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Synthesis of 7-cyano- and 7-acetamido-indoles via cyanocarbonation/hydrogenation of 7-formyl indole

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Abstract—A procedure for the synthesis of 7-cyano and 7-acetamido indoles via cyanocarbonation/hydrogenation of 7-formyl indole is presented. The process can be efficiently scaled up to provide multigram quantities of the desired compounds in good yield. A small survey of substrate scope indicates that the reaction may prove generally useful for the synthesis of aryl acetonitriles.

1. Introduction

Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids such as **1** represent an important structural class of compounds with diverse biological activity.[1] Efforts in our laboratories have previously reported novel 6-substituted indolocarbazoles and aryl[*a*]pyrrolo[3,4-*c*]carbazoles that were highly potent and selective Cyclin D1/CDK4 inhibitors. Further evaluation of the SAR around this class of compounds identified the 'inversed' indolocarbazoles **2** as a novel series for development (Fig. 1).

To advance this series into clinical development we required a process to prepare multi-gram quantities of **2** (Scheme 1). Retrosynthetically, **2** is prepared from the corresponding bis-indolyl maleimides (BIMs) **4** via 2′,2′-bond formation. (Scheme 1). The BIM **4** is in turn prepared from aryl acetamide **6** and methyl indole-3-glyoxylate **5**.[2,3] While our efforts on the total synthesis of this class of compounds will be reported in the near future, we would like to provide a preliminary report of new methodology that we identified for the synthesis of aryl acetamides **6**. Although aryl acetamides are generally prepared from aryl acetic acids by a two step procedure, for the 'inversed' indolocarbazoles **2** and **3** this would require the use of 7-indole acetic acid which is not readily accessible. However, due to the commercial availability of 7-formyl indole (**7**) we developed a new method for synthesis of **6** from the corresponding aldehyde. This manuscript will describe, for the first time, the results of this work.

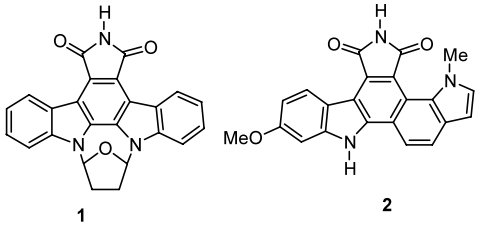
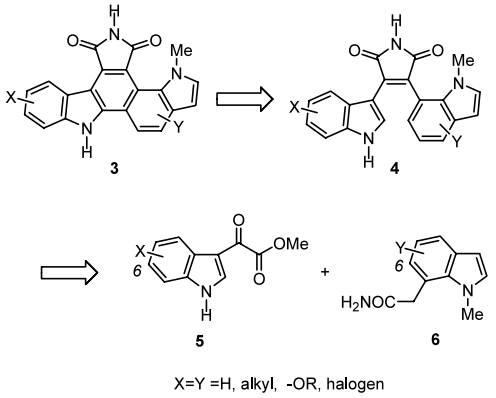


Figure 1.

2. Results and discussion

Methods for the one-carbon homologation of aldehydes to nitriles are rare.[4–6] Usually one must rely on reduction of the aldehyde to the alcohol. Once constructed, the alcohol can be directly displaced with



X=Y =H, alkyl, -OR, halogen

Scheme 1.

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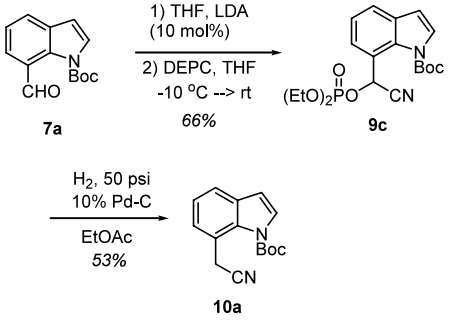
MCN (M = Na, K, Li) in the presence of TMSCl and NaI[7] or is activated by conversion to a mesylate, halide or other suitable leaving group and displaced with MCN (Scheme 2).[8–11]

The most straightforward route to 7-indole acetamides such as **6** involves direct reduction of 7-formyl indole to its corresponding alcohol followed by displacement with an alkalai metal cyanide (Scheme 2, strategy A). However, experience in our own hands as well as literature precedent,[12,13] indicates that this approach is not as straightforward as it would appear. In our experiments with mesylates and other activated derivatives (**8a** and **8b**, Strategy A, Scheme 1), we observed very low (<10%) yields of the desired compound (**10** and **11**). Instead, dimers, trimers and oligomers were the major products observed (as determined by LC-MS). These observations are in good accord with what is known in the field; Black has demonstrated that in fact the most effective method for synthesizing macrocyclic indole-type compounds is through activation of a benzylic indole 2- or 7-position as its mesylate or halide derivative.

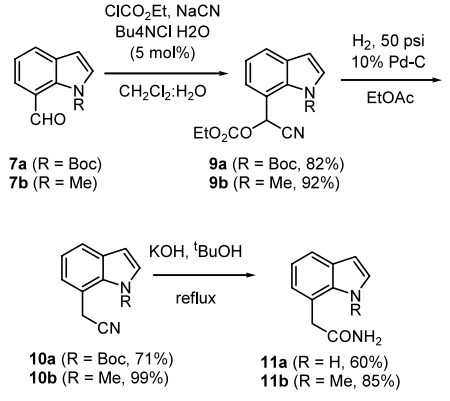
A variety of alternative methods exist for the transformation of aldehydes to nitriles via cyanohydrin derivatives.[4,14–19] Interestingly, many procedures involve the direct conversion of an aldehyde to a one-carbon homologated nitrile without the need for isolation of an intermediate protected cyanohydrin. Although they occur over a single step, these procedures involve the use of specialized reagents such as polymeric sulfonylhydrazones or isothiocyanates that are either unstable or unavailable commercially. In addition, many of the procedures are characterized by the significant formation of by-products as well as low yields of the desired aryl acetonitrile. A more viable approach involves the cyanophosphonation of 7-formyl indole followed by reductive removal of the phosphonate group with SmI_2.[6,20] Although feasible on small scale this approach involved the stoichiometric (or excess) use of LiCN and SmI_2 and would present challenges on large scale due to cost and ease of handling. Therefore we examined a number of alternatives; specifically, we decided to examine a more convenient reduction for removal of the phosphonate group. Recourse to the literature led us to consider one of the many cyanophosphonation/hydrogenation protocols that have been used extensively in the past.[5,21,22] To avoid the use of LiCN,[23] we turned our attention to the catalytic LDA cyanophosphonation procedure developed by Harusawa.[21] Scheme 3 details our attempts at cyanophosphonation of *N*-substituted indoles. Although neither 7-formyl indole[24] or 1-methyl-7-formyl indole participated in the reaction, we were delighted to determine that 1-*tert*-butoxy carbonyl-7-formyl indole (**7a**) did react cleanly to afford the corresponding cyanophosphonate (**9c**) in 66% yield after chromatography. Subsequent, hydrogenation of **6** in ethyl acetate liberated 7-cyanomethyl indole-1-carboxylic acid *tert*-butyl ester (**10a**) in 53% yield.

While this procedure worked well, we were interested in examining other alternatives that would afford **10** in higher overall yield. A variety of reagents and procedures may be used to replace the phosphonate group[15,17,25] but we were attracted to the cyanocarbonation procedure developed by Au (which employs NaCN and ethylchloroformate) because of its directness and simplicity.[26] We were gratified to find that unlike the cyanophosphonation procedure, both 7-formyl-indole-1-carboxylic acid *tert*-butyl ester (**7a**) and 7-formyl-1-methyl indole (**7b**) could be cleanly converted to their corresponding cyanocarbonates **9a** and **9b** in 82 and 92% yield (Scheme 4). Moreover, hydrogenation under the conditions previously used resulted in the isolation of the corresponding indole acetonitriles **10a** and **10b** in 71 and 99% yields, respectively.

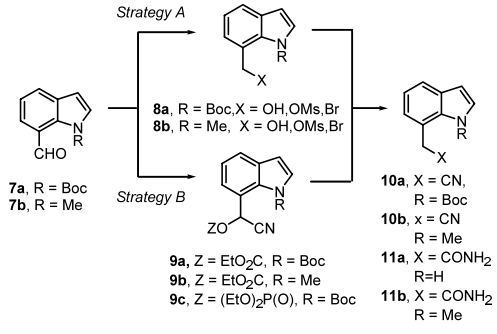
Having obtained high yields for the formation of the indole acetonitriles **10**, we proceeded to scale this chem-



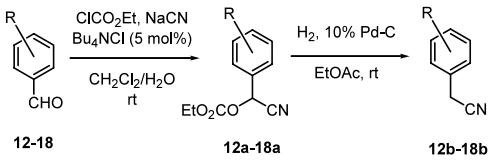
Scheme 3.



Scheme 4.



Scheme 2.



Scheme 5.

Table 1. Cyanocarbonation of aryl aldehydes

Entry	Aldehyde	Yield (%) (**12a–18a**)	Yield (%) (**12b–18b**)
1	2-Naphthaldehyde	57	99
2	2,6-Dimebenzaldehyde	73	40
3	2-Fluorobenzaldehyde	85	31
4	2-Methoxybenzaldehyde	95	69
5	7-Formylbenzofuran	78	74
6	Cyclohexane carboxaldehyde	95	0
7	Acetophenone	Nr	Na

istry up to demonstrate its robustness and utility.[27] Several improvements to the procedure were implemented during this scale-up run. Firstly, it was determined that it was not necessary to purify the crude cyanocarbonate **10a** before implementing the hydrogenation reaction, and secondly a crystallization procedure was developed for the purification of **10b**. This improved two-step process afforded **10b** in 75% yield from 7-formyl indole. Removal of the Boc-group under standard conditions proceeded in quantitative yield to provide 7-cyanomethyl-1*H*-indole. Alternatively, we were able to achieve a one-pot Boc-removal and nitrile hydrolysis to generate 2-(1*H*-Indole-7-yl)-acetamide in moderate yield (60–65%). Compound **10b** was hydrolyzed to the amide under similar conditions in 85% yield (Scheme 4).

To explore the versatility of this method, a variety of substrates were examined (Table 1). The reaction was successful for both aryl and heteroaryl acetaldehydes substituted with both electron donating and withdrawing groups to afford the corresponding aryl nitriles in 31–99% yield. However, for alkyl-substituted aldehydes (e.g. cyclohexane carboxaldehyde, entry 6) the cyanocarbonation reaction was successful (yield 95%), but we have been unable to identify conditions to reduce intermediate **17a** to the desired nitrile **17b**.[28] Not surprisingly, acetophenone failed to participate as a substrate in the cyanocarbonation reaction (Scheme 5).

In conclusion, we have developed a new method for the synthesis of aryl acetonitriles and acetamides that is operationally simple to implement and proceeds from readily available commercial reagents. Cyanocarbonation/hydrogenation of 7-formyl indoles has been implemented on scale to produce multi-gram quantities ($\sim$100 g) of 7-cyanomethyl-indole-1-carboxylic acid *tert*-butyl ester. For the indole substrates examined, this method proved superior to other protocols. Examination of substrate scope indicated that this cyanocarbonation/hydrogenation procedure could be effective for the synthesis of a range of aryl acetonitriles that are important precursors to the 'inversed' indolocarbazoles, highly potent inhibitors of Cyclin D1/CDK4.

Acknowledgements

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24. 1.1 equiv. of LDA was used for compound **5** where R = H.
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27. The experimental procedure for a large-scale preparation is as follows: Preparation of **9a**: 7-formyl-1-*tert*-butoxycarbonyl indole (**7a**) (114 g, 465 mmol) is dissolved in CH_2Cl_2 (900 mL) and Bu_4NCl H_2O (6.6 g, 24 mmol) and ethyl chloroformate (46 mL, 481 mmol) are added. The solution is stirred, and NaCN (47.2 g, 963 mmol) in water (900 mL) is added dropwise over a period of 90 min. The biphasic solution is stirred at room temperature until HPLC indicates that no starting material remains. The mixture is transferred to a separatory funnel with the aid of 4-L CH_2Cl_2 and 4-L DI H_2O, and the organic layer is separated. The organic layer is washed with 2×4 L satd $NaHCO_{3(aq)}$ and 2×4 L satd $NaCl_{(aq)}$. The organic layer is separated, dried (Na_2SO_4) and filtered through a pad of SiO_2 to provide **9a** (140.4 g, 88%) as a brown oil. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 7.73 (dd, J = 1.2 Hz, 8.1 Hz, 1H), 7.43 (dd, J = 0.9 Hz, 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 3 Hz, 1H), 6.81 (s, 1H), 6.55 (d, J = 3.0 Hz, 1H), 4.21–4.37 (m, 2H), 4.09 (s, 3H), 1.33 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 132.6, 130.8, 123.8, 123.3, 118.8, 116.7, 114.2, 101.1, 65.3, 64.5, 35.8, 13.8; IR (KBr, cm^{-1}): 3022, 2985, 1758, 1372, 1342, 1332, 1250, 1153, 1021; anal calcd for $C_{14}H_{14}N_2O_3$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.68; H, 5.68; N, 8.10; mass spectrum: molecular ion: m/z = 344.0; base peak: m/z = 344.0; Preparation of **10a**: Cyanocarbonate **9a** (139 g, 404 mmol) is dissolved in EtOAc (5.1 L) and 10% Pd–C (35 g) is added. The slurry is hydrogenated at 50°C and 50 psi H_2. When HPLC indicates that **9a** has been consumed, the reaction mixture is cooled to rt and is filtered through Hyflo. The solvent is removed in vacuo and the product **10a** (93 g, 85%) is isolated as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, J = 5.2 Hz, 1H), 7.54 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 7.21–7.29 (m, 2H), 6.58 (d, J = 4.8 Hz, 1H), 4.32 (s, 2H), 1.65 (s, 9H); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 149.1, 132.5, 132.3, 128.7, 126.7, 123.4, 121.3, 118.9, 117.8, 107.5, 84.2, 27.5, 23.5; IR (KBr, cm^{-1}): 3010, 2984, 2936, 2255, 1746, 1425, 1732, 1337, 1259, 1154, 1102, 1024, 1014; HRMS calculated for $C_{15}H_{16}N_2O_2$: 256.1212; Found: 256.1212.
28. Alternative reducing agents were not examined to effect this chemistry.