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The preparation of 5-indolyl-Mannich bases: an expedient source of 5-(chloromethyl)indoles

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Abstract

Regioisomeric analogues of gramine, 5-(dialkylaminomethyl)indole-2-carboxylates were prepared by the Fischer indolization of 4-(dialkylaminomethyl)phenylhydrazones easily obtained from diazotized 4-(dialkylaminomethyl)anilines by the Japp–Klingemann reaction. These formal Mannich bases are valuable synthetic intermediates affording 5-(chloromethyl)indoles on reaction with acetyl chloride at rt within a few minutes in quantitative yields.

For well over a 100 years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for their preparation have been developed.[1] A particular indole synthesis is often a result of a compromise between starting material availability, functional group tolerance and regioselectivity. In some cases, specific substitution patterns remain difficult to be obtained by standard indole-forming reactions; thus, new methodologies emerge. However, not to lose the knowledge and experience accumulated during the applications of old methods, it is important to explore and broaden the functional group tolerance, regioselectivity or starting material availability of these traditional methods to fit new requirements.

For over 100 years, the Fischer indole reaction has remained an extremely important and useful method for the synthesis of a variety of indole intermediates and biologically active compounds.[2] In the case of heterocycles with benzylic substituents, however, owing to the rather harsh conditions in the indolization step either low yields or no products result.[3] We have disclosed that the sulfomethyl group, as an extremely stable substituent in the Fischer synthesis of indole-2-carboxylates, can serve as a convenient pre-substituent for the chloromethyl group at the benzenoid part of the heterocycle.[4] This type of chemistry is based on our observation that the sulfomethyl group of indole-2-carboxylates can be easily transformed into a chloromethyl group with $SOCl_2$ under the conditions of sulfonyl chloride formation. These 4-, 5-, 6- and 7-(chloromethyl)indole-2-carboxylates proved to be highly reactive, very useful advanced indole intermediates.[5] However, the use of $SOCl_2$ and the low solubility of the indolemethanesulfonic acids in common solvents impeding manipulations on the indole nucleus are the drawbacks of the procedure, which have to be circumvented.

To broaden the synthetic utility of (chloromethyl)indoles as synthetic intermediates, it was necessary to find a functionality which is as stable as the SO_3H group but one that can be transformed to a chloromethyl group under milder conditions. In addition, it should provide a lipophilic indole nucleus.

In this Letter, we disclose our results on the synthesis of 5-(dialkylaminomethyl)indole-2-carboxylates and their facile conversion to 5-(chloromethyl)indoles.

It is well known that tertiary amines containing a benzyl group can be easily transformed to secondary amines under the influence of alkyl chloroformates with the benzyl group being eliminated. The main application of this reaction is to produce secondary amines from tertiary amines[6] but

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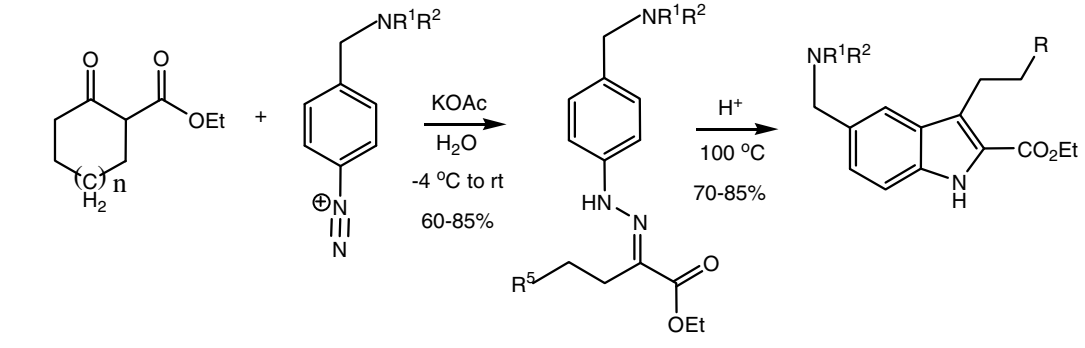
sometimes it is used to provide benzyl chlorides from dialkylbenzylamines, at least in the case of electron-rich aromatic rings.[7] The idea has arisen that tertiary 5-(indolylmethyl)amines may serve as a source of 5-(chloromethyl)indoles in an analogous reaction. The synthesis and the reactivity of 3-(dialkylaminomethyl)indoles (i.e., gramine) are well documented.[1a] The analogous 5-(dialkylaminomethyl)indoles, however, have not received an equal amount of attention, which can be attributed to the difficulties surrounding their synthesis. These compounds are available through the transformation of indoles bearing 5-cyano[8] or carboxamido groups[9] as the direct introduction of the 5-aminomethyl group through Mannich condensation is accomplished only in the case of 4-hydroxyindoles.[10] Thus, the need for easier access to these potentially useful indole building blocks still remains.

Our new method for the preparation of 5-(dialkylaminomethyl)indoles[11] (Scheme 1) started with the Japp–Klingemann reaction of diazotized *para*-(dialkylaminomethyl)anilines[12] **2**, **3**, **4** and **5** with β-oxoester derivatives **1a**,**b** to yield hydrazones **6a**,**b**; **7a**,**b**; **8a**,**b** and **9a**,**b**. KOAc was used to adjust the pH to 4–5 during the condensation, the hydrazones were either separated from the reaction mixture or isolated by evaporating the aqueous solution to dryness and extracting the solid residue with ethyl acetate–ethanol (10:1). The exact structure of the hydrazones was not investigated. The Fischer indolization was carried out in acetic acid–hydrogen chloride at reflux. The resulting 5-(dialkylaminomethyl)indoles **10a**,**b**; **11a**,**b**; **12a**,**b** and **13a**,**b** were isolated by evaporating the solvent, then the crude acids were esterified in ethanol–hydrogen chloride at rt and then purified by either crystallization from hexane–ethyl acetate (20:1) or flash chromatography in good overall yields. Although (alkylphenyl)hydrazones have the propensity to undergo rearrangement during Fischer indolization, amines **10**, **11**, **12** and **13** were the only indoles formed.

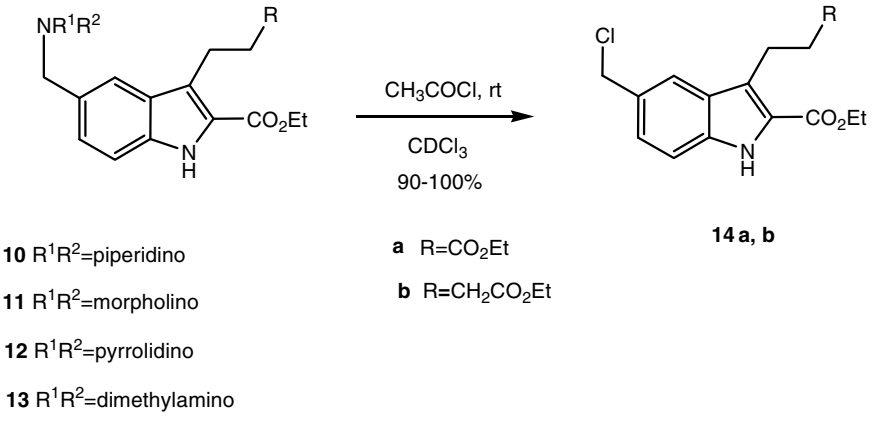
The behaviour of these formal Mannich bases was investigated in the presence of methyl, and ethyl chloroformates, or carboxylic acid chlorides. With the former reagents complex reaction mixtures were obtained which did not seem attractive for further consideration, a clean reaction occurred with acetyl chloride at room temperature within a few minutes in $CDCl_3$ yielding the respective (chloromethyl)indoles **14a**,**b**, quantitatively (Scheme 2). These reactions were carried out in an NMR tube in dry $CDCl_3$: one drop of acetyl chloride was added to the solutions containing 10–14 mg of Mannich-base then the ^1H NMR spectrum was measured within a few minutes at 18 °C. The samples indicated that the ^1H NMR spectra of pure (chloromethyl)indoles were superimposed with those of the respective acetamide (and excess acetyl chloride). The presence of both the (chloromethyl)indole and the acetamide was verified by adding authentic samples of these compounds which resulted in no change in the spectra except an increase in the intensity compared to the other cleavage product. On a preparative scale, (piperidinomethyl)indole (**10b**, 2 g, 5 mmol) was treated with acetyl chloride (1.1 mL, 15 mmol) in dry CH_2Cl_2 (40 mL) at rt for 10 min (Scheme 2). The reaction mixture was evaporated to dryness to give (chloromethyl)indole **14b** which was either dissolved in MeOH yielding (indolylmethyl)methyl ether[11] **15**, quantitatively, or treated with NaCN in DMF to yield cyanomethylindole[11] **16** in 61% yield (Scheme 3).

In spite of their easy transformation to (chloromethyl)indoles, these 5-(dialkylaminomethyl)indoles are stable compounds: 5-(dimethylaminomethyl)indole **13a** when refluxed in piperidine, did not undergo aminolysis.

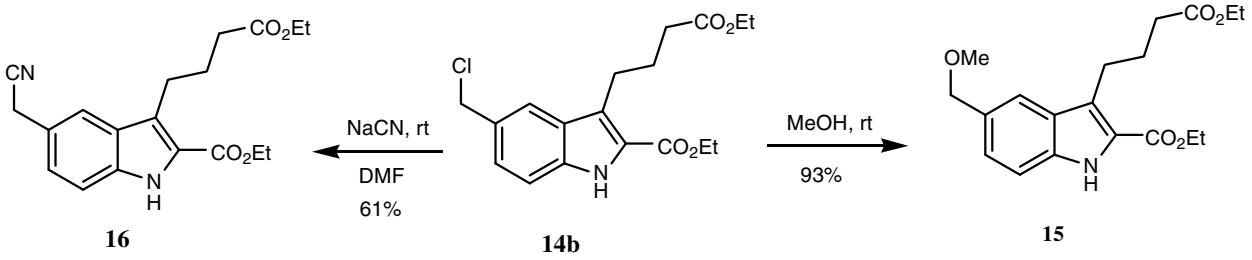
To the best of our knowledge, 5-(dialkylaminomethyl)indoles have not been used to furnish (chloro-



Scheme 1.



Scheme 2.



Scheme 3.

methyl)indoles, as yet. They have been subjected to nucleophilic substitution in an indirect manner, following quaternization: trimethyl-(5-indolylmethyl)ammonium iodide was used for the N-alkylation of the anion of 1,1-dioxo-5-methyl-1,2,5-thiadiazolidine at 80–90 °C in DMF.[8]

In summary, the method described above enables the facile and regioselective introduction of a dialkylaminomethyl group at C5 of indole-2-carboxylates. The dialkylamino group of these regioisomers of gramine or its analogues, while extremely stable in refluxing acetic acid–hydrogen chloride or ethanol–hydrogen chloride, is easily replaced by chlorine, quantitatively, in the presence of acetyl chloride at rt. Thus, the mild reaction conditions used to obtain (chloromethyl)indoles endow our procedure with extremely good functional group tolerance.

Acknowledgement

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11. *Representative example*: (4-Morpholinomethyl)aniline (1.4 g, 7.3 mmol) dissolved in water (20 mL) and concd HCl (3.5 mL) was diazotized by adding $NaNO_2$ (0.504 g, 7.3 mmol) at −4 °C over a period of 20 min. Ethyl 2-cyclohexanonecarboxylate (**1b**, 1.4 g, 8 mmol) was then added at −4 °C while stirring vigorously. The pH of the reaction mixture was adjusted to 6–7 by adding NaOAc at −4 °C. The yellow solution was allowed to warm to rt and stirred for 18 h. The resulting red solution was evaporated to dryness and the solid residue was extracted with EtOAc (50 mL) to separate hydrazone **7b** from inorganic salts. The solvent was removed in vacuo and the residue (red oil) was dissolved in AcOH–HCl(g) (50 mL, 1.5% HCl(g)) and kept at 95–98 °C for 2 h. After the evaporation of the solvent in vacuo, the residue (brown solid) was dissolved in EtOH–HCl(g) (30 mL, 0.2% HCl) and kept at rt for 24 h. The solution was evaporated to dryness in vacuo and the residue (brown solid) was

dissolved in water (10 mL), basified with solid Na_2CO_3 and extracted with EtOAc (3 × 15 mL). After the evaporation of the solvent, the residue (pale oil) was chromatographed on Alumina (neutral) with hexane–EtOAc (10:1) to give **11b** (white solid, 1.9 g, 66%). All new compounds gave the correct NMR, MS and elemental analysis data. Melting points, ^1H, ^{13}C NMR (500, 75 MHz, respectively, in $CDCl_3$) and elemental analysis data of representative examples **10b**, **11b**, **15** and **16**. Compound **10b**: δ 1.24 (t, $J = 7$ Hz, 3H), 1.42 (m, 5H), 1.57 (m, 4H), 2.02 (m, 2H), 2.36 (m, 2H), 2.44 (m, 4H), 3.15 (m, 2H), 3.56 (s, 2H), 4.11 (q, $J = 7$ Hz, 2H), 4.41 (q, $J = 7$ Hz, 2H), 7.31 (m, 2H), 7.55 (s, 1H), 8.77 (s, 1H); ^{13}C NMR: 14.42, 14.58, 24.15, 24.46, 25.89, 26.17, 34.17, 54.47, 60.36, 60.89, 64.22, 111.67, 121.42, 123.79, 123.87, 127.86, 128.02, 129.71, 135.49, 162.50, 173.04. Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99%. Found: C, 68.76; H, 7.90; N, 6.95%; mp: 82–83 °C (hexane). Compound **11b**: δ 1.25 (t, $J = 7$ Hz, 3H), 1.43 (t, $J = 7$ Hz, 3H), 2.03 (m, 2H), 2.37 (m, 2H), 2.48 (m, 4H), 3.16 (m, 2H), 3.60 (s, 2H), 3.73 (m, 4H), 4.12 (q, $J = 7$ Hz, 2H), 4.42 (q, $J = 7$ Hz, 2H), 7.33 (s, 2H), 7.58 (s, 1H), 8.70 (s, 1H); ^{13}C NMR: 14.43, 14.58, 24.14, 26.17, 34.15, 53.80, 60.37, 60.91, 64.02, 67.19, 111.78, 121.26, 123.80, 123.86, 127.55, 128.06, 129.58, 135.52, 162.49, 173.79. Anal. Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96%. Found: C, 65.48; H, 7.62; N, 6.95%; mp: 98–102 °C (hexane). Compound **15**: δ 1.22 (t, $J = 7$ Hz, 3H), 1.36 (t, $J = 7$ Hz, 3H), 2.00 (m, 2H), 2.31 (m, 2H), 3.10 (m, 2H), 3.35 (s, 3H), 4.05 (q,$J = 7$ Hz, 2H), 4.35 (q, $J = 7$ Hz, 2H), 4.49 (s, 2H), 7.25 (m, 2H), 7.57 (s, 1H), 8.92 (s, 1H); ^{13}C NMR: 13.71, 13.88, 23.45, 25.47, 33.47, 57.36, 59.67, 60.24, 74.79, 111.32, 119.69, 123.32, 125.60, 127.40, 129.48, 135.08, 162.29, 173.54. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03%. Found: C, 65.53; H, 7.26; N, 4.01%; mp: 42–43 °C (hexane). Compound **16**: δ 1.24 (t, $J = 7$ Hz, 3H), 1.43 (t, $J = 7$ Hz, 3H), 2.02 (m, 2H), 2.36 (m, 2H), 3.15 (m, 2H), 3.85 (s, 2H), 4.12 (q, $J = 7$ Hz, 2H), 4.42 (q, $J = 7$ Hz, 2H), 7.25 (d, $J = 8$ Hz, 1H), 7.38 (d, $J = 8$ Hz, 1H), 7.63 (s, 1H), 8.85 (s, 1H); ^{13}C NMR: 14.41, 14.54, 23.90, 24.04, 26.12, 34.04, 60.44, 61.14, 112.80, 118.63, 120.30, 121.76, 123.66, 124.62, 125.53, 128.43, 135.44, 162.31, 173.71. Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48, N, 8.18%. Found: C, 66.47; H, 6.42; N, 8.13%; mp: 104-106 °C (hexane).

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