Reaction of aromatic isocyanides with triethylamine: a new method for the synthesis of indole betaines

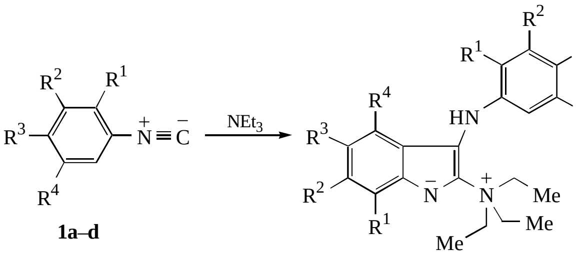
Maxim A. Mironov* and Vladimir S. Mokrushin

Department of Technology of Organic Synthesis, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 3432 74 5483; e-mail: crocus@htf.ustu.ru

A new reaction between aromatic isocyanides containing electron-withdrawing substituents and triethylamine is described which allows 2-triethylammonium-3-arylaminoindolates to be obtained. The structure of the compounds was determined by X-ray analysis, NMR and mass spectroscopy.

The indole structure is central to a great number of biologically active compounds. Various cyclisations of aromatic isocyanides are convenient methods for the synthesis of indole derivatives. For example, dianyl indigo is a major product of oligomerisation of phenyl isocyanide.[1] The interaction of aryl and naphthyl isocyanides with ketones in the presence of an acid catalyst leads to anilides of 3*H*-indolecarboxylic-2-acid.[2] The intramolecular cyclisation of 2-alkylphenyl isocyanides is a convenient method for the preparation of 3-alkylindoles.[3]

We have found that refluxing of 3,5-bis(trifluoromethyl)-phenyl isocyanide **1a** in hexane with triethylamine results in the formation of 2-triethylammonium-3-(3′,5′-bistrifluoromethyl)-phenylamino-4,6-bistrifluoromethylindolate **2a** in 85% yield (Scheme 1),† in contrast to the methods described in the literature dealing with the synthesis of indole derivatives from isocyanides.[1–3] The ^{1}H NMR spectrum of the compound exhibited resonance signals of two non-equivalent aromatic rings at δ 6.3–8.1 ppm, a triplet of three methyl groups at δ 1.05 ppm and two multiplets of three methylene groups at δ 3.6–4.1 ppm. The mass spectrum of compound **2a** exhibits a molecular ion peak *m*/*z* 579 $[M]^+$ corresponding to the dimeric composition of the starting isocyanide plus a fragment of triethylamine. The main fragmentation ions are $[M - 29]^+$ and $[M - 86]^+$. These data suggest that indolate **2a** results from the reaction of isocyanide **1a** with triethylamine. However, ^{1}H NMR and mass spectral data proved to be insufficient to provide unequivocal evidence of the structure of this unexpected product.



1a–d

2a–d

a $R^1 = R^3 = H$, $R^2 = R^4 = CF_3$
b $R^1 = Br$, $R^2 = R^4 = H$, $R^3 = NO_2$
c $R^1 = R^4 = H$, $R^2 = CF_3$, $R^3 = Cl$
d $R^1 = H$, $R^2 = R^3 = R^4 = Cl$

Scheme 1

An X-ray crystallographic analysis of compound **2a** was therefore performed.‡ Two crystallographic molecules (A and B) in the compound **2a** feature similar structures. The dihedral angle between the planes of the indole group and the phenyl ring [C(11)–C(16)] turned out to be 80.1° and 87.1° in molecules A and B, respectively. Most of the geometric parameters of molecules A and B are of standard nature,[4] but the high value of the anisotropic temperature factor of the fluorine atoms can be assigned to the various positions of the trifluoromethyl groups.

The reaction of aromatic isocyanides, bearing electron-withdrawing substituents (2-bromo-4-nitro **1b**, 3-trifluoromethyl-4-chloro **1c** and 3,4,5-trichlorophenyl isocyanide **1d**) with triethylamine proceeds similarly leading to the corresponding 2-triethylammonium-3-arylaminoindolates **2b**–**d**. ^{1}H NMR and mass spectral data for compounds **2b**–**d** are similar to those for compound **2a**. Phenyl isocyanide and 4-bromophenyl isocyanide do not interact with triethylamine under these conditions.

The starting isocyanides **1a**–**d** were obtained according to a well-known method.[5]

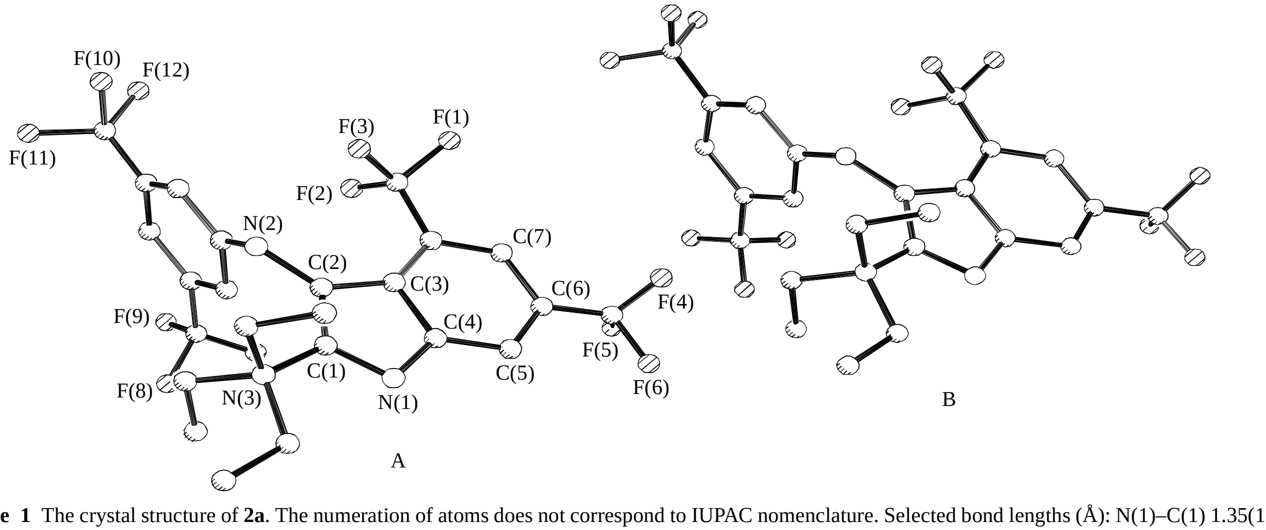


Figure 1 The crystal structure of **2a**. The numeration of atoms does not correspond to IUPAC nomenclature. Selected bond lengths (Å): N(1)–C(1) 1.35(1), N(l)–C(4) 1.37(1), N(2)–C(2) 1.42(9), N(2)–C(11) 1.40(1), N(3)–C(1) 1.50(1), C(1)–C(2) 1.38(1), C(2)–C(3) 1.43(1), C(3)–C(4) 1.43(1), C(3)–C(8) 1.40(1), C(4)–C(5) 1.39(1), C(5)–C(6) 1.37(1), C(6)–C(7) 1.41(1), C(7)–C(8) 1.39(1); selected bond angles (°): C(1)–N(1)–C(4) 102.8(6), C(2)–N(2)–C(11) 121.0(6), N(1)–C(1)–N(3) 117.6(6), N(1)–C(1)–C(2) 116.0(7), N(3)–C(1)–C(2) 126.2(7), N(2)–C(2)–C(1) 127.4(7), N(2)–C(2)–C(3) 128.0(6), C(1)–C(2)–C(3) 104.4(6), C(2)–C(3)–C(4) 104.0(6), C(2)–C(3)–C(8) 137.5(7), C(4)–C(3)–C(8) 118.5(7), N(l)–C(4)–C(3) 112.8(6), N(l)–C(4)–C(5) 125.7(7), C(3)–C(4)–C(5) 121.5(7), C(4)–C(5)–C(6) 118.5(8), C(5)–C(6)–C(7) 121.4(8), C(7)–C(6)–C(10) 118.5(8), C(6)–C(7)–C(8) 120.3(7).

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[†] *General procedure for the synthesis of* 2-*triethylammonium*-3-(3′,5′-*bistrifluoromethyl)phenylamino*-4,6-*ditrifluoromethylindolate* **2a**. A solution of 3,5-bis(trifluoromethyl)phenyl isocyanide **1a** (1 g, 4.2 mmol) and triethylamine (0.35 ml, 2.5 mmol) in hexane (20 ml) was refluxed for 4 h. The resulting precipitate was filtered off, washed with hexane and recrystallised from acetonitrile. Yield 85%, mp 200–201 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.05 (t, 9H, 3Me), 3.66–4.09 (m, 6H, 3CH$_2$), 6.31 (s, 1H, 2′-H), 7.11 (s, 1H, 6′-H), 7.34 (s, 1H, 4′-H), 7.50 (s, 1H, 7-H), 7.93 (s, 1H, 5-H), 8.13 (s, 1H, NH). MS, *m*/*z*: 579 (100%, M$^+$), 550 (67), 322 (21), 277 (21), 213 (44), 86 (40).

Some physical characteristics for other compounds are given below:

2b: mp 224–226 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.10 (t, 9H, 3Me), 3.66–4.05 (m, 6H, 3CH$_2$), 6.32 (d, 1H, 6′-H, J 9.2 Hz), 7.90 (d, 1H, 4-H, J 2.2 Hz), 7.93 (dd, 1H, 5′-H, $J_{5'\text{-H},6'\text{-H}}$ 9.2 Hz, $J_{5'\text{-H},3'\text{-H}}$ 2.6 Hz), 7.95 (d, 1H, 6-H, J 2.2 Hz), 8.26 (s, 1H, NH), 8.40 (d, 1H, 3′-H, J 2.6 Hz). MS, *m*/*z*: 555 (3%, M$^+$), 526 (13), 525 (48), 217 (31), 215 (33), 86(100).

2c: mp 245–246 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.06 (t, 9H, 3Me, J 6.9 Hz), 3.87 (q, 6H, 3CH$_2$, J 6.9 Hz), 6.60 (d, 1H, 6′-H, J 8.7 Hz), 6.99 (s, 1H, 2′-H), 7.05 (s, 1H, 7H), 7.33 (d, 1H, 5′-H, J 8.7 Hz), 7.72 (s, 1H, NH), 7.81 (s, 1H, 4-H). MS, *m*/*z*: 513 (66%, M + 2), 511 (100%, M$^+$), 484 (59), 482 (89), 454 (32), 86 (49).

2d: mp 283–284 °C. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.05 (t, 9H, 3Me), 3.68–3.99 (m, 6H, 3CH$_2$), 6.00 (d, 1H, 2′-H, J 2.5 Hz), 7.05 (d, 1H, 6′-H, J 2.5 Hz), 7.48 (s, 1H, NH), 7.88 (s, 1H, 4-H). MS, *m*/*z*: 513 (77%, M + 2) and other isotopic peaks, 511 (42%, M$^+$), 484 (100), 456 (41), 179 (55), 86 (61), 72 (73).

[‡] The experimental X-ray crystallographic data for **2a** were obtained on an Enraf-Nonius, Cad-4 diffractometer (λMoKα, graphite monochromator, $\theta/2\theta$-scan, $2\theta_{\max} = 46°$). The structure was solved by a direct method and refined by a full-matrix least-squares method with an anisotropic approximation using the programs SHELX-93 to $R = 0.078$ ($wR2 = 0.227$) for 3689 independent reflections with $F^2 > 3\sigma I$; GOOF = 1.042. Empirical formula $C_{24}H_{21}F_{12}N_3$, monoclinic crystals, space group $P2_1/c$, $a = 12.188(3)$ Å, $b = 21.093(6)$ Å, $c = 19.733(6)$ Å, $\beta = 90.50(5)°$, $V = 5073(5)$ Å^3, $d_{\text{calc}} = 1.517$ g cm^{-3}, $Z = 8$, $\mu = 0.152$ mm^{-1}. Full lists of atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see ‘Notice to Authors’, *Mendeleev Communications*, 1998, Issue1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/30.