New synthesis of indoles containing the isocyanide group

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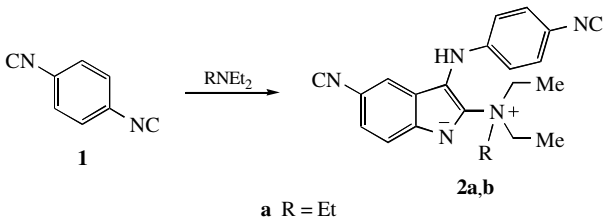
A new method was proposed for the synthesis of indoles containing the isocyanide group by the reaction between aromatic isocyanides and trialkylamines.

The indole nucleus is present in a wide range of natural products, and the synthesis of this important ring system is of interest. Indoles containing the isocyanide group are produced by certain *Pseudomonas* species.[1] Antibiotic B 371 and its derivatives are important examples that possess high levels of antibacterial and antifungal activity.[2] Structure–activity studies have established that the isocyanide group is essential for the biological activity of these compounds.[3] The limited number of convenient methods available for the synthesis of indoles with isocyanide substituents is a serious obstacle for the continuation of studies in this area, since classical methods have often failed.[4] We propose the reaction[5] between aromatic isocyanides and trialkylamines, a practical and mild procedure for the construction of diverse isocyanoindoles. In this case, the synthesis of the indole nucleus and the introduction of the isocyanide group proceed simultaneously.

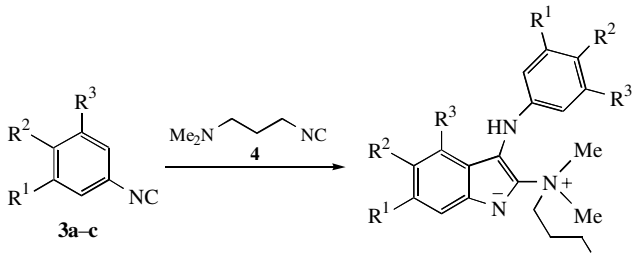


1 **2a**,**b**

a R = Et
b R = Me

Scheme 1

For the synthesis of indoles containing the isocyanide group in aromatic rings, commercial 1,4-diisocyanobenzene **1** was used. We have found that the keeping of 1,4-diisocyanobenzene **1** and triethylamine (two equivalents) in benzene at 60 °C results in the formation of only one product without any detectable polymerization† (Scheme 1). The structure of 2-triethylammonio-3-(4-isocyano)phenylamino-5-isocyanoindolate **2a** was assigned to this product on the basis of NMR, IR and mass spectrometry data. The ^{1}H NMR spectrum of this compound exhibited resonance signals of two non-equivalent aromatic rings at δ 6.4–7.4 ppm, a singlet of the NH group at δ 7.72 ppm, a triplet of three methyl groups at δ 1.04 ppm and a quartet of three methylene groups centered at δ 3.85 ppm. The mass spectrum of **2a** exhibits a molecular ion peak with *m*/*z* 357. Moreover,



3a–c **5a–c**

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

Scheme 2

compound **2a** showed two expected IR absorption bands at 2113 and 2117 cm^{-1} due to isocyanide stretching. These data confirm that the two isocyanide groups remained unchanged in the final product. The yields of indolates **2** depend strongly on the structure of starting tertiary amines. Thus, the reaction of **1** with *N*-methyldiethylamine affords corresponding indolate **2b** in only 20% yield while the use of *N*-methylpiperidine did not give a product. It may be assumed that easy polymerization of starting isocyanide **1**, as well as product **2**, have an influence on the yields of the products. Indeed, a considerable prolongation of the reaction time results in a decrease in the yield; therefore, in every case, the optimal reaction time and temperature should be found.

The aliphatic isocyanides can be introduced as a trialkylammonium group at the 2-position of the indolate. The synthesis of these compounds is based upon the reaction between aromatic isocyanides **3a–c** and 3-dimethylpropyl isocyanide **4**. All starting isocyanides **3**, **4** were obtained according to a well-known method.[6] The reaction between aromatic isocyanides **3a–c** and aliphatic isocyanide **4** results in the formation of isocyanoindolates **5a–c** in good yields‡ (Scheme 2). The typical

† *General procedure for the synthesis of indolates* **2a**,**b**. A solution of 1,4-diisocyanobenzene **1** (0.26 g, 2 mmol) and trialkylamine (0.35 ml, 2.5 mmol) in benzene (5 ml) was kept at 60 °C for 2 h. The resulting precipitate was filtered off and washed with hexane.

For **2a**: yield 42%, mp 190–191 °C. IR, ν/cm^{-1}: 2113, 2117 (NC). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.04 (t, 9H, 3Me, *J* 6.9 Hz), 3.85 (q, 6H, 3CH_2, *J* 6.9 Hz), 6.49 (br. s, 2H, 2′-H and 6′-H), 6.83 (dd, 1H, 6-H, $J_{6\text{-H},5\text{-H}}$ 8.2 Hz, $J_{6\text{-H},4\text{-H}}$ 2.0 Hz), 6.96 (d, 1H, 4-H, $J_{4\text{-H},6\text{-H}}$ 1.9 Hz), 7.22 (d, 2H, 3′-H and 5′-H, *J* 8.85 Hz), 7.32 (d, 1H, 7-H, $J_{7\text{-H},6\text{-H}}$ 8.1 Hz), 7.72 (s, 1H, NH). MS, *m*/*z*: 357 (M$^+$, 14%), 328 (14), 277 (100), 238 (19), 199 (26), 183 (19), 145 (53). Found (%): C, 73.62; H, 6.58; N, 19.58. Calc. for $C_{22}H_{23}N_5$ (%): C, 73.92; H, 6.49; N, 19.59.

For **2b**: yield 20%, mp 213–214 °C. IR, ν/cm^{-1}: 2115, 2118 (NC). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.08 (t, 6H, 2Me, *J* 6.9 Hz), 3.40 (s, 3H, Me), 3.68 (q, 2H, CH_2, *J* 6.9 Hz), 4.12 (q, 2H, CH_2, *J* 6.9 Hz), 6.51 (br. s, 2H, 2′-H and 6′-H), 6.80 (dd, 1H, 6-H, $J_{6\text{-H},5\text{-H}}$ 8.5 Hz, $J_{6\text{-H},4\text{-H}}$ 1.8 Hz), 7.01 (d, 1H, 4-H, $J_{4\text{-H},6\text{-H}}$ 1.7 Hz), 7.11 (d, 2H, 3′-H and 5′-H, *J* 8.9 Hz), 7.27 (d, 1H, 7-H, $J_{7\text{-H},6\text{-H}}$ 8.5 Hz), 7.63 (s, 1H, NH).

‡ *General procedure for the synthesis of indolates* **5a–c**. A solution of 4-nitroisocyanobenzene **3a** (0.3 g, 2 mmol) and 3-dimethylaminopropyl isocyanide **4** (0.42 ml, 4 mmol) in benzene–hexane (1:1, 6 ml) was refluxed for 4 h. Product **5a** was collected by filtration and washed with hexane. Yield 65%, mp 258–259 °C. IR, ν/cm^{-1}: 2150 (NC). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.81–1.96 (m, 2H, CH_2), 3.42 (br. t, 2H, CH_2, *J* 6.4 Hz), 3.61 (s, 6H, 2Me), 3.99 (br. t, 2H, CH_2, *J* 6.5 Hz), 6.65 (br. s, 2H, 2′-H and 6′-H), 7.34 (d, 1H, 7-H, $J_{7\text{-H},6\text{-H}}$ 8.85 Hz), 7.71 (dd, 1H, 6-H, $J_{6\text{-H},5\text{-H}}$ 8.85 Hz, $J_{6\text{-H},4\text{-H}}$ 2.1 Hz), 7.94 (d, 1H, 4-H, $J_{4\text{-H},6\text{-H}}$ 2.1 Hz), 7.97 (d, 2H, 3′-H and 5′-H, *J* 9.1 Hz), 8.47 (s, 1H, NH). MS, *m*/*z*: 408 (M$^+$, 48%), 392 (24), 367 (58), 355 (34), 339 (100), 292 (41), 278 (53), 232 (43), 203 (54), 106 (82). Found (%): C, 58.79; H, 4.88; N, 20.72. Calc. for $C_{20}H_{20}N_6O_4$ (%): C, 58.87; H, 4.90; N, 20.58.

For **5b**: yield 52%, mp 247–248 °C. IR, ν/cm^{-1}: 2150 (NC). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.65–1.91 (m, 2H, CH_2), 3.46 (br. t, 2H, CH_2, *J* 6.5 Hz), 3.52 (s, 3H, Me), 3.59 (s, 3H, Me), 3.73–4.03 (m, 2H, CH_2), 6.09 (br. s, 1H, 2′-H), 7.07 (br. s, 1H, 6′-H), 7.50 (s, 1H, 7-H), 7.83 (s, 1H, NH). MS, *m*/*z*: 524 ([M + 2]$^+$, 70%) and other isotopic peaks, 522 (M$^+$, 37%), 510 (23), 457 (64), 413 (20), 302 (58), 261 (100), 195 (41), 181 (34).

For **5c**: yield 56%, mp 122–123 °C. IR, ν/cm^{-1}: 2150 (NC). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.65–1.90 (m, 2H, CH_2), 3.43 (br. t, 2H, CH_2, *J* 7.0 Hz), 3.54 (s, 3H, Me), 3.64 (s, 3H, Me), 3.82–4.18 (m, 2H, CH_2), 6.37 (s, 1H, 2′-H), 6.99 (s, 1H, 6′-H), 7.31 (s, 1H, 7-H), 7.40 (s, 1H, 4′-H), 7.86 (s, 1H, 5-H), 7.94 (s, 1H, NH). MS, *m*/*z*: 590 (M$^+$, 52%), 576 (19), 549 (22), 523 (100), 477 (34), 336 (18), 295 (20), 213 (39).

^{1}H NMR spectrum of **5a** exhibited the resonance signals of two non-equivalent aromatic rings at δ 6.6–8.0 ppm, a singlet of the NH group at δ 8.47 ppm and the signals of the two methyl groups and three methylene groups of the aliphatic isocyanide residue as a singlet at δ 3.61 ppm, two triplets (at δ 3.42 and 3.99 ppm) and one multiplet (1.81–1.96 ppm), respectively. Each of compounds **5a–c** showed strong IR absorption at 2150 cm^{-1} due to isocyanide stretching. By this methodology, only aromatic isocyanides take part in the reaction with tertiary amines, and aliphatic isocyanides are introduced into the 2-position of indolates **5** without any changes.

In conclusion, the reaction of aromatic isocyanides with tertiary amines allowed us to introduce the isocyanide group into an aromatic ring, as well as into the aliphatic part, of indolate molecules. These compounds with active isocyanide groups can be used in diverse chemical transformations (cycloaddition, multicomponent condensation and polymerization).

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