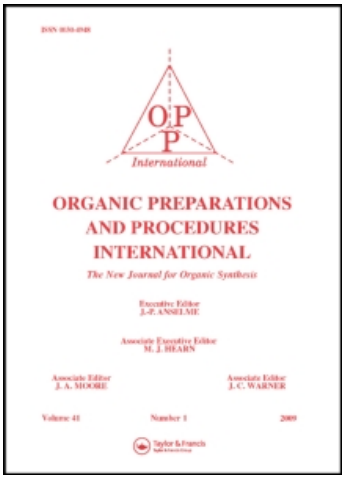

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SYNTHESIS OF N-PROTECTED 1*H*-INDOLE-5-CARBOXYLIC ACIDS WITH ALDOSE REDUCTASE INHIBITORY POTENTIAL

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SYNTHESIS OF N-PROTECTED 1*H*-INDOLE-5-CARBOXYLIC ACIDS WITH ALDOSE REDUCTASE INHIBITORY POTENTIAL

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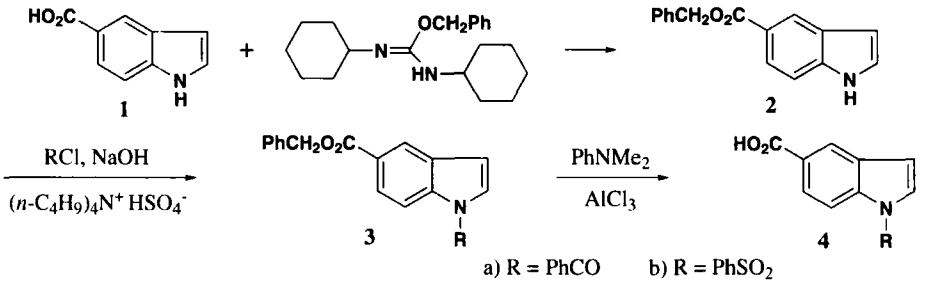
Indole carboxylic acids are useful building blocks for the preparation of bioactive compounds.[1-3] In these syntheses, selective functionalization of either the carboxylic acid or the indolyl-NH is often required. Based on the above considerations, the present work describes the preparation of 1-benzoyl- and 1-benzenesulfonyl-1*H*-indole-5-carboxylic acids (**4a** and **4b**). We consider these compounds as useful organic synthons and they contain important functionalities for a putative aldose reductase enzyme inhibitory activity.[4] Aldose reductase (ALR2) is implicated in chronic diabetic complications.[5]

Our initial attempt to synthesize these compounds involved a haloform reaction[6] of 1-benzoyl- or 1-benzenesulfonyl-5-acetylindoles. This route was selected because we had recently reported[7] a convenient two-step preparation of 5-acetylindole from indole. However, all attempts to isolate the desired carboxylic acids were unsuccessful, due to the extensive decomposition under these conditions. An alternative synthetic strategy involving the condensation of the commercially available 1*H*-indole-5-carboxylic acid (**1**) with O-benzyl-1,3-dicyclohexylisourea,[8-10] gave the corresponding benzyl ester **2** in excellent yield; no substitution on the heterocyclic ring was observed. In addition, this procedure gives better results than the previously reported Mitsunobu type esterification.[3] The introduction of the N-benzoyl- or the N-benzenesulfonyl-substituent was achieved under phase-

transfer catalysis conditions.[11] Finally, the selective cleavage of the benzyl ester bond of **3a** and **3b** was accomplished with the combination of N,N-dimethylaniline and aluminum chloride.[12] All attempts to hydrogenolytically cleave these esters using hydrogen transfer reagents[13,14] or by catalytic hydrogenation in a Parr apparatus,[10] in various solvents invariably resulted in either no reaction or in partial reduction to the indoline in addition to hydrogenolysis. In contrast, it is worth noting that it has been reported that the hydrogenolysis of 1-benzoyl-1*H*-indole-4-carboxylic acid benzyl ester proceeded in nearly quantitative yield in ethyl acetate,[10] without indoline formation.



Finally, compounds **4a** and **4b** were screened for their ability to inhibit partially purified ALR2 obtained from rat lens.[5] We found that at a concentration of 100 μM, they inhibited the enzyme by 57% (SEM = 4, n = 3) and 43% (SEM = 5, n = 3), respectively. Thus, they might become useful synthetic units in the preparation of ALR2 inhibitors.

EXPERIMENTAL SECTION

Mps are uncorrected and were determined in open glass capillaries using a Mel-Temp II apparatus. UV spectra were recorded on a Perkin-Elmer 554 spectrophotometer, IR spectra were obtained on a Perkin-Elmer 597 spectrophotometer and ^{1}H NMR spectra on a Bruker AW-80 spectrometer with internal TMS standard. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer.

1*H*-Indole-5-carboxylic Acid Benzyl Ester (2).- A mixture of 1*H*-indole-5-carboxylic acid (**1**) (2.5 g, 15.5 mmol) and 2-benzyl-1,3-dicyclohexylisourea[8] (5.35 g, 17 mmol) in dioxane (100 mL), was heated for 3 h at 65-70°, under a N_2 atmosphere. Then 200 mL of CH_2Cl_2 were added and the resulted mixture was filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ solution (1 x 100 mL), saturated NaCl solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from toluene/petroleum ether to yield 3.12 g (80%) of a white solid, mp. 126-127°, *lit.*[3] 127-129°. IR (Nujol, cm^{-1}): 3300 (NH), 1675 (CO). ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 2H, $COOCH_2$), 6.50-6.70 (m, 1H, indole C-3-H), 7.15-7.60 (m, 7H, indole C-2-H, C-7-H and phenyl-H), 7.80-8.05 (m, 2H, indole C-4-H and C-6-H), 8.45 (br s, 1H, NH).

N-Substituted Indole-5-carboxylic Acid Benzyl Esters (3). General Procedure.- To a well stirred suspension of 1*H*-indole-5-carboxylic acid benzyl ester (**2**) (5 mmol), powdered NaOH (0.71 g, 17.8

mmol) and tetrabutylammonium hydrogen sulfate (0.024 g, 0.07 mmol) in CH_2Cl_2 (30 mL), a solution of benzoyl chloride or benzenesulfonyl chloride (5.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise, under a N_2 atmosphere, while the temperature of the reaction mixture was maintained below 15°. Stirring was continued for an additional hour at the same temperature. The resulting suspension was filtered by gravity and the filtrate was evaporated under reduced pressure. The residue was recrystallized from toluene/petroleum ether.

Benzoyl-1H-indole-5-carboxylic acid benzyl ester (**3a**), 70% yield of colorless solid, mp. 101-102°. IR (Nujol, cm^{-1}): 1695, 1660 (CO). ^1H NMR ($CDCl_3$): δ 5.35 (s, 2H, $COOCH_2$), 6.50-6.70 (m, 1H, indole C-3-H), 7.20-8.40 (m, 14H, Ar-H).

Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.52; H, 4.78; N, 4.04

Benzenesulfonyl-1*H*-indole-5-carboxylic acid benzyl ester (**3b**), 82% yield of colorless solid, mp. 115-116°. IR (Nujol, cm^{-1}): 1700 (CO). ^1H NMR, ($CDCl_3$): δ 5.35 (s, 2H, $COOCH_2$), 6.65-6.80 (m, 1H, indole C-3-H), 7.25-8.30 (m, 14H, Ar-H).

Anal. Calcd for $C_{22}H_{17}NO_4S$: C, 67.50; H, 4.38; N, 3.58. Found: C, 67.19; H, 4.14; N, 3.78.

N-Substituted Indole-5-carboxylic Acids (4). General Procedure.- To a solution containing either compound **3a** or compound **3b** (3.8 mmol) and N,N-dimethylaniline (2.3 g, 19 mmol) in CH_2Cl_2 (15 mL), was added anhydrous aluminum chloride (1.52 g, 11.4 mmol) and the resulting mixture was stirred for 2 h at room temperature under a N_2 atmosphere. It was poured into a mixture of H_2O and ice (~20 mL), the two phases were separated and the aqueous layer was extracted with EtAc (2 x 30 mL). The combined organic layer and extracts were washed with an 1N solution of HCl (2 x 50 mL), saturated NaCl solution, dried over $NaSO_4$ and concentrated under reduced pressure. The residue was recrystallized from toluene/petroleum ether.

Benzoyl-1*H*-indole-5-carboxylic acid (**4a**), 56% yield of colorless solid, mp. 241°. IR (Nujol, cm^{-1}): 3300-2500 (OH), 1670 (CO), 1655 (CO). ^1H NMR ($CDCl_3$/DMSO-d_6): δ 6.65-6.85 (m, 1H, indole C-3-H), 7.30-8.45 (m, 10H, ArH and COOH).

Anal. Calcd for $C_{16}H_{11}NO_3 \cdot 0.3H_2O$: C, 71.00; H, 4.31; N, 5.17. Found: C, 70.95; H, 4.26; N, 5,18

Benzenesulfonyl-1*H*-indole-5-carboxylic acid (**4b**), 73% yield of colorless solid, mp. 193-195°. IR (Nujol, cm^{-1}): 3300-2500 (OH), 1670 (CO). ^1H NMR, ($CDCl_3$): δ 6.75-6.90 (m, 1H, indole C-3-H), 7.45-8.45 (m, 10H, ArH and COOH).

Anal. Calcd for $C_{15}H_{11}NO_4S \cdot 0.4H_2O$: C, 58.39; H, 3.85; N, 4.54. Found: C, 58.42; H, 3.82; N, 4.48

Aldose Reductase Enzyme Assay.- The assay was performed as previously described.[5] The test compounds were dissolved in 10% Me_2SO. Sorbinil was used as a reference compound.

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PREPARATION OF 3-(TRIFLUOROMETHYL)COUMARINS

Submitted by (11/10/01)

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Coumarins constitute an important class of naturally occurring compounds with useful pharmacological activity.[1,2] Numerous coumarins were used as steroid receptor modulators[3] and photopolymerization initiators[4]. Some attention has been paid to trifluoromethyl substituted coumarins as fluorescent markers for synthetic proteinases[5,6] and also as laser dyes.[7] Recently, a