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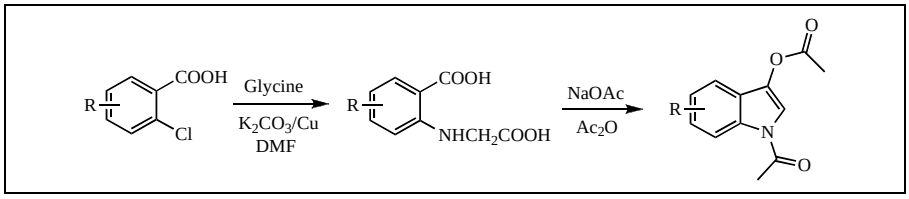

An efficient two steps procedure for the synthesis of 1-acetyl-1*H*-indol-3-yl acetates, starting from 2-chlorobenzoic acids, was developed and in general, moderate to good yields were obtained.

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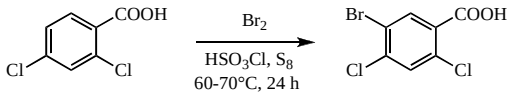
INTRODUCTION

Different indoxyl moieties are present as aglicons in different chromogenic compounds which are very useful to identify certain microorganisms [1,2,3]. In the literature [4] the preparation of most of them consists of five to six steps of synthesis starting from the commercially available toluidines or anthranilic acids. For this procedure long reaction time is required for the aminoalkylation step and poor yields are obtained [5], even in the case of 1-acetyl-1*H*-indol-3-yl acetate [6]. In a previous work we described an improved two steps procedure for obtaining **3b** starting from 2,4-dichlorobenzoic acid [7]. Encouraged by this result, we decided to carry out the preparation of other substituted 1-acetyl-1*H*-indol-3-yl acetate derivatives starting from the corresponding 2-chloro benzoic acids.

RESULTS AND DISCUSSION

Most of the 2-chlorobenzoic acids employed in this work are commercially available. 5-Bromo-2,4-dichlorobenzoic acid (**1a**) had to be prepared. The only procedure described in literature to synthesize **1a** does not give full experimental details, used a large quantity of chlorosulfonic acid and **1a** was only characterized by its melting point [8]. In order to carry out the synthesis of **1a** we followed the described procedure using less than the half of chlorosulfonic acid from the literature. The reaction took place with total consumption of the bromine and almost all the starting 2-chlorobenzoic acid within 24 hours giving **1a** in 95 % yield (Scheme I).

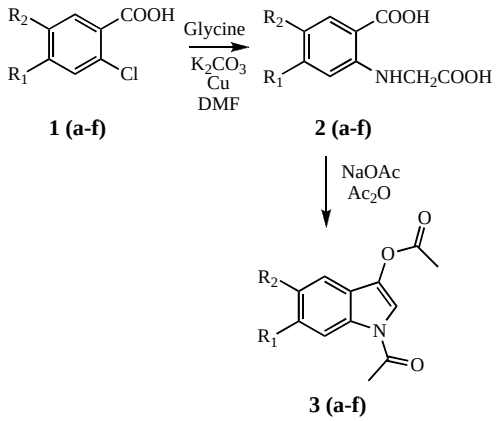
Scheme I



1a

The condensation step between 2-chlorobenzoic acids (**1a-f**) and glycine took place from two to six hours with good yields and purity of the obtained 2-[(carboxymethyl) amino]benzoic acids (**2a-f**) (Scheme II).

Scheme II



1 (a-f) **2 (a-f)** **3 (a-f)**

a R_1 = Cl, R_2 = Br; **b** R_1 = Cl, R_2 = H; **c** R_1 = H, R_2 = Cl; **d** R_1, R_2 = H; **e** R_1 = H, R_2 = NO_2; **f** R_1 = NO_2, R_2 = H

Subsequent Rössing cyclodecarboxylation [9] with sodium acetate in acetic anhydride at reflux gave the corresponding 1-acetyl-1*H*-indol-3-yl acetates (**3a-f**) with moderated to good yields. Only for compound **3d** lower yields were obtained. In general no further purification was necessary.

Table 1

Analytical data of prepared 2-[(carboxymethyl) amino] benzoic acids

Compound	Time (h)	Yield (%)	Mp_{lit} (°C) Mp_{obt} (°C)	NMR data.
2a	4	71	230 [4] 238	^{1}H nmr: δ 13.06 (s, 2H, 2COOH), 8.22 (s, 1H, N-H), 8.00 (s, 1H, 6-H), 6.90 (s, 1H, 3-H), 4.05 (s, 2H, CH_2) ^{13}C nmr: δ 171.00, 167.69, 149.59, 138.63, 135.55, 113.21, 111.30, 104.56, 44.10
2b	6	84	228 [10] 225	^{1}H nmr: δ 7.88 (d, 1H, 6-H, J= 8.5), 6.62 (dd, 1H, 4-H, $J_{4,6}$ = 8.5, $J_{4,3}$ = 1.9), 6.53 (d, 1H, 3-H, $J_{1,3}$ = 1.9), 3.97 (s, 2H, CH_2) ^{13}C nmr: δ 171.6, 169.6, 150.3, 140.3, 133.3, 115.3, 110.5, 109.2, 44.67.
2c	3	87	210 [5] 210-215	^{1}H nmr: δ 8.15 (s, 1H, N-H), 7.62 (d, 1H, 6-H, J=2.53), 7,24 (dd, 1H, 4-H, J=2.53 and J=8.95), 6.82 (d, 1H, 3-H, J=8.95), 4.16 (s, 2H, CH_2) ^{13}C nmr: δ 171.62, 168.10, 149.57, 133.26, 129.71, 122.40, 120.92, 118.45, 47.46.
2d	2	53	220 [11] 220	^{1}H nmr: δ 7.91 (d, 1H, Ph-H, J= 7.95), 7.33 (m, 1H, Ph-H), 6.57 (m, 2H, Ph-H), 3.95 (s, 2H, CH_2). ^{13}C nmr: δ 172.28, 150.49, 134.94, 132.15, 129.77, 129.08, 115.26, 112.03, 44.67.
2e	2	97	226-227 [12] 222-223	^{1}H nmr: δ 8.05 (m, 2H, Ph-H), 7.37 (m, 2H, Ph-H), 4.10 (s, 2H, CH_2) ^{13}C nmr: δ 171.04, 168.65, 154.31, 135.47, 129.59, 128.68, 112.64, 109.92, 44.54.
2f	2	75	240-242 [13][a] 243-244[b]	^{1}H nmr: δ 8.35 (s, 1H, N-H), 8.00 (d, 1H, Ph-H, J=8.5), 7.34-7.30 (m, 2H, Ph-H), 4.10 (s, 2H, CH_2) ^{13}C nmr: δ: 171.77, 168.99, 151.67, 150.72, 133.82, 115.92, 109.02, 106.38, 44.66.

[a] From water [b] From absolute ethanol.

Table 2

Analytical Data of prepared 1-acetyl-1*H*-indol-3-yl acetates

Compound	Yield (%)	Mp_{lit} (°C) Mp_{obt} (°C).	NMR data
3a	64	176 [4] 171-172	^{1}H nmr: δ 8.51 (s, 1H, Ph-H), 7.99 (s, 2H, Ph-H and pyrrole-H), 2.62 (s, 3H, $NCOCH_3$), 2.39 (s, 3H, $OCOCH_3$) ^{13}C nmr: δ 172.24, 169.86, 132.29, 131.89, 129.92, 124.33, 122.84, 118.37, 117.52, 116.28, 23.76, 20.71.
3b	45	112-113 [4] 111-113	^{1}H nmr: δ 8.34 (d, 1H, 7-H, J= 1.9), 7.90 (s, 1H, 2-H), 7.52 (d, 1H, 4-H, J= 8.5), 7.34 (dd, 1H, 5-H, J= 1.9, J= 8.5), 2.61 (s, 3H, CH_3, $NCOCH_3$), 2.28 (s, 3H, $OCOCH_3$) ^{13}C nmr: δ 169.36, 167.95, 133.02, 132.57, 130.08, 123.56, 122.27, 119.06, 116.33, 115.59, 23.36, 20.25.
3c	45	130 [4] 134-135	^{1}H nmr: δ 8.3 (d, 1H, Ph-H, J= 8.95), 7.91 (s, 1H, pyrrole-H), 7.57 (d, 1H, Ph-H, J= 2.07), 7.36 (dd, 1H, J= 8.95 and J= 2.07), 2.62 (s, 3H, $NCOCH_3$), 2.39 (s, 3H, $OCOCH_3$) ^{13}C nmr: δ 169.96, 168.91, 133.14, 131.56, 131.57, 128.53, 126.03, 125.58, 118.05, 117.95, 24.06, 20.98.
3d	10	83 [4], 88 [14] 84-86	^{1}H nmr: δ 8.36 (d, 1H, Ph-H, J= 7.9), 7.90 (s, 1H, Pyrrole-H), 7.41 (m, 3H, Ph-H), 2.62 (s, 3H, $NCOCH_3$), 2.39 (s, 3H, $OCOCH_3$) ^{13}C nmr: δ 169.29, 168.18, 133.43, 132.44, 125.53, 123.46, 123.34, 117.64, 115.90, 115.50, 23.57, 20.37.
3e	70	219-220 [12] 221-222	^{1}H nmr: δ 8.55 (m, 2H, Ph-H), 8.27 (d, 1H, Ph-H, J= 9.15), 8.15 (s, 1H, Pyrrole-H), 2.68 (s, 3H, $NCOCH_3$), 2.44 (s, 3H, $OCOCH_3$) ^{13}C nmr: δ 170.14, 168.66, 143.72, 135.50, 133.64, 124.04, 120.89, 119.58, 116.94, 114.62, 24.04, 20.79.
3f	57	195 [15] 195-198	^{1}H nmr: δ 9.18 (d, 1H, Ph-H, J= 1.83), 8.29 (s, 1H, Pyrrole-H), 8.21-8.17 (m, 1H, Ph-H), 7.77 (d, 1H, Ph-H, J= 9.15), 2.70 (s, 3H, $NCOCH_3$), 2.48 (s, 3H, $OCOCH_3$) ^{13}C nmr: δ: 169.73, 168.14, 144.92, 132.62, 130.95, 128.09, 121.60, 118.57, 118.40, 111.82, 23.46, 20.31.

The 1-acetyl-1*H*-indol-3-yl acetates (**3a**, **3b**, **3c**, **3e** and **3f**) were synthesized with an overall yield ranging from 38% to 68%.

EXPERIMENTAL

Thin layer chromatography (TLC) were performed on Silicagel plates ALUGRAM Sil G/UV 254 and $CHCl_3$:AcOEt:AcOH (8:6:1) as the solvent system. The TLC plates were visualized by means of a Bioblock lamp with a wavelength of 254 nm. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250F spectrometer in deuterated dimethylsulfoxide as solvent. The coupling constants are in Hz. Melting points were determined on a Stuart Scientific SMP 3 capillary melting point apparatus and were uncorrected

Synthesis of 5-bromo-2,4-dichloro benzoic acid (1a). 5 g (26.2 mmol) of 2,4-dichlorobenzoic acid were added to 20 mL of chlorosulfonic acid and when all was disolved, 0.05 g (0.2 mmol) of sulfur and 0.67 mL (13.1 mmol) of bromine were added. The mixture was heated at 60-70°C during 24 h. After total consumption of bromine the mixture was carefully poured onto ice. The mixture was stirred and the precipitate obtained was collected, washed with cold water and dried at 50°C to constant weight. The white powder was recrystallized from cyclohexane yielding 6.7 g (95 %) of **1a** as colorless crystals, mp. 177-178°C, lit.[8] 187-189°C (from water). ^1H nmr: δ 8.15 (s, 1H, *H*-Ph), 7.96 (s, 1H, *H*-Ph). ^{13}C nmr: δ 164.87, 137.00, 135.32, 132.17, 132.11, 131.70, 120.51.

General procedure for the synthesis of 2-[(carboxymethyl) amino] benzoic acids. To a suspension of 11.11 mmol of the corresponding 2-chlorobenzoic acid (**1a**, **1b**, **1c**, **1d**, **1e**, **1f**), 28.11 mmol of glycine and 1.27 mmol of copper powder in 10.6 mL of dimethylformamide, was slowly added 33.3 mmol of potassium carbonate. The mixture was heated at reflux with a good stirring between 2 and 6 hours (see Table 1). When all the corresponding 2-chlorobenzoic acid had been consumed, the mixture was poured onto 30 mL of cold 6 *M* hydrochloric acid and stirred for 30 min. The precipitate obtained was collected and washed with cold water until neutral pH. The solid was dried at 50°C to constant weight affording the product (see yields in Table 1).

General procedure for the synthesis of 1-acetyl-1*H*-indol-3-yl acetates from 2-[(carboxymethyl) amino] benzoic acids. A mixture 8.36 mmol of the corresponding 2-[(carboxymethyl)-amino]benzoic acid (**2a**, **2b**, **2c**, **2d**, **2e**, **2f**) 12.8 mL of acetic anhydride and 32.06 mmol of dry sodium acetate were heated at reflux. When the gas evolution had finished, the mixture while still hot was poured into a beaker and left to cool overnight at 0°C. The precipitate was collected and poured into 35 mL of ice water and stirred for 1 h, collected again and dried in vacuum to yield the corresponding 1-acetyl-1*H*-indol-3-yl acetates (**3a**, **3b**, **3c**, **3d**, **3e**, **3f**) (see Table 2).

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