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Rapid synthesis of diversely functionalized 3,4,7-trisubstituted indoles

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ABSTRACT

Synthetic approaches are described for the synthesis of 4-alkoxyindole-7-carboxamides and 4-alkoxy-3-cyanoindole-7-carboxamides, which are useful intermediates in medicinal chemistry research. Two strategies were employed, highlighted by a Bartoli indole synthesis or a sequential and regioselective use of chlorosulfonyl isocyanate to install both the 3-cyano and 7-carboxamido groups. These routes are scalable and afford diversely functionalized indoles for further elaboration.

Indoles are commonly found in natural products and medicinally active compounds, and the synthesis and functionalization of the indole core is of great interest to the synthetic chemistry community. During the course of a medicinal chemistry effort we prepared indoles of general structure **1** (Fig. 1), in which R^1 was hydrogen or cyano, and R^2 was a point of broad diversity. This communication describes the chemistry that we developed for the synthesis of these compounds. Noteworthy is the rapid and selective functionalization of 4-alkoxyindoles using chlorosulfonyl isocyanate.

Our initial route to compound **1** (R^1 = H) is shown in Scheme 1. The indole ring was formed by reaction of nitrobenzene **2** with vinylmagnesium bromide according to the Bartoli method.[1] Cyanation of **3** using copper(I) cyanide followed by demethylation with sodium ethanethiolate afforded the 4-hydroxyindole **4**. The R^2 group was then installed either by a Mitsunobu reaction or by base-promoted alkylation. Hydration of nitrile **5** under Katritzky conditions[2] cleanly afforded indole-7-carboxamide **6**.

Although this synthesis was relatively short, it was not very efficient (3 steps, 18% yield to the key intermediate **4**) and several of the steps were problematic. The Bartoli reaction was low yielding and difficult to purify, the copper(I) cyanide and sodium ethanethiolate reactions involved toxic reagents and harsh conditions, and the work-up of the cyanation reaction was very tedious even on modest scales. Consequently, we sought an improved synthesis of a key intermediate similar to **4** that could be used to explore substitution of the indole ring at the 3-, 4-, and 7-positions.

A second generation synthesis was developed to circumvent some of these shortcomings (Scheme 2). Exchanging the methyl ether in **2** for a benzyl ether prior to indole formation averted the later use of sodium ethanethiolate. The Bartoli reaction was retained to generate indole **8**, but the cyanation step was replaced with a carbonylation reaction.[3] This four-step sequence (22% yield) was more scalable than the first generation route, providing >10 g of ester **9**, a useful intermediate for further elaboration of the 3-, 4-, and 7-positions.

During the course of our work, we also required access to the 3-cyanoindole scaffold (**1**, R^1 = CN). While many methods for the synthesis of 3-cyanoindoles rely on prior aldehyde formation by Vilsmeier formylation, direct cyanation protocols also exist.[4] We found that the desired 3-cyano group could be conveniently installed in one step from indole **9** using chlorosulfonyl isocyanate[5]

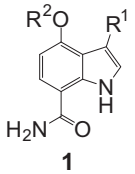
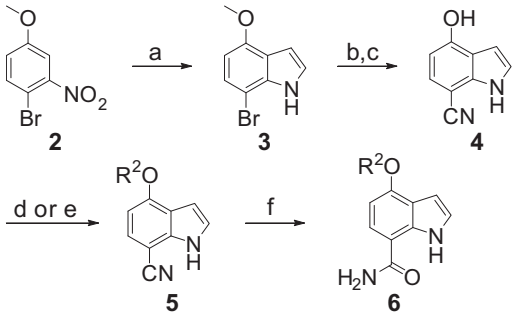


Figure 1. General structure of indole-7-carboxamides of interest.



Scheme 1. Reagents and conditions: (a) vinylmagnesium bromide, THF, <5 °C, 41%; (b) CuCN, DMF, 160 °C, 57%; (c) NaSEt, DMF, 120 °C, 76%; (d) R^2OH, polymer-PPh_3, DIAD, THF; (e) R^2X, Na_2CO_3, DMF; (f) H_2O_2, K_2CO_3, DMSO.

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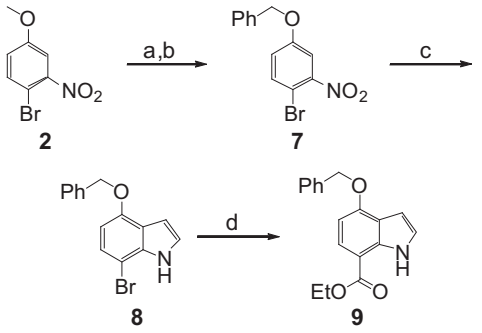
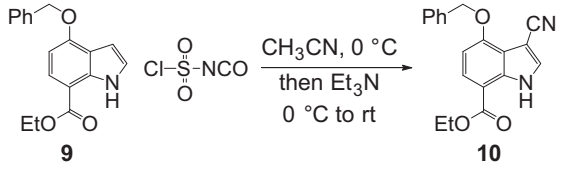


Scheme 2. Reagents and conditions: (a) BBr_3, DCM, −78 °C to rt, 83%; (b) BnBr, K_2CO_3, acetone, 91%; (c) vinylmagnesium bromide, THF, <5 °C, 37%; (d) $Cl_2Pd(dppf)\cdot CH_2Cl_2$, dppf, Et_3N, EtOH, 35 bar CO, 130 °C, 78%.



Scheme 3. Direct cyanation of indole **9** with CSI.

(CSI) at 0 °C, according to the method developed by Vorbrüggen[6] (Scheme 3), in 80% yield.[7]

While tri-substituted indole **10** was generated through the routes shown in Schemes 2 and 3 (5 steps, 17% yield), we surmised that targeting 3-substituted indoles would provide synthetic opportunities to circumvent the Bartoli indole synthesis and/or decrease the step count. We hypothesized that a mono-substituted 4-alkoxyindole could be functionalized sequentially at the 3- and 7-positions. Accordingly, direct cyanation of commercially available 4-benzyloxyindole with CSI led to 3-cyano-4-benzyloxyindole in good yield (**12**, Scheme 4) when the intermediate *N*-chlorosulfonylcarboxamide was quenched with DMF according to the Lohaus method.[8] In analogy to our 2nd generation synthesis, iodination of the 7-position,[9] followed by carbonylation[10] with $Mo(CO)_6$ afforded ester **10**. This sequence provided much more efficient access to key intermediate **10** (3 steps, 39% yield).

In addition, we sought a facile route to the indole-7-carboxamide, and considered a direct aminocarbonylation[11] at C-7 of **12**. We recognized that CSI may be used for such a functionalization,[5,12] and we hypothesized[13] that we could employ it to directly access the desired indole-7-carboxamide. Consequently, we resubjected 3-cyano-4-benzyloxyindole (**12**) to CSI, allowing the reaction to warm to room temperature, which resulted in a second addition of CSI. This time the intermediate *N*-chlorosulfonylcarboxamide (**14**) was hydrolyzed with dilute acid, which led directly to the indole-7-carboxamide **15**.[14] Thus, CSI was used to sequentially and regioselectively install first a 3-cyano group followed by a 7-carboxamido group, as shown in Scheme 4. Interestingly, while many examples exist of the addition of strong carbon electrophiles to C-7 of an indole (e.g., Vilsmeier reactions,[15] Friedel–Crafts reactions,[15c,16] and addition of oxalyl chloride[15a,15c,17]), this is the first reported example of the use of chlorosulfonyl isocyanate to functionalize C-7 of an indole.

Deprotection of the benzyl group of **15** provided intermediate **16** in only three steps from commercially available starting materials[18] with an overall yield of 66%. By comparison, the synthesis of compound **16** by the route described in Schemes 2 and 3 would have required eight steps. Importantly, this short and efficient synthesis was scalable, and was used for the synthesis of >50 g of **16**, a versatile intermediate for the preparation of diverse indoles.

In conclusion, we have developed synthetic routes for the preparation of 4-alkoxyindole-7-carboxamides bearing either a hydrogen or cyano group at C-3. Of particular note, we developed an operationally simple, three-step synthesis of 3-cyano-4-hydroxyindole-7-carboxamide (**16**) highlighted by the use of chlorosulfonyl isocyanate to sequentially and regioselectively install both the cyano and carboxamide groups. Compounds such as **4**, **9**, **13**, and **16** posses multiple orthogonal functionalities amenable to extensive elaboration and diversification.

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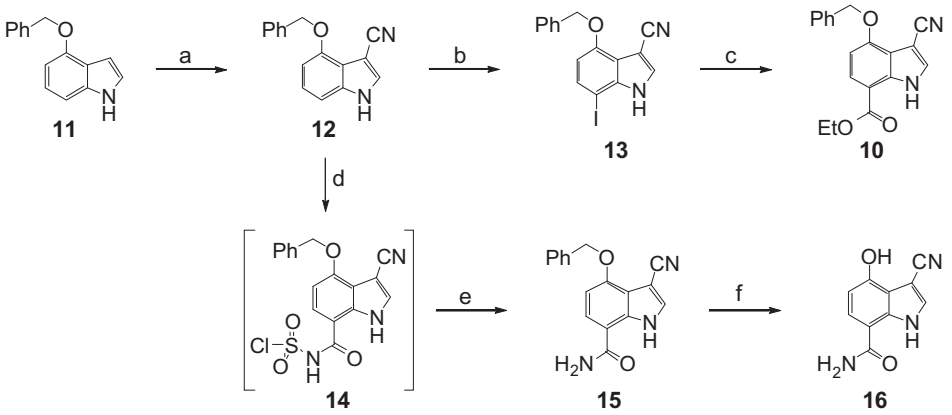
7. The yield of **10** is based on the NMR purity of a crude weight.



Scheme 4. Reagents and conditions: (a) CSI, CH_3CN, −45 °C, then DMF, −45 °C to rt, 72%; (b) ICl, AcOH, 83%; (c) $Mo(CO)_6$, 10% Pd/C, DMAP, DIPEA, EtOH, dioxane, 120 °C, 66%; (d) CSI, CH_3CN, 0 °C to rt; (e) 1 M HCl, 96%; (f) H_2, 10% Pd/C, DMF, 96%.

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13. In some of our previous cyanations with CSI we had noticed two minor byproducts, one corresponding to the indole-3-carboxamide, and another which appeared to result from a second addition of CSI to the indole.
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15. For example: (a) Brown, V. H.; Skinner, W. A.; DeGraw, J. I. *J. Heterocycl. Chem.* **1969**, *6*, 539–543; (b) Black, D. S. C.; Kumar, N.; Wong, L. C. H. *Synthesis* **1986**, 474–476; (c) Jones, A. W.; Wahyuningsih, T. D.; Pchalek, K.; Kumar, N.; Black, D. S. C. *Tetrahedron* **2005**, *61*, 10490–10500.
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18. *Experimental procedure for the synthesis of* **16**: Chlorosulfonyl isocyanate (4.08 mL, 47.0 mmol) in acetonitrile (10 mL) was added dropwise over 15 min to an acetontrile/CO_2-cooled (ca. −45 °C), stirred solution of 4-benzyloxy-1*H*-indole (10.0 g, 44.8 mmol) in acetonitrile (100 mL). Over the course of the addition a fine precipitate formed. The mixture was stirred at ca. −45 °C under nitrogen for 10 min. DMF (100 mL) was then slowly added, and the mixture was removed from the bath and allowed to warm to room temperature. It was then poured into a mixture of ice and water (500 mL), and extracted with ethyl acetate (3 × 250 mL). The combined organics were washed with water, satd $NaHCO_3$, and brine, then dried ($MgSO_4$), filtered, and evaporated. The crude material was purified by dissolving in chloroform and passing through silica gel (10 cm diam. × 10 cm thick), eluting with 0–3% ethyl acetate in chloroform to give 4-benzyloxy-3-cyano-1*H*-indole (**12**, 8.03 g, 32.3 mmol, 72%) as an off-white solid. LC–MS (ES) m/z = 271 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 2H), 6.74 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.58–7.67 (m, 3H), 8.93 (br s, 1H). Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 76.98; H, 4.80; N, 11.16. A solution of CSI (1.5 mL, 17.3 mmol) in acetonitrile (20 mL) was added dropwise via addition funnel to a mechanically stirred solution of **12** (3.79 g, 15.3 mmol) in acetonitrile (100 mL) at 0 °C under nitrogen, and the mixture was allowed to stir and warm to room temperature over 7 h, after which a precipitate had formed. The mixture was then quenched with 1 M HCl (60 mL, initial dissolution of reaction mixture followed by rapid precipitation) and stirred at room temperature overnight. Water (ca. 100 mL) was then added and the solid was collected by vacuum filtration, washed with ether, and dried to give 4-benzyloxy-3-cyano-1*H*-indole-7-carboxamide (**15**, 4.27 g, 14.7 mmol, 96%) as a white solid. LC–MS (ES) m/z = 292 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.39 (s, 2H), 6.90 (d, J = 8.3 Hz, 1H), 7.29–7.45 (m, 4H), 7.60 (d, J = 7.1 Hz, 2H), 7.83 (d, J = 8.3 Hz, 1H), 7.98–8.11 (br s, 1H), 8.04 (d, J = 3.0 Hz, 1H), 12.02 (s, 1H). Anal. Calcd for $C_{17}H_{13}N_3O_2{\cdot}0.15H_2O$: C, 69.45; H, 4.56; N, 14.29. Found: C, 69.40; H, 4.40; N, 14.31. A suspension of **15** (4.27 g, 14.7 mmol) and 10 wt % Pd/C (428 mg) in DMF (100 mL) was stirred under an atmosphere of hydrogen (balloon) for 7 h, then degassed and filtered through a pad of Celite. The filtrate was concentrated in vacuo then triturated with ether. The solid was collected by vacuum filtration to give 3-cyano-4-hydroxy-1*H*-indole-7-carboxamide (**16**, 3.00 g, 6 wt % DMF present by ^{1}H NMR, 14.0 mmol, 96%) as an off-white solid. LC–MS (ES) m/z = 202 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.57 (d, J = 8.3 Hz, 1H), 7.25 (br s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.91 (br s, 1H), 7.95 (d, J = 3.0 Hz, 1H), 10.65 (s, 1H), 11.88 (br s, 1H). Anal. Calcd for $C_{10}H_7N_3O_2{\cdot}0.1H_2O$: C, 59.17; H, 3.58; N, 20.70. Found: C, 58.97; H, 3.37; N, 20.50.