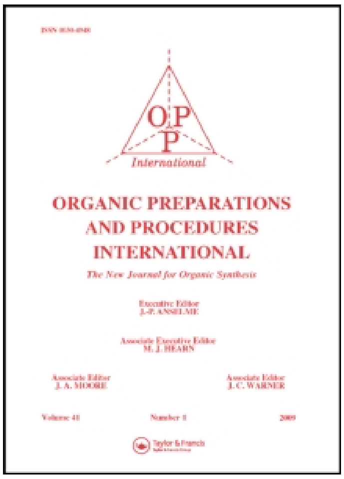

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AN IMPROVED SYNTHESIS OF INDOLE-3-CARBOXYLIC ACIDS

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AN IMPROVED SYNTHESIS OF INDOLE-3-CARBOXYLIC ACIDS

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The more useful of the numerous methods available for preparation of indole-3-carboxylic acids III involve carbonation of metal salts of indoles,[1,2,3,4] decarbonylation and hydrolysis of 3-indoleglyoxaloyl chlorides,[4,5] reaction of potassium salts of isatic acids with dimethylsulfonium methylide,[6] and basic hydrolysis of 3-indolyltrifluoromethyl ketones (II).[7]

The intermediate ketones II of the last named procedure have been prepared in moderate yield by treatment of indoles with trifluoroacetonitrile (modified Hoesch reaction) and more recently by heating a variety of indoles with trifluoroacetic anhydride in sealed vessels.[8] Improved yields of II with the latter reagent have now been obtained in polar, water-miscible solvents, such as dimethylformamide (DMF) and tetrahydrofuran (THF), without the use of sealed vessels.

The preparation of III from indoles via II (see Tables 1 and 2) has thus become a convenient and efficient procedure.

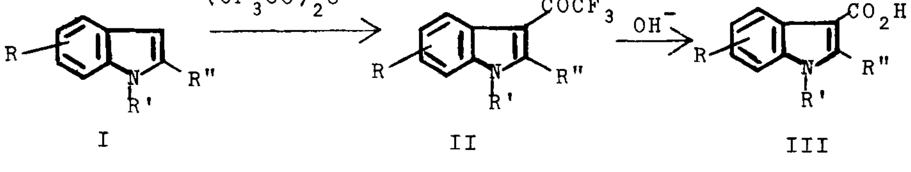

TABLE 1[a]

3-Indolyltrifluoromethyl Ketones

Substituents on Indole Ring				%	Recrystal-	
R	R'	R"	Solvent	Yield of II	lization Solvent	mp.[b]
H	H	H	DMF, THF, MeCN, DMSO, DMAC, Me_2CO	85-95	ether-benzene	209-212[c]
H	$-(CH_2)_2CO_2H$	H	DMF	90	ether-hexane	186-189
H	Me	H	DMF	63	benzene-hexane	101-102[d]
5-MeO	H	Me	DMF	82	benzene	186.5-188.5[e]
5-Br	H	H	DMF	85	methanol	253-255
5,6-OCH_2O-	H	H	DMF	80	methanol	272-275[f]

a) Analytical and physical data on compounds in both tables with mp. marginally different from literature values are in agreement with the designated structures; b) uncorrected mp.; c) lit.,[7] mp. 214°; d) lit.,[7] mp. 105°; e) lit.,[8] mp 185-185.5°; f) lit.,[7] mp. 268°.

TABLE 2

Indole-3-Carboxylic Acids

Substituents on Indole Ring			% Yield of	Overall % Yield of III	
R	R'	R"	III from II	From Indole I	mp.[a]
H	H	H	94	80-89	234-237 (dec.)[b]
H	H	H		74[c]	234-236 (dec.)
H	$-(CH_2)_2CO_2H$	H	85	76	197-200 (dec.)
H	Me	H	75	47	202-205 (dec.)[d]
5-MeO	H	Me	13[e]	11	189-192 (dec.)[f]
5-Br	H	H	79	67[g]	230-232 (dec.)[h]
5,6-OCH_2O-	H	H	73	58	215-217 (dec.)[i]

a) uncorrected mp.; b) lit.,[9] mp. 245-246° (dec.); c) Base hydrolysis was carried out on the indole-trifluoroacetic anhydride-DMF reaction mixture without isolation of 3-indolyltrifluoromethyl ketone; d) lit.,[10] mp. 205-206° (dec.); e) 74% of 2-methyl-5-methoxyindole isolated; f) lit.,[11] mp. 208° (dec.); g) Recrystallized from aqueous acetone; h) lit.,[4] mp. 238-240° (dec.); i) lit.,[7] mp. 239-240° (dec.).

EXPERIMENTAL SECTION

3-Indolyltrifluoromethyl Ketones. General Procedure.

A 30% solution of the indole in, preferably, DMF or THF is cooled in an ice bath and protected from moisture; 1.2 equivalents of trifluoroacetic anhydride is added dropwise with stirring. The solution is poured into 10 volumes of H_2O; the product is separated, washed with H_2O, dried at 80° under reduced pressure, and recrystallized from a suitable solvent (see Table 1).

3-Trifluoroacetyl-1-indolepropionic Acid.

Anal. Calcd for $C_{13}H_{10}F_3NO_3$: C, 54.74; H, 3.54; N, 4.91; F, 19.98. Found: C, 54.65; H, 3.30; N, 4.90; F, 20.17. Mol wt 285 (mass spectrum).

IR (nujol) C=O at 1709 cm^{-1} (carboxylic acid) and 1653 cm^{-1} (ketone); NMR (DMSO d_6) δ 2-proton triplet (J = 6.5 Hz) at 2.93 ($\rangle$N-CH_2-), 2-proton triplet (J = 6.5 Hz) at 4.64 (-CH_2-CO_2H), 5-proton multiplet between 7.33 and 8.60 (aromatic), very broad D_2O exchangeable absorption below 10.0.

5-Bromo-3-indolyl Trifluoromethyl Ketone.

Anal. Calcd for $C_{10}H_5BrF_3NO$: C, 41.12; H, 1.72; N, 4.79; F, 19.51. Found: C, 41.33; H, 1.89; N, 4.78; F, 19.77. Mol wt 292 (mass spectrum).

IR (nujol) N-H band at 3195 cm^{-1}, C=O at 1637 cm^{-1} (ketone). NMR (DMSO d_6) δ 5-proton multiplet at 7.40 to 8.37 (aromatic), 1-proton broad multiplet (exchangeable with D_2O) at 12.84 ($\rangle$N-H).

Hydrolysis of 3-Indolyltrifluoromethyl Ketones to Indole-3-carboxylic Acids. General Procedure.

A 10% solution of the indolyltrifluoromethyl ketone in 20% aq. NaOH is heated under reflux for 1 hr. The cooled solution is acidified with conc. HCl; the precipitated indole-3-carboxylic acid is separated, washed with H_2O, and dried at 100° in air.

3-Carboxy-1-indolepropionic Acid.

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.57; H, 4.70; N, 6.26. Mol wt 233 (mass spectrum).

IR (nujol) C=O at 1689 and 1626 cm^{-1} (carboxylic acids). NMR (DMSO d_6) δ 2-proton triplet (J = 6.5 Hz) at 2.87 ($>N-CH_2-$), 2-proton triplet (J = 6.5 Hz) at 4.51 ($-CH_2-CO_2H$), 5-proton multiplet at 7.18 to 8.30 (aromatic) and 2-proton broad singlet (exchangeable with D_2O) at 12.00 (2 CO_2H).

5-Methoxy-2-methyl-3-indolecarboxylic Acid.

mp. 189-192° (dec.) (lit.,[11] mp. 208°, dec.).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.14; H, 5.14; N, 6.77. Mol wt 205 (mass spectrum).

IR (nujol) N-H band at 3311 cm^{-1}, C=O at 1639 cm^{-1} (carboxylic acid). NMR (DMSO d_6) δ 3-proton singlet at 2.70 ($C-CH_3$), 3-proton singlet at 3.81 ($O-CH_3$), 3-proton multiplet at 6.70 to 7.62 (aromatic) and 2-proton broad singlet (exchangeable with D_2O) at 11.56 ($>N-H$ + $-CO_2H$).

5,6-Methylenedioxy-3-indolecarboxylic Acid.

mp. 215-127° (dec.) (lit.,[7] mp. 239-240°, dec.).

Anal. Calcd for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.45; H, 3.46; N, 6.59. Mol wt 205 (mass spectrum).

IR (nujol) N-H band at 3400 cm^{-1}, C=O at 1642 cm^{-1}. NMR (DMSO d_6) δ 2-proton singlet at 6.02 ($-O-CH_2-O-$), 1-proton singlet at 7.05 (C-4 proton), 1-proton singlet at 7.50 (C-7 proton), 1-proton doublet (*J* = 3 Hz) at 7.89 (C-2 proton), and 2-proton broad singlet (exchangeable with D_2O) at 11.62 ($>$N-H + CO_2H).

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