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SYNTHESIS OF 5-SUBSTITUTED INDOLE DERIVATIVES, PART 5.[1] A SYNTHESIS OF 5-FORMYL-1*H*-INDOLE-2-CARBOXYLATES: THE CH_2SO_3H FUNCTIONALITY AS A MASKED FORMYL GROUP

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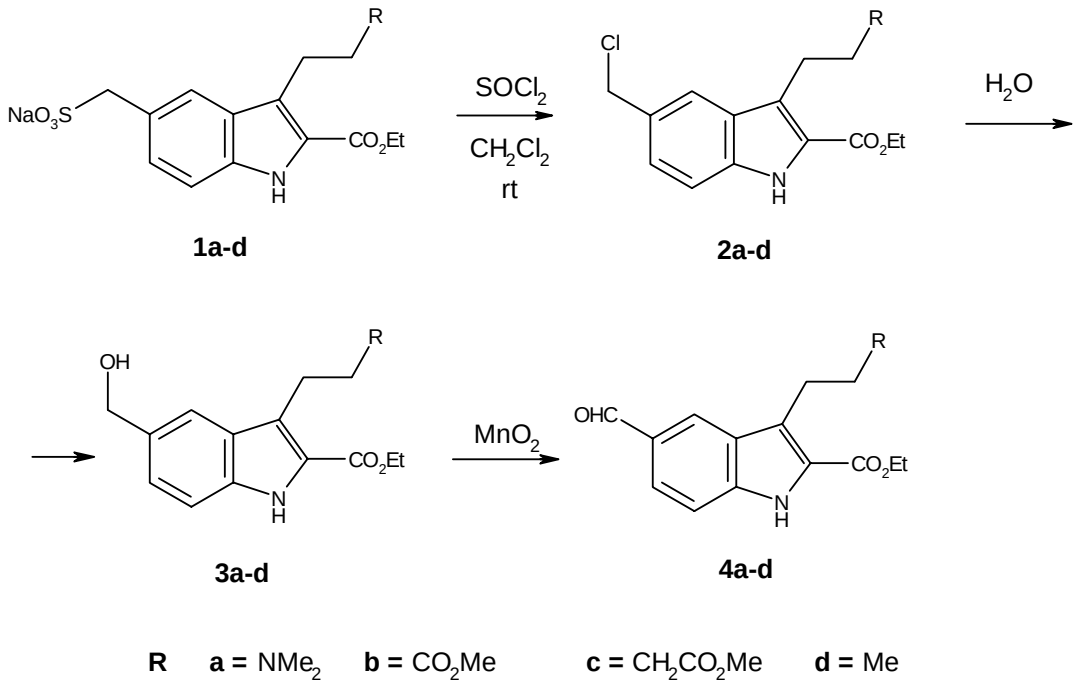
Abstract - New synthetic intermediates, ethyl 5-formyl-1*H*-indole-2-carboxylates (**4**) were prepared from 2-ethoxycarbonyl-1*H*-indole-5-methanesulfonic acids (**1**). The transformation of the sulfomethyl group to formyl function was accomplished through elimination of SO_2 to yield ethyl 5-chloromethyl-1*H*-indole-2-carboxylates (**2**), hydrolysed to ethyl 5-hydroxymethyl-1*H*-indole-2-carboxylates (**3**), then oxidized to aldehydes (**4**).

A wide variety of biologically active, or naturally occurring indoles contain substituents in the benzenoid portion of the indole nucleus. The 4-, 5-, 6-, and 7-formylindoles are important intermediates for these compounds. As a part of our ongoing research on the synthesis of Naratriptan,[1] a 5-$HT_{1B/1D}$ receptor agonist, we studied the synthesis of 5-formylindoles. Condensation of the formyl group with methanesulfonamides offers a simple approach to the aminosulfonylethyl-side chain of Naratriptan. In this paper we want to reveal our results on the facile preparation of ethyl 5-formyl-1*H*-indole-2-carboxylates (**4a-d**) from 5-chloromethyl-1*H*-indole-2-carboxylates (**2a-d**).[2]

The known syntheses of 5-formylindoles, *i.e*. the one starting from 5-bromoindoles is effected by the sequence of lithiation with *t*-BuLi and condensation with DMF.[3] An alternative procedure starts from 5-alkoxycarbonylindoles reduced by $LiAlH_4$ to benzyl alcohols followed by MnO_2 mediated oxidation.[4] These strongly basic conditions exclude other base-sensitive functionalities from the targeted 5-formylindoles. The importance of 5-substituted indoles[5] prompted us to develop a new, simple and efficient synthetic approach to 5-formylindoles avoiding basic conditions. In a preceding paper[2] we showed that 2-ethoxycarbonyl-1*H*-indole-5-methanesulfonates (**1a-d**) are easily transformed to ethyl 5-

chloromethylindole-2-carboxylates (**2a-d**) with $SOCl_2$ in excellent yields (Scheme 1). Chloromethyl-indoles (**2a-d**) undergo facile transformation to formylindoles (**4a-d**):

Scheme 1

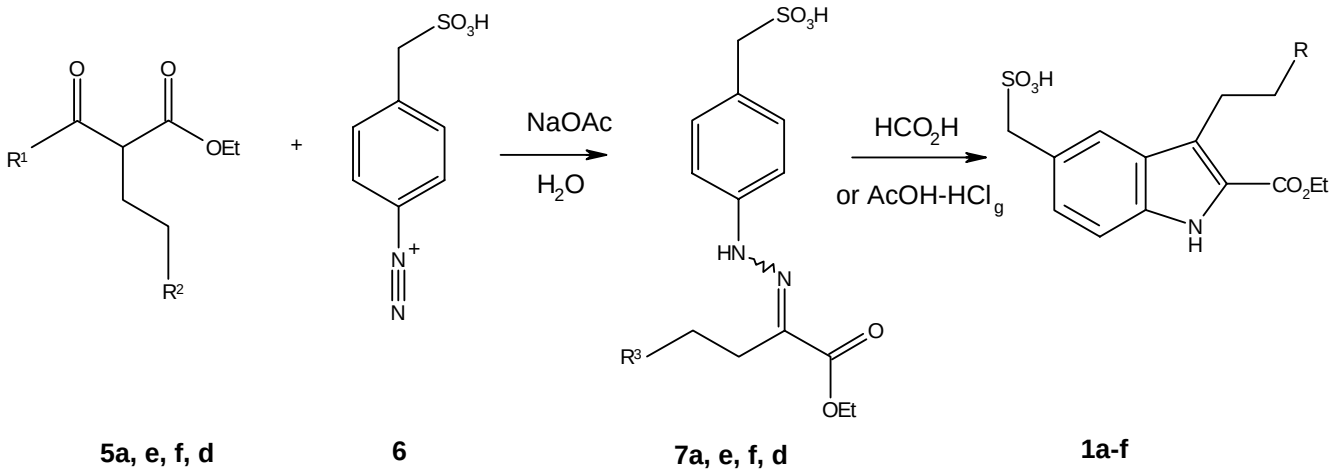


R **a =** NMe_2 **b =** CO_2Me **c =** CH_2CO_2Me **d =** Me

The hydrolysis takes place smoothly in water at 0 ^oC in the absence of base as chlorides (**2a-d**) are very reactive compounds. The alcohols (**3a-d**) can be isolated by extraction with CH_2Cl_2 at pH=8-9 in 75-93% yields. With respect to yields and purity to effect oxidation to aldehydes (**4a-d**), the best method is the activated MnO_2 mediated one, other oxidizing agents - $KMnO_4$, $K_2Cr_2O_7$, $KBrO_3$ - being less effective. Attempted direct conversion of chlorides (**2a-d**) to aldehydes (**4a-d**) either failed (with hexamethylenetetramine) or resulted in low yields (with DMSO and $NaHCO_3$ at 110 ^oC). As indole-5-methanesulfonic acids (**1a-d**) are easily accessible from diazotized 4-aminophenylmethanesulfonic acid (**6**) in 60-80% yield through the Japp-Klingemann method followed by Fischer synthesis[2] (Scheme 2), the overall procedure to 5-formylindoles applies only acidic or neutral conditions. The Fischer indolization of hydrazones (**7e**) and (**7f**) gives carboxylic acids (**1e**) and (**1f**), respectively. In order to avoid the formation of acid chlorides, the carboxyl group has to be protected as CO_2Me to give **1b** and **1c**, respectively, prior to the reaction with $SOCl_2$ (Scheme 2).

In summary, the transformation of indole-5-methanesulfonates (**1a-d**) to chloromethylindoles (**2a-d**) followed by hydrolysis and oxidation provides a general and regioselective methodology to achive the synthesis of highly substituted 5-formylindoles (**4a-d**). This method has the advantages of ready accessibility of the reagents, absence of side reactions, good yields and experimental simplicity.

Scheme 2



5a, e, f, d **6** **7a, e, f, d** **1a-f**

5a R^1=Me, R^2=CH_2NMe_2
e R^1+R^2=CH_2
f R^1+R^2=$(CH_2)_2$
d R^1=OH, R^2=Et

7a R^3=CH_2NMe_2
e R^3=CH_2CO_2H
f R^3=$(CH_2)_2CO_2H$
d R^3=Et

1a R=NMe_2
e R=CO_2H → i → **b** R=CO_2Me
f R=CH_2CO_2H → i → **c** R=CH_2CO_2Me
d R=Me

Reagents and conditions: i) MeOH, $SOCl_2$, -15 ^oC to 40 ^oC, 4 h

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EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded at 250 MHz and 62.5 MHz, respectively, on a Bruker AC 250 spectrometer. All δ values are given in ppm, in $CDCl_3$ as solvent, TMS was used as an internal standard. HRMS spectra were measured on a MAT 312 instrument equipped with a MASPEC II[32] data system (FAB, V/E scan). IR spectra were measured on Perkin-Elmer 1600 series FTIR spectrophotometer in KBr discs. All chemicals were reagent grade and used without further purification. Compounds (**1a-f**) and (**2a-d**) were prepared as described in ref (2).

General Procedure for preparation of **3a-d**:

The chloromethylindole (**2a-d,** 1 mmol) was dissolved (in case of **2a** suspended) in dry CH_2Cl_2 (30 mL) and added dropvise to the stirring mixture of ice (10 g) and $KHCO_3$ (3 g) over a period of 10 min. In case of **2a**, K_2CO_3 (0.3 g) was then added to the aqueous phase. Stirring was continued for 10 min, then the

organic phase was separated and dried over $MgSO_4$ to give, after rotary evaporation, pure **3a-d**. **3a** (89%), mp: 128-130 ^{O}C (EtOH); ^{1}H NMR: 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); ^{13}C NMR: δ 14.96, 22.82, 45.27, 60.37, 60.82, 64.31, 112.91, 118.43, 121.26, 124.10, 125.46, 127.63, 134.45, 136.33, 162.42; IR: 3330, 1674, 1259 cm^{-1}; *Anal*. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 65.81; H, 7.59; N, 9.48.

3b (93%), mp: 116-118 ^{O}C (hexane-EtOAc 5:1); ^{1}H NMR: δ 1.42 (3H, t, *J*=7 Hz), 2.68 (2H, m), 3.39 (2H, m), 3.65 (3H, s), 4.42 (2H, q, *J*=7 Hz), 4.73 (2H, s), 7.36 (2H, s), 7.70 (1H, s), 8.92 (1H, s); ^{13}C NMR: δ 14.29, 20.38, 35.16, 47.55, 51.64, 61.03, 112.54, 120.85, 122.55, 124.31, 126.52, 127.42, 129.40, 135.76, 162.14, 173.63; IR: 3328, 1737, 1689, 1262 cm^{-1}; HRMS Found: 305.1262. Calcd for $C_{16}H_{19}NO_5$ (M^+): 305.12632.

3c (75%), mp: 107-109 ^{O}C (EtOAc); ^{1}H NMR: δ 1.42 (3H, t, *J*=7 Hz), 2.02 (2H, m), 2.37 (2H, m), 3.14 (2H, m), 3.65 (3H, s), 4.41 (2H, q, *J*=7 Hz), 4.73 (2H, s), 7.35 (1H, s), 7.36 (1H, s), 7.67 (1H, s), 8.82 (1H, s); ^{13}C NMR: δ 14.36, 23.90, 25.90, 33.57, 47.52, 51.83, 60.93, 112.41, 121.00, 123.76, 124.23, 126.53, 127.84, 129.37, 135.70, 162.30, 174.04; IR: 3331, 1736, 1688, 1257 cm^{-1}; *Anal*. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.54; H, 6.68; N, 4.28.

3d (92%), mp: 140-142 ^{O}C (hexane-EtOAc 9:1); ^{1}H NMR: δ 0.98 (3H, t, *J*=5 Hz), 1.42 (3H, t, *J*=7 Hz), 1.66 (2H, m), 3.06 (2H, m), 4.40 (2H, q, *J*=7 Hz), 4.74 (2H, s), 7.35 (2H, s), 7.67 (1H, s), 8.81 (1H, s); ^{13}C NMR: δ 14.20, 14.36, 24.24, 26.66, 47.62, 60.84, 112.31, 121.24, 124.05, 125.26, 126.41, 128.04, 129.13, 135.72, 162.57; IR: 3312, 1680, 1263 cm^{-1}; *Anal*. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.84; H, 7.48; N, 5.21.

General Procedure for preparation of **4a-d**:

The alcohol (**3a-d**, 1 mmol) was stirred in CH_2Cl_2 (40 mL) with activated MnO_2 (2 g) at rt for 48 h, then the reaction mixture was filtered, the MnO_2 washed with CH_2Cl_2 (10 mL) and the combined solution was evaporated to give pure **4a-d**. **4a** (87%), mp: 123-125 ^{O}C (hexane); ^{1}H NMR: δ 1.39 (3H, t, *J*=7 Hz), 2.38 (6H, s), 2.64 (2H, m), 3.30 (2H, m), 4.39 (2H, q, *J*=7 Hz), 7.31 (1H, d, *J*=8.6 Hz), 7.76 (1H, dd, *J*=8.6 Hz, *J*=1.3 Hz), 8.17 (1H, d, *J*=1.3 Hz), 9.97 (1H, s), 10.12 (1H, br s); ^{13}C NMR: δ 14.42, 22.95, 45.33, 60.15, 61.16, 112.60, 123.72, 124.82, 125.49, 126.47, 127.68, 129.67, 139.31, 161.98, 192.02; IR: 3312, 1687, 1262 cm^{-1}; HRMS Found: 289.1557. Calcd for $C_{16}H_{21}N_2O_3$ $(M+H)^+$: 289.15522. *Anal*. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.60; H, 6.88; N, 9.61.

4b (81%), mp: 126-128 ^{O}C (EtOAc); ^{1}H NMR: δ 1.42 (3H, t, *J*=7 Hz), 2.69 (2H, m), 3.38 (2H, m), 3.62 (3H, s), 4.40 (2H, q, *J*=7 Hz), 7.42 (1H, d, *J*=8.6 Hz), 7.84 (1H, d, *J*=8.6 Hz), 8.25 (1H, s), 9.72 (1H, br s),

10.02 (1H, s); ^{13}C NMR: δ 14.27, 20.28, 35.03, 51.67, 61.36, 112.66, 124.25, 124.97, 125.31, 126.70, 127.44, 129.95, 139.05, 161.80, 173.34, 192.07; IR: 3304, 2917, 1733, 1686, 1257 cm^{-1}; HRMS Found: 303.1110. Calcd for $C_{16}H_{17}NO_5$ (M^+): 303.11067. *Anal*. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 62.95; H, 5.58; N, 4.40.

4c (85%), mp: 109-111 ^{O}C (EtOAc); ^{1}H NMR: δ 1.43 (3H, t, *J*=7 Hz), 2.04 (2H, m), 2.38 (2H, m), 3.20 (2H, m), 3.65 (3H, s), 4.43 (2H, q, *J*=7 Hz), 7.46 (1H, d, *J*=8.6 Hz), 7.87 (1H, d, *J*=8.6 Hz), 8.23 (1H, s), 9.16 (1H, br s), 10.04 (1H, s); ^{13}C NMR: δ 14.35, 23.86, 25.93, 33.52, 51.53, 61.24, 112.53, 125.17 (two overlapping signals), 125.37, 126.54, 127.82, 129.92, 139.01, 161.86, 173.84, 192.00; IR: 3307, 1732, 1672, 1260 cm^{-1}; HRMS Found: 317.1257. Calcd for $C_{17}H_{19}NO_5$ (M^+): 317.12632. *Anal*. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.14; H, 6.10; N, 4.24.

4d (88%), mp: 131-133 ^{O}C (hexane); ^{1}H NMR: δ 0.98 (3H, t, *J*=5 Hz), 1.43 (3H, t, *J*=7 Hz), 1.76 (2H, m), 3.07 (2H, m), 4.43 (2H, q, *J*=7 Hz), 7.45 (1H, d, *J*=8.3 Hz), 7.85 (1H, d, *J*=8.3 Hz), 8.22 (1H, s), 9.36 (1H, br s), 10.03 (1H, s); ^{13}C NMR: δ 14.15, 14.31, 24.32, 26.64, 61.14, 112.51, 125.02, 125.10, 126.65, 126.78, 128.00, 129.70, 139.22, 162.32, 192.12; IR: 3314, 1672, 1260 cm^{-1}; HRMS Found: 259.1204. Calcd for $C_{15}H_{17}NO_3$ (M^+): 259.12084. *Anal*. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.17; H, 6.55; N, 5.32.

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