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Synthesis of 5-substituted indole derivatives. Part 3: A facile synthesis of 5-chloromethyl-1*H*-indole-2-carboxylates: replacement of sulfonic acid functionality by chlorine†

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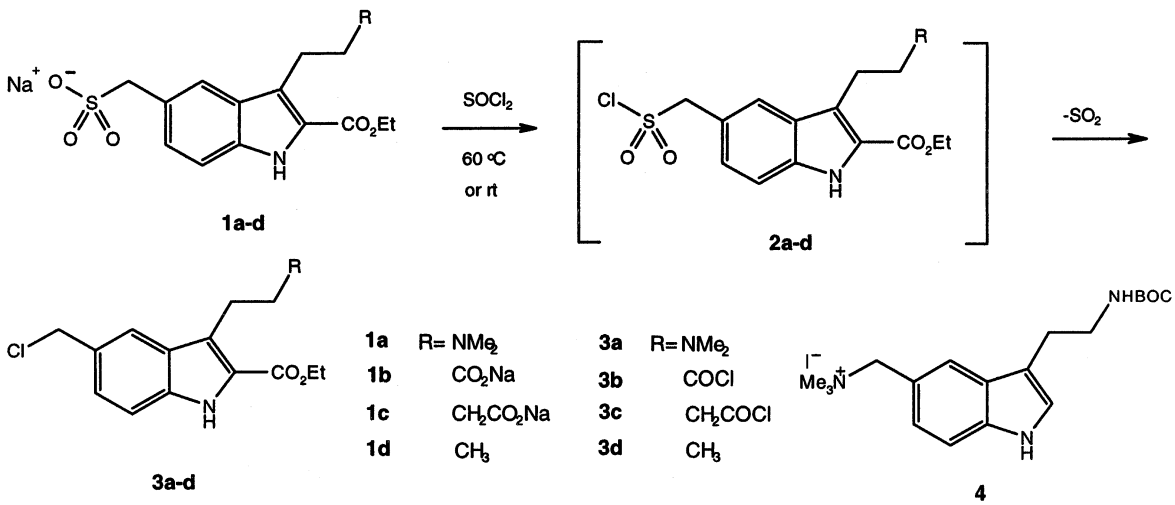
Abstract—Valuable new synthetic intermediates, 5-chloromethyl-1*H*-indole-2-carboxylates, were prepared by the elimination of SO_2 from 2-ethoxycarbonyl-1*H*-indole-5-methanesulfonic acids, which are easily accessible by Fischer-type indolization. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of functionalized indoles has been of interest to organic chemists for many years due to the large number of natural products that contain this structural element. More importantly, indole-containing compounds have pronounced effects in many physiological processes, and indoles having 5-HT receptor activity as agonists[2] or antagonists[3] have aroused considerable synthetic interest during the last decade in many research groups. Although the 5-indolylcarbinyl unit is a common structural element of these compounds, their synthesis is carried out in a different way: the latent 5-substituent had been introduced prior to the indolization step.[3,4] This approach is impractical; instead a common advanced intermediate suitable for facile derivatization to generate a diverse group of 5-substituted indoles is required. An obvious target to fulfill these requirements would be the 5-halomethyl indoles. In this paper we disclose our results on the



Scheme 1.

Keywords: Fischer synthesis; 3,5-disubstituted 2-carboxyindoles; desulfination.

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† For Part 2, see Ref. 1.

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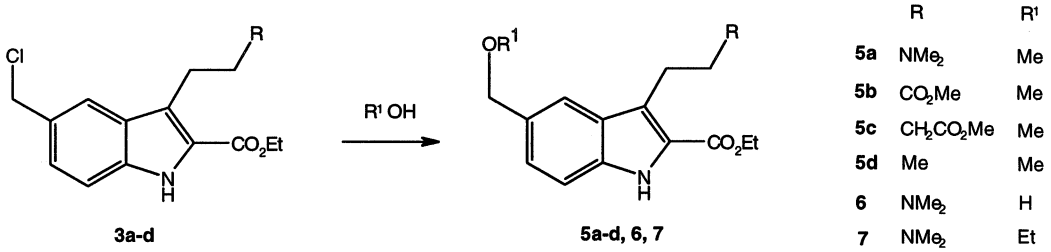

Scheme 2.

facile synthesis of ethyl 5-chloromethyl-1*H*-indole-2-carboxylates **3a–d**. The preparation of compounds **3a–d** is based on our observation that the SO_3H group of the indole-5-methanesulfonic acids **1a–d** is easily replaced by chlorine under the circumstances of the formation of sulfonyl chlorides (Scheme 1). Such a type of 'functional group chemistry' is rare in the literature, and unprecedented in the chemistry of the indoles. To the best of our knowledge, only two examples exist where this type of transformation has been used for preparative purposes: Barber and co-workers developed a general method for the preparation of aryloxymethyl chlorides from aryloxymethanesulfonates and PCl_5 at rt.[5] Moreover, a number of 2-benzimidazolyl chlorides were prepared in good yields from the corresponding 2-benzimidazolyl sulfonic acids by treatment with PCl_5 and $POCl_3$.[6]

The formation of alkyl chlorides and even alkyl amines has been observed by the elimination of SO_2 from alkyl sulfonyl chlorides[7] or sulfonamides,[8] respectively, but the reactions have not been shown to have any synthetic utility.

The advantages related to our process are obvious: the sulfo group of **1a–d**,[9] as one of the most chemically stable, allows for a broad range of transformations of the indole nucleus. The chloromethyl functionality can then be introduced under mild conditions.

The chloromethyl indoles **3a–d** are very reactive compounds that easily undergo hydrolysis or alcoholysis[10] at rt even in the absence of bases (Scheme 2).

Castro and Matassa[11] have already proved that the 5-indolylcarbinyl carbon has a high reactivity, similar to that of the 3-indolylcarbinyl carbon (e.g. in gramine) by synthesizing the tryptamine **4**. This high reactivity toward nucleophilic substitution is the result of resonance interaction, quite similar to that operating in the case of the 3-indolylcarbinyl carbon. This type of resonance stabilization must facilitate the loss of SO_2 from sulfonyl chlorides **2a–d**, if elimination proceeds through an ionic intermediate. Evidence has already been presented for the intermediacy of an episulfonium ion in the thermal desulfination of 2-(phenylthio)ethanesulfonyl chloride by McManus et al.[7a] The probable driving force for the loss of SO_2 on attempted chlorination of aryloxymethanesulfonates[5] is the formation of the resonance-stabilized intermediate $[ArO^+{=}CH_2]$. On the other hand, as a precedent for the concerted loss of SO_2 and formation of halides, we recall the thermal desulfination of allylic sulfonyl halides.[12] Whether the displacement of the chlorosulfonyl group of **2a–d** by chloride follows a nucleophilic path or occurs simultaneously is not yet clear and needs further investigation.

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9. General procedure for **1a–d**: (4-Nitrophenyl)-methanesulfonic acid[13] was prepared from (4-nitrophenyl)methyl chloride and Na_2SO_3 and was then reduced using catalytic hydrogenation (Pd/C) to afford (4-aminophenyl)methanesulfonic acid (62% overall from (4-nitrophenyl)methyl chloride). The sulfonic acids **1a–d**[14,15] were prepared as sodium salts as follows: first hydrazones were prepared in the Japp–Klingemann reaction of diazotized (4-aminophenyl)methanesulfonic acid with the appropriate C–H acids: **1a**: ethyl 2-(3-dimethylaminopropyl)oxobutanoate; **1b**: ethyl 2-oxo-cyclopentanecarboxylate; **1c**: ethyl 2-oxo-cyclohexanecarboxylate; **1d**: butylmalonic acid monoethylester. The hydrazones were then subjected to Fischer-type indolization in AcOH–HCl at rt (**1a**) or in 80% HCO_2H (**1b–d**) at reflux. Overall yields: **1a**: 61%; **1b**: 80%; **1c**: 76%; **1d**: 73%.
10. General procedure for **5a–d**,[14,15] and **6**, **7**:[14,15] The sulfonate salt (**1a–d**, 1 mmol) was stirred in $CHCl_3$ (30 ml)

containing $SOCl_2$ (1 ml, 14 mmol) and DMF (0.03 ml), at rt for 24 h (**3b–d**), or at reflux for 4 h (**3a**) and the solution was evaporated to dryness to give **3a–d**.[14] The solid residue was dissolved in MeOH (**5a–d**) or aqueous dioxane (1:1, **6**) or EtOH (**7**). After standing for 3 h at rt, the solvent was rotary evaporated to give the products. Overall yields from **1a–d**, respectively: **5a** (88%), **5b** (72%), **5c** (80%), **5d** (66%), **6** (82%), **7** (94%).

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14. Melting points and ^1H NMR data (500 MHz, in D_2O for compounds **1a–d** and $CDCl_3$ for compounds **3a–d**, **5a–d**, **6** and **7**): Compound **1a**: δ 1.29 (3H, t, $J=7$ Hz), 2.69 (6H, s), 2.8–3.2 (4H, m), 3.96 (2H, s), 4.25 (2H, q, $J=7$ Hz), 7.22 (1H, d, $J=8.5$ Hz), 7.33 (1H, d, $J=8.5$ Hz), 7.62 (1H, s); mp: 280–284°C (H_2O). Compound **1b**: δ 1.48 (3H, t, $J=7$ Hz), 2.66 (2H, m), 3.32 (2H, m), 4.37 (2H, q, $J=7$ Hz), 4.40 (2H, s), 7.42 (2H, s), 7.73 (1H, s); mp: 272–276°C (H_2O). Compound **1c**: δ 1.53 (3H, t, $J=7$ Hz), 2.04 (2H, m), 2.58 (2H, m), 3.04 (2H, m), 4.43 (2H, q, $J=7$ Hz), 4.50 (2H, s), 7.53 (2H, s), 7.78 (1H, s); mp: 237–240°C (H_2O). Compound **1d**: δ 1.22 (3H, t, $J=5$ Hz), 1.65 (3H, t, $J=7$ Hz), 1.83 (2H, m), 3.18 (2H, m), 4.50 (2H, s), 4.56 (2H, q, $J=7$ Hz), 7.60 (2H, s), 7.92 (1H, s); mp: 238–242°C (H_2O). Compound **3a**: δ 1.40 (3H, t, $J=7$ Hz), 2.92 (3H, s), 2.95 (3H, s), 3.20 (2H, m), 3.65 (2H, m), 4.42 (2H, q, $J=7$ Hz), 4.72 (2H, s), 7.40 (2H, s), 7.88 (1H, s), 9.18 (1H, s). Compound **3b**: δ 1.32 (3H, t, $J=7$ Hz), 3.16 (2H, m), 3.35 (2H, m), 4.32 (2H, q, $J=7$ Hz), 4.63 (2H, s), 7.28 (2H, s), 7.60 (1H, s), 8.83 (1H, s). Compound **3c**: δ 1.30 (3H, t, $J=7$ Hz), 1.98 (2H, m), 2.85 (2H, m), 3.05 (2H, m), 4.35 (2H, q, $J=7$ Hz), 4.62 (2H, s), 7.28 (2H, s), 7.53 (1H, s), 8.88 (1H, s). Compound **3d**: δ 0.89 (3H, t, $J=5$ Hz), 1.33 (3H, t, $J=7$ Hz), 1.60 (2H, m), 2.97 (2H, m), 4.30 (2H, q, $J=7$ Hz), 4.65 (2H, s), 7.27 (2H, s), 7.58 (1H, s), 8.90 (1H, s). Compound **5a**: δ 1.44 (3H, t, $J=7$ Hz), 2.95 (6H, s), 3.22 (2H, m), 3.41 (3H, s), 3.66 (2H, m), 4.41 (2H, q, $J=7$ Hz), 4.55 (2H, s), 7.40 (2H, s), 7.78 (1H, s), 8.92 (1H, s); mp: 158–160°C (EtOH). Compound **5b**: δ 1.40 (3H, t, $J=7$ Hz), 2.65 (2H, m), 3.38 (3H, s), 3.40 (2H, m), 3.63 (3H, s), 4.40 (2H, q, $J=7$ Hz), 4.57 (2H, s), 7.32 (2H, m), 7.66 (1H, s), 8.88 (1H, s); mp: 70–72°C (hexane). Compound **5c**: δ 1.35 (3H, t, $J=7$ Hz), 2.00 (2H, m), 2.30 (2H, m), 3.09 (2H, m), 3.34 (3H, s), 3.59 (3H, s), 4.34 (2H, q, $J=7$ Hz), 4.40 (2H, s), 7.25 (2H, m), 7.57 (1H, s), 9.08 (1H, s); mp: 48–50°C (hexane). Compound **5d**: δ 0.98 (3H, t, $J=5$ Hz), 1.42 (3H, t, $J=7$ Hz), 1.69 (2H, m), 3.07 (2H, m), 3.40 (3H, s), 4.37 (2H, q, $J=7$ Hz), 4.55 (2H, s), 7.27 (2H, m), 7.64 (1H, s), 9.09 (1H, s); mp: 74–76°C (hexane). Compound **6**: δ 1.40 (3H, t, $J=7$ Hz), 2.37 (6H, s), 2.58 (2H, m), 3.30 (2H, m), 4.40 (2H, q, $J=7$ Hz), 4.77 (2H, s), 7.35 (2H, s), 7.68 (1H, s), 8.82 (1H, s); mp: 128–130°C (EtOH). Compound **7**: δ 1.25 (3H, t, $J=7$ Hz), 1.44 (3H, t, $J=7$ Hz), 2.89 (3H, s), 2.91 (3H, s), 3.24 (2H, m), 3.54 (2H, q, $J=7$ Hz), 3.64 (2H, m), 4.40 (2H, q, $J=7$ Hz), 4.58 (2H, s), 7.39 (2H, s), 7.77 (1H, s), 9.00 (1H, s); mp: 188–190°C (EtOH).
15. ^{13}C NMR was used for the structure elucidation of compounds **1a–d**, and **5a–d**, **6** and **7**, and low-resolution MS for compounds **5a–d**, **6** and **7**. IR also confirmed the loss of the SO_3 group in all cases.