Simple *N*-Alkylation and *N*-Acylation of 3-Acetylindole and 3-Indolecarbaldehyde

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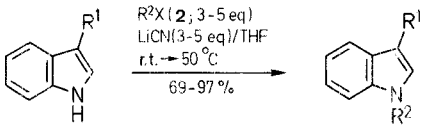
Using lithium cyanide a simple method for the transformation of 3-acetylindole into the *N*-alkyl, *N*-acyl, and *N*-*p*-toluenesulfonyl derivatives in good yield is reported. 3-Indolecarbaldehyde is also *N*-alkylated by the same procedure.

The methods reported for the synthesis of N-alkylindole-3-carbaldehydes involve the use of strong bases such as potassium *t*-butoxide in anhydrous *t*-butanol,[1] and potassium carbonate in dimethylformamide.[2] 3-(Pyrrolidinylmethylene)-3*H*-indole,[3] prepared from 3-indolecarbaldehyde and pyrrolidine in benzene under reflux with azeotropic removal of water, has been reported as an efficient intermediate for the preparation of *N*-alkyl and *N*-acyl-3-indolecarbaldehydes. Bohlmann observed that 4-(dimethylamino)pyridine is an effective catalyst for the *N*-acetylation of substituted pyrroles and indoles.[4] On the other hand, it is known that 3-acetylindole is alkylated by dialkylsulfate in aqueous sodium sulfate at elevated temperature.[5] Although a few methods for the *N*-alkylation and *N*-acylation of 3-acylindoles are available, no general synthetic method has been observed. Recently we reported a simple one-pot synthesis of silylated and acylated cyanohydrins of a variety of carbonyl compounds using lithium cyanide.[6] Application of this method (using acylchlorides and lithium cyanide) to 3-indolecarbaldehyde gave 1-acyl-3-(α-acyloxy)indoleacetonitriles, which are described in the preceding paper.[7]

In continuation of our studies on the utility of lithium cyanide in organic synthesis, we applied this method for the *N*-alkylation, acylation, and sulfonylation of 3-acetylindole as well as the *N*-alkylation of 3-indolecarbaldehyde. The scope of the new *N*-



1a $R^1 = COCH_3$
b $R^1 = CHO$

3a-3l

substitution procedures is shown in the Table. The alkylations of 3-acylindoles **1a, b** are in general performed by using 3–5 equivalents of lithium cyanide and 3 equivalents of alkylhalides, respectively, at room temperature in the cases of **1b** and at 50 °C in the cases of **1a** in tetrahydrofuran in high yields. Anhydrous acetonitrile can also be used as solvent, and reaction temperature (50 °C) brought about a considerable reduction in time (within 3 h) for the alkylation of **1b**. Acylations of **1a** were achieved very smoothly at room temperature, while it took longer reaction time for sulfonylation, and the yield was not satisfactory.

In summary, the advantage of the procedure described herein over that of others is that *N*-alkylation and *N*-acylation of 3-acylindoles proceed in a one-pot procedure under neutral reaction conditions without using any base.

1-Alkyl-3-acylindoles and 1-Acyl-3-acylindoles; General Procedure:
Lithium cyanide is added to a magnetically stirred solution of 3-acylindoles (1 mmol) in dry tetrahydrofuran (10 ml) at room tempera-

Table 1. *N*-Alkylation and Acylation of 3-Acetyl- and 3-Formylindoles

Product	R^1	R^2 [X]	Molar Ratio of **1**/**2**	Molar Ratio of **1**/LiCN	Reaction Conditions Time (h)/Temp. (°C)	Yield (%)	m.p. (°C)	Molecular Formula[a] or Lit. m.p. (°C)
3a	CH_3CO	CH_3 [I]	3	5	15/50	97	94–96	95[4]
3b	CH_3CO	CH_3CH_2 [I]	3	5	30/50	90	88–89	88[4]
3c	CH_3CO	CH_2=$CHCH_2$ [Br]	3	5	30/50	92	oil	$C_{13}H_{13}NO$ (199.2)
3d	CH_3CO	$C_6H_5CH_2$ [Br]	3	5	10/50	75	102–103	$C_{17}H_{15}NO$ (249.3)
3e	CHO	CH_3 [I]	3	3	5/25	95	66–68	68–69[1,3]
3f	CHO	CH_3CH_2 [I]	3	5	15/25	78	83–84	$C_{11}H_{11}NO$[8] (173.2)
3g	CHO	CH_2=$CHCH_2$ [Br]	3	5	4/25	89	65–66	$C_{12}H_{11}NO$ (185.2)
3h	CHO	$C_6H_5CH_2$ [Br]	3	5	5/25	85	108–109	113–114[2]
3i	CH_3CO	CH_3CO [Cl]	5	5	1/25	94	148–149	150–151[9]
3j	CH_3CO	CH_3CH_2CO [Cl]	3	3	3/25	95	116–117	$C_{13}H_{13}NO_3$ (231.2)
3k	CH_3CO	C_6H_5CO [Cl]	3	3	3/25	87	125–126	119[4]
3l	CH_3CO	$CH_3C_6H_4SO_2$ [Cl]	5	5	15/25	69	145–146	$C_{17}H_{15}NO_3S$ (313.4)

[a] Satisfactory microanalyses obtained: C ±0.18, H ±0.26, N ±0.15.

Table 2. Spectral Data of New 1-Alkyl- and 1-Acyl-3-Acyl Indoles Prepared

Product	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ (ppm)
3c	1640 (C=O)[a] 1610 (C=C)	2.53 (s, 3H, CH_3); 4.77 (m, 2H, CH_2); 5.20 (br d, 1H, J = 18 Hz, =CHH); 5.31 (br d, 1H, J = 10 Hz, =CHH); 6.03 (m, 1H, CH=CH_2); 7.31 (m, 3H$_{arom}$); 7.74 (s, 1H, 2-H); 8.40 (m, 1H, 4-H)
3d	1635 (C=O)	2.52 (s, 3H, CH_3); 5.36 (s, 2H, CH_2); 7.1–7.4 (m, 8H$_{arom}$); 7.76 (s, 1H, 2-H); 8.40 (m, 1H, 4-H)
3f[8]	1630 (C=O)	1.54 (t, 3H, J = 7.3 Hz, CH_2CH_3); 2.53 (s, 3H, CH_3); 4.20 (q, 2H, J = 7.3 Hz, CH_2CH_3); 7.31 (m, 3H$_{arom}$); 7.77 (s, 1H, 2-H); 8.39 (m, 1H, 4-H)
3g	1650 (C=O), 1610 (C=C)	4.79 (m, 2H, CH_2); 5.23 (br d, 1H, J = 17 Hz, =CHH); 5.35 (br d, 1H, J = 10 Hz, =CHH); 6.03 (m, 1H, CH=CH_2); 7.35 (m, 3H$_{arom}$); 7.72 (s, 1H, 2-H); 8.31 (m, 1H, 4-H); 10.01 (s, 1H, CHO)
3j	1755, 1665 (C=O)	1.52 (t, 3H, J = 7.3 Hz, CH_2CH_3); 2.58 (s, 3H, CH_3); 4.56 (q, 2H, J = 7.3 Hz, CH_2CH_3); 7.40 (m, 2H, 5-H, 6-H); 8.17 (m, 1H, 7-H); 8.17 (s, 1H, 2-H); 8.38 (m, 1H, 4-H)
3l	1660 (C=O), 1380, 1160 (SO_2)	2.37 (s, 3H, CH_3); 2.57 (s, 3H, CH_3); 7.2–7.9 (m, 7H$_{arom}$); 8.21 (s, 1H, 2-H); 8.32 (m, 1H, 4-H)

[a] Measured as film.

ture. After being stirred for 5 min, a solution of the halide (alkyl halides, acyl halides, or *p*-toluenesulfonyl chloride) in tetrahydrofuran (5 ml) is added. The reaction is monitored by TLC [silica gel (Merck Art. 5715), using benzene/ethyl acetate, 10:1, as eluent]. After the starting material has been consumed, the tetrahydrofuran is evaporated. The residue is partitioned between water (10 ml) and ethyl acetate (30 ml). The organic layer is separated, washed with water (2 × 10 ml), and dried with sodium sulfate. After concentrating the ethyl acetate layer, the residue is chromatographed on silica gel (Merck Art. 7734) column chromatography using benzene/ethyl acetate (10:1). The new compounds are recrystallized from isopropanol (Tables 1 and 2).

Received: 1 September 1986
(Revised form: 14 October 1986)

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