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Synthesis of 3-iminoindole derivatives by the reactions of aromatic isocyanides with *N,N*-dialkylbenzylamines

Maxim A. Mironov,* Maria I. Tokareva and Vladimir S. Mokrushin

Department of Technology of Organic Synthesis, Urals State Technical University, 620002 Ekaterinburg, Russian Federation. Fax: +7 343 375 4135; e-mail: mironov@mail.ustu.ru

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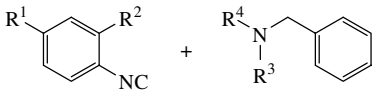
The reaction of *N,N*-dialkylbenzylamines with aromatic isocyanides leading to 2-dialkylamino-3-aryliminoindole derivatives with the subsequent formation of zwitter ionic indolates has been discovered; the structures of final products have been confirmed by X-ray analysis.

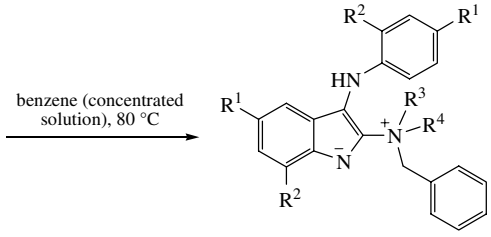
3-Iminoindoles are promising reagents for the synthesis of polycyclic structures including indole alkaloids.[1] 2,3-Diiminoindoles can be used as an antioxidant for synthetic and mineral oil compositions.[2] Due to the easy transfer from imino to amino group and backwards, indoles of this type are interesting for electrochemical research.[3] Some 3-aminoindoles exhibit antibacterial activity,[4] while other were tested as CNS drugs.[5] Synthetic pathways to 3-imino- and 3-aminoindoles are characterised by low yields and various side processes.[6] Note that 3-aminoindoles are unstable compounds, which are usually handled as salts, alkyl/acyl derivatives or 3-imino precursors.[3]

This study was devoted to the syntheses of indole derivatives from aromatic isocyanides.[7]

We found that the reaction of *N*,*N*-dimethylbenzylamine **1a** with two equivalents of isocyanide **2a** in a concentrated benzene solution leads to corresponding indolate **3a** in good yield (Scheme 1). The structures of the compounds were determined by NMR spectroscopy and mass spectrometry.† The ^{1}H NMR spectra of compounds exhibited the signals of protons typical of indolates:[7] two aromatic and one indole residue signals (6.45–7.92 ppm); a NH group signal (8.50 ppm); methylene (5.20 ppm) and alkyl group signals. In this case, the second product was not isolated owing to its formation in low yield. In contrast, when we carried out this reaction in a dilute benzene solution with long refluxing (10–15 h), target product **4a** was obtained in 64% yield (Scheme 2), while indolate only in 10%. The results depended on the solubility of indolates in benzene.

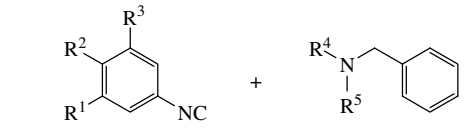


2a $R^1 = NO_2$, $R^2 = H$ **1a** $R^3 = R^4 = Me$
2e $R^1 = NO_2$, $R^2 = Br$ **1c** $R^3 + R^4 = (CH_2)_5$

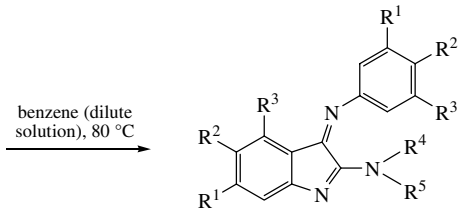


3a $R^1 = NO_2$, $R^2 = H$, $R^3 = R^4 = Me$
3b $R^1 = NO_2$, $R^2 = Br$, $R^3 + R^4 = (CH_2)_5$

Scheme 1 Synthesis of indolates **3**.



2a $R^1 = R^3 = H$, $R^2 = NO_2$ **1a** $R^4 = R^5 = Me$
2b $R^1 = R^2 = R^3 = Cl$ **1b** $R^4 = R^5 = Et$
2c $R^1 = CF_3$, $R^2 = Cl$, $R^3 = H$ **1c** $R^4 + R^5 = (CH_2)_5$
2d $R^1 = R^3 = H$, $R^2 = CN$



4a $R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 = R^5 = Me$
4b $R^1 = R^2 = R^3 = Cl$, $R^4 = R^5 = Me$
4c $R^1 = CF_3$, $R^2 = Cl$, $R^3 = H$, $R^4 = R^5 = Me$
4d $R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 = R^5 = Et$
4e $R^1 = R^3 = H$, $R^2 = NO_2$, $R^4 + R^5 = (CH_2)_5$
4f $R^1 = R^2 = R^3 = Cl$, $R^4 + R^5 = (CH_2)_5$
4h $R^1 = R^3 = H$, $R^2 = CN$, $R^4 + R^5 = (CH_2)_5$

Scheme 2 Synthesis of 3-arylimino-3*H*-indoles **4**.

† *General procedure for the synthesis of indolates* **3a**,**b**. A solution of *N*,*N*-dimethylbenzylamine **1a** (0.135 ml, 1.0 mmol) and 4-nitrophenylisocyanide **2a** (0.3 g, 2.0 mmol) in benzene (1.0 ml) was refluxed for 2 h. The product was collected by filtration and washed with hexane to yield **3a**. Yield 50%, mp 197–198 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.36 (s, 6H, NMe_2), 5.20 (s, 2H, CH_2), 6.45 (br. s, 2H, H_{Ar}-2,6), 7.13–7.25 (m, 5H, Ph), 7.39 (d, 2H, H_{Ar}-3,5, *J* 8.5 Hz), 7.42 (d, 1H, H-7, *J* 9.2 Hz), 7.75 (dd, 1H, H-6, *J* 9.2 Hz, *J* 2.4 Hz), 7.92 (d, 1H, H-4, *J* 2.4 Hz), 8.50 (s, 1H, NH). MS, *m*/*z*: 431 (29%, M^+), 340 (100), 339 (76), 91 (18). Found (%): C, 64.42; H, 4.76; N, 16.37. Calc. for $C_{23}H_{21}N_5O_4$ (%): C, 64.23; H, 4.92; N, 16.23.

For **3b**: yield 59%, mp 220–221 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.43–2.54 [m, 6H, $(CH_2)_3$], 3.34–3.65 (m, 2H, NCH_2), 4.34–4.57 (m, 2H, NCH_2), 4.89 (d, 1H, CH_2, *J* 12.2 Hz), 5.09 (d, 1H, CH_2, *J* 12.2 Hz), 6.21 (d, 1H, H_{Ar}-6, *J* 9.5 Hz), 6.94–7.29 (m, 5H, Ph), 7.19 (s, 1H, NH), 7.78 (dd, 1H, H_{Ar}-5, *J* 9.5 Hz, *J* 2.4 Hz), 7.83 (d, 1H, H-4, *J* 2.1 Hz), 7.96 (d, 1H, H-6, *J* 2.1 Hz), 8.34 (d, 1H, H_{Ar}-3, *J* 2.4 Hz). MS, *m*/*z*: 629 (24%, M^+), 538 (55), 459 (58), 458 (39), 457 (59), 413 (29), 91 (100), 84 (84). Found (%): C, 49.55; H, 3.74; N, 11.28. Calc. for $C_{26}H_{23}Br_2N_5O_4$ (%): C, 49.63; H, 3.68; N, 11.13.

Dilution has a negative influence on reaction rate; therefore, we used a three-fold excess of *N*,*N*-dialkylbenzylamines to smooth this effect. Thus, the reaction of *N*,*N*-dialkylbenzylamines **1a–c** with isocyanides **2b–d** resulted in the formation of the second product in high yield.

The structure of the target product was determined using X-ray analysis, NMR spectroscopy and mass spectrometry. The formation of 2-dialkylamino-3-aryliminoindoles (Scheme 2) as a second product in the reaction of aromatic isocyanides with *N*,*N*-dialkylbenzylamines was found.‡,§ Thus, the parent mass peak for compounds **4a–h** corresponds to the molecular formula of an indolate minus the fragment C_7H_8. The ^{1}H NMR spectra of these compounds are also characterised by the absence of NH and benzyl group signals; only two groups of signals (aromatic residue and *N*,*N*-dialkylamino group protons) were present. The X-ray analysis of compound **4b** suggested the elimination of a benzyl group (Figure 1). The structure of the dimethylamino group is almost flat (the sum of three angles is 359.7°). This fact suggests a conjugation of double bonds in the five-membered ring system.[8] The aryl fragment is turned at 69.1° regarding indole fragment, while the angle C(2)–N(2)–C(9) is 124.5° that open the way to existence of two isomers for this structure. Note that we detected the signals of only one isomer in the ^{1}H NMR spectra of compounds **4a–h**.

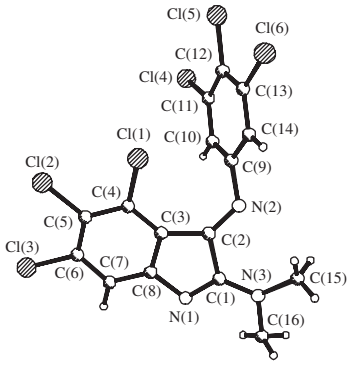


Figure 1 X-ray structure of **4b**. Selected bond lengths (Å): N(1)–C(1) 1.31, N(3)–C(1) 1.33, N(2)–C(2) 1.27.

2-Dialkylamino-3-aryliminoindoles result from the reductive dealkylation of indolates. To prove this suggestion, we carried out an experiment, where pure indolate **3a** was refluxed in acetonitrile under argon. As a result, we obtained a mixture containing 3-iminoindole **4a**, toluene and polymers.¶ The moderate yield (43%) of target compound **4a** in the absence of oxygen and, at the same time, the presence of toluene in the reaction mixture can be a good corroboration for our hypothesis. It is likely that we found a special type of reductive dealkylation, where the elimination of benzyl group is conjugated with the oxidation of amino function in indolates.

We obtained the target 2-dialkylamino-3-aryliminoindoles in aprotic solvents such as benzene, toluene and acetonitrile, while in protic polar solvents the reaction leads to a complex mixture of polymers. The substituents in isocyanides and benzylamines have an influence on the results of this synthesis. Thus, only isocyanides bearing electron-withdrawing groups like cyano, nitro, trifluoromethyl or chloro took part in the reaction; the cause of this fact is the subsequent formation of indolates **3**, which are formed in reaction of π-deficient isocyanides with tertiary amines. In addition, the introduction of substituents in the *ortho* position of isocyanides has a negative effect on the formation of 2-dialkylamino-3-aryliminoindoles. Thus, we did not obtain product **4** from isocyanide **2e** owing to the high stability of corresponding indolate **3b**. An *ortho* substituent may be a hindrance for the oxidation of amino function in indolate **3b**. The use of *N*,*N*-dialkylbenzylamines with electron-

‡ *General procedure for the synthesis of 2-dialkylamino-3-aryliminoindoles* **4a–f**. An excess of *N*,*N*-dimethylbenzylamine **1a** (0.2 ml, 1.5 mmol) was added to a solution of 4-nitrophenylisocyanide **2a** (0.15 g, 1.0 mmol) in benzene (15.0 ml), and the resulting mixture was refluxed for 12 h. The reaction mixture was concentrated to 2–3 ml. The product was collected by filtration and washed with hexane to yield **4a**. Yield 64%, mp 170–171 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.39 (s, 3H, NMe), 3.58 (s, 3H, NMe), 6.87 (d, 1H, H-4, *J* 2.2 Hz), 7.02 (d, 1H, H-7, *J* 8.7 Hz), 7.32 (d, 2H, H_{Ar}-2,6, *J* 8.7 Hz), 8.13 (dd, 1H, H-6, *J* 2.2 Hz, *J* 8.7 Hz), 8.42 (d, 2H, H_{Ar}-3,5, *J* 8.7 Hz). MS, *m*/*z*: 339 (100%, M^+), 324 (15), 278 (34), 203 (18), 76 (31). Found (%): C, 56.49; H, 3.97; N, 20.50. Calc. for $C_{16}H_{13}N_5O_4$ (%): C, 56.64; H, 3.86; N, 20.64.

For **4b**: yield 48%, mp 260–261 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.04 (s, 6H, NMe_2), 7.06 (s, 1H, H-7), 7.32 (s, 2H, H_{Ar}-2,6), 7.36 (s, 3H, $0.5C_6H_6$). MS, *m*/*z*: 453 (17%, M^+) and other isotopic peaks, 440 (10), 425 (8), 262 (94), 260 (100), 233 (27), 143 (19). Found (%): C, 41.98; H, 2.03; N, 9.38. Calc. for $C_{16}H_9Cl_6N_3$ (%): C, 42.15; H, 1.99; N, 9.22.

For **4c**: yield 46%, mp 217–218 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.44 (s, 3H, NMe), 3.52 (s, 3H, NMe), 6.27 (s, 1H, H-4), 7.18 (s, 1H, H-7), 7.30 (dd, 1H, H_{Ar}-6, *J* 8.4 Hz, *J* 2.4 Hz), 7.44 (d, 1H, H_{Ar}-2, *J* 2.4 Hz), 7.76 (d, 1H, H_{Ar}-5, *J* 8.4 Hz). MS, *m*/*z*: 453 (100%, M^+), 455 (64, $[M + 2]^+$), 438 (31), 389 (23), 260 (47), 179 (47). Found (%): C, 47.72; H, 2.35; N, 9.13. Calc. for $C_{18}H_{11}Cl_2F_6N_3$ (%): C, 47.60; H, 2.44; N, 9.25.

For **4d**: yield 55%, mp 149–150 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.15–1.46 [m, 6H, $N(CH_2\mathit{Me})_2$], 3.78 [s, 2H, $N(C\mathit{H}_2Me)_2$], 4.05 [s, 2H, $N(C\mathit{H}_2Me)_2$], 6.88 (s, 1H, H-4), 7.03 (d, 1H, H-7, *J* 7.9 Hz), 7.35 (d, 2H, H_{Ar}-2,6, *J* 9.2 Hz), 8.13 (d, 1H, H-6, *J* 7.9 Hz), 8.41 (d, 2H, H_{Ar}-3,5, *J* 9.2 Hz). MS, *m*/*z*: 367 (42%, M^+), 352 (100), 338 (17), 292 (26), 166 (62), 118 (57), 76 (25), 72 (28). Found (%): C, 58.70; H, 4.56; N, 18.93. Calc. for $C_{18}H_{17}N_5O_4$ (%): C, 58.85; H, 4.66; N, 19.06.

For **4e**: yield 55%, mp 149–150 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.71 [s, 6H, $(CH_2)_3$], 3.98 (br. s, 2H, NCH_2), 4.37 (br. s, 2H, NCH_2), 6.84 (d, 1H, H-4, *J* 2.1 Hz), 7.00 (d, 1H, H-7, *J* 8.9 Hz), 7.33 (d, 2H, H_{Ar}-2,6, *J* 8.9 Hz), 8.10 (dd, 1H, H-6, *J* 8.9 Hz, *J* 2.1 Hz), 8.40 (d, 2H, H_{Ar}-3,5, *J* 8.9 Hz). MS, *m*/*z*: 379 (71%, M^+), 257 (7), 138 (16), 118 (40), 84 (24). Found (%): C, 59.99; H, 4.53; N, 18.63. Calc. for $C_{19}H_{17}N_5O_4$ (%): C, 60.15; H, 4.52; N, 18.46.

For **4f**: yield 48%, mp 252–253 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.69 [br. s, 6H, $(CH_2)_3$], 3.97 [br. s, 4H, $N(CH_2)_2$], 7.00 (s, 1H, H-7), 7.10 (s, 2H, H_{Ar}-2,6). MS, *m*/*z*: 493 (31%, M^+) and other isotopic peaks, 316 (27), 314 (26), 273 (27), 179 (43), 143 (29), 84 (15). Found (%): C, 45.95; H, 2.56; N, 8.52. Calc. for $C_{19}H_{13}Cl_6N_3$ (%): C, 46.01; H, 2.64; N, 8.47.

For **4h**: yield 36%, mp 184–185 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.69 [s, 6H, $(CH_2)_3$], 3.90 (br. s, 2H, NCH_2), 4.30 (br. s, 2H, NCH_2), 6.23 (d, 1H, H-4, *J* 1.8 Hz), 6.99 (d, 1H, H-7, *J* 8.2 Hz), 7.23 (d, 2H, H_{Ar}-2,6, *J* 8.2 Hz), 7.62 (dd, 1H, H-6, *J* 8.2 Hz, *J* 1.8 Hz), 7.97 (d, 2H, H_{Ar}-3,5, *J* 8.2 Hz). MS, *m*/*z*: 339 (100%, M^+), 338 (30), 296 (22), 102 (36), 84 (12), 310 (15), 255 (6). Found (%): C, 74.19; H, 5.09; N, 20.75. Calc. for $C_{19}H_{17}N_5$ (%): C, 74.32; H, 5.05; N, 20.62.

§ *X-ray diffraction data for* **4b**. Formula $C_{16}H_9Cl_6N_3 \cdot 1/2C_6H_6$, M = 495.02, triclinic, space group $P\bar{1}$, a = 9.656(7), b = 11.429(3) and c = 11.470(4) Å, V = 1046.3(9) Å^3, Z = 2, d_{calc} = 1.571 g cm^{-3}, μ = 0.832 mm^{-1}, $F(000)$ = 498. Data collection was performed at 293 K within the θ range from 2.05 to 26.98°; a total of 4702 (of which 4557 were unique) reflections were collected [R(int) = 0.0244] and used to refine 304 parameters. The structure was solved with the program SHELXS-97 and refined using SHELXL-97[9] to R_1 = 0.0396 and wR_2 = 0.1085 [$I > 2\sigma(I)$].

CCDC 602994 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2007.

¶ *Preparation of compound* **4a** *in the absence of oxygen and HPLC analysis of the reaction mixture*. A solution of indolate **3a** (0.2 g, 0.5 mmol) in acetonitrile (20.0 ml) was refluxed for 24 h under argon. The final mixture was analysed by reversed-phase HPLC with detection at 230 nm (a Hewlett-Packard HP 1090 apparatus equipped with a diode-array detector). A reversed-phase column was used (Hypersil® BDS C18, 3μ, 50×4.6 mm) under an optimised binary acetonitrile–water gradient, flow rate of 1 ml min^{-1}. Simultaneously, target compound **4a** was isolated by flash chromatography in 43% yield (silica 40/5 μ; chloroform–methanol, 20:1).

withdrawing groups was unsuccessful because the reaction resulted in the formation of a complex polymer mixture. In contrast, various alkyl groups can be used here. The reaction allowed us to obtain a wide range of 2-dialkylamino-3-aryliminoindoles **4** containing electron-withdrawing substituents.

In summary, a new reaction of aromatic isocyanides with *N*,*N*-dialkylbenzylamines was discovered. The reaction leads to the derivatives of 3-iminoindoles in good yields.

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