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ARTICLE TYPE

Observation by NMR of cationic Wheland-like intermediates in the de-iodination of protected 1-iodonaphthalene-2,4-diamines in acidic media

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1-Iodonaphthalene-2,4-diamines in trifluoroacetic acid / chloroform give stable Wheland-like tetrahedral cationic species observable by NMR, through an initial intramolecular protonation. Dynamic equilibria allow proton-deuterium exchange of aromatic protons and provide a mechanism for deiodination of 1-iodonapthalene-2,4-diamines.

Introduction

Cyclopropabenzindoles (CBI) are more biologically potent, stable and synthetically accessible analogues of cyclopropapyrrolo-indole (CPI) antitumour antibiotics, such as duocarmycin-SA **1** and CC1065 **2** (Figure 1).[1,2] These compounds are exquisitely potent cytotoxins (**1** shows IC_{50} = 10 pM against L1210 cells)[3] but it is this very potency that makes them difficult to develop as selective anticancer drugs. Recently, much effort has gone into developing prodrugs (*e.g.* **3**,**4**) for selective delivery of CPIs and CBIs to tumours.[2,4] Efficient routes to the required hydroxy-*seco*-CBIs are available but access to the corresponding amino-*seco*-CBIs is more challenging.[5,6]

As part of our research towards a general route to amino-*seco*-CBIs, di-Boc-1-iodonaphthalene-2,4-diamine **11** was prepared from 2,4-dinitronaphthalen-1-ol **6** in five steps, as shown in Scheme 1. Inexpensive Martius Yellow **6** was triflated at oxygen, forming **7**.[5] S_NAr displacement of the triflate with iodide then produced the iodonaphthalene **8** in good yield. Unfortunately, reduction of the nitro groups of **8** was accompanied by complete loss of the iodine to form the naphthalenediamine **9**, which was converted into the di-Boc-protected derivative **10**. The iodine was restored electrophilically with an I^+-equivalent generated from N-iodosuccinimide and toluenesulfonic acid, affording the key intermediate **11**. For our route, we needed to discriminate between the two amine nitrogens in **11** to access either **12** or **13** or to form the diamine **14** (for later selective reprotection) by treatment with a dilute (0.85%, one equiv.) solution of trifluoroacetic acid in dichloromethane (Scheme 1). However even prolonged reaction (*ca.* 7 days, 20°C) only resulted in the isolation of **10**, from unanticipated loss of iodine but retention of the normally acid-labile Boc groups. Further attempts with more concentrated solutions of CF_3CO_2H removed both Boc groups but the iodine was lost, giving **9**. To understand the process more fully, a series of NMR-scale experiments was undertaken, leading to identification of un-

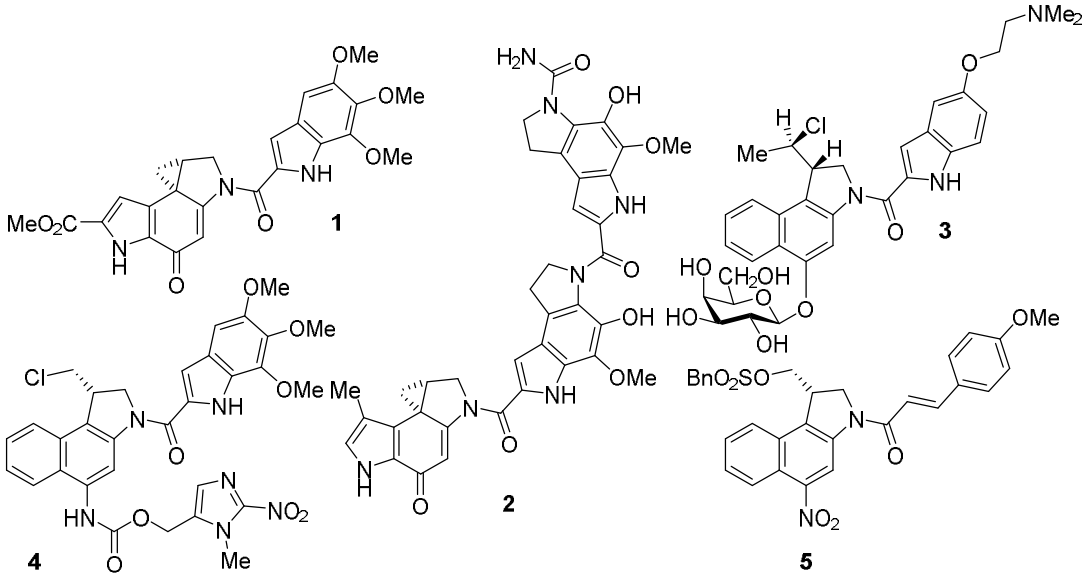
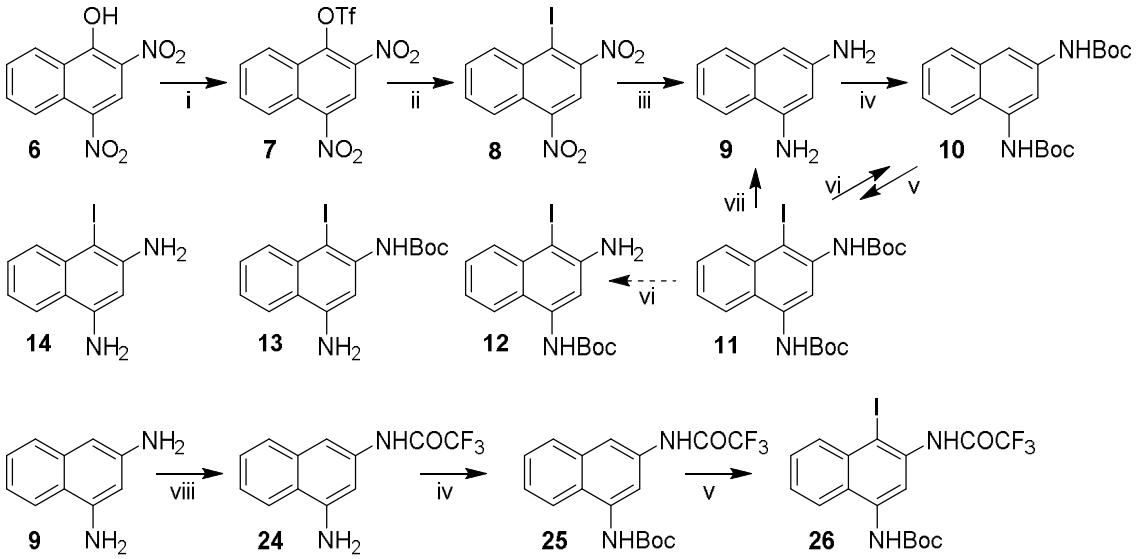


Figure 1. Structures of duocarmycin-SA **1**, CC1065 **2** and representative prodrugs of CBIs **3**-**5**.



Scheme 1. Syntheses of protected 1-iodo-2,4-dinitronaphthalenes **11** and **26** used in the study and reaction of **11** with CF_3CO_2H. *Reagents*: i, Tf_2O, Et_3N, CH_2Cl_2; ii, NaI, acetone, Δ; iii, $SnCl_2$, EtOAc; iv, Boc_2O, THF, Δ; v, N-iodosuccinimide, TsOH, THF, MeOH; vi, 0.85% CF_3CO_2H in CH_2Cl_2; vii, >5% CF_3CO_2H in CH_2Cl_2; viii, $(CF_3CO)_2O$, Pr^i_2NEt, THF.

expected cationic Wheland-like intermediates.

Results and discussion

Compound **11** was dissolved in deuteriochloroform (150 μL) and CF_3CO_2H (450 μL) at 0°C in a 5 mm NMR tube and introduced to the pre-cooled spectrometer probe. The course of the reaction was followed by ^{1}H NMR at 0°C for 120 min, during which time both Boc groups were cleaved to give **15** in good yield (>90%, by ^{1}H NMR) (Scheme 2). Although the NMR spectrum of **10** is clear, it was noted that new peaks upfield of the signals for the aromatic protons of **15** were slowly appearing. Raising the temperature to 20°C caused these new signals to become dominant until, after 2 h at 20°C, they were present at >90%, with loss of the peaks for **15**; selected ^{1}H NMR spectra from this experiment are shown in Figure 2. The new compound was fully assigned through 1-D and 2-D NMR experiments and was identified as the Wheland intermediate-like tetrahedral cationic species **16**.‡ Most significant is the signal at δ 9.64 in the ^{13}C spectrum, arising from an sp^3 carbon, with an associated proton signal at δ 6.50, as shown by HSQC. The upfield shift of the aromatic proton can be attributed to the loss of aromaticity, the stabilisation of the positive charge in the compound and the shielding effects of the iodine. 3-H$^{\#}$ also experiences a significant upfield shift of 2.06 ppm. Cation **16** is relatively stable in CF_3CO_2H / chloroform solution, with little change during 7 d at 20°C. However, all attempts at isolation afforded only the de-iodinated product **9**.

More information about the reaction was obtained using CF_3CO_2D. The overall course of the reaction was similar, with removal of both Boc groups at 0°C at 2 h and at 20°C, a tetrahedral cationic species again formed. However, both the signal at δ 6.50 (1-H) and the signal at δ 6.05 (3-H) show smaller than expected intensity, as a result of H→D exchange. Interestingly, this effect is seen even when only small amounts of **18** have been formed. Initially, the signal for 1-H integrates for 0.24 H (*i.e.* 76% of the 1-H have been replaced with deuterium), whereas 3-H integrates for only 0.10 H. The presence of D at the 1- and 3-positions was confirmed by the ^{13}C showing as a triplet owing to ^{13}C-D coupling. Over time, the intensity of the 1-H signal decreased further; ultimately the ratio of the signals for the aromatic protons to these signals is close to 10:1, which reflects of the overall ratio of exchangeable D to H in solution. The presence of a larger signal for protium at 1-H than for the overall ratio in solution at early time points provides mechanistic information. Addition of a deuteron to 2-N is rapid but H/D exchange at this nitrogen is slow, so that full equilibration of H and D is not complete in the time taken to obtain the first NMR data. It follows that the protonation at the 1-C is likely to be *intra*molecular from the N^+H_2D or the Bu^t cation is the source; if it were *inter*molecular from the trifluoroacetic acid, then the ratio of H/D in the Wheland-like species would reflect the overall solution ratio from the start. Since 3-H displays this ratio at all times, exchange at this position is much more rapid and may proceed directly from solvent. It is likely that the solution contains a mixture of dications and monocations but only the monocations have sufficient electron density to react (thus only the reactive monocations are shown in Scheme 2).

Similar experiments were undertaken with **9**, with CF_3CO_2H and with CF_3CO_2D (Scheme 2). Treatment of **9** with CF_3CO_2H / deuteriochloroform at 20°C afforded a mixture of two compounds, assigned as the di-protonated naphthalenediamine **20** and a tetrahedral species **21**, in ratio *ca.* 4:1, as shown by NMR. Of particular note is the presence of a CH_2 in **21**, confirmed by a phase-sensitive HSQC spectrum with a correlation peak at δ 4.13 in ^{1}H and δ 33.27 in ^{13}C. As with the iodo-compound **11**, the aromatic protons show a marked up-field shift in moving to the the cationic Wheland species. There was little or no change in the ratio **20** : **21** in CF_3CO_2H during 7 d at 20°C. When the experiment was repeated with CF_3CO_2D, deuterium was found to wash into both the 1- and 3-positions of **23** and, significantly, into the 1- and 3-positions of **22**. This provides confirmation that **22** and **23** are in equilibrium. Surprisingly, the initial spectral data for **23** showed that the signal for 1-H integrates to almost two protons

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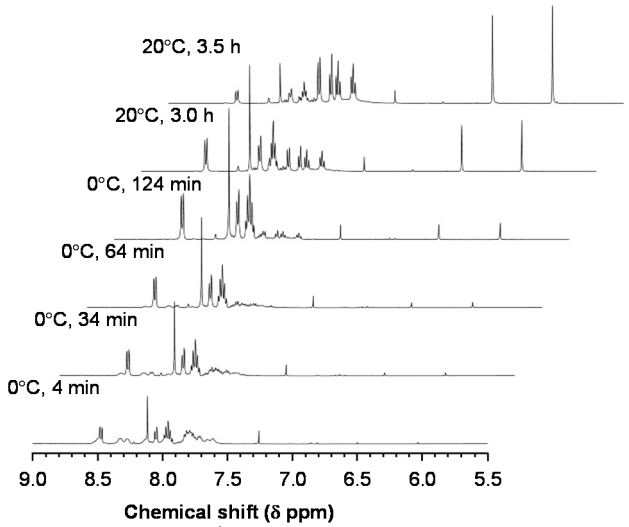


Figure 2. Time-course of ^{1}H NMR spectra of reaction of **11** with CF_3CO_2H / $CDCl_3$ (3:1).

relative to the other aromatic protons and thus has very little deuterium incorporated when first formed. As with the formation of **16** / **18**, this gives strong evidence for an intramolecular mechanism of protonation at 1-C, as the Bu^t cation is absent from this reaction mixture. After 48 h, this signal had reduced in size and a new triplet, slightly upfield at δ 4.14, arose. This peak correlated with a signal for a carbon with one proton attached (from the DEPT135 spectrum) and is assigned as *C*HD. The signal for 3-H also diminishes rapidly as deuterium was incorporated; at 4 min, the 3-H signal integrated for 0.18 H, whereas 1-H integrated for 1.0 H. Exchange at 3-H is much more rapid than for 1-H. Incorporation of D has a marked effect on the ^{13}C signals for 1-C and 3-C.

To explore the effect of a non-acid-labile amide group at N^3, the N^1-Boc-N^3-TFA differentially protected naphthalenediamine **26** was prepared (Scheme 1). Treatment of **9** with stoichiometric trifluoroacetic anhydride in dilute solution in THF achieved selective protection of the less-hindered amine in 15% yield. Interestingly, Hawkins *et al.*[7] reported selective introduction of Boc at this position with Boc-ON but in only 8% yield of crude material. Masking the remaining amine with Boc and introduction of the iodine gave **26**. With trifluoroacetamide adjacent to the iodine, treatment of **26** with CF_3CO_2H in deuteriochloroform did not lead to NMR-observable concentrations of any tetrahedral cation. Following loss of Boc, only **27** was observed and, after 48 h, iodine was lost to afford **28**, shown by the presence of a signal at δ 8.29 for 1-H. Significantly, when CF_3CO_2D was used, both this peak and 3-H showed a reduced intensity after 48 h, indicating that deuterium is incorporated. A transient Wheland cationic species may be involved but the equilibrium concentration is too low for observation. Deuterium was also incorporated into **29** / **30**.

In each case where Boc was lost, the NMR spectra showed that the Bu^t was trapped by solvent as Bu^t trifluoroacetate. With CF_3CO_2D, deuterium was incorporated, giving clearly identifiable $F_3CCO_2C(CH_3)(CH_3)(CH_2D)$, $F_3CCO_2C(CH_3)(CH_2D)$-(CH_2D) and $F_3CCO_2C(CH_3)(CH_3)(CHD_2)$ species, showing that 2-methylpropene is an intermediate.

Electrophilic aromatic substitution proceeds *via* an initial π-complex, which converts to a "σ-complex"; the latter is better recognised as the covalent Wheland intermediate. Several σ-complexes have been identified by their charge-transfer UV-vis absorptions and by crystallography.[8] The vast majority of Wheland intermediates are extremely transient, owing to rapid deprotonation, only being observed by fs time-resolved laser absorption spectroscopy. A few examples have sufficient lifetime to be characterised by NMR. 1,3,5-Trimethylbenzene and hexamethylbenzene react with $NO_2^+BF_4^-$ in super-acid media at -70°C to give NMR-observable Wheland intermediates but these decompose on warming.[9] Wheland intermediates have been isolated with carboranyl counter-anions (characterised by NMR at low temperature)[10] and where the molecule contains both Wheland-like cations and Meisenheimer-like anions.[11] The formation of Wheland intermediates from 1,3,5-tris(dialkylamino)benzenes under acidic conditions has been studied and reviewed by Effenberger.[12] Wheland intermediate cations have also been observed by NMR in azo-coupling reactions of these molecules with arenediazonium salts.[13] UV spectroscopy and thermochemical studies have been reported to show Wheland-like structures from protonation of benzene-1,3,5-triamine.[14]

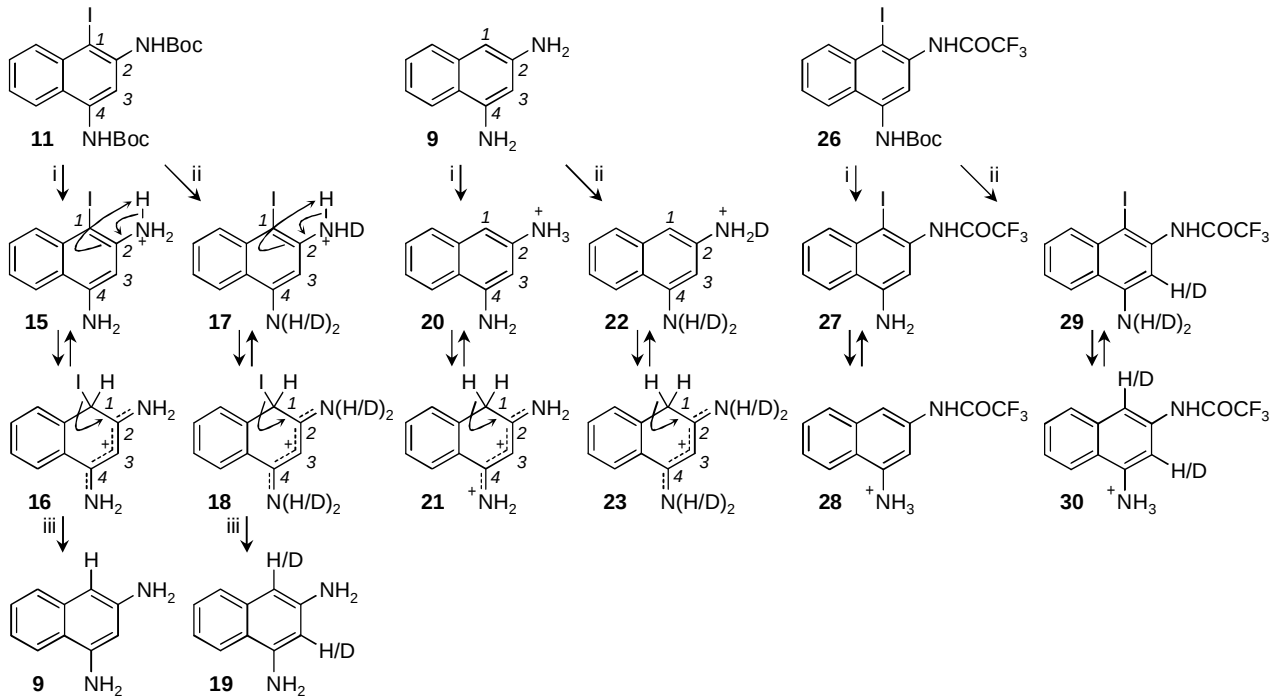
We believe that this is the first direct observation by NMR of Wheland-like intermediates derived from naphthalenes; these cations are remarkably stable, even at room temperature, but decompose on attempted isolation. The formation of these stable carbocationic species provides a partial explanation for the unexpected loss of iodine in attempts to cleave Boc groups from **6**. The iodine must be lost from the cationic species as an electrophilic I^+-equivalent. Presumably, the trapping nucleophile is trifluoroacetate, although, at very long time-points (>7 d), the solutions turn dark red, suggesting the presence of I_2.

The abundant tetrahedral Wheland-like species **16** / **18**, observed by NMR, is stabilised both by delocalisation of charge (including with the nitrogens) and by relief of steric compression between the very large iodine (R = 1.98 Å) and the *peri* 8-H as it moves from the sp^2-hybridised educt to the sp^3-hybridised 1-C in the cation. However, the presence of iodine in the molecule is not essential for the formation of these cationic species, as shown by the formation of **21** / **23** and the reactions of **27** / **29**. Figure 3 shows space-filling representations of MM2-minimised structures of **15** and **16**, to illustrate this point.

Conclusions

Here we report the generation of Wheland-like intermediates from (Boc-protected) naphthalenediamines. When the adjacent amine lacks an electron-withdrawing carbonyl, these intermediates are present in high concentrations in trifluoroacetic acid, characterisable by ^{1}H and ^{13}C NMR at 0°C and at 20°C, much higher than have been used previously for less-stabilised benzenium cations. Strikingly, the source of the proton at the new tetrahedral carbon is shown to be intramolecular, through a 1,3-proton shift. These studies provide evidence for the mechanism of protio-deiodination of *ortho*-iodoanilines and *ortho*-iodoanilides.

Experimental



Scheme 2. Reactions of **11**,**9** and **26** with CF_3CO_2H and with CF_3CO_2D in $CDCl_3$, showing intramolecular 1,3-proton shifts to form Wieland-like intermediates **16**,**18**,**21** and **23** and numbering scheme used throughout. *Reagents*: i, CF_3CO_2H / $CDCl_3$ (3:1); ii, CF_3CO_2D / $CDCl_3$ (3:1); iii, aq. work-up.

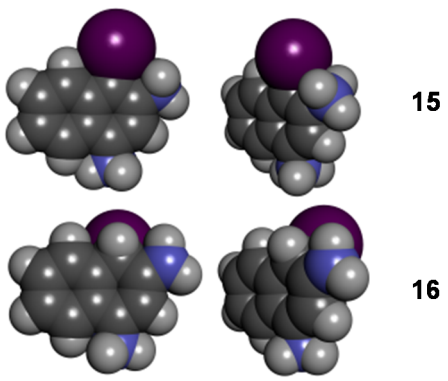


Figure 3. Space-filling representations of MM2-minimised structures of **15** and **16**, showing relief of steric crowding on moving to tetrahedral sp^3 1-C in **16**.

NMR experiments were performed using a Bruker Avance III spectrometer operating at 500.13 MHz (^{1}H), 125.77 MHz (^{13}C) and 470.52 MHz (^{19}F). The residual solvent peak was used as an internal reference for ^{1}H (δ = 7.26 ppm for $CDCl_3$) and ^{13}C (δ = 77.0 ppm) and ^{19}F was referenced externally to $BF_3.OEt_2$ (δ = -132.0 ppm). Mass spectrometry was carried out on a micrOTOF^{TM} from Bruker Daltonics (Bremen, Germany) using an electrospray source (ESI-TOF). Melting points were obtained using a Reichert-Jung heated-stage microscope. IR spectra were recorded on a Perkin-Elmer 782 infra-red spectrometer using potassium bromide discs. TLC was carried out on Merck aluminium-backed TLC plates Silicagel 60 F_{254} and viewed using UV light (λ = 254 nm). Experiments were conducted at ambient temperature, unless otherwise noted. Solvents were evaporated under reduced pressure. Solutions in organic solvents were dried with magnesium sulfate. All reagents and solvents were of commercial reagent grade and were used without further purification. The brine was saturated.

2,4-Dinitronaphthalen-1-yl trifluoromethanesulfonate (7)

Martius Yellow (2,4-dinitronaphthalen-1-ol) **6** (501 mg, 2.14 mmol) and triethylamine (562 mg, 5.6 mmol) in dichloromethane (10 mL) were cooled in an ice bath and treated dropwise with trifluoromethanesulfonic anhydride (784 mg, 2.8 mmol). The mixture was stirred at 20°C for 2 h under N_2. Aq. HCl (0.5 M, 10 mL) was added in one portion and the mixture was stirred for 30 min. The aqueous phase was separated and extracted with dichloromethane. The combined organic phases were washed with sat. aq. sodium hydrogen carbonate and brine. Drying, evaporation and chromatography (dichloromethane) gave **7** (484 mg, 62%) as a yellow solid: mp 117-119°C (lit.[5] mp 105-107°C); ν_{max} 1532 (NO_2), 1365 (-SO_2-O-), 1349 (NO_2); δ_H ($(CD_3)_2SO$) 7.72 (1 H, ddd, *J* 8.2, 7.1, 1.0 Hz, 7-H), 7.91 (1 H, ddd, *J* 8.4, 7.0, 1.4 Hz, 6-H), 8.51 (1 H, d, *J* 8.4 Hz, 8-H), 8.57 (1 H, d, *J* 8.6 Hz, 5-H), 8.87 (1 H, s, 3-H); δ_C ($(CD_3)_2SO$) 120.65 (q, *J* 322.3 Hz, CF_3), 122.31 (3-C), 123.32 (5-C), 125.58 (8-C), 127.49 (2-C), 127.76 (8a-C, 7-C), 128.00 (4a-C), 133.09 (6-C), 134.75 (4-C), 158.70 (1-C); δ_F ($CDCl_3$) -71.85 (s, CF_3).

1-Iodo-2,4-dinitronaphthalene (8)

Compound **7** (4.28 g, 11.7 mmol) was heated under reflux with sodium iodide (5.99 g, 40 mmol) in acetone (170 mL) for 2 h. The evaporation residue, in ethyl acetate, was washed with sat. aq. sodium thiosulfate and dried. Evaporation and chromatogra-

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phy (dichloromethane) gave **8** (2.98 g, 74%) as a yellow solid: mp 183-186°C (lit.[5] mp 194-195°C); ν_{max} 1530 (NO_2), 1333 (NO_2); δ_H ($(CD_3)_2SO$) 7.98 (2 H, m, 6,7-H_2), 8.32 (1 H, dd, *J* 7.1, 1.7 Hz, 5-H), 8.52 (1 H, dd, *J* 7.7, 2.0 Hz, 8-H), 8.73 (1 H, s, 3-H); δ_C ($(CD_3)_2SO$) 102.55 (1-C), 117.53 (3-C), 123.35 (5-C), 124.01 (4a-C), 131.39 (6-C), 132.32 (7-C), 135.07 (8-C), 135.12 (8a-C), 147.21 (4-C), 151.91 (2-C).

Naphthalene-1,3-diamine (9)

Compound **8** (1.05 g, 2.9 mmol) and tin(II) chloride dihydrate (9.84 g, 44 mmol) in ethyl acetate (100 mL) were heated under reflux for 17 h. The mixture was added to ice and sodium hydrogen carbonate was added until the aqueous layer was basic. The mixture was extracted with ethyl acetate and the combined extracts were washed with water and dried. Evaporation gave crude **9** as a dark brown solid: δ_H ($CDCl_3$) 3.71 (2 H, s, NH_2), 4.08 (2 H, s, NH_2), 6.23 (1 H, d, *J* 2.1 Hz, 2-H), 6.50 (1 H, d, *J* 1.9 Hz, 4-H), 7.18 (1 H, ddd, *J* 8.2, 6.8, 1.2 Hz, 7-H), 7.34 (1 H, ddd, *J* 8.0, 6.8, 1.0 Hz, 6-H), 7.53 (1 H, d, *J* 8.2 Hz, 5-H), 7.64 (1 H, d, *J* 8.4 Hz, 8-H); δ_H ($CDCl_3$) 100.67 (4-C), 100.58 (2-C), 118.65 (8a-C), 120.67 (8-C), 121.36 (7-C), 126.39 and 126.42 (5-C and 6-C), 136.01 (4a-C), 143.28 (1-C), 144.71 (3-C).

N,N'-Bis(*tert*-butoxycarbonyl)naphthalene-1,3-diamine (10)

The above crude **9** was heated under reflux with di-*tert*-butyl dicarbonate (3.11 g, 14.2 mmol) in tetrahydrofuran (30 mL) for 17 h. Evaporation and chromatography (dichloromethane) gave **10** (769 mg, 74%) as a pale buff solid: mp 127-130°C (lit.[5] mp 129-131°C); ν_{max} 3254 (NH), 1716 (C=O), 1685 (C=O); δ_H ($CDCl_3$) 1.54 (9 H, s, Bu^t), 1.56 (9 H, s, Bu^t), 6.63 (1 H, s, NH), 6.91 (1 H, s, NH), 7.34 (1 H, ddd, *J* = 8.1, 6.8, 1.3 Hz, 6-H), 7.44 (1 H, ddd, *J* 7.9, 6.9, 1.1 Hz, 7-H), 7.73 (1 H, d, *J* 8.2 Hz, 5-H), 7.77 (2 H, m, 1,8-H_2), 7.93 (1 H, s, 3-H); δ_C ($CDCl_3$) 28.37 (2 × C*Me*$_3$), 80.63 (*C*Me$_3$), 80.92 (*C*Me$_3$), 110.65 (3,8-C_2), 119.69 (5-C), 122.5 (4a-C), 124.41 (6-C), 126.49 (7-C), 128.52 (1-C), 133.76 (4-C), 134.82 (8a-C), 135.81 (2-C), 152.76 (C=O), 153.13 (C=O).

N,N'-Bis(*tert*-butoxycarbonyl)-1-iodonaphthalene-2,4-diamine (11)

Compound **10** (417 mg, 1.28 mmol) was treated with N-iodosuccinimide (431 mg, 1.9 mmol) and 4-methylbenzenesulfonic acid hydrate (457 mg, 2.4 mmol) in tetrahydrofuran (7 mL) and methanol (7 mL) at -78°C. The mixture was allowed to warm slowly to 20°C over 4 h and was then diluted with aq. sodium thiosulfate (5%) and stirred at 20°C for 15 min. The mixture was extracted with ethyl acetate. The combined organic extracts were dried and the solvents were evaporated. Chromatography (dichloromethane) gave **11** (400 mg, 71%) as a pale buff solid: mp 166-168°C (lit.[5] mp 154-156°C); ν_{max} 3384 (NH), 3229 (NH), 1733 (C=O), 1683 (C=O); δ_H ($CDCl_3$) δ 1.55 (9 H, s, Bu^t), 1.57 (9 H, s, Bu^t), 6.86 (1 H, s, 4-NH), 7.17 (1 H, s, 2-NH), 7.43 (1 H, dd, *J* 8.0, 6.9 Hz, 6-H), 7.51 (1 H, dd, *J* 7.9, 1.1 Hz, 7-H), 7.76 (1 H, d, *J* 8.2 Hz, 5-H), 8.09 (1 H, d, *J* 8.4 Hz, 8-H); δ_C ($CDCl_3$) 28.38 (2 × C*Me*$_3$), 81.03 (*C*Me$_3$), 81.28 (*C*Me$_3$), 87.36 (1-C), 113.71 (3-C), 121.40 (5-C), 124.88 (4a-C), 125.32 (6-C), 128.15 (7-C), 132.58 (8-C), 134.65 (4-C or 8a-C), 134.82 (8a-C or 4-C), 138.22 (2-C), 152.68 (C=O), 153.21 (C=O).

N-(1-Aminonaphthalen-3-yl)-2,2,2-trifluoroacetamide (24)

Naphthalene-1,3-diamine **9** (1.29 g, 8.16 mmol) was stirred in dry tetrahydrofuran (100 mL) under nitrogen at 0°C. N,N-Di*iso*propylethylamine (4.23 g, 32.6 mmol) was added, followed by dropwise addition of trifluoroacetic anhydride (1.71 g, 8.16 mmol) in dry tetrahydrofuran (100 mL) during 2 h. The mixture was allowed to warm slowly to 20°C during 16 h. The evaporation residue, in ethyl acetate, was washed with water and brine. Drying, evaporation and chromatography (petroleum ether / ethyl acetate 9:1 → 1:1) gave **24** (309 mg, 15%) as a buff solid: mp 168-169°C; ν_{max} 3482, 3374, 3324 (NH), 1721, 1706 (C=O); δ_H ($CDCl_3$) 5.99 (2 H, s, NH_2), 7.01 (1 H, d, *J* 2.0 Hz, 2-H), 7.39 (1 H, ddd, *J* 8.2, 6.8, 1.3 Hz, 7-H), 7.47 (1 H, ddd, *J* 8.1, 6.8, 1.2 Hz, 6-H), 7.49 (1 H, d, *J* 1.4 Hz, 4-H), 7.75 (1 H, d, *J* 7.7 Hz, 5-H), 8.10 (1 H, d, *J* 8.4 Hz, 8-H), 11.17 (1 H, s, NH); δ_C ($CDCl_3$) 101.31 (2-C), 106.51 (4-C), 115.88 (q, *J* 289.0 Hz, CF_3), 120.89 (8a-C), 122.24 (8-C), 123.46 (7-C), 126.34 (6-C), 127.78 (5-C), 134.09 (4a-C), 134.67 (3-C), 145.56 (1-C), 154.41 (q, *J* 36.6 Hz, C=O); δ_F ($(CD_3)_2SO$) -73.69 (s, CF_3); *m/z* (ES^+) 277.0554 (M + Na) ($C_{12}H_9F_3N_2NaO$ requires 277.0565).

***tert*-Butyl N-(3-trifluoroacetamidonaphthalen-1-yl)carbamate (25)**

Compound **24** (330 mg, 1.30 mmol) was boiled under reflux with di-*tert*-butyl dicarbonate (1.43 g, 6.55 mmol) in dry tetrahydrofuran (10 mL) under N_2 for 16 h. Evaporation and chromategraphy (petroleum ether → petroleum ether / ethyl acetate 19:1) gave **25** (381 mg, 83%) as a pale buff solid. mp 206-208ºC; ν_{max} 3297 (NH), 3244 (NH), 1711 (C=O), 1683 (C=O); δ_H ($(CD_3)_2SO$) 1.57 (9 H, s, Bu^t), 7.54 (1 H, td, *J* 8.2, 1.4 Hz, 7-H), 7.58 (1 H, td, *J* 8.0, 1.2 Hz, 6-H), 7.94 (1 H, d, *J* 8.1 Hz, 5-H), 8.00 (1 H, d, *J* 2.0 Hz, 2-H), 8.13 (1 H, d, *J* 8.2 Hz, 8-H), 8.20 (1 H, d, *J* 1.8 Hz, 4-H), 9.39 (1 H, s, N*H*Boc), 11.50 (1 H, s, N*H*$COCF_3$); δ_C ($(CD_3)_2SO$) 28.13 (C*Me*$_3$), 79.26 (*C*Me$_3$), 114.63 (2-C), 114.73 (4-C), 115.79 (q, *J* 288.8 Hz, CF_3), 122.64 (8-C), 125.27 (8a-C), 125.33 (7-C), 126.75 (6-C), 128.03 (5-C), 133.52 (4a-C), 133.56 (3-C), 134.92 (1-C), 153.76 (Boc C=O), 154.68 (q, *J* 37.1 Hz, CF_3C=O); δ_F ($(CD_3)_2SO$) -73.76 (s, CF_3); *m/z* (ES^+) 377.1120 (M + Na) ($C_{17}H_{17}F_3N_2NaO_3$ requires 377.1089).

***tert*-Butyl N-(1-iodo-2-(trifluoroacetamido)naphthalen-4-yl)-carbamate (26)**

Compound **25** (336 mg, 0.95 mmol) in dry tetrahydrofuran (10 mL) was cooled to -78°C and stirred under N_2. N-Iodosuccinimide (309 mg, 1.4 mmol) in dry tetrahydrofuran (2.0 mL) was added followed by 4-methylbenzenesulfonic acid hydrate (370 mg, 1.9 mmol) in dry tetrahydrofuran (2.0 mL). The temperature of the mixture was allowed to rise slowly to 20°C during 20 h. The reaction was quenched by addition of sat. aq. sodium hydrogen carbonate. The mixture was diluted with water and extracted with ethyl acetate. Drying, evaporation and chromatography (petroleum ether → petroleum ether / ethyl acetate 4:1) gave **26** (344

mg, 75%) as a pale buff solid: mp 198-199°C; ν_{max} 3323, 3209 (NH), 1721 (C=O), 1698 (C=O); δ_H ($CDCl_3$) δ 1.57 (9 H, s, Bu^t), 6.95 (1 H, s, N*H*Boc), 7.54-7.61 (2 H, m, 6,7-H_2), 7.82 (1 H, d, *J* 8.1 Hz, 5-H), 8.14 (1 H, d, *J* 8.6 Hz, 8-H), 8.58 (1 H, s, N*H*$COCF_3$), 8.71 (1 H, s, 3-H); δ_C ($CDCl_3$) 28.31 (CMe_3), 81.63 (CMe_3), 89.87 (1-C), 113.26 (3-C), 115.77 (q, *J* 289.3 Hz, CF_3), 121.09 (8-C), 125.43 (8a-C), 126.86 (7-C), 128.73 (6-C), 133.17 (5-C), 134.52 (4a-C), 134.90 (4-C), 135.20 (2-C), 152.82 (Boc C=O), 155.05 (q, *J* 38.0 Hz, CF_3C=O); δ_F ($(CD_3)_2SO$) -74.13 (s, CF_3); *m/z* (ES^+) 503.0100 (M + Na) ($C_{17}H_{16}F_3IN_2NaO_3$ requires 503.0055), 498.0542 (M + $^+NH_4$) ($C_{17}H_{20}F_3IN_3O_3$ requires 498.0500).

Notes and references

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‡ NMR spectroscopic data for **16**. ^{1}H NMR ($CDCl_3$ / CF_3CO_2H, 293 K) δ 6.05 (1 H, s, 3-H), 6.51 (1 H, s, CHI), 7.58 (1 H, t, *J* = 7.8 Hz), 7.75 (1 H, d, *J* = 7.8 Hz), 7.70 (1 H, t, *J* = 7.8 Hz), 7.84 (1 H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$ / CF_3CO_2D, 293K) δ 9.79 (CHI), 91.49 (CH), 121.68 (C_q), 124.16 (CH), 129.93 (CH), 131.48 (CH), 135.01 (CH), 141.25 (C_q), 164.30 (CNH_3^+), 173.50 (CNH_3^+).

To avoid confusion, all positions on the naphthalene ring are numbered in the discussion according to the iodonaphthalene educts, with N-containing groups at 2- and 4-positions.

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