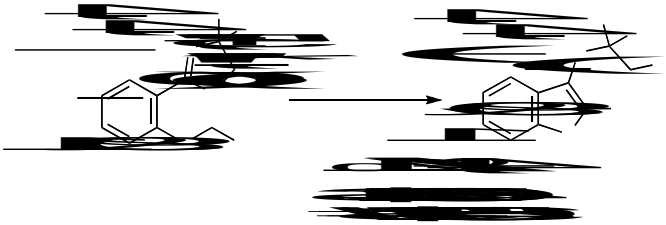
Base-induced Cyclisation of *ortho*-Substituted 2-Phenyloxazolines to Give 3-Aminobenzofurans and Related Heterocycles

R. Alan Aitken*
Andrew D Harper
Alexandra M. Z. Slawin

EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, U.K.

raa@st-and.ac.uk



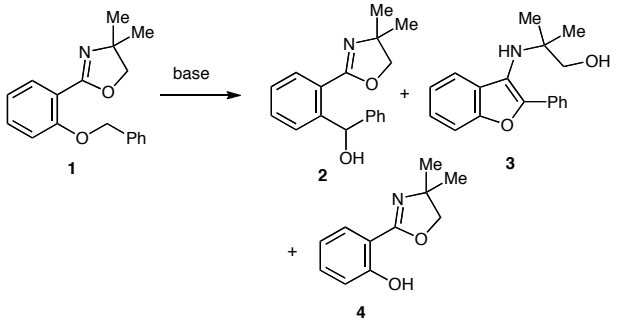
Received:
Accepted:
Published online:
DOI:

Abstract Treatment of *ortho*-benzyloxyphenyloxazolines with butyllithium and potassium *t*-butoxide results in cyclisation with ring-opening of the oxazoline to give 2-aryl-3-aminobenzofurans. The reaction also occurs with the corresponding benzylthio- and benzylamino-compounds to give benzothiophenes and indoles, respectively. Use of an *ortho*-allyloxyphenyloxazoline gives the corresponding 2-vinylbenzofuran, while both α-methylbenzyloxy and benzylsulfonyl compounds form stable spirooxazolidine products. The X-ray structure of an aminobenzothiophene product has been determined.

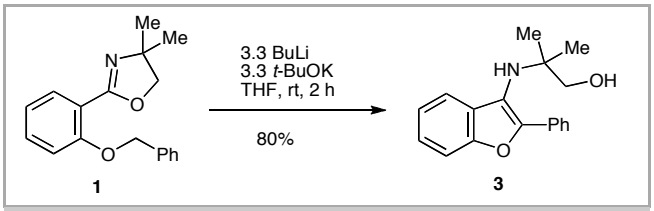
Key words cyclisation, oxazoline, benzofuran, benzothiophene, indole, Schlosser's base, spiro heterocycle

Although the chemistry of 4,5-dihydrooxazoles (2-oxazolines) has been extensively developed over the last 40 years,[1–3] new useful reactions facilitated by this auxiliary group continue to be discovered. We have recently examined the ability of this group to facilitate the [1,2]-Wittig rearrangement of an adjacent benzyl ether in compounds such as **1** and the success of this strategy will be reported elsewhere. However, in the course of this work, it was discovered that treatment of **1** with both *n*-butyllithium and potassium *t*-butoxide ("Schlosser's base") resulted in unexpected cyclisation with ring opening of the oxazoline to give the 3-aminobenzofuran **3** in high yield.[4] Optimisation of the process is shown in Table 1. While the Wittig rearrangement product **2** was formed using BuLi in THF, 2.2 equivalents were required to obtain a good yield and this gave **3** as a major byproduct. Most other solvents gave mixtures with lower selectivity for **2** *vs.* **3** and the only two that gave complete reaction, MTBE and toluene, actually favoured the debenzylation product **4**. Better selectivity for **3** was obtained using the BuLi / t-BuOK mixture but 1.1 equivalents gave mostly starting material and it was only with just over 3 equivalents that high conversion with excellent selectivity for **3** was achieved (Scheme 1). We interpret this in terms of the mechanism shown in Scheme 2 where initial *ortho*-metallation is followed by deprotonation of the benzyl group allowing equilibration with cyclised forms, but it is only the third deprotonation leading to formation of the aromatic furan ring that decisively leads to product **3**.

Table 1 Optimisation of the reaction for formation of **3**

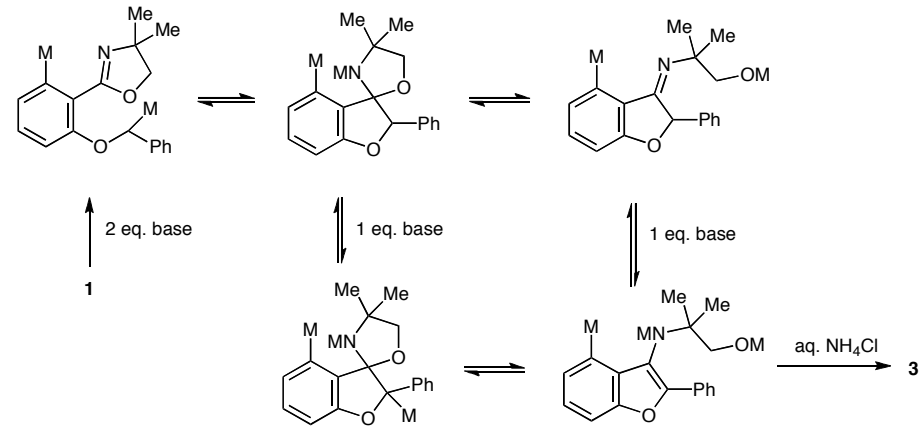


Conditions	Ratio of products (%)			
	1	**2**	**3**	**4**
1.1 eq. BuLi, THF	57	29	8	6
1.1 eq. NaH, THF	100	0	0	0
2.2 eq. BuLi, THF	0	75	19	6
2.2 eq. BuLi, Et_2O	13	38	39	10
2.2 eq. BuLi, t-BuOMe	0	24	27	49
2.2 eq. BuLi, 2-MeTHF	39	47	6	8
2.2 eq. BuLi, dioxane	4	64	19	13
2.2.eq. BuLi, DME	42	17	30	11
2.2 eq. BuLi, PhMe	0	13	29	58
1.1.eq. BuLi, t-BuOK, THF	57	4	33	6
2.2 eq. BuLi, t-BuOK, THF	17	0	79	4
3.3 eq. BuLi, t-BuOK, THF	3	0	95	2

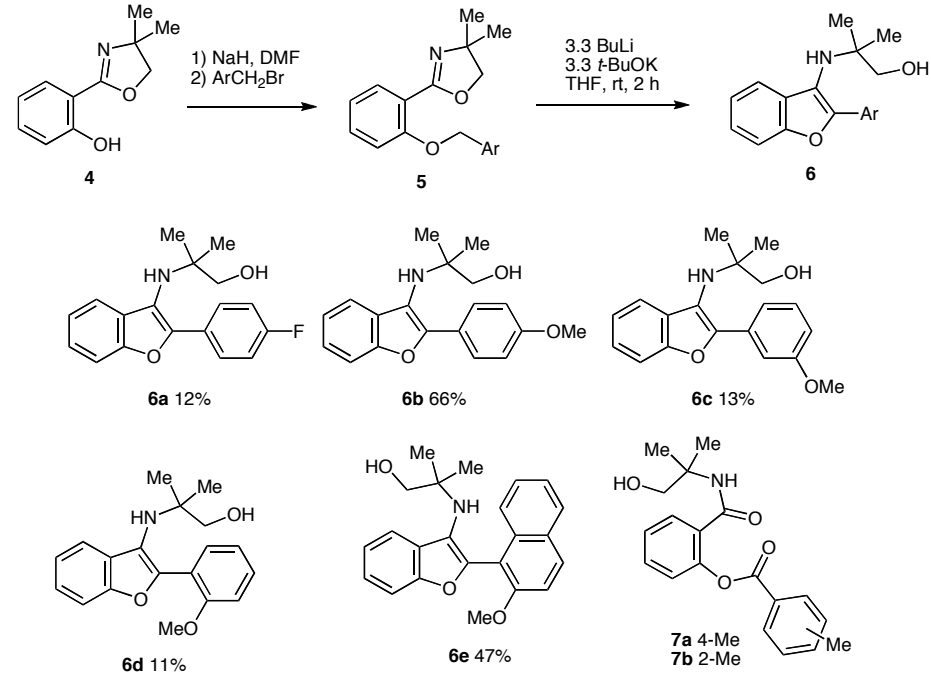


Scheme 1 Optimised conditions for cyclisation of **1** to give **3**.

As far as we are aware, the only previous examples of intramolecular base-induced cyclisation of a carbanion onto an oxazoline resulting in ring-opening of the latter are a single example of naphtho[2,3-*b*]thiophene formation upon treatment of a 1-bromo-2-naphthyloxazoline with the sodium salt of 4-chlorobenzylmercaptan,[5] and two reports in which fluorenone products are formed as byproducts in treatment of an *ortho*-lithiated phenyloxazoline with an aryne.[6,7] The current process does bear a close resemblance to the Gewald reaction,[8] in which an *ortho*-alkoxybenzonitrile is treated with base leading to a 3-aminobenzofuran. Although this process originally required a strongly electron-withdrawing substituent on the alkoxy group, more recent examples show that it also works with less stabilised anions,[9–11] including the cyclisation of 2-benzyloxy-3-cyanopyridine.[12] It might also be



Scheme 2 Proposed mechanism for conversion of **1** into **3**.



Scheme 3 Preparation of compounds **5a–j** and their reaction to give **6a–e** and **7a,b**

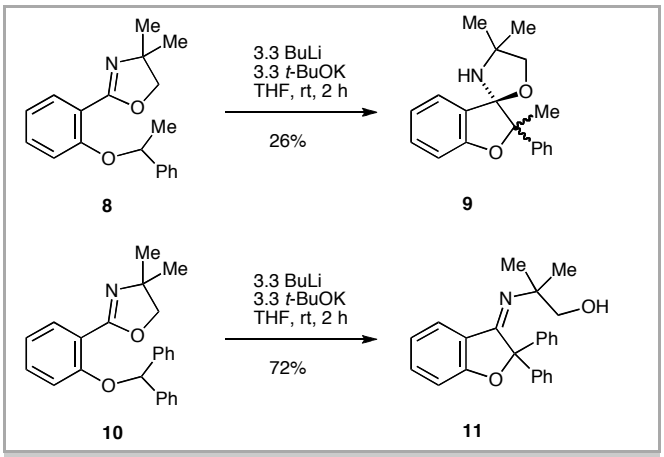
mentioned that heterocycle formation by intramolecular cyclisation of both alkoxide[13] and imide[14] anions onto 2-oxazolines are well known, giving phthalides and isoquinolines respectively after hydrolysis. There are relatively few direct cyclization routes to 3-aminobenzofurans but one notable recent method involves treatment of 2-alkynylphenols with *O*-benzoylhydroxylamines and a copper catalyst under basic

conditions, although this was only used to obtain 3-dialkylamino products.[15,16]

Although the starting oxazoline **1** was readily prepared by conventional step-wise construction of the oxazoline ring with the benzyl group already in place, a range of examples with substituted benzyl groups were more conveniently synthesised from the phenol **4**, itself derived from dealkylation of the allyl compound **12** (*vide infra*). In this way compounds **5a–j** were prepared and characterised (Scheme 3).

When these were subjected to the conditions of Scheme 1, a varied pattern of reactivity was observed. Compounds **5a–e** all gave the expected benzofurans **6a–e** in moderate to low yield with the latter being caused by extensive decomposition during chromatographic purification. In the case of **5f** and **5g**, the products isolated were those of oxidative cleavage of the benzofuran ring, **7a** and **7b**, and it is likely that similar 2-benzoyloxybenzamides were also formed in many of the other cases. The ready oxidative C2-C3 bond cleavage of a 3-hydroxybenzofuran was noted as early as 1916,[17] and the same process has been reported more recently for 2,3-diaminobenzofurans.[18] For the nitro-containing compounds **5h–j**, base treatment resulted in extensive decomposition and no useful products were obtained.

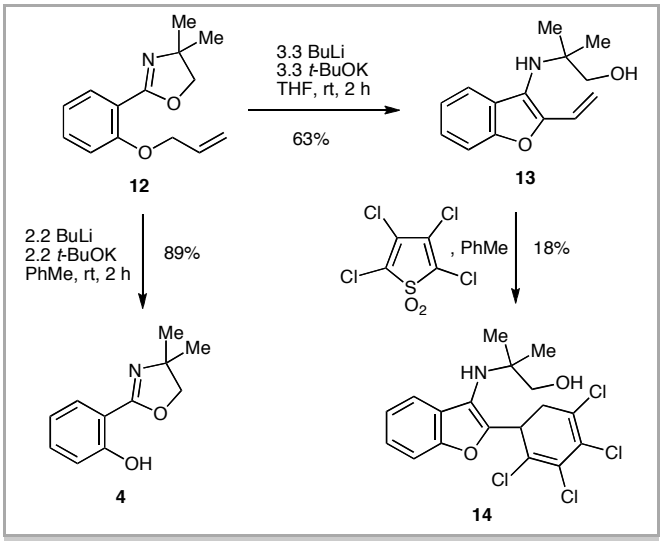
The oxazolines **8** and **10** with secondary alkoxy groups were readily prepared by alkylation of **4** and also underwent cyclisation. The products were, respectively, the spiro oxazolidine **9** obtained as a 5:3 mixture of diastereomers and the dihydrobenzofuran-3-imine **11** (Scheme 4). The potential of chiral oxazoline analogues of **8** for the synthesis of 2-chiral benzofuran-3-ones is currently being investigated.



Scheme 4 Reactions observed with secondary alkoxy groups

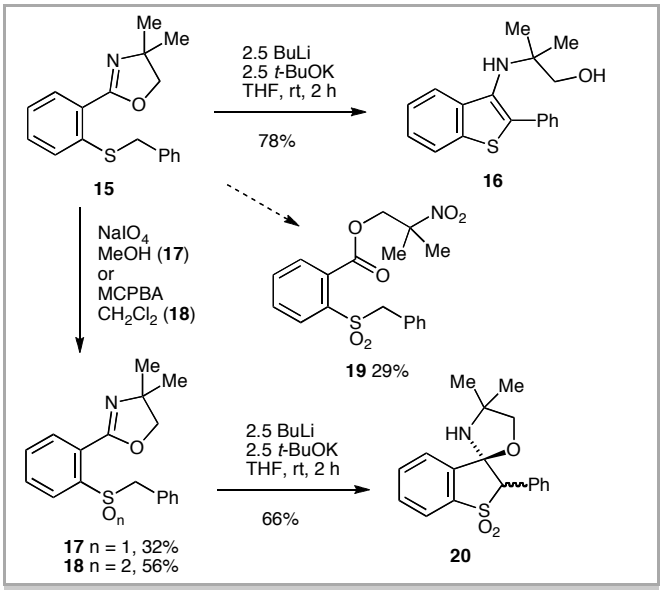
The 2-allyloxyphenyloxazoline **12** was also found to undergo the same process giving the 2-vinylbenzofuran **13** (Scheme 5). While we were unable to get this to react as a diene with a wide range of dienophiles, it did undergo a Diels Alder reaction as the dienophile with tetrachlorothiophene dioxide[19] with extrusion of SO_2 to give adduct **14**.

A most useful observation was that by changing the reaction solvent to toluene, treatment of **12** with just over two equivalents of BuLi/KOBu^t gave the phenol **4** in high yield, presumably with elimination of hept-1-ene and this was the method used to obtain **4** for synthesis of **5a–j**, **8** and **10**, effectively using *O*-allyl as a protecting group through the oxazoline formation.



Scheme 5 Reactions of the 2-allyloxyphenyloxazoline

The method is also applicable to formation of 3-aminobenzothiophenes from 2-(benzylthio)phenyloxazolines and conversion of **15** into **16** proceeded in good yield with 2.5 equivalents of BuLi/KOBu^t (Scheme 6). The structure of product **16** was confirmed by X-ray diffraction, which also showed an interesting pattern of hydrogen bonding involving the amino alcohol function.[20] The sulfide **15** was oxidised to both the sulfoxide **17** and the sulfone **18** using standard methods and, in the latter case, there was partial breakdown of the oxazoline to give the nitro ester **19** as a byproduct. This is a known reaction of oxazolines with mCPBA.[21] Base treatment of the sulfoxide **17**

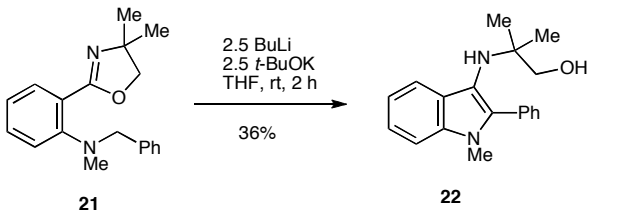


Scheme 6 Cyclisation of sulfur-containing oxazolines

led to extensive decomposition and gave no useful products while the sulfone **18** reacted cleanly to give the spiro compound **20** as a 3:2 mixture of diastereomers. The formation of 3-

aminobenzothiophenes by the base-induced cyclisation of 2-(benzylthio)benzonitrile as well as the corresponding sulfoxide and sulfone has been reported,[22] and there are numerous other reports of Gewald-type benzothiophene formation[11,23-27] but, apart from the example already mentioned,[5] none involving cyclisation onto an oxazoline.

Finally the method was extended to indole formation. The oxazoline **21** was prepared by nucleophilic substitution of the 2-methoxyphenyloxazoline[28] with *N*-methylbenzylamine and, upon treatment with 2.5 equivalents of BuLi/KOBu^t, gave the aminoindole **22** (Scheme 7). There have been several reports of aminoindole formation by Gewald cyclisation of *ortho*-aminobenzonitriles,[10,11,29] and in the last case, involving cyclisation of an *N*-benzyl group, it was noted that the 3-amino-2-phenylindoles could not be isolated as such due to instability and they were instead directly acylated before isolation. This perhaps goes some way to explain the low yield obtained for **22**. The copper catalyzed cyclisation of 2-alkynylanilines with *O*-benzoylhydroxylamines also gives 3-aminoindoles but is restricted to 3-dialkylamino products.[16]



21 22

Scheme 7 Cyclisation of a benzylaminophenyloxazoline to an indole

In summary we have developed a convenient new route to form 2-aryl-3-aminobenzofurans, also applicable to the corresponding benzothiophenes and indoles. Extension of the method to other fused ring heterocycles, such as various isomeric thienofurans, is currently being investigated and will be reported shortly.

Funding Information

We thank EPSRC (UK) for a DTA studentship (Grant No. EP/L505079/1) and the EPSRC UK National Mass Spectrometry Facility at Swansea University

Supporting Information

Full experimental procedures and spectroscopic data for all compounds, copies of ^{1}H and ^{13}C NMR spectra and details of X-ray structure for **16**.

Primary Data

(No)

References and Notes

(1) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
(2) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
(3) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137.
(4) Typical experimental procedures:
A solution of 2-(benzyloxy)benzoic acid (10.00 g, 43.8 mmol) and thionyl chloride (6.4 mL, 10.44 g, 87.7 mmol) in toluene (90 mL) was heated under reflux for 3 h and then cooled and evaporated to give 2-(benzyloxy)benzoyl chloride (10.80 g, 100%) as a pale yellow oil which was used without further purification.
This was dissolved in CH_2Cl_2 (40 mL) and added dropwise to a solution of 2-amino-2-methylpropan-1-ol (7.81 g, 87.6 mmol) in CH_2Cl_2 (50 mL) stirred at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to rt for 18 h before being poured into water. The two layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 (× 2). The combined organic layers were washed successively with 2 M HCl, 2 M NaOH and water before being dried and evaporated to give the amide (12.68 g, 97%) as a colourless solid, mp 115–117 °C, which was used without further purification.
Thionyl chloride (3.7 mL, 6.03 g, 50.7 mmol) was added to a solution of 2-(benzyloxy)-*N*-(1-hydroxy-2-methylpropan-2-yl)benzamide (12.68 g, 42.4 mmol) in CH_2Cl_2 (210 mL) and the reaction mixture was stirred at rt for 18 h. The mixture was washed with 2 M NaOH and water before being dried and evaporated to give, after purification by Kugelrohr distillation (185 °C/9.2 Torr), **1** (10.14 g, 85%) as a colourless oil which formed a low-melting solid on standing. IR: 1718, 1645, 1038, 967, 871, 848, 751, 733, 695 cm^{-1}. ^{1}H NMR (500 MHz): δ = 7.72 (dd, *J* = 7.5, 2.0 Hz, 1 H), 7.52 (d, *J* = 7.5 Hz, 2 H), 7.38–7.35 (m, 3 H), 7.29 (t, *J* = 7.3 Hz, 1 H), 7.01–6.97 (m, 2 H), 5.18 (s, 2 H, OCH_2Ar), 4.11 (s, 2 H, oxazoline CH_2), 1.41 (s, 6 H, CH_3). ^{13}C NMR (125 MHz): δ = 161.2 (C=N), 157.3 (C–O), 137.0 (C), 131.9 (CH), 131.1 (CH), 128.2 (2 CH), 127.5 (CH), 126.7 (2 CH), 120.6 (CH), 118.6 (C), 113.5 (CH), 78.8 (oxazoline CH_2), 70.5 (OCH_2Ar), 67.5 (C), 28.4 (CH_3). HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{20}NO_2$ [M+H]$^+$: 282.1489; found: 282.1478.
Under a nitrogen atmosphere, *n*-butyllithium (2.5 M in hexane, 6.6 mL, 16.5 mmol) was added to a stirred mixture of 2-(2-(benzyloxy)phenyl)-4,4-dimethyl-4,5-dihydrooxazole **1** (1.41 g, 5.01 mmol) and potassium *tert*-butoxide (1.88 g, 16.8 mmol) in dry THF (50 mL). The reaction mixture was stirred at rt for 2 h before being quenched by addition of sat. aq. NH_4Cl and extracted with Et_2O (× 3). The combined organic layers were dried and evaporated to give, after purification by column chromatography (Al_2O_3, gradient elution, Et_2O/hexane 3:2 to EtOAc), **3** (1.13 g, 80%) as orange crystals, mp 59–63 °C. IR: 3325, 2974, 2933, 1605, 1452, 1362, 1256, 1043, 1026, 739, 694 cm^{-1}. ^{1}H NMR (400 MHz): δ = 8.08–8.05 (m, 2 H), 7.64–7.62 (m, 1 H), 7.46–7.41 (m, 3 H), 7.34–7.30 (m, 1 H), 7.29–7.25 (m, 1 H), 7.24–7.20 (m, 1 H), 3.42 (s, 2 H, CH_2), 2.65 (br s, 2 H, NH and OH), 1.07 (s, 6 H, CH_3). ^{13}C NMR (125 MHz): δ = 153.0 (C), 148.5 (C), 131.1 (C), 129.5 (C), 128.5 (2 CH), 128.0 (CH), 126.5 (2 CH), 124.4 (CH), 122.5 (CH), 122.2 (C), 119.6 (CH), 111.2 (CH), 70.3 (CH_2), 58.1 (C), 24.7 (CH_3). HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{20}NO_2$ [M+H]$^+$: 282.1489; found: 282.1482.
(5) Baker, R. W.; Hockless, D. C. R.; Pocock, G. R.; Sargent, M. V.; Skelton, B. W.; Sobolev, A. N.; Twiss (née Stanojevic), E.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2615.
(6) Yalcouye, B.; Berthelot-Bréhier, A.; Augros, D.; Panossian, A.; Choppin, S.; Chessé, M.; Colobert, F.; Leroux, F. R. *Eur. J. Org. Chem.* **2016**, 725.
(7) Augros, D.; Yalcouye, B.; Berthelot-Bréhier, A.; Chessé, M.; Choppin, S.; Panossian, A.; Leroux, F. R. *Tetrahedron* **2016**, *72*, 5208.
(8) Gewald, K.; Jänsch, H.-J. *J. Prakt. Chem.* **1973**, *315*, 779.
(9) Sarodnick, G.; Kempter, G. E. Ger. Pat. DD292001, **1991**; *Chem. Abstr.* **1991**, *115*, 232294.
(10) Radl, S.; Hezky, P.; Urbánková, J; Váchal, P.; Krejcí, I. *Collect. Czech. Chem. Commun.* **2000**, *65*, 280.
(11) Radl, S.; Obadalova, I. *Arkivoc* **2005**, part xv, 4.
(12) Yang, J.; Wangweerawong, A.; Dudley, G. B. *Heterocycles* **2012**, *85*, 1603.
(13) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991.
(14) Poindexter, G. S. *J. Org. Chem.* **1982**, *47*, 3787.
(15) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395–2397.

(16) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617–625
(17) von Auwers, K. *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 820.
(18) Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron Lett.* **2007**, *48*, 401.
(19) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856.
(20) Crystal data for **16**: $C_{18}H_{19}NOS$, M = 297.41, colourless prism, crystal dimensions 0.20 × 0.20 × 0.20 mm, monoclinic, space group $P2_1/c$, a = 11.976(2), b = 12.4118(15), c = 20.997(3) Å, β = 95.825(6)°, V = 3105.0(8) Å^3, Z = 8, D_c = 1.272 Mg m^{-3}, T = 173 K, R = 0.0345, R_W = 0.0801 for 4529 reflections with $I>2\sigma(I)$ and 395 variables. Data were collected using graphite monochromated Mo-Kα radiation, λ = 0.71075 Å and have been deposited at the Cambridge Crystallographic Data Centre as CCDC 1540330.
(21) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1976**, *41*, 3237.
(22) Beck, J. R. *J. Heterocycl. Chem.* **1978**, *15*, 513.
(23) Carrington, D. E. L.; Clarke, K.; Scrowston, R. M. *J. Chem. Soc. (C)* **1971**, 3903.
(24) Beck, J. R. *J. Org. Chem.* **1972**, *37*, 3224.
(25) Beck, J. R.; Yahner, J. A. *J. Org. Chem.* **1974**, *39*, 3440.
(26) Markert, J.; Hagen, H. *Liebigs Ann. Chem.* **1980**, 768.
(27) Kobayashi, K.; Yamashita, K. *Heterocycles* **2017**, *94*, 772.
(28) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
(29) Seong, C. M.; Park, C. M.; Choi, J.; Park, N. S. *Tetrahedron Lett.* **2009**, *50*, 1029.