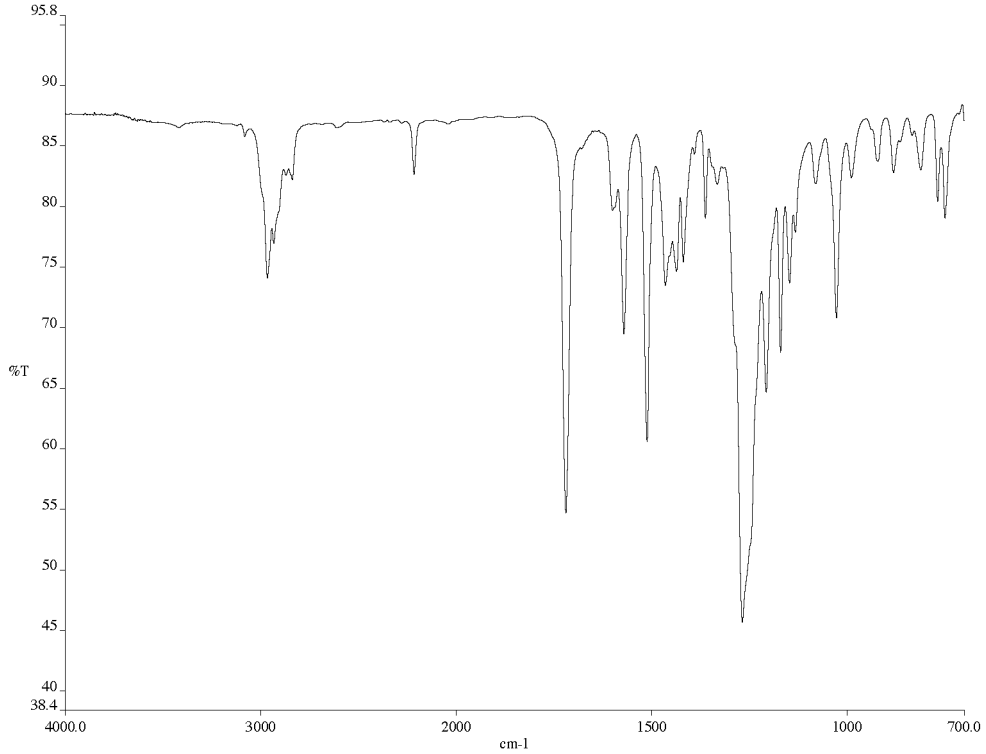


Figure A6.39.2 Infrared spectrum (thin film/NaCl) of iminoindenone **698f**.

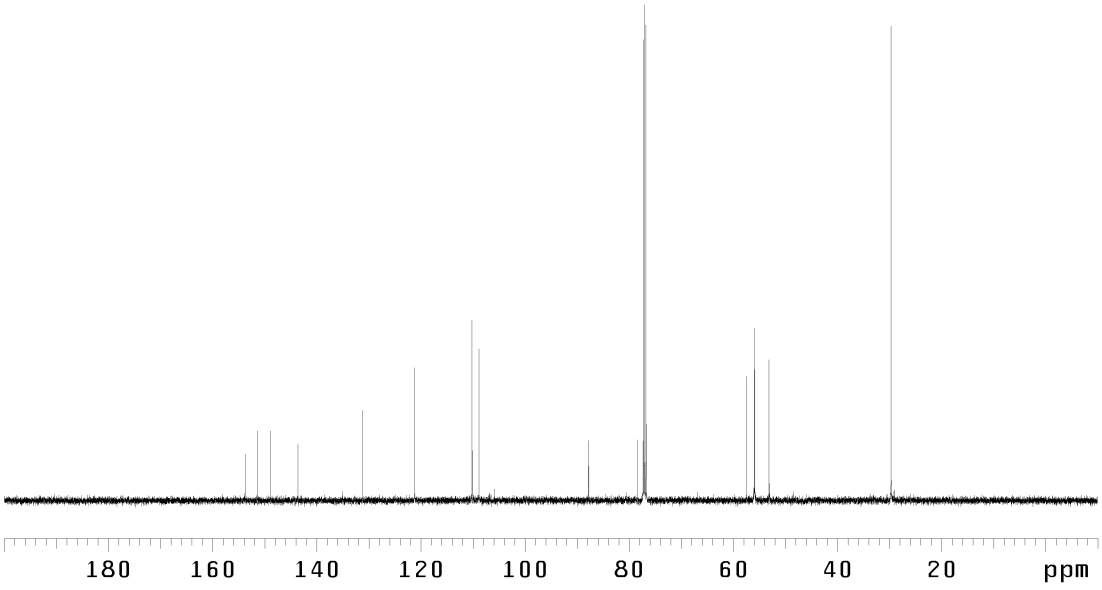


Figure A6.39.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **698f**.

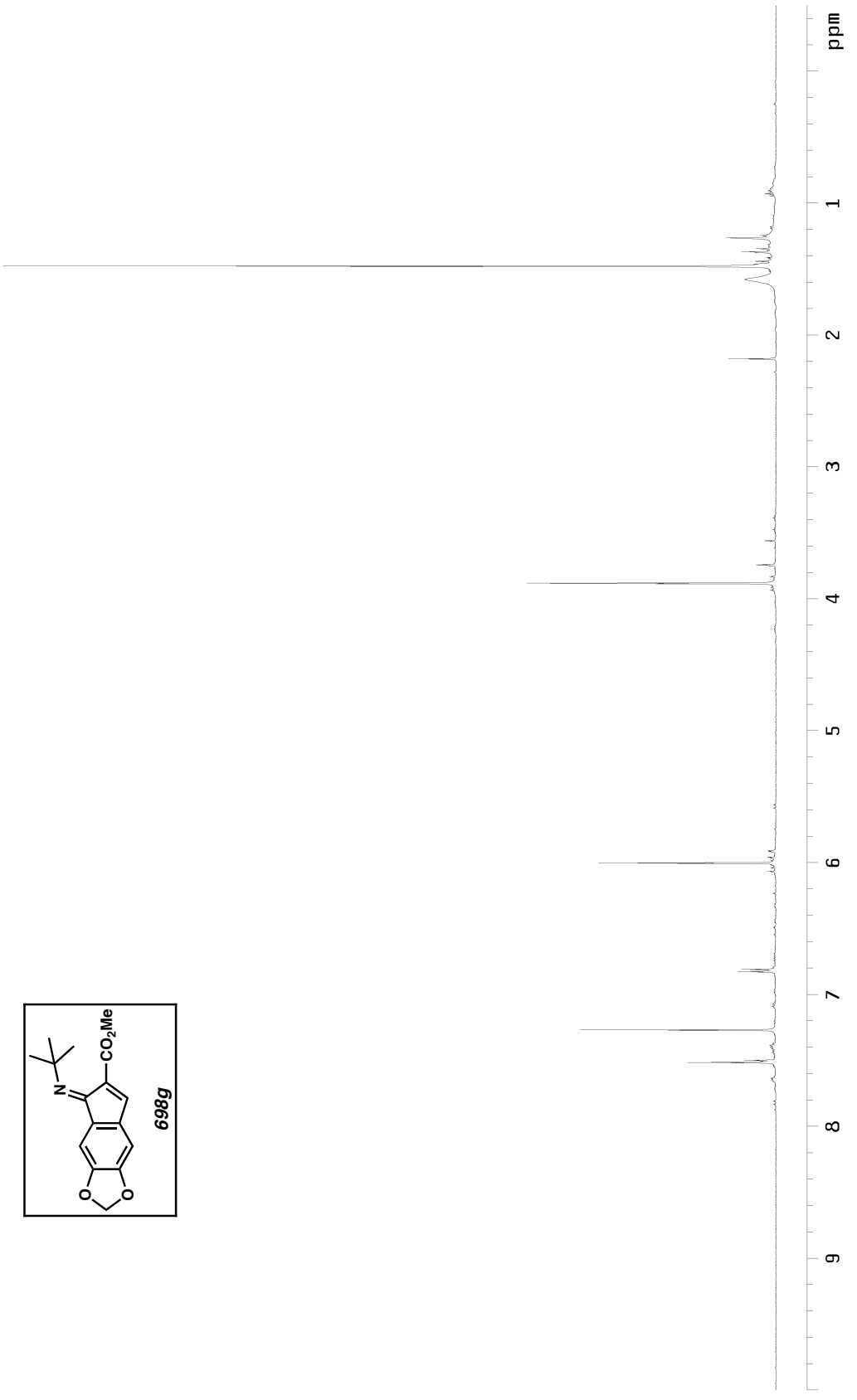


Figure A6.40.1 ^{1}H NMR (500 MHz, $CDCl_3$) of iminoindenone **698g**.

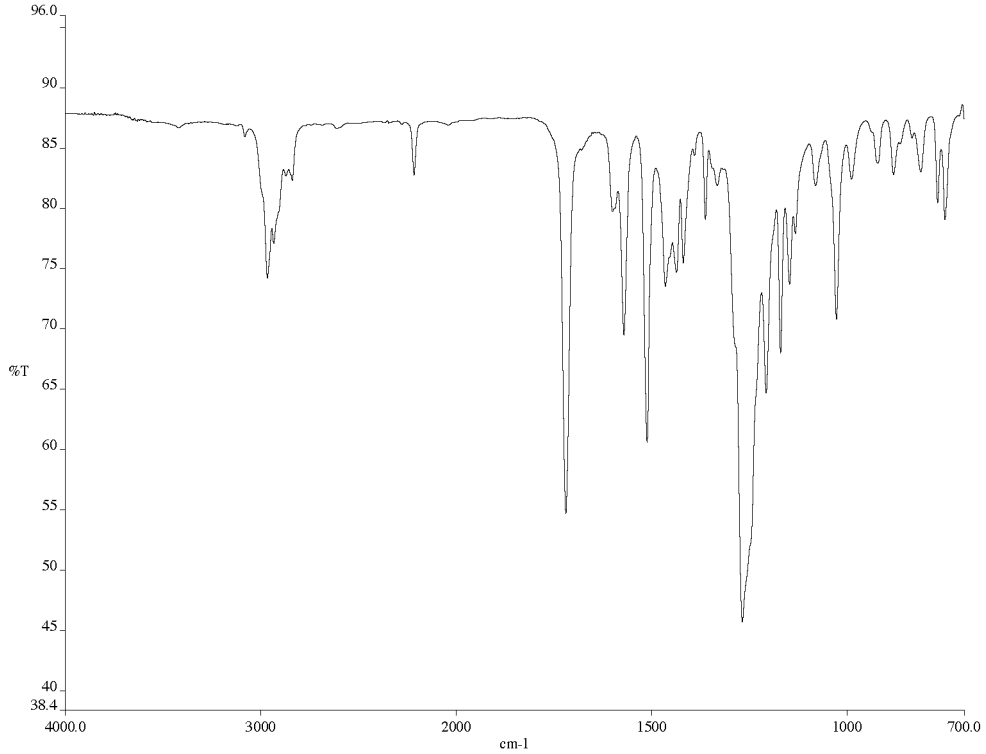


Figure A6.40.2 Infrared spectrum (thin film/NaCl) of iminoindenone **698g**.

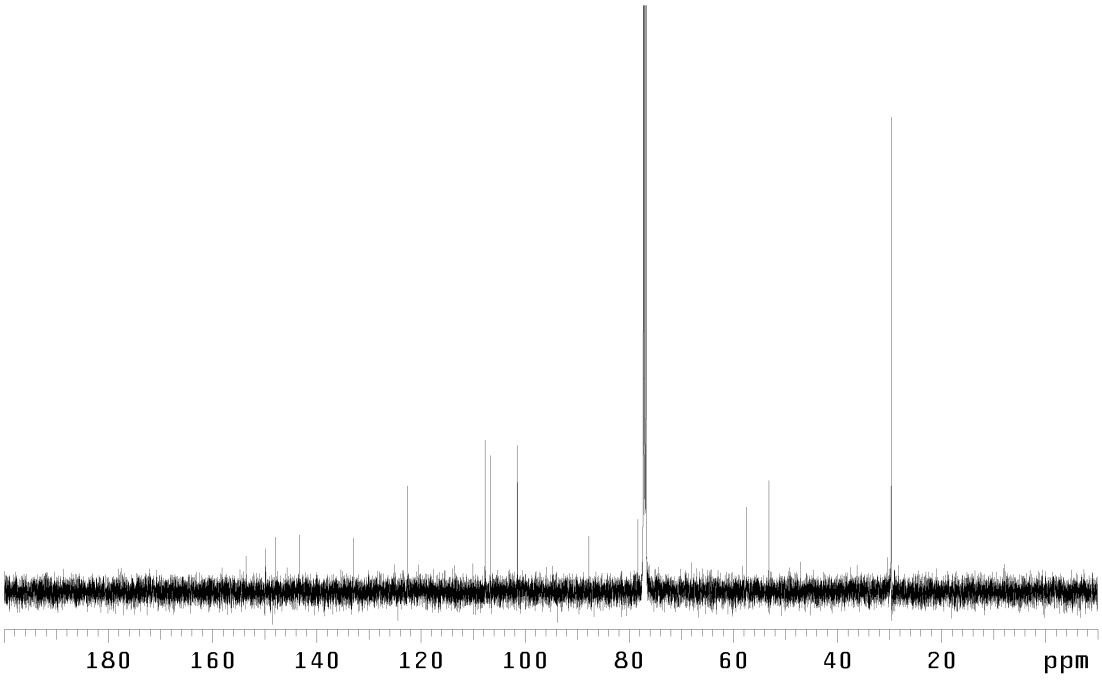


Figure A6.40.3 ^{13}C NMR (125 MHz, $CDCl_3$) of iminoindenone **698g**.

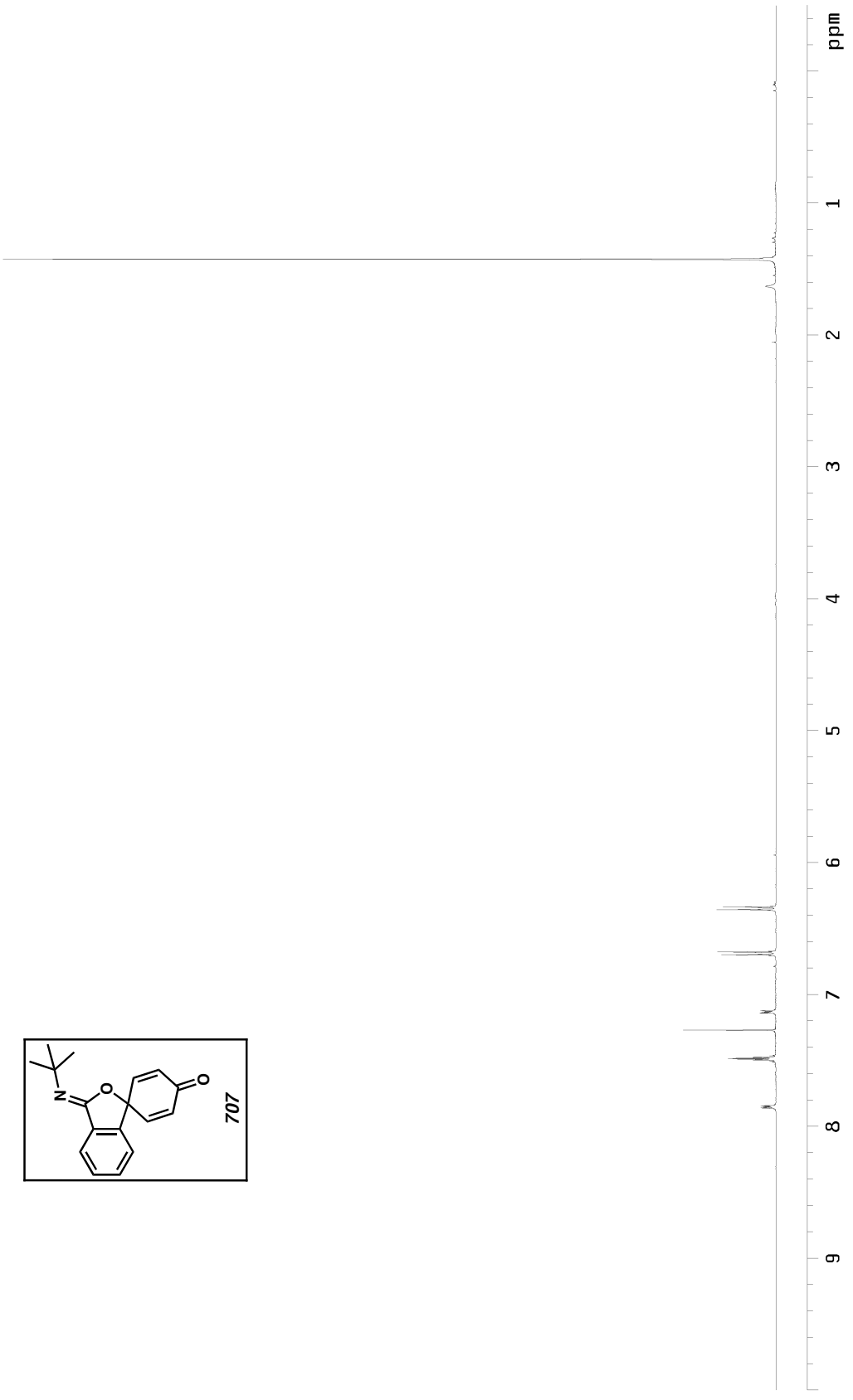


Figure A6.42.1 ^{1}H NMR (500 MHz, $CDCl_3$) of spirocycle **707**.

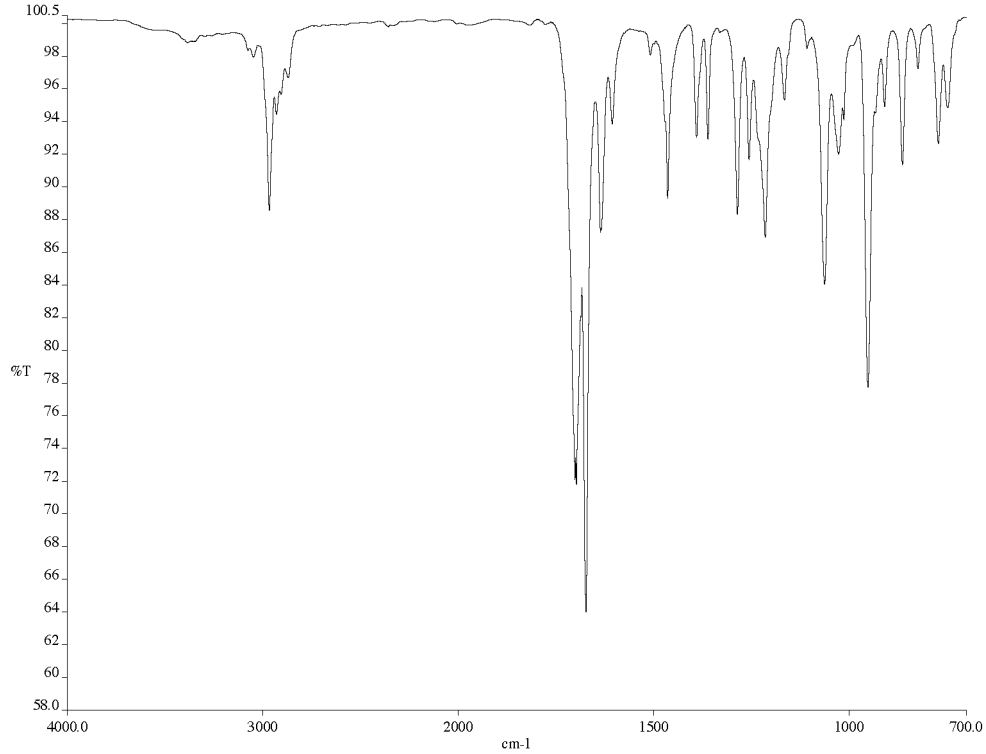


Figure A6.42.2 Infrared spectrum (thin film/NaCl) of spirocycle **707**.

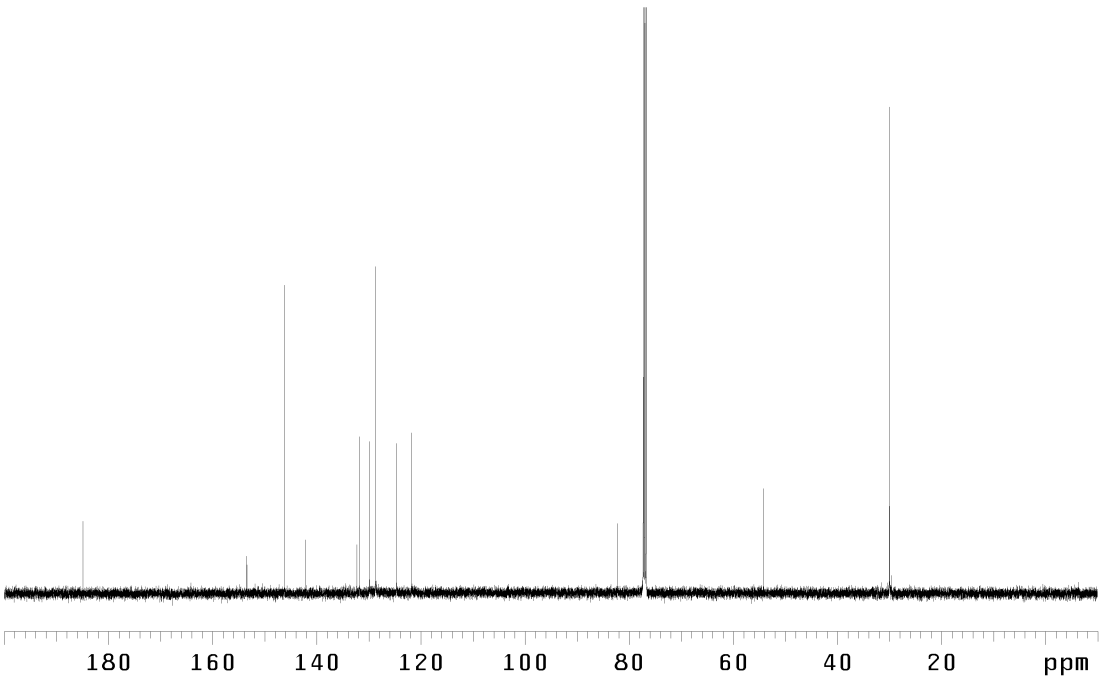


Figure A6.42.3 ^{13}C NMR (125 MHz, $CDCl_3$) of spirocycle **707**.

Figure A6.43.1 ^{1}H NMR (500 MHz, $CDCl_3$) of spirocycle **709**.

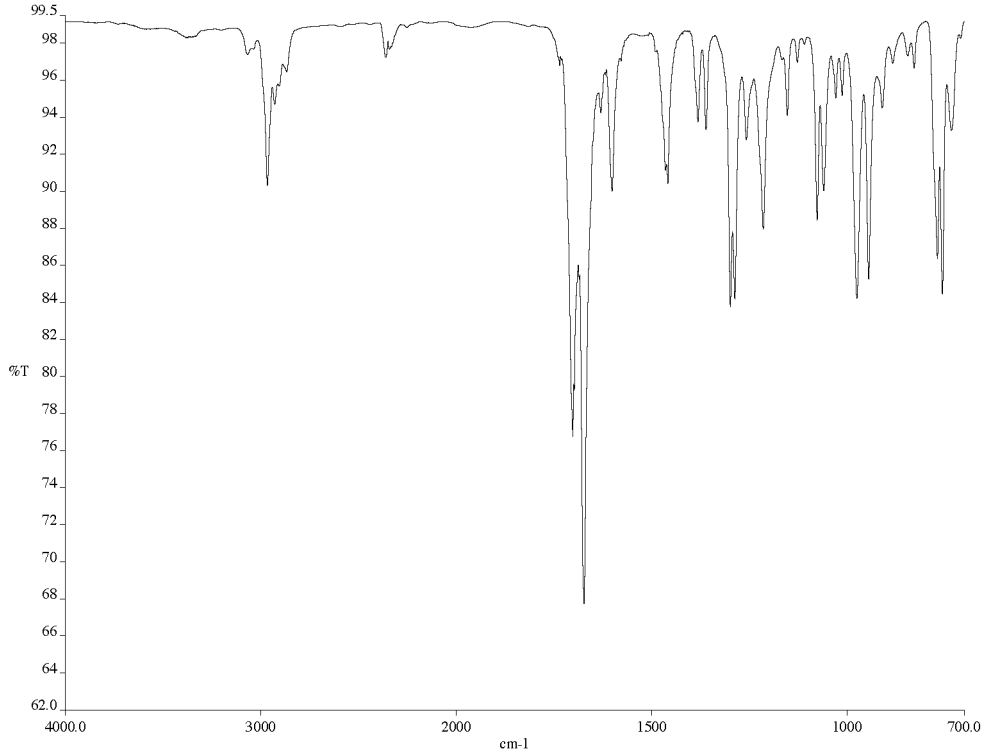


Figure A6.43.2 Infrared spectrum (thin film/NaCl) of spirocycle **709**.

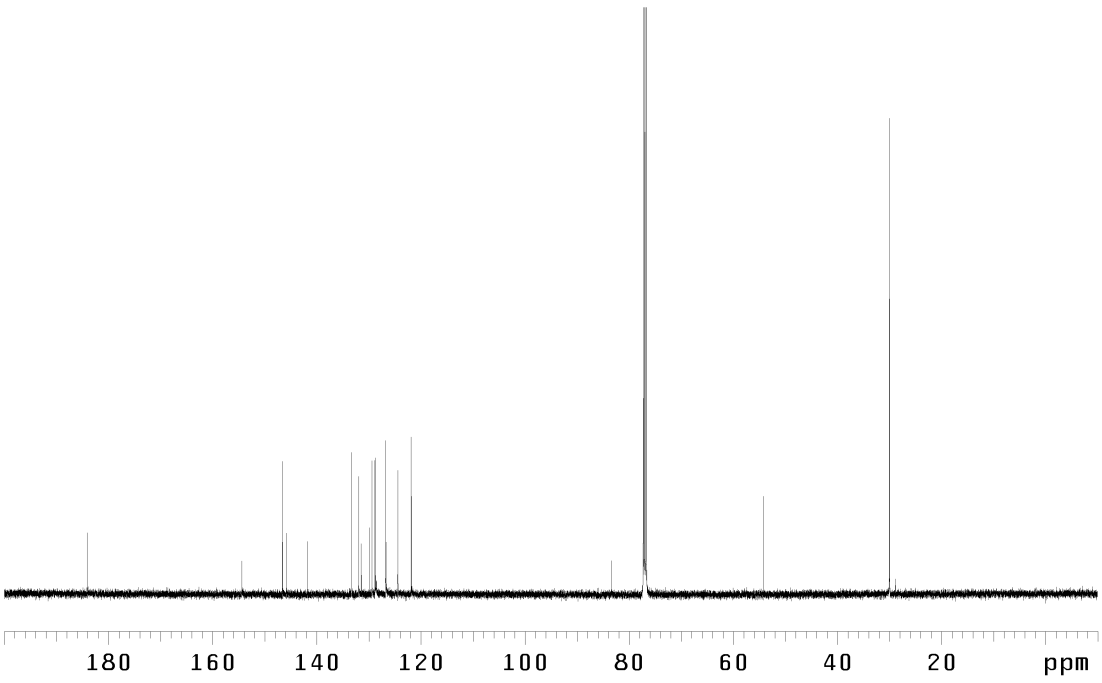


Figure A6.43.3 ^{13}C NMR (125 MHz, $CDCl_3$) of spirocycle **709**.

Figure A6.44.1 ^{1}H NMR (500 MHz, $CDCl_3$) of spirocycle **711**.

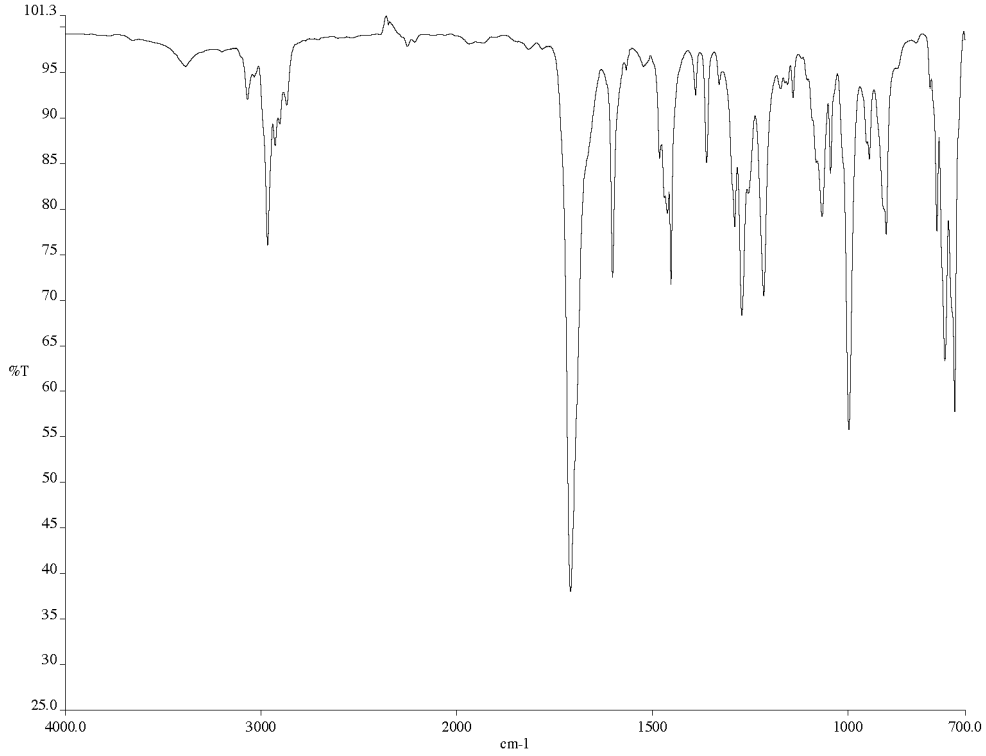


Figure A6.44.2 Infrared spectrum (thin film/NaCl) of spirocycle **711**.

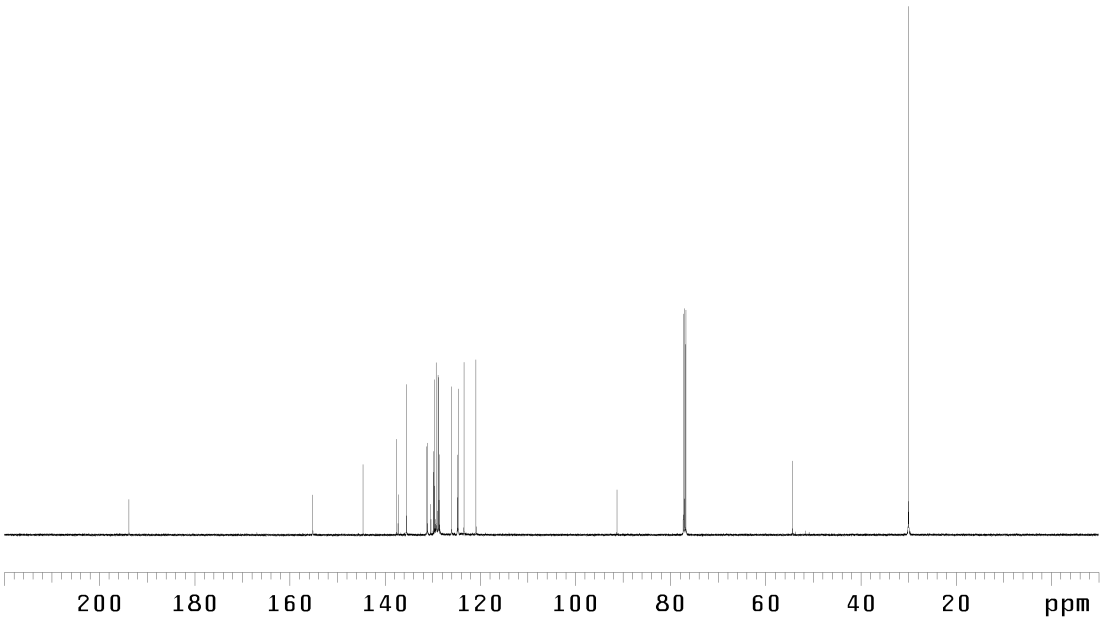


Figure A6.44.3 ^{13}C NMR (125 MHz, $CDCl_3$) of spirocycle **711**.

APPENDIX 7

X-Ray Crystallography Reports Relevant to Appendix 6

A7.1 CRYSTAL STRUCTURE OF PHENOXY IMINOISOBENZOFURAN 683p

Figure A7.1. ORTEP drawing of phenoxy iminoisobenzofuran ***683p*** *(shown with 50% probability ellipsoids)*
NOTE: Crystallographic data have been deposited in the Cambridge Database (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 739396.

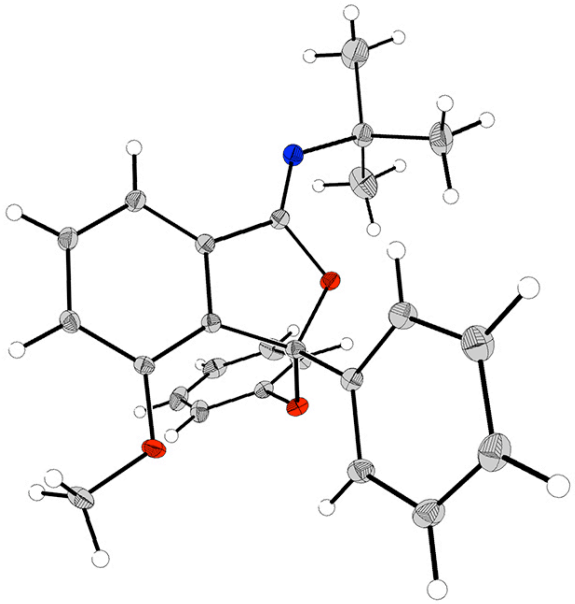
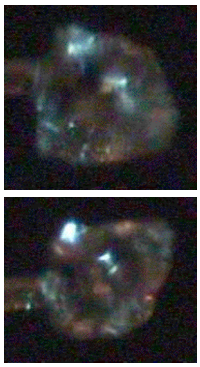


*Table A7.1. Crystal data and structure refinement for phenoxy iminoisobenzofuran **683p** (CCDC 739396)*

Empirical formula	$C_{25}H_{25}NO_3$
Formula weight	387.46
Crystallization Solvent	$CDCl_3$
Crystal Habit	Block
Crystal size	0.31 x 0.27 x 0.25 mm^3
Crystal color	Colorless



Data Collection

Type of diffractometer	Bruker KAPPA APEX II	
Wavelength	0.71073 Å MoKα	
Data Collection Temperature	100(2) K	
θ range for 9578 reflections used in lattice determination	2.48 to 38.91°	
Unit cell dimensions	a = 8.4862(3) Å b = 9.8342(3) Å c = 13.1013(4) Å	α= 77.791(2)° β= 77.424(2)° γ = 80.138(2)°
Volume	1033.97(6) $Å^3$	
Z	2	
Crystal system	Triclinic	
Space group	P-1	
Density (calculated)	1.245 Mg/m^3	
F(000)	412	
Data collection program	Bruker APEX2 v2.1-0	
θ range for data collection	2.14 to 39.22°	
Completeness to θ = 39.22°	95.3 %	
Index ranges	$-14 \le h \le 14$, $-15 \le k \le 17$, $-22 \le l \le 23$	
Data collection scan type	ω scans; 18 settings	
Data reduction program	Bruker SAINT-Plus v7.34A	
Reflections collected	51220	
Independent reflections	11606 [R_{int}= 0.0801]	
Absorption coefficient	0.081 mm^{-1}	
Absorption correction	None	
Max. and min. transmission	0.9800 and 0.9752	

Table A7.1. (cont.)

Structure solution and Refinement

Structure solution program	SHELXS-97 (Sheldrick, 2008)
Primary solution method	Direct methods
Secondary solution method	Difference Fourier map
Hydrogen placement	Difference Fourier map
Structure refinement program	SHELXL-97 (Sheldrick, 2008)
Refinement method	Full matrix least-squares on F^2
Data / restraints / parameters	11606 / 0 / 362
Treatment of hydrogen atoms	Unrestrained
Goodness-of-fit on F^2	1.891
Final R indices [I>2σ(I), 8945 reflections]	R1 = 0.0431, *w*R2 = 0.1014
R indices (all data)	R1 = 0.0581, *w*R2 = 0.1036
Type of weighting scheme used	Sigma
Weighting scheme used	$w=1/\sigma^2(Fo^2)$
Max shift/error	0.001
Average shift/error	0.000
Largest diff. peak and hole	0.648 and -0.292 e.Å^{-3}

Special Refinement Details

Crystals were mounted on a glass fiber using Paratone oil then placed on the diffractometer under a nitrogen stream at 100K.

Refinement of F^2 against ALL reflections. The weighted R-factor (*w*R) and goodness of fit (S) are based on F^2, conventional R-factors (R) are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on ALL data will be even larger.

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Figure A7.2. Phenoxy iminoisobenzofuran ***683p***

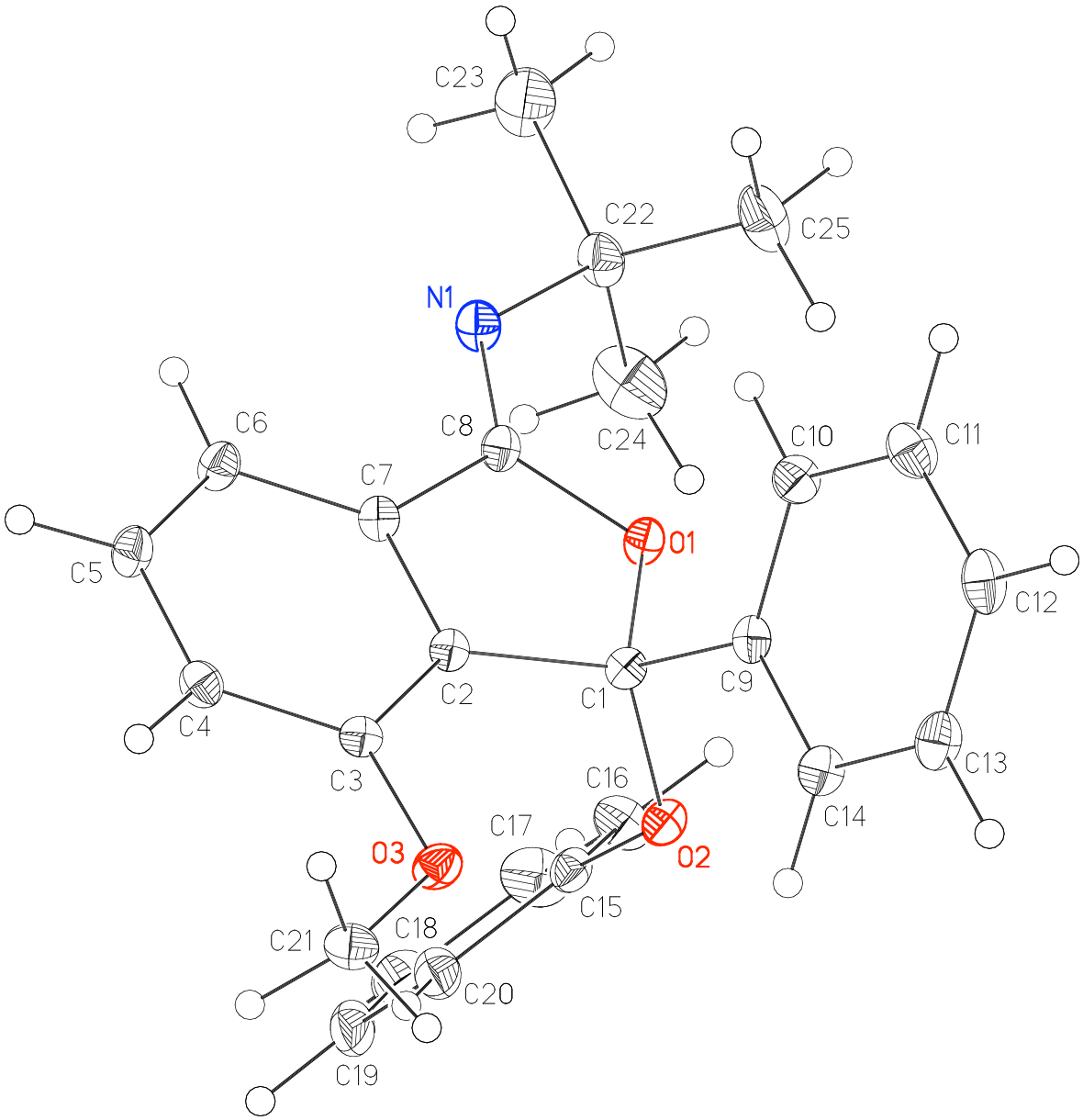


Table A7.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for ***683p*** *(CCDC 739396). U(eq) is defined as the trace of the orthogonalized U^{ij} tensor*

	x	y	z	U_{eq}
O(1)	3472(1)	9014(1)	1779(1)	12(1)
O(2)	5165(1)	9139(1)	2930(1)	12(1)
O(3)	2639(1)	9400(1)	5108(1)	15(1)
N(1)	1898(1)	7586(1)	1261(1)	14(1)
C(1)	3544(1)	9449(1)	2754(1)	11(1)
C(2)	2329(1)	8643(1)	3583(1)	11(1)
C(3)	1846(1)	8646(1)	4671(1)	11(1)
C(4)	591(1)	7865(1)	5232(1)	13(1)
C(5)	-124(1)	7092(1)	4714(1)	14(1)
C(6)	360(1)	7080(1)	3636(1)	14(1)
C(7)	1594(1)	7881(1)	3088(1)	11(1)
C(8)	2302(1)	8109(1)	1950(1)	11(1)
C(9)	3117(1)	11036(1)	2619(1)	11(1)
C(10)	1992(1)	11714(1)	1985(1)	15(1)
C(11)	1592(1)	13170(1)	1848(1)	18(1)
C(12)	2320(1)	13954(1)	2340(1)	18(1)
C(13)	3425(1)	13278(1)	2980(1)	17(1)
C(14)	3820(1)	11817(1)	3134(1)	14(1)
C(15)	5864(1)	7735(1)	3005(1)	12(1)
C(16)	6663(1)	7253(1)	2082(1)	19(1)
C(17)	7442(1)	5878(1)	2155(1)	24(1)
C(18)	7425(1)	5014(1)	3138(1)	23(1)
C(19)	6657(1)	5516(1)	4060(1)	22(1)
C(20)	5858(1)	6889(1)	3996(1)	17(1)
C(21)	2051(1)	9494(1)	6203(1)	16(1)
C(22)	2651(1)	7806(1)	125(1)	17(1)
C(23)	1637(1)	7108(1)	-400(1)	32(1)
C(24)	4405(1)	7088(1)	-15(1)	30(1)
C(25)	2593(1)	9360(1)	-384(1)	25(1)

*Table A7.3. Bond lengths [Å] and angles [°] for **683p** (CCDC 739396)*

O(1)-C(8)	1.3962(7)	C(24)-H(24A)	0.954(13)
O(1)-C(1)	1.4473(8)	C(24)-H(24B)	0.999(13)
O(2)-C(15)	1.3989(7)	C(24)-H(24C)	1.014(14)
O(2)-C(1)	1.4153(8)	C(25)-H(25A)	0.970(12)
O(3)-C(3)	1.3597(7)	C(25)-H(25B)	1.003(12)
O(3)-C(21)	1.4299(8)	C(25)-H(25C)	1.002(11)
N(1)-C(8)	1.2599(8)		
N(1)-C(22)	1.4726(9)	C(8)-O(1)-C(1)	111.20(5)
C(1)-C(2)	1.5160(8)	C(15)-O(2)-C(1)	116.66(4)
C(1)-C(9)	1.5218(8)	C(3)-O(3)-C(21)	117.04(5)
C(2)-C(7)	1.3826(8)	C(8)-N(1)-C(22)	124.50(5)
C(2)-C(3)	1.3961(9)	O(2)-C(1)-O(1)	109.11(4)
C(3)-C(4)	1.4012(8)	O(2)-C(1)-C(2)	114.67(5)
C(4)-C(5)	1.4006(9)	O(1)-C(1)-C(2)	103.49(4)
C(4)-H(4)	0.975(10)	O(2)-C(1)-C(9)	106.51(4)
C(5)-C(6)	1.3843(9)	O(1)-C(1)-C(9)	108.83(5)
C(5)-H(5)	0.975(9)	C(2)-C(1)-C(9)	114.05(5)
C(6)-C(7)	1.3956(8)	C(7)-C(2)-C(3)	120.56(5)
C(6)-H(6)	0.972(10)	C(7)-C(2)-C(1)	109.08(5)
C(7)-C(8)	1.4655(9)	C(3)-C(2)-C(1)	130.25(5)
C(9)-C(10)	1.3914(9)	O(3)-C(3)-C(2)	117.35(5)
C(9)-C(14)	1.3970(9)	O(3)-C(3)-C(4)	125.00(6)
C(10)-C(11)	1.3961(9)	C(2)-C(3)-C(4)	117.65(5)
C(10)-H(10)	0.987(10)	C(3)-C(4)-C(5)	120.70(6)
C(11)-C(12)	1.3930(10)	C(3)-C(4)-H(4)	120.1(5)
C(11)-H(11)	0.977(11)	C(5)-C(4)-H(4)	119.2(5)
C(12)-C(13)	1.3849(11)	C(6)-C(5)-C(4)	121.75(6)
C(12)-H(12)	0.963(10)	C(6)-C(5)-H(5)	121.2(6)
C(13)-C(14)	1.3996(9)	C(4)-C(5)-H(5)	117.0(6)
C(13)-H(13)	0.995(11)	C(5)-C(6)-C(7)	116.73(6)
C(14)-H(14)	0.970(10)	C(5)-C(6)-H(6)	122.9(6)
C(15)-C(16)	1.3861(9)	C(7)-C(6)-H(6)	120.4(6)
C(15)-C(20)	1.3851(10)	C(2)-C(7)-C(6)	122.60(6)
C(16)-C(17)	1.3929(9)	C(2)-C(7)-C(8)	108.60(5)
C(16)-H(16)	0.990(11)	C(6)-C(7)-C(8)	128.78(6)
C(17)-C(18)	1.3846(12)	N(1)-C(8)-O(1)	127.00(6)
C(17)-H(17)	0.947(12)	N(1)-C(8)-C(7)	125.45(5)
C(18)-C(19)	1.3877(12)	O(1)-C(8)-C(7)	107.54(5)
C(18)-H(18)	0.973(10)	C(10)-C(9)-C(14)	119.65(5)
C(19)-C(20)	1.3978(10)	C(10)-C(9)-C(1)	119.45(5)
C(19)-H(19)	0.958(13)	C(14)-C(9)-C(1)	120.90(6)
C(20)-H(20)	0.966(12)	C(9)-C(10)-C(11)	120.24(6)
C(21)-H(21A)	0.970(10)	C(9)-C(10)-H(10)	119.6(6)
C(21)-H(21B)	0.958(9)	C(11)-C(10)-H(10)	120.2(6)
C(21)-H(21C)	1.026(11)	C(12)-C(11)-C(10)	120.19(7)
C(22)-C(24)	1.5246(11)	C(12)-C(11)-H(11)	120.4(5)
C(22)-C(25)	1.5293(10)	C(10)-C(11)-H(11)	119.4(5)
C(22)-C(23)	1.5306(11)	C(13)-C(12)-C(11)	119.57(6)
C(23)-H(23A)	1.033(13)	C(13)-C(12)-H(12)	120.3(7)
C(23)-H(23B)	1.006(13)	C(11)-C(12)-H(12)	120.1(7)
C(23)-H(23C)	1.005(14)	C(12)-C(13)-C(14)	120.65(6)

C(12)-C(13)-H(13)	121.6(7)	H(21A)-C(21)-H(21C)	108.9(8)
C(14)-C(13)-H(13)	117.7(7)	H(21B)-C(21)-H(21C)	111.6(9)
C(9)-C(14)-C(13)	119.68(6)	N(1)-C(22)-C(24)	109.65(6)
C(9)-C(14)-H(14)	120.0(5)	N(1)-C(22)-C(25)	112.64(5)
C(13)-C(14)-H(14)	120.3(5)	C(24)-C(22)-C(25)	110.30(7)
C(16)-C(15)-C(20)	121.38(6)	N(1)-C(22)-C(23)	105.06(6)
C(16)-C(15)-O(2)	118.70(6)	C(24)-C(22)-C(23)	110.07(7)
C(20)-C(15)-O(2)	119.72(6)	C(25)-C(22)-C(23)	108.99(7)
C(15)-C(16)-C(17)	119.13(7)	C(22)-C(23)-H(23A)	108.6(8)
C(15)-C(16)-H(16)	119.3(6)	C(22)-C(23)-H(23B)	110.6(6)
C(17)-C(16)-H(16)	121.6(6)	H(23A)-C(23)-H(23B)	107.1(10)
C(18)-C(17)-C(16)	120.15(7)	C(22)-C(23)-H(23C)	110.4(7)
C(18)-C(17)-H(17)	120.4(8)	H(23A)-C(23)-H(23C)	111.0(10)
C(16)-C(17)-H(17)	119.5(8)	H(23B)-C(23)-H(23C)	109.0(12)
C(17)-C(18)-C(19)	120.31(6)	C(22)-C(24)-H(24A)	110.2(8)
C(17)-C(18)-H(18)	120.8(7)	C(22)-C(24)-H(24B)	109.7(7)
C(19)-C(18)-H(18)	118.7(7)	H(24A)-C(24)-H(24B)	106.2(10)
C(18)-C(19)-C(20)	120.02(7)	C(22)-C(24)-H(24C)	112.6(8)
C(18)-C(19)-H(19)	120.1(6)	H(24A)-C(24)-H(24C)	107.6(12)
C(20)-C(19)-H(19)	119.8(6)	H(24B)-C(24)-H(24C)	110.2(10)
C(15)-C(20)-C(19)	118.98(7)	C(22)-C(25)-H(25A)	110.6(7)
C(15)-C(20)-H(20)	119.2(7)	C(22)-C(25)-H(25B)	110.6(6)
C(19)-C(20)-H(20)	121.8(7)	H(25A)-C(25)-H(25B)	108.2(10)
O(3)-C(21)-H(21A)	111.1(7)	C(22)-C(25)-H(25C)	113.0(7)
O(3)-C(21)-H(21B)	105.3(6)	H(25A)-C(25)-H(25C)	106.5(9)
H(21A)-C(21)-H(21B)	109.5(8)	H(25B)-C(25)-H(25C)	107.8(9)
O(3)-C(21)-H(21C)	110.6(6)		

Table A7.4. Anisotropic displacement parameters ($Å^2$ x 10^4) for ***683p*** *(CCDC 739396). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$*

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	130(2)	128(2)	105(2)	-46(1)	-1(2)	-40(1)
O(2)	100(2)	105(2)	174(2)	-44(2)	-28(2)	-3(1)
O(3)	151(2)	196(2)	119(2)	-70(2)	-24(2)	-45(2)
N(1)	172(2)	145(2)	104(2)	-52(2)	-10(2)	-32(2)
C(1)	102(2)	120(2)	104(2)	-37(2)	-15(2)	-13(2)
C(2)	103(2)	109(2)	105(2)	-35(2)	-12(2)	-7(2)
C(3)	111(2)	121(2)	107(2)	-40(2)	-24(2)	-2(2)
C(4)	134(2)	148(2)	104(3)	-33(2)	-7(2)	-13(2)
C(5)	145(3)	164(2)	126(3)	-38(2)	8(2)	-50(2)
C(6)	146(3)	146(2)	132(3)	-53(2)	-1(2)	-49(2)
C(7)	115(2)	115(2)	105(2)	-42(2)	-3(2)	-12(2)
C(8)	117(2)	106(2)	113(2)	-39(2)	-7(2)	-16(2)
C(9)	113(2)	106(2)	115(3)	-32(2)	1(2)	-11(2)
C(10)	155(3)	133(2)	161(3)	-36(2)	-36(2)	-1(2)
C(11)	187(3)	143(3)	177(3)	-22(2)	-32(2)	25(2)
C(12)	212(3)	113(2)	178(3)	-39(2)	21(2)	-4(2)
C(13)	200(3)	129(2)	186(3)	-67(2)	-2(2)	-34(2)
C(14)	153(3)	135(2)	153(3)	-50(2)	-22(2)	-17(2)
C(15)	106(2)	109(2)	159(3)	-30(2)	-27(2)	-12(2)
C(16)	221(3)	163(3)	166(3)	-53(2)	-46(2)	37(2)
C(17)	273(4)	185(3)	275(4)	-113(3)	-93(3)	76(2)
C(18)	206(3)	129(3)	371(5)	-42(3)	-111(3)	10(2)
C(19)	155(3)	186(3)	280(4)	64(3)	-56(3)	-24(2)
C(20)	130(3)	184(3)	174(3)	6(2)	-20(2)	-10(2)
C(21)	174(3)	201(3)	120(3)	-72(2)	-38(2)	-9(2)
C(22)	229(3)	178(3)	103(3)	-51(2)	-11(2)	-49(2)
C(23)	500(6)	392(5)	148(4)	-90(3)	-54(4)	-231(4)
C(24)	295(4)	383(4)	175(4)	-97(3)	29(3)	71(3)
C(25)	369(4)	209(3)	143(3)	-3(2)	-26(3)	-58(3)

Table A7.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ***683p*** *(CCDC 739396)*

	x	y	z	U_{iso}
H(4)	195(11)	7865(9)	5989(8)	16(2)
H(5)	-949(11)	6529(9)	5152(8)	19(2)
H(6)	-126(12)	6554(10)	3263(9)	24(2)
H(10)	1514(12)	11163(10)	1610(9)	24(2)
H(11)	817(12)	13634(10)	1389(9)	22(2)
H(12)	2027(12)	14956(10)	2256(9)	24(2)
H(13)	3978(13)	13807(11)	3336(9)	28(3)
H(14)	4579(11)	11346(9)	3594(8)	15(2)
H(16)	6670(12)	7893(10)	1388(9)	24(2)
H(17)	7961(15)	5535(12)	1525(11)	40(3)
H(18)	8013(13)	4068(11)	3201(9)	31(3)
H(19)	6660(14)	4920(11)	4740(10)	34(3)
H(20)	5290(14)	7260(11)	4623(10)	35(3)
H(21A)	899(12)	9846(10)	6330(9)	22(2)
H(21B)	2656(12)	10148(10)	6345(8)	20(2)
H(21C)	2231(12)	8528(10)	6677(9)	24(2)
H(23A)	1742(16)	6048(13)	-88(12)	51(4)
H(23B)	2069(15)	7207(12)	-1187(11)	38(3)
H(23C)	467(18)	7546(13)	-279(12)	58(4)
H(24A)	5072(16)	7598(13)	224(12)	51(4)
H(24B)	4858(14)	7095(11)	-786(10)	37(3)
H(24C)	4511(17)	6092(14)	400(12)	55(4)
H(25A)	1484(14)	9829(11)	-271(10)	37(3)
H(25B)	3018(13)	9472(10)	-1169(10)	28(3)
H(25C)	3247(13)	9878(11)	-80(10)	31(3)

APPENDIX 8

Notebook Cross-Reference

NOTEBOOK CROSS-REFERENCE FOR NEW COMPOUNDS

The following notebook cross-reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this thesis. For each compound, both hard copy and electronic characterization folders containing the original ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and IR spectra have been created. All notebooks and spectroscopic data are stored in the Stoltz research group archive.

Table A8.1. Compounds in Chapter 2 – Orthogonal Synthesis of Indolines and Isoquinolines via Aryne Annulation

Compound	^{1}H NMR	^{13}C NMR	IR
167	CDGVII-93D	CDGVII-93Dc	CDGVII-119
170a, b	CDGVII-123E	CDGVII-123Dc	CDGVI-225
170c	CDGVII-117B	CDGVII-121Bc	CDGVII-117
170d	CDGVI-219B	CDGVII-219Bc	CDGVII-065_Phe
176	CDGVII-47G	CDGVII-47Gc	CDGVII-47
181a	CDGVI-299_char	CDGVI-299c_char	CDGVI-299
181b	CDGVII-65	CDGVII-65c	CDGVII-65
181c	CDGVII-211_char	CDGVII-211c_char	CDGVII-211
181d	CDGV-275G-2	CDGV-275G-2c	CDGV-275
181e	CDGVI-265E-2	CDGVI-265E-2c	CDGVI-265
181f	CDG-CF3_isoquin	CDGVII-CF3c	CDG-CF3IQ
181g	KMA-X-229.2	KMA-X-229.2c	KMA-X-229.2
181h	CDGVII-149_char	CDGVII-149c_char	CDGVII-149
182a	CDGVI-257E	CDGVI-257Ec	CDGVI-257
182b, c	CDGV-287E	CDGV-287Ec	CDGV-287
182d	CDGV-291_char	CDGV-291Gc	CDGVI-291_sesam
182e	CDGVII-31	CDGVII-31c	CDGVII-031
182f	CDGVIII-57B-6	CDGVIII-57C	CDGVIII-57D
187a	CDGVII-221	CDGVII-221C	CDGVI-273
187b	KMA-X-35.4	KMA-X-35.4c	KMA-IX-35.4

187c	KMA-X-175.5	KMA-X-175.5c	KMA-X-175.5
A1-1	KMA-X-175.2	KMA-X-175.2c	KMA-X-175.2
187d	KMA-X-179.4	KMA-X-179.4c	KMA-X-179.4
A1-2	KMA-X-179.1.1	KMA-X-179.1.1c	KMA-X-179.1.1
187e	CDGVII-243B-5	CDGVII-243B-5c	CDGVII-243
187f	KMA-IX-191.2	KMA-IX-191.2c	KMA-IX-163.1
A1-4	KMA-IX-265.3	KMA-IX-265.3c	KMA-IX-265.2
A1-5	KMA-IX-171.5	KMA-IX-171.5c	KMA-IX-171.2
195	KMA-IX-261.2	KMA-IX-261.2c	KMA-IX-177.2
196	KMA-IX-271.6	KMA-IX-269.2c	KMA-IX-235.2
197	KMA-IX-273.5	KMA-IX-273.4c	KMA-IX-255.5
202a	KMA-XVII-75.1	KMA-XVII-75.1c	KMA-XVII-75.1
202b	KMA-XVII-57.1	KMA-XVII-57.1c	KMA-XVII-57.1
209	KMA-XVI-219.2	KMA-XVI-219.2c	KMA-XVI-219.1
202c	KMA-XVII-95.1	KMA-XVII-95.1c	KMA-XVII-95.1

Table A8.2. Compounds in Chapter 4 – A Concise Total Synthesis of (–)-Quinocarcin via Aryne Annulation

Compound	^{1}H NMR	^{13}C NMR	IR
***syn*-382**	KMA-VI-135.1	KMA-VI-135.1c	ERA-XIV-241.1
381	KMA-VIII-185.2	KMA-VIII-185.2c	KMA-VIII-185.2
380	KMA-XVII-185.3	KMA-XVII-185.3c	KMA-XVII-185.3
392	KMA-VIII-125.2	KMA-VIII-125.3c	KMA-VIII-125.2
405a	KMA-XIII-127.6	KMA-XIII-127.3-13C	KMA-XIII-127.5
402	KMA-XIII-115.3	KMA-XIII-115.2-13C	KMA-XIII-115.3
406	KMA-XIII-125.6	KMA-XIII-125.6c	KMA-XIII-125.6
407	KMA-XIII-127.5	KMA-XIII-127.5c	KMA-XIII-131.14
411	KMA-XIII-131.8a	KMA-XIII-131.8-13C	KMA-XIII-131.6
415a	KMA-XIII-171.2	KMA-XIII-171.1-13C	KMA-XIII-171.1
415b	KMA-XIII-179.10	KMA-XIII-179.9c	KMA-XIII-179.9
414	KMA-XIII-181.1	KMA-XIII-181.1c	KMA-XIII-163.2
378	KMA-XIII-191.4	KMA-XIII-191.4c	KMA-XIII-191.4
211	KMA-XIII-213.2-2	KMA-XIII-213.4c	KMA-XIII-213.2

Table A8.3. Compounds in Chapter 5 – Expedient Synthesis of 3-Hydroxyisoquinolines and 2-Hydroxy-1,4-Naphthoquinones via One-Pot Aryne Acyl-Alkylation / Condensation

Compound	^{1}H NMR	^{13}C NMR	IR
575h	KMA-XIV-227.2	KMA-XIV-227.2c	KMA-XIV-227.1
575i	KMA-XV-63.3	KMA-XV-63.3c	KMA-XV-63.1
575j	KMA-XV-55.3	KMA-XV-55.3c	KMA-XV-55.1
575k	KMA-XV-35.3	KMA-XV-35.2c	KMA-XV-35.2
569	KMA-XV-219.1	KMA-XV-219.1c	KMA-XV-219.1
571a	KMA-XIV-269.2	KMA-XIV-269.2c	KMA-XIV-269.2
571b	KMA-XIV-271.1	KMA-XV-221.2c	KMA-XV-221.1
571c	KMA-XIV-273.1	KMA-XIV-273.1c	KMA-XV-223.1
571d	KMA-XIV-275.2	KMA-XIV-275.2c	KMA-XV-225.1
571e	KMA-XV-227.1	KMA-XV-227.1c	KMA-XV-227.1
571f	KMA-XVI-31.2	KMA-XVI-31.2c	KMA-XVI-31.2
576a	KMA-XV-101.1	KMA-XV-101.1c	KMA-XV-101.4
576b	KMA-XV-99.1	KMA-XV-99.1c	KMA-XV-99.1
576c	KMA-XIV-291.6	KMA-XIV-291.2c	KMA-XIV-291.6
576d	KMA-XIV-261.3	KMA-XIV-261.3c	KMA-XIV-261.3
576e	KMA-XIV-263.3	KMA-XIV-263.3c	KMA-XIV-263.3
576f	KMA-XIV-225.2	KMA-XIV-295.2c	KMA-XIV-225.2
576g	KMA-XIV-217.5	KMA-XIV-217.5c	KMA-XIV-217.4
576h	KMA-XV-83.2	KMA-XV-83.3c	KMA-XV-83.4
576i	KMA-XV-169.3	KMA-XV-169.3	KMA-XV-169.1
576j	KMA-XIV-243.1	KMA-XIV-243.1c	KMA-XIV-243.1
576k	KMA-XV-71.3	KMA-XV-71.3c	KMA-XV-71.2
576l	KMA-XV-61.2	KMA-XV-61.2c	KMA-XV-61.2
576m	KMA-XV-41.6	KMA-XV-121.2c	KMA-XV-121.2
A5-1	KMA-XVI-185.1	KMA-XVI-185.1c	KMA-XVI-185.1
578	KMA-XVI-191.1	KMA-XVI-191.1c	KMA-XVI-191.1
579	BDHI-OTfd=2	BDHI-OTfd=2-13C	BDH-I-OTf
588a	KMA-XIV-303.2	KMA-XIV-303.2c	KMA-XIV-303.2
588b	KMA-XV-25.2	KMA-XV-25.2c	KMA-XV-25.2
588c	KMA-XIV-179.5	KMA-XIV-179.5c	KMA-XV-49.1
588d	KMA-XV-203.1	KMA-XV-203.1c	KMA-XV-203.1

588e	KMA-XVI-35.2	KMA-XVI-35.2c	KMA-XVI-35.1
588f	KMA-XV-205.4	KMA-XV-205.4c	KMA-XV-205.4
588g	KMA-XV-31.2	KMA-XV-31.2c	KMA-XV-31.2
588h	KMA-XV-107.1	KMA-XV-107.1c	KMA-XV-107.1
588i	KMA-XV-33.1	KMA-XV-33.1c	KMA-XV-33.1
588j	KMA-XV-45.1	KMA-XV-45.1c	KMA-XV-45.1
588k	KMA-XV-73.2	KMA-XV-73.2c	KMA-XV-73.1

Table A8.4. Compounds in Chapter 6 – Multicomponent Aryne Reactions

Compound	^{1}H NMR	^{13}C NMR	IR
680	KMA-XI-43.3	KMA-XI-43.3c	KMA-XI-187.2
683a	KMA-XIV-35.2	KMA-XIV-35.2c	KMA-XIV-35.2
683b	KMA-XI-45.3	KMA-XI-45.3c	KMA-XIV-31.2
683c	KMA-XI-47.3	KMA-XI-47.3c	KMA-XIII-301.4
683d	KMA-XI-111.4	KMA-XI-111.4c	KMA-XI-111.2
683e	KMA-XIII-263.5	KMA-XIII-263.5c	KMA-XIII-263.6
683f	KMA-XII-27.5	KMA-XII-27.5c	KMA-XII-27.3
683g	KMA-XV-279.1	KMA-XV-279.1c	KMA-XIV-63.1
683h	KMA-XV-283.3	KMA-XV-283.1c	KMA-XV-283.1
683i	KMA-XII-75.2	KMA-XII-75.2c	KMA-XII-75.2
683j	KMA-XIV-65.2	KMA-XIV-65.5c	KMA-XIV-65.2
683k	KMA-XIII-271.4	KMA-XIII-271.4c	KMA-XIII-271.4
683l	KMA-XVI-139.3	KMA-XVI-139.4c	KMA-XVI-139.4
683m	KMA-XVI-137.3	KMA-XVI-137.4c	KMA-XVI-137.4
683n	KMA-XVI-75.3	KMA-XVI-75.1c	KMA-XVI-75.3
683o	KMA-XVI-77.2	KMA-XVI-77.1c	KMA-XVI-77.2
683p	KMA-XIV-139.1	KMA-XIV-139.1c	KMA-XIV-139.1
683q	KMA-XVI-41.1	KMA-XVI-41.1c	KMA-XVI-41.1
683r	KMA-XVI-21.7	KMA-XVI-21.7c	KMA-XVI-21.7
683s	KMA-XIV-117.3	KMA-XIV-117.6.c	KMA-XIV-117.6
683t	KMA-XIV-141.2	KMA-XIV-141.2c	KMA-XIV-141.2
683u	KMA-XVI-29.5	KMA-XVI-29.5c	KMA-XVI-29.5
669a	KMA-XVI-87.1	KMA-XVI-87.1c	KMA-XVI-87.1

669b	KMA-XVI-85.1	KMA-XVI-85.1c	KMA-XVI-85.1
669c	KMA-XVI-145.5	KMA-XVI-145.5c	KMA-XVI-145.5
669d	KMA-XVI-161.7	KMA-XVI-161.7c	KMA-XVI-161.7
669e	KMA-XVI-57.2	KMA-XVI-57.2c	KMA-XVI-57.2
669f	KMA-XVI-173.6	KMA-XVI-173.6c	KMA-XVI-173.6
669g	KMA-XVI-175.5	KMA-XVI-175.5c	KMA-XVI-175.5
687a	KMA-XVI-169.1	KMA-XVI-169.1c	KMA-XVI-169.1
687b	KMA-XVI-179.1	KMA-XVI-179.1c	KMA-XVI-179.1
687c	KMA-XVI-177.1	KMA-XVI-177.1c	KMA-XVI-177.1
691	CDGXV-141	CDGXV-141-C13	CDGXV-141
698a	CDGXV-133	CDGXV-133-C13	CDGXV-133
698b	CDGXV-127	CDGXV-127-C13	CDGXV-127
675c	CDGXV-175	CDGXV-175-C13	CDGXV-175
675d	CDGXV-165C	CDGXV-165C-C13	CDGXV-165C
675e	CDGXV-289	CDGXV-289-C13	CDGXV-289
675f	CDGXV-287-hplcA-3	CDGXV-287-C13	CDGXV-287
675g	CDGXV-169	CDGXV-169-C13	CDGXV-169
707	KMA-XVI-59.3	KMA-XVI-59.3c	KMA-XVI-59.3
709	KMA-XVI-141.1	KMA-XVI-141.1c	KMA-XVI-141.1
711	KMA-XVI-143.1	KMA-XVI-143.1c	KMA-XVI-143.1

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ABOUT THE AUTHOR

Kevin McCormack Allan was born in Fullerton, California on July 14th, 1982, to John R. and Susan M. Allan. Growing up in sunny Southern California with his younger brother Brian, he spent much of his time riding his bike to the neighborhood comic book store and playing outdoors. He remembers his first true contact with science to be the fifth grade project his father helped him to conduct, monitoring the effects of different fertilizers on radish growth. In 1996, Kevin began attending Sunny Hills High School. Never the gifted athlete, he joined the band in his freshman year and played tenor saxophone for the next four years as part of the marching alliance and jazz ensemble. In high school, he also came to appreciate (if not yet love) chemistry in Mrs. Miller's general and AP chemistry courses. Though never easy, these classes provided the impetus to apply to college as a chemistry major.

After graduating in 2000, Kevin moved north to the University of California, Berkeley. In his sophomore year, he would have the good fortune to enroll in Chem 112A, the introductory organic chemistry course taught by Dr. Ahamindra Jain. While unquestionably quirky, Dr. Jain conveyed an enthusiasm for the science that his students could not help but absorb. Kevin would go on to take an organic synthesis laboratory course taught by Dr. Jain before joining his research group in the spring of 2003. There he would design and synthesize polyfluorinated derivatives of the flu drug, Oseltamivir, and use fluorimetry to measure their binding affinities with viral neuraminidase. In 2004, he graduated with a Bachelor of Science degree in Chemistry.

Later that fall, Kevin moved back to the Los Angeles area to begin his doctoral studies with Professor Brian Stoltz at the California Institute of Technology. His research there included the development of new methods for the annulation of reactive aryne intermediates and the application of these methods to the total synthesis of biologically active alkaloids. In May 2010, Kevin will move to Chicago, Illinois, to begin a postdoctoral position in the labs of Professor Viresh Rawal at the University of Chicago.