A Simple Synthesis of *N*-Alkylindoles

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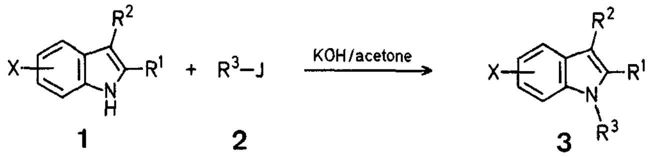
The most general method for the synthesis of *N*-alkylindoles and -pyrroles is the alkylation using either strong bases such as potassium[1] or sodium amide[2] in anhydrous solvents or potassium hydroxide in dimethyl sulfoxide[3]. Recently, it has been reported that the *N*-alkylation of indole derivatives is achieved using tetraalkylammonium salts[4] or crown ethers[5] as phase-transfer catalysts.

In the course of studies on the introduction of a methoxy group on to the benzene ring of indole derivatives[6], we required several *N*-alkylated indole derivatives (**3**). In a search for the most facile synthesis of *N*-alkylindole derivatives, we applied the method described in the preceding paper[7] with replacement of the acyl chlorides by alkyl iodides or benzyl chloride **2**. In the case of dimethoxyethane or tetrahydrofuran as solvent, the *N*-alkylation did not proceed in satisfactory yields; on the other hand, in acetone rapid and smooth *N*-alkylation of indole derivatives (**1**) was observed.



$R^3 = CH_3, C_2H_5, C_6H_5{-}CH_2{-}$

The reactions were complete within a few min at room temperature on using alkyl iodides (**2**). According to the literature[5,8], alkylation of metalloindole derivatives sometimes results in the formation of 1- and 3-alkylindole derivatives. In our case only 1-methylindole was obtained from the reaction of indole with methyl iodide; however, gas chromatographic analysis of the reaction mixture showed the presence of a trace of 3-methylindole. Although several methods of the *N*-alkylation of indole derivatives are available, our method has the advantages of mild reaction conditions, short reaction time, and easy work-up.

1-Ethylindole (3; R^1, R^2, X = H, $R^3 = C_2H_5$); Typical Procedure:
To an acetone solution (12 ml) of indole (**1**; R^1, R^2, X = H; 496 mg, 4.24 mmol) is added powdered potassium hydroxide (1.19 g, 21.2 mmol) with cooling. After few min, ethyl iodide (**2**; $R^3 = C_2H_5$; 1.32 g, 8.46 mmol) is added to the acetone solution with vigorous stirring and the reaction mixture is stirred for 10 min at room temperature. Benzene (90 ml) is added to the reaction mixture and insoluble materials are removed by filtration. The benzene solution is washed with saturated sodium chloride solution (20 ml) and dried with sodium sulfate. Benzene is evaporated and the residue is purified by silica gel column chromatography using benzene/hexane (1:1) for elution to give 1-ethylindole; yield: 541 mg (88%); b.p. 120 °C/21 torr; Ref.[4], b.p. 81–82 °C/0.5 torr.

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Table. *N*-Alkylation[a] of Indoles **1** by Methyl or Ethyl Iodide or Benzyl Chloride **2**

Product No.	R^1	R^2	X	R^3	Molar ratio of **1**:**2**	Reaction time [min]	Yield[b] [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	
								found	reported
3a	H	H	H	CH_3	1.1	10	80 (17)[c]	95°/8	73–74°/2[4]
3b	H	H	H	C_2H_5	2.0	10	88	120°/21	81–82°/0.5[4]
3c	H	H	H	$C_6H_5CH_2$	2.0	120	85 (11)	43–44° (ligroin)	44°[9]
3d	CH_3	H	H	CH_3	3.3	10	59 (26)	52–53° (ligroin)	54–55°[10]
3e	H	CH_3	H	CH_3	2.0	10	70 (21)	112°/8	119–120°/7[11]
3f	H	$CH_2COOC_2H_5$	H	CH_3	1.5	40	78	120°/0.095	165°/1[12]
3g	$—(CH_2)_4—$		4-Br	CH_3	1.1	8	83	100.5–101.5° (ether)	$C_{13}H_{14}BrN$ (264.2)[d]
3h	$—(CH_2)_4—$		5-Br	CH_3	1.1	8	76	73–74° (hexane)	$C_{13}H_{14}BrN$ (264.2)[d]
3i	$—(CH_2)_4—$		6-Br	CH_3	1.1	8	92	118–119° (hexane)	$C_{13}H_{14}BrN$ (264.2)[d]

[a] Acetone as solvent.

[b] Figures in brackets are amounts (%) of starting material recovered.

[c] In dimethoxyethane the yield is 35% (63%)[b] and in tetrahydrofuran 13% (71%)[b].

[d] Satisfactory microanalyses obtained (C, H, N ±0.3).

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