SHORT PAPER

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Cyclisation of *N*-alkyl-2,4-dinitro-6-trifluoromethylanilines†

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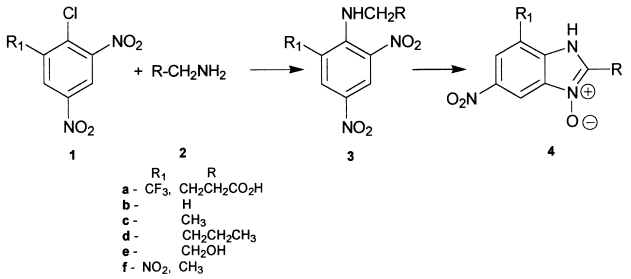
Examples of cyclisation of the title compounds leading to 2-alkyl substituted benzimidazole *N*-oxides are reported.

Keywords: nitro compounds, cyclisation, benzimidazole *N*-oxides, trifluoromethyl compounds

Recently we have been involved in the investigations concerning the use of ^{19}F NMR spectroscopy for the determination of the presence of organic bases (*e.g.* aminoacids) in biofluids (*e.g.* urine). As one of the fluorine markers 1-chloro-2,4-dinitro-6-trifluoromethylbenzene **(1)** was chosen. This commercially available compound shows satisfactory reactivity towards nitrogen bases and possesses good properties for ^{19}F resonance measurements. The products of the nucleophilic substitution of chlorine in 1 by several aminoacids have been prepared and characterised by their ^{1}H, ^{13}C and ^{19}F NMR spectra. The results of this investigation will be published elsewhere. We now report the unexpected behaviour of the product obtained in the reaction of **1** with γ-aminobutyric acid, **2a** (Scheme 1).



Scheme 1

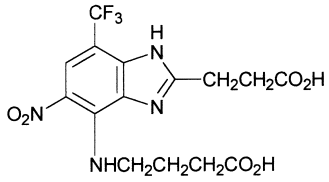
It was observed that side products were formed during the synthesis of **3a**, one of them in appreciable amount. The higher the molar ratio of sodium bicarbonate the higher was the yield of this product. The same compound was also obtained in almost quantitative yield when pure **3a** was heated in dilute alcohol in the presence of $NaHCO_3$. The product was purified by preparative TLC (SiO_2, ether/methanol = 9/1) and characterised by ^{1}H, ^{13}C NMR and MS. The obtained data are in accord with the structure **4a**.

To check the generality of this observed phenomenon the cyclisation of compounds **3b–f** was studied. Compounds **4b–f** were thus obtained in high yields (*ca* 80%). It was also found that using ethanol as a solvent and potassium carbonate as a base the reaction was faster and the products less contaminated.

The cyclisation of *N*- and arene ring substituted *o*-nitroanilines have been extensively investigated in terms of preparative as well as mechanistic aspects.[1-19] To our knowledge the reactions which proceed under conditions similar to those here are the compounds for which R = CO_2R[10-15], CN[10-13,15-18] or C_6H_5[19] (see Scheme 1). One of the reaction stages is inevitably proton abstraction from the CH_2 group. The presence of the above substituents stabilises the resulting negative charge and certainly facilitates this process. Our results show that the reaction goes well also when the substituents R do not possess carbanion-stabilising character.

We tried also to cyclise the compounds obtained by reaction of **2a** and **2c** with 2,4-dinitrochlorobenzene. Both compounds appeared to be very stable and besides a small amount of 2,4-dinitrophenol resulting from hydrolysis no other compounds were formed even after several hours heating in the presence of $NaHCO_3$. Also an attempt at cyclisation of the *N,N*-diethyl substituted analogue of **3** ($R_1 = CF_3$) failed. It seems that in the case of compounds for which R = alkyl, the cyclisation demands the presence of the NH proton and its acidity must be sufficiently high.

Besides of **4a** another minor side product of reaction **1** + **2a** → **3a** was separated by preparative TLC. Its tentative structure **(5)**, based on ^{1}H, ^{13}C NMR and MS data, is shown below.



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Experimental

All NMR spectra in $CDCl_3$ or $^{2}H_6$-DMSO solutions were recorded using a Varian Gemini 2000 spectrometer operating at 4.7 T. Residual solvent signals were used as chemical shift references for proton (δ_{CHCl3} = 7.26 ppm, δ_{DMSO} = 2.49 ppm) and carbon spectra (δ_{CHCl3} = 77.00 ppm, δ_{DMSO} = 39.5 ppm). The assignment of resonance signals was based on the chemical shifts, intensities and the values of H,F or ^{13}C,F coupling constants. In the case of ^{13}C spectra the multiplicity of signals in the proton coupled spectra (**4a** and **4c**) was taken into consideration. Symbols m were used for the assignment of multiplet like signals. Mass spectra were obtained under electron impact.

4-(2,4-Dinitro-6-trifluoromethylphenylamino)butyric acid, **3a:** A mixture of **1** (0.68 g, 2.5 mmol), **2a** (0.52 g, 5 mmol), sodium hydrocarbonate (0.63 g, 7.5 mmol), ethanol (7 ml) and water (7 ml) was refluxed for 3 h. After cooling and diluting with water the mixture was extracted with ether to remove substances insoluble in alkaline water, then acidified with hydrochloric acid and extracted with ether again. The ether solution was washed with brine, dried (MgSO4) and concentrated to ca. 5 ml. A precipitated solid (**4a**, *ca* 0.40 g) was filtered off. The filtrate was evaporated to dryness and resulting oil was extracted with toluene to give **3a** (*ca* 0.25 g). The residue insoluble in toluene solidified. It contained mainly **4a** and **5** (*ca* 0.10 g). Analytical samples of **3a, 4a** and **5** were purified by preparative TLC (Merck Kiesigel 60 F_{254}, ether:methanol = 9:1, v/v, R_f = 1, 0.5 and 0.3, respectively).

3a: m.p. 89–92°C, HRMS: $C_{11}H_{10}O_6N_3F_3$ requires *M*, 337.0522, found: 337.0527. ^{1}H NMR ($^{2}H_6$-DMSO): 10.5 (bs, 1H. CO_2H), 8.794 (d, 1H, $H_{3'}$, $J_{3',5'}$ = 3.0 Hz), 8.434 (bd, 1H, $H_{5'}$), 7.506 (bt, $J_{NH,4}$ = 5.4

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Hz), 3.082 (q, 2H, H_4), 2.230 (t, 2H, H_2, $J_{2,3}$ = 7.2 Hz), 1.819 (pent, 2H, H_3). ^{13}C NMR ($^2H_6$-DMSO) 174.17 (CO_2H), 144.77 (q, $C_{1'}$, $J_{1',F}$ = 1.0 Hz), 134.33 ($C_{2'}$ or $_{4'}$), 136.19 ($C_{4'\text{ or }2'}$), 127.13 ($C_{3'}$), 126.96 (q, $C_{5'}$, $J_{5',F}$ = 6.1 Hz), 122.67 (q, CF_3, $J_{C,F}$ = 272.9 Hz), 116.32 (q, $C_{6'}$, $J_{6',F}$ = 31.7 Hz), 46.70 (q, C_4, $J_{4,F}$ = 1.5 Hz), 30.72 (C_2), 24.37 (C_3).

5: m.p. 213°C dec., HRMS: $C_{15}H_{15}F_3N_4O_6$ requires *M* 404.0944, found 404.0920. ^1H NMR ($^2H_6$-DMSO): 13.01 (bs, 1H, NH), 12.8-10.8 (vbs, 2H, 2 × CO_2H), 9.203 (bt, 1H, NH unresolved), 8.125 (t, 1H, H_{Ar}, $J_{C,F}$ = 1.2 Hz), 4.215 (q, 2H), 3.060 (t, 2H), 2.790 (t, 2H), 2.321 (t, 2H), 1.895 (sext, 2H), $^{13}C\{^1H\}$ NMR 174.34, 173.60, 153.95 (q, $J_{C,F}$ = 4.5 Hz), 141.91 (q, $J_{C,F}$ = 2.9 Hz), 133.53, 131.47, 126.12, 124.61, 123.44 (q, $J_{C,F}$ = 269.5 Hz), 119.53 (q, $J_{C,F}$ = 4.9 Hz), 101.38 (q, $J_{C,F}$ = 34.7 Hz), 44.22, 31.03, 30.87, 25.82, 23.37.

Synthesis of N-substituted 2,4-dinitro-6-(trifluoromethyl)anilines, ***3b-e****, and N-ethyl-2,4,6-trinitroaniline* ***3f:*** An ethanol solution of **1** was treated with an excess of the appropriate amine or its ethanol solution and the mixture was left at room temperature for 1 h. The progress of the reaction was monitored by TLC (SiO_2, ether:hexane = 1:1). After the spot of **1** vanished the solution was evaporated to dryness under reduced pressure. The residues (crystals for **3b** and **3f**; oil for **3c, 3d** and **3e**). were found by ^1H NMR spectra to be pure enough for use in further reactions.

3b: m.p. 69–71°C, ^1H NMR ($CDCl_3$) 9.072 (d, 1H, $H_{3'}$, $J_{3',5'}$ = 2.8 Hz), 8.640 (dq, 1H, $H_{5'}$, $J_{5',F}$ = 0.6 Hz), 8.28 (bs, 1H, NH), 3.082 (dq, 3H, CH_3, $J_{CH3,NH}$ = 5.4, $J_{CH_3,F}$ = 1.8 Hz).

3c: oil; ^1H NMR ($CDCl_3$) 9.073 (d, 1H, $H_{3'}$, $J_{3',5'}$ = 3.0 Hz), 8.638 (dq, 1H, $H_{5'}$, $J_{5',F}$ = unresolved), 7.86 (bs, 1H, NH), 3.427 (m, 2H, CH_2), 1.390 (t, 3H, CH_3, $JCH_{2,CH3}$ = 7.0 Hz), $^{13}C\{^1H\}$ NMR ($CDCl_3$) 146.25 ($C_{1'}$), 134.68 ($C_{2'\text{ or }4'}$), 135.17 ($C_{4'\text{ or }2'}$), 129.25 (q, $C_{5'}$, $J_{5',F}$ = 6.9 Hz), 126.93 ($C_{3'}$), 122.64 (q, CF_3, $J_{C,F}$ = 272.7 Hz), 116.89 (q, $C_{6'}$, $J_{6',F}$ = 33.1 Hz), 42.08 (q, CH_2, $J_{4,F}$ = 4.9 Hz), 15.59 (CH_3).

3d: ^1H NMR ($CDCl_3$) 9.025 (d, 1H, $H_{3'}$, $J_{3',5'}$ = 2.8 Hz), 8.602 (dq, 1H, $H_{5'}$, $J_{5',F}$ = 0.6 Hz), 7.78 (bt, 1H, NH), 3.082 (q, 2H, NCH_2), 1.715 (pent, 2H, CH_2), 1.414 (sext, 2H, CH_2), 0.949 (t, 3h, CH_3, J_{CH_3,CH_2} = 7.2 Hz), $^{13}C\{^1H\}$ NMR ($CDCl_3$) 146.46 ($C_{1'}$), 134.64 ($C_{2'\text{ or }4'}$), 135.14 ($C_{4'\text{ or }2'}$), 129.28 (q, $C_{5'}$, $J_{5',F}$ = 6.7 Hz), 126.96 ($C_{3'}$), 122.69 (q, CF_3, $J_{C,F}$ = 273.3 Hz), 116.91 (q, $C_{6'}$, $J_{6',F}$ = 33.2 Hz), 46.90 (q, NCH_2, $J_{4,F}$ = 5.2 Hz), 32.24 (CH_2), 19.74 (CH_2), 13.51 (CH_3).

3e: ^1H NMR ($CDCl_3$) 9.077 (d, 1H, H_3, $J_{3,5}$ = 2.8 Hz), 8.652 (bd, 1H, H_5), 3.928 (t, 2H, OCH_2, J_{CH_2,CH_2} = 5.0 Hz), 3.515 (q, 2H, OCH_2).

N-Ethyl-2,4,6-trinitroaniline **(3f)**: m.p. 82–84°C (lit.[20] 83.5–84°C), ^1H NMR ($CDCl_3$): 9.028 (s, 2H, H_3, H_5), 8.952 (bs, 1H, NH), 3.167 (dq, 2H, CH_2, $J_{CH_2,\ NH}$ = 4.8 Hz, J_{CH_2,CH_3} = 7.0 Hz), 1.410 (t, 3H, CH_3).

3-(5-Nitro-3-oxy-7-trifluoromethyl-1H-benzimidazol-2-yl)propanoic acid, ***4a****, 2-Alkyl-5-nitro-7-trifluoromethyl-1H-benzimidazole 3-oxides,* ***4b–e*** *and 2-methyl-5,7-dinitro-1H-benzimidazole 3-oxide* ***4f:*** A mixture of **3a** (0.5 mmol) and $NaHCO_3$ (1.2 mmol) in 10 ml of 50% aqueous ethanol was refluxed for 1 h. Because in such conditions side-products (phenol and probably products of CF*3* hydrolysis) were formed, for cyclisation of **3b–3f** (0.5 mmol) anhydrous ethanol (10 ml) and potassium carbonate (1 mmol) as a base were used. The solution was diluted with water (5 ml) and extracted with ether to remove non-acidic compounds. The water layer was acidified with few drops of concentrated hydrochloric acid and extracted again. The extract was dried and evaporated to dryness under reduced pressure. The resulting solid contained more than 90% of desired product **4** (from ^1H NMR). Yield *ca* 80%.

4a: m.p. 217°C dec., HRMS: $C_{11}H_8O_5N_3F_3$ requires *M*, 319.0416, found 319.0414. ^1H NMR ($^2H_6$-DMSO) 12.46 (bs, 2H, CO_2H + NH), 8.550 (dq, 1H, $H_{4'}$, $J_{4',6'}$ = 2.3 Hz, $J_{4',F}$ = 0.6 Hz), 8.275 (dq, 1H, $H_{6'}$, $J_{6',F}$ = 0.7 Hz), 3.179 (t, 2H, CH_2), 2 850 (t, 2H, CH_2CO_2), ^{13}C NMR ($^2H_6$-DMSO) 173.12 (m, CO_2H), 157.74 (m, $C_{2'}$), 141.44 (t, $C_{5'}$, $J_{C5',H4'H6'}$ = 4.3 Hz), 138.42 (bt, $C_{7a'}$, $J_{C7a',\ H4'H6'}$ = 6 Hz, $J_{C7a',F}$ = 1.3 Hz – from $^{13}C\{^1H\}$ spectrum), 132.84 (d, $C_{3a'}$, $J_{C3a,H4}$ = 2.4 Hz), 122.88 (dq, CF_3, $J_{CF_3,\ H6'}$ = 5.2 Hz, $J_{C,F}$ = 272.7 Hz), 118.33 (q, $C_{7'}$, $J_{C7',F}$ = 33.5 Hz), 114.38 (ddq, $C_{6'}$, $J_{C6',H6'}$ = 169.6 Hz, $J_{C6',H4'}$ = 4.9 Hz, $J_{C6',F}$ = 5.3 Hz), 109.33 (dd, $C_{4'}$, $J_{C4',H4'}$ = 173.7 Hz, $J_{C4',H6'}$ = 4.8 Hz), 29.96 (t, C_2, $J_{C2,H2}$ = 131.5 Hz), 21.34 (t, C_3, $J_{C3,H3}$ = 125.0 Hz).

4b: m.p. 239°C dec., ^1H NMR ($^2H_6$-DMSO): 12.83 (bs, 1H, NH), 8.946 (s, 1H, H_2), 8.662 (dq, 1H, H_4, $J_{4,6}$ = 2.2 Hz, $J_{4,F}$ = 0.6Hz), 8.320 (dq, 1H, H_6, $J_{6,F}$ = 0.8 Hz), $^{13}C\{^1H\}$ NMR ($^2H_6$-DMSO) 146.05 (C_2), 142.14 (C_5), 139.24 (C_{7a}), 131.77 (C_{3a}), 122.67 (q, CF_3, $J_{C,F}$ = 272.7 Hz), 119.49 (q, C_7, $J_{C7,F}$ = 33.5 Hz), 114.63 (q, C_6, $J_{C6,F}$ = 5.2 Hz), 110.35 (C_4).

4c: m.p. 252°C dec., ^1H NMR: C 12.57 (bs, 1H, NH), 8.530 (dq, 1H, H_4, $J_{4,6}$ = 2.0 Hz, $J_{4,F}$ = 0.6Hz), 8.259 (dq, 1H, H*6*, $J_{6,F}$ = 0.8 Hz), 2.629 (s, 3H, CH_3), ^{13}C NMR ($^2H_6$-DMSO) 156.67 (q, C_2, $J_{C2,CH3}$ = 7.2 Hz), 141.31 (t, C_5, $J_{C5,H4H6}$ = 4.2 Hz), 138.49 (t unresolved, C_{7a}), 132.55 (d, C_{3a}, $J_{C3a,H4}$ = 2.3 Hz), 122.89 (dq, CF_3, $J_{CF_3,\ H6}$ = 5.1 Hz, $J_{C,F}$ = 272.6 Hz), 118.07 (q, C_7, $J_{C7,F}$ = 33.1 Hz), 114.36 (ddq, C_6, $J_{C6,H6}$ = 169.3 Hz, $J_{C6,H4}$ = 5.0 Hz, $J_{C6,F}$ = 5.3 Hz), 109.27 (dd, $C_{4'}$, $J_{C4',H4'}$ = 173.3 Hz, $J_{C4',H6'}$ = 4.9 Hz), 12.37 (q, CH_3, $J_{C,H}$ = 130.5 Hz).

4d: m.p. 213°C dec., HRMS: $C_{11}H_{10}F_3N_3O_3$ requires *M*, 289.0674, found 289.0671. ^1H NMR ($^2H_6$-DMSO): 12.57 (bs, 1H, NH), 8.495 (dq, 1H, H_4, $J_{4,6}$ = 2.2 Hz, $J_{4,F}$ = 0.6Hz), 8.228 (dq, 1H, H_6, $J_{6,F}$ = 0.8 Hz), 2.923 (t, 2H, C**H**$_2$ CH_2 CH_3, J_{CH_2,CH_2} = 7.8 Hz), 1.813 (sext, 2H, CH_2 C**H**$_2$ CH_3), 0.965 (t, 3H, CH_3, J_{CH_2,CH_3} = 7.6 Hz). $^{13}C\{^1H\}$ NMR ($^2H_6$-DMSO): 158.59 (C_2), 141.35 (C_5), 138.49 (q, C_{7a}, $J_{C7a,F}$ = 1.6 Hz), 132.63 (C_{3a}), 122.91 (q, CF_3, $J_{C,F}$ = 272.9 Hz), 118.25 (q, C_7, $J_{C7,F}$ = 33.2 Hz), 114.38 (q, C_6, $J_{C6,F}$ = 5.1 Hz), 109.36 (C_4), 27.61 (**C**$H_2CH_2CH_3$), 19.98 (CH_2**C**H_2CH_3), 13.68 (CH_3).

4e: m.p. 172°C dec., ^1H NMR ($^2H_6$-DMSO): 12.70 (bs, 1H, NH), 8.610 (d, 1H, H_4, $J_{4,6}$ = 2.2 Hz), 8.288 (bd, 1H, H_6), 4.9 (vbs, 1H, OH), 4.780 (s, 2H, CH_2), $^{13}C\{^1H\}$ NMR ($^2H_6$-DMSO) 157.17 (C2), 141.83 (C5), 138.15 (q, C_{7a}, $J_{C7a,F}$ = 1.5 Hz), 132.70 (C_{3a}), 122.87 (q, CF_3, $J_{C,F}$ = 272.9 Hz), 118.98 (q, C_7, $J_{C7,F}$ = 33.3 Hz), 114.59 (q, C_6, $J_{C6,F}$ = 5.2 Hz), 109.90 (C_4), 54.51 (CH_2).

4f: m.p. 265°C dec., ^1H NMR ($^2H_6$-DMSO): 8.744 (d, 1H, H_6, $J_{4,6}$ = 2.2 Hz), 8.636 (d, 1H, H_4), 2.669 (s, 3H, CH_3).

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