A Convenient Synthesis of 2-Cyano-3-Substituted Indoles

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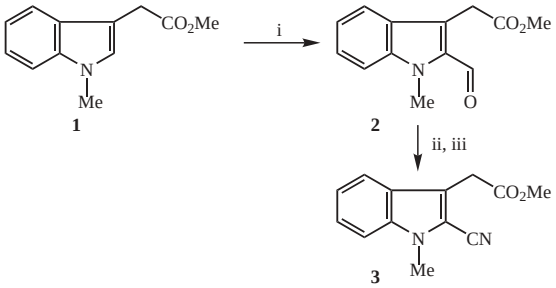
Abstract: A new and mild method for the synthesis of 2-cyano-3-substituted indoles is described which is effective on *N*-unsubstituted indoles.

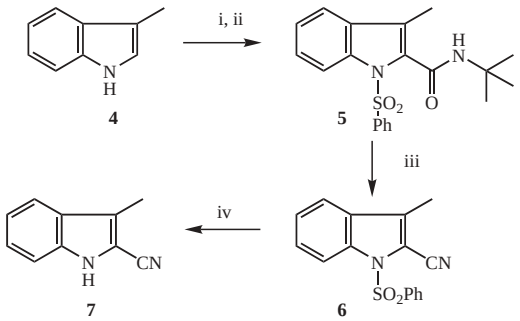
Key words: electrophilic cyanation, cyanoindoles, heterocycles, Lewis acids, nitriles

Substituted cyanoindoles are important intermediates in the synthesis of heteroaromatic molecules and have found some use in the synthesis of biologically active compounds.[2,3] Incorporation of the nitrile functionality into substituted indoles has been accomplished via a variety of methods which often involve multi-step routes and harsh, expensive or toxic reagents.[2,4–15] During our investigations into the synthesis of monoterpene indole alkaloids and spirocyclic oxindoles via nucleophilic free-radical chemistry, it was necessary to incorporate an electron withdrawing cyano-group at the 2-position of our 3-substituted indole precursors.[16,17] The initial synthetic route was based on Vilsmeier formylation of protected indole **1**, followed by oxime formation and dehydration (Scheme 1). However, the formylation step gave low yields (ca. 50%) and required extensive purification of the product.



Scheme 1 *Reagents and conditions*: (i) DMF–$POCl_3$, 40 °C (48%); (ii) NH_2OH, Et_3N (99%); (iii) Ac_2O, pyridine, reflux (73%).

In related studies, we had previously synthesised 3-methyl-2-cyano indole **7** following the reported method of Gribble and co-workers.[10] This involved protection and activation of 3-methylindole **4** as a phenylsulfonamide derivative, followed by treatment with LDA and *tert*-butyl isocyanate to give the amide **5** in 68% yield. Subsequent treatment with phosphorous oxychloride in benzene gave



Scheme 2 *Reagents and conditions*: (i) LDA, THF, –78 °C, $PhSO_2Cl$ (85%); (ii) LDA, THF, –78 °C, *t*-BuNCO (68%); (iii) $POCl_3$, PhH (83%); (iv) NaH–PhSH, THF, reflux (72%).

the 2-cyano protected indole **6** in 83% yield. Treatment with sodium thiophenoxide finally gave the desired 2-cyano-3-methylindole **7** (Scheme 2).[14]

The main drawback involved in the synthesis of both 3-substituted-2-cyanoindoles was the need for early protection of the indole nitrogen. As a result of the multistep syntheses and low overall yields obtained in the synthesis of our substituted 2-cyanoindoles we decided to investigate alternative methods for the introduction of the nitrile functionality into indole. Herein we now report a new approach to 3-substituted-2-cyanoindoles.

Our initial investigation was based on the reaction between indole-3-acetic acid methyl ester **8** and *tert*-butyl isocyanate. There are two possible means whereby the reaction can be encouraged: (i) activation of indole, (already achieved by Gribble and Katritzky via lithiation at the C-2 position of indole)[5,10] (ii) activation of the isocyanate. An example of this is the use of chlorosulfonyl isocyanate,[4] which has a strong electron-withdrawing group on the isocyanate nitrogen making it very reactive and thus more difficult to work with. However, we felt that *tert*-butyl *iso*cyanate could be activated by the use of a Lewis acid. Addition of 1 equivalent of boron trifluoride diethyl etherate to a solution of **8** and *tert*-butyl isocyanate resulted in a 62% yield of amide **9** (Scheme 3). Following the initial success, we optimised the reaction conditions by increasing the amount of Lewis acid used to 2 equivalents and carried out the reaction in dichloromethane at 0 °C, which gave the amide **9** in 97% yield.[18] This was subsequently converted to the 2-cyanoindole ester **10** by heating a solution of the amide **9** at reflux with $POCl_3$ in either benzene or toluene (77%).[19] Electron-donating groups at C-5 are commonly found in biologically-active indole

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derivatives and there was concern that reaction may occur in the benzene ring of such indoles. However, reaction of **11** gave the corresponding amide **12** in good yield (80%), which was then converted to the nitrile **13** in excellent yield (92%). In the case of **14** where the indole nitrogen carries a methyl group, only 60% of the corresponding amide **15** was isolated. Presumably, the *N*-alkyl group reduces the nucleophilicity of the C-2 position of indole, resulting in lower yields of amide **15**. The resultant amide was readily converted to the *N*-protected 2-cyanoindole ester **16** (88%). In the case of 3-methylindole **4**, amide **17** was prepared in 85% yield, and then converted to 2-cyano-3-methylindole **7** in 90% yield. Thus in contrast to our previous 4-step synthesis of **7**, only 2 steps were required and no protecting group strategy was necessary.

An unexpected result occurred in the case of **18** where we obtained a 1:2 ratio of **19**:**20** (85%) using standard conditions. Heating the reaction mixture at reflux did not change the ratio of products. Although it is well established that there is competition between *N*- and *C*-acylation in indole derivatives, given the results obtained with compounds **4**, **8** and **11**, it is possible that the acetoxy group participates in the reaction in some way. The amide **19** could be isolated from the mixture by chromatography in moderate yield (25%) and was converted to the 2-cyano-3-substituted indole **21** in good yield (79%).

In summary, we have developed a new, mild and efficient synthesis of 2-cyano-3-substituted indoles in two steps, which is effective on *N*-unsubstituted indoles. The use of boron trifluoride enables the more conveniently handled reagent, *tert*-butyl isocyanate to be used and the synthesis can also be conducted on a relatively large scale (ca. 100 g for **8**) and with a significant reduction in the number of steps previously required.

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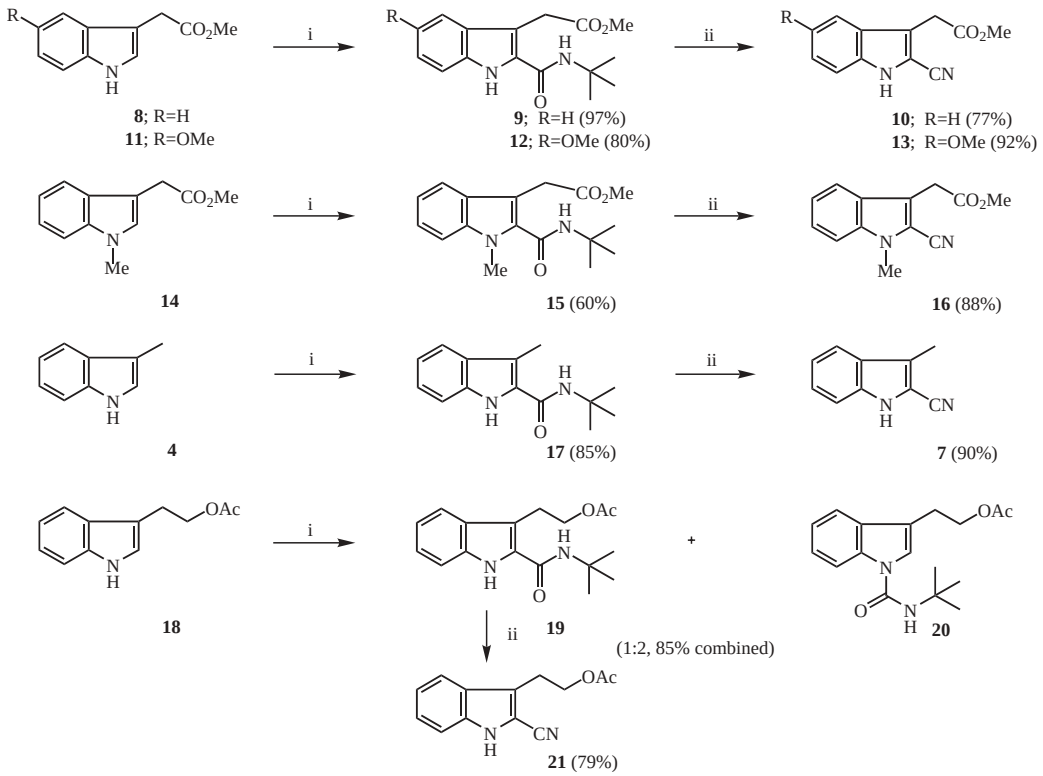

Scheme 3 *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, *t*-BuNCO, 0 °C; (ii) $POCl_3$, PhH, reflux.

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(18) **Representative Procedure: (2-*t*-Butylcarbamoyl-1*H*-indol-3-yl)-acetic Acid Methyl Ester (9):** Boron trifluoride diethyl etherate (7.2 mL, 8.1 g, 57.5 mmol) was added to a stirred solution of indole-3-acetic acid methyl ester (**8**, 5.4 g, 28.8 mmol) and freshly distilled *t*-butyl isocyanate (4.9 mL, 4.3 g, 43.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction was allowed to stir for 18 h whereupon organic solvent was removed under reduced pressure and the residue taken up in CH_2Cl_2 (100 mL) and washed with a solution of sat. NH_4Cl (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts washed with brine (200 mL), dried ($MgSO_4$), filtered and organic solvent removed under reduced pressure. The crude product was purified by flash column chromatography (3:1, hexane–EtOAc) to give amide **9** as colourless crystalline needles (8.00 g, 97%); mp 159.5–160.5 °C; R_f = 0.31 (3:1, hexane–EtOAc); (*m/z* calcd for $C_{16}H_{20}N_2O_3$ [M^+]: 288.1474. Found: 288.1473 [M^+]). IR: ν_{max} = 3273.1 (NH), 1720.1 (CO_2CH_3), 1638.0 (CONH*t*-Bu) cm^{-1}. ^1H NMR: (300 MHz, $CDCl_3$): δ = 1.91 [9 H, s, C(CH_3)$_3$], 3.75 (3 H, s, OCH_3), 3.98 (2 H, s, $CH_2CO_2CH_3$), 7.17 (1 H, td, *J* = 8.0 and 1.0 Hz, C-5*H*), 7.29 (1 H, td, *J* = 8.0 and 1.0 Hz, C-6*H*), 7.53 (1 H, d, *J* = 8.0 Hz, C-7*H*), 7.70 (1 H, d, *J* = 8.0 Hz, C-4*H*), 8.13 (1 H, br s, N*H*), 10.68 (1 H, br s, CON*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.04 [C(CH_3)$_3$], 31.05 ($CH_2CO_2CH_3$), 52.17 [C(CH_3)$_3$], 52.68 (CO_2CH_3), 106.86 (C-3), 112.27 (C-7), 119.53 (Ar-*C*-H), 120.13 (Ar-*C*-H), 124.15 (Ar-*C*-H), 127.76 (quaternary C), 131.32 (quaternary C), 135.36 (C-7a), 161.89 (CONH), 173.80 (CO_2CH_3). MS: *m/z* (%) = 288.15 (87.6) [M^+], 215.04 (95.4), 200.05 (92.1), 188.07 (56.1), 183.03 (62.1), 156.04 (89.5), 128.05 (100.0), 58.16 (67.4).
(19) **Representative Procedure: (2-Cyano-1*H*-indol-3-yl)-acetic Acid Methyl Ester (10):** A solution of ester **9** (48.90 g, 0.20 mol) and phosphorus oxychloride (50.0 mL, 82.30 g, 0.54 mol) in benzene (300 mL) was heated under reflux for 7 h. Organic solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 (200 mL) and a solution of sat. $NaHCO_3$ (200 mL) and stirred for 1 h. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered and solvent removed under reduced pressure. The crude product was purified by flash column chromatography (5:1, hexane–EtOAc) to give nitrile **10** as a colourless crystalline solid (26.87 g, 77%); mp 88.0–89.5 °C.[9]

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