REGIO- AND CHEMOSELECTIVE ALKYLATION OF 2,3-DIALKYLINDOLES. A CONVENIENT PREPARATION OF 2,3,3-TRIALKYL-3H-INDOLES

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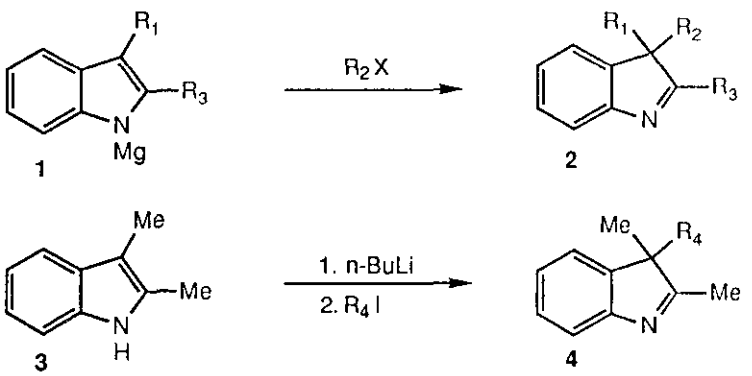
Abstract - Various 3-alkyl-2,3-dimethyl-3H-indoles were prepared by addition of an alkyl iodide to a solution of the lithium salt of 2,3-dimethylindole. In contrast, reaction with ethyl chloroformate or trimethylsilyl chloride afforded the N-substituted indoles exclusively. The reaction failed with cyclohexylcarboxaldehyde.

In connection with our interest in the cycloaddition chemistry of indolium methylides[1,2] we required access to a variety of 2,3,3-trialkyl-3H-indoles (**2**). Although a number of routes to this system have been reported,[3] the most common method appeared to be alkylation of the corresponding 2,3-dialkylindole magnesium salt[4] (**1**) (Scheme 1).



Scheme 1

However, although this reaction has been investigated with various alkyl halides[5] (usually bromides) we noted a severe limitation in the use of long chain alkyl iodides which completely failed to alkylate. This, coupled with the rather vigorous conditions also associated with the indole Grignard procedure prompted us to search for a more convenient and milder general alkylation method.

We describe here a simple and short procedure for the direct formation of 3-alkyl-2,3-dimethyl-3H-indoles (4) from the lithium salt of 2,3-dimethylindole.[3]

It was found that the lithium salt of 2,3-dimethylindole could be conveniently generated by the addition of a solution of n-butyllithium to a solution of 2,3-dimethylindole (**3**) in tetrahydrofuran (THF) at -78°C. After stirring for 30 min at -78°C the electrophile was added and the solution allowed to warm to room temperature and stirred for 2.5 h. Work up followed by flash chromatography[6] of the crude product afforded the corresponding 3-alkyl-2,3-dimethyl-3H-indole derivative (**4**). The results of a number of such experiments are summarised in Table 1.

Interestingly, the initial concentration of 2,3-dimethylindole was found to be critical. At initial concentration of less than 0.07 M no alkylated products could be isolated. However, an initial concentration of 0.28 M was found to be optimum; increasing the concentration further did not lead to any appreciable improvement in yield and led to inhomogeneity of the reaction mixture.

As can be seen from Table 1, alkyl iodides clearly favour formation of the C-3 alkylated product.[7] The reaction of allyl bromide similarly favours C-3 alkylation. The successful alkylation with hexyl iodide and 6-iodohexene is noteworthy since, as noted earlier, these electrophiles completely failed to undergo alkylation of the 2,3-dimethylindole magnesium salt. Reaction with secondary iodides affords 3-alkylated products in similar yield to those obtained with the indole Grignard.[8] Chemoselectivity is possible between mixed dihaloalkanes as shown by the formation of the 3-(3-chloropropyl)-3H-indole and allows selectivity not found with the indole Grignard reagent. In addition, the lithium salt of **3** is unreactive towards aldehydes as implied by the failure of the attempted addition to cyclohexylcarboxaldehyde. This contrasts with the behaviour of the corresponding indole Grignard[9] and may allow further chemoselectivity with polyfunctional electrophiles. In contrast to the alkylations, acylation with ethyl chloroformate occurred

Table 1. Alkylation of 2,3-DimethylIndoleLithium Salt

electrophile	conditions	conc *a*	product *b*	yield (%)
EtI	-78 -> rt	2.75	3	45
EtI	rt	2.75	3	58
EtI (2 eq.)	-78 -> rt	2.75	3	65
EtI	-78 -> rt	6.89	3	68
MeI	-78 -> rt	2.75	3	58
*i*PrI	-78 -> rt	2.75	3	36
allyl Br	-78 -> rt	2.75	3	70
hexyl I	-78 -> rt	2.75	3	46
hexenyl I	-78 -> rt	2.75	3	54
$Cl(CH_2)_3I$	-78 -> rt	2.75	3 $(CH_2)_3Cl$	65
EtO_2CCl	-78 -> rt	2.75	N	96
EtO_2CCl	-78 -> rt	2.75	N	98
TMSCl	-78 -> rt	2.75	N	89
$C_6H_{11}CHO$	-78 -> rt	2.75	_	_ *c*

a Concentration of lithium salt expressed as number of mmol in 10 ml of THF. *b* Position of alkylation.

c Quantitative recovery of 2,3-dimethylindole.

exclusively at nitrogen to give 1-ethoxycarbonyl-2,3-dimethylindole[10] in quantitative yield. Similarly, quenching the lithium salt of **3** with trimethylsilyl chloride afforded only N-trimethylsilyl-2,3-dimethyl-1-trimethylsilylindole[11] in high yield.

In conclusion, this method offers distinct advantages over previously reported indole C-3 alkylation procedures in that it is quicker, simpler, milder and may allow some chemoselectivity with other functional groups.

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Experimental Section

General. Unless otherwise stated, all reagents were used as obtained from commercial sources. Tetrahydrofuran (THF) was distilled immediately prior to use from sodium / benzophenone. All reactions were carried out in flame dried glassware under a constant positive flow of dry argon. Purification was accomplished after chromatography by reduced pressure bulb to bulb distillation. All ^{1}H nmr spectra were recorded in $CDCl_3$ on a JEOL FX90Q (90 MHz) or a BRUKER AM400 (400 MHz) spectrometer and were referenced to a singlet designated 0.0 ppm attributed to Tetramethylsilane (TMS). ^{13}C nmr were recorded on the above spectrometers at 22.5 & 100 MHz respectively and referenced to the central peak of a triplet occurring at 77 ppm attributed to solvent ($CDCl_3$). Infrared spectra were recorded on a Perkin Elmer 1420 ratio recording spectrophotometer and referenced to polystyrene (1601 cm^{-1}). Mass spectra were recorded on a KRATOS D5 electron impact spectrometer and are tabulated as m/z (intensity expressed as % of total ion current). Elemental analysis was performed by the University of Leeds Micro Analytical Unit. Butyllithium concentration was determined by titration of a solution of diphenylacetic acid in THF.[12]

General Procedure for the Alkylation of 2,3-Dimethylindole : To a solution of 2,3-dimethylindole (400 mg, 2.75 mmol) in THF (10 ml) at -78°C was added a solution of n-butyllithium (1.57 M, 2.75 mmol, 1.75 ml). The solution was stirred at -78°C for 30 min before the electrophile (2.75 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2.5 h before pouring into water (10 ml) and extracting with ether (2 x 20 ml). The ether layers were washed with saturated brine (20 ml) and dried ($MgSO_4$). Chromatography of the residue (ether / hexane,1:1) afforded the desired 3H-indole which was further purified by Kugelrohr distillation.

2,3-Dimethyl-3-ethyl-3H-indole. Isolated as a colourless oil: bp 54°C / 0.1 mm Hg (lit.[5b] 56°C / 0.25 mm Hg) ; ^{1}H nmr (90 MHz) δ: 0.35 (t, J=7.5Hz, 3H), 1.2 (s, 3H), 1.8 (2 overlapping q, J=7.5Hz, 2H), 2.2 (s, 3H), 7.1-7.6 (m, 4H).^{13}C nmr (100 MHz) δ: 8.3, 15.5, 22.2, 22.6, 29.8, 58.1, 119.5, 121, 127.3, 143, 154.4, 186.7. Ir υ: 2980, 1580, 1380, 1200, 1110, 1000, 860, 760. Ms: 173 (M+ 63 %), 158 (100), 144 (52), 117 (35), 103 (21), 91 (25), 77 (51), 51 (32).

2,3,3-Trimethyl-3H-indole. Isolated as a colourless oil: bp 56°C / 1.0 mm Hg (lit.[13] 113°C / 21 mm Hg) ; ^{1}H nmr (90 MHz) δ: 1.2 (s, 6H), 2.2 (s, 3H), 7.2-7.6 (m, 4H). Identical to a commercially available sample.

2,3-Dimethyl-3-isopropyl-3H-indole. Isolated as a colourless oil: bp 65°C / 0.03 mm Hg (lit.[13] 100-110°C /11 mm Hg); ^{1}H nmr (400 MHz) δ: 0.35 (d, J=7Hz,3H), 1.1 (d, J=7Hz, 3H), 1.2 (s, 3H), 2.0 (septet, J=7Hz,1H), 2.2 (s, 3H), 7.0-7.3 (m, 3H), 7.5 (d, J=10Hz, 1H). ^{13}C nmr (100 MHz) δ: 17.1, 17.2, 20.5, 33.4, 36.8, 60.9, 119.5, 122.7, 124.3, 128, 142, 154.7, 187.4. Ir υ: 2980, 1580, 1460, 1380, 1260, 1020, 870, 760. Ms: 187 (M+ 45 %), 172 (33), 158 (11), 144 (100), 130 (40), 115 (20), 103 (17), 91 (20), 72 (54), 51 (32), 43 (64), 41 (62).

3-Allyl-2,3-dimethyl-3H-indole. Isolated as a colourless oil: bp 80°C / 0.04 mm Hg (lit.[13] 128-132°C / 12 mm Hg); ^{1}H nmr (400 MHz) δ: 1.3 (s, 3H), 2.2(s, 3H), 2.4 (ddt, J_1=14Hz, J_2=8Hz, J_3=~1Hz, 1H), 2.6

(ddt, J_1=14Hz, J_2=6.5Hz, J_3=~1Hz, 1H), 4.85 (ddt, J_1=10Hz, J_2=J_3=~1Hz, 1H), 4.95 (ddt, J_1=17Hz, J_2=J_3=~1Hz, 1H), 5.15 (dddd, J_1=17Hz, J_2=10Hz, J_3=8Hz, J_4=6.5Hz, 1H), 7.1-7.5 (m, 3H), 7.6 (d, J=10Hz, 1H). ^{13}C nmr (100 MHz) δ: 15.3, 21.3, 40.6, 57, 117, 119, 121.2, 124, 127, 132, 142.8, 153.8, 186. Ir υ: 2950, 1580, 1450, 1380, 1200, 1000, 920, 760. Ms: 185 (M+ 56 %), 170 (17), 144 (100), 128 (21), 115 (16), 103 (16), 77 (61), 51 (41), 41 (34). Anal. Calcd for $C_{13}H_{15}N$ C 84.28, H 8.16, N 7.56: Found C 84.40, H 8.20, N 7.80.

2,3-Dimethyl-3-hexyl-3H-indole. Isolated as a colourless oil: bp 93°C / 0.02 mm Hg; ^{1}H nmr (400 MHz) δ: 0.55 (m, 1H), 0.65 (m, 1H), 0.75 (td, J_1=7Hz, J_2=3Hz, 3H), 1.05 (m, 6H), 1.2 (s, 3H), 1.65 (tt, J_1=13Hz, J_2=5Hz, 1H), 1.8 (tt, J_1=13Hz, J_2=5Hz, 1H), 2.2 (s, 3H), 7.0-7.3 (m, 3H), 7.4 (d, J=8Hz, 1H). ^{13}C nmr (100 MHz) δ: 13.7, 15.4, 22, 22.5, 23.7, 29.1, 31.1, 36.9, 57.6, 119, 121, 124, 127, 143.6, 154. IR υ: 2980, 2940, 1580, 1460, 1400, 1370, 1200, 1000, 750. Ms: 229 (M+ 21 %), 158 (58), 144 (100), 130 (13), 115 (21), 103 (12), 91 (19), 77 (26), 63 (39). Anal. Calcd for $C_{16}H_{23}N$ C 83.78, H 10.11, N 6.11: Found C 83.80, H 10.05, N 6.35.

2,3-Dimethyl-3-hexenyl-3H-indole: Isolated as a pale yellow oil: bp 93°C / 0.07 mm Hg; ^{1}H nmr (90 MHz) δ: 0.4-1.9 (m, 8H), 1.2 (s, 3H), 2.1 (s, 3H), 4.8 (m, 2H), 5.7 (m, 1H), 7.0-7.6 (m, 4H). ^{13}C nmr (22.5 MHz) δ: 15, 22, 23, 28, 32.5, 36, 114, 119, 121, 124, 127, 138, 143, 154, 186. Ir υ: 2960, 2820, 1580, 1450, 920, 760, 740. Ms: 227 (M+29 %), 212 (43), 201 (12), 184 (10), 172 (18), 158 (74), 144 (100),130 (17), 115 (26), 103 (14), 91 (19), 77 (25). Anal. Calcd for $C_{16}H_{21}N$ C 84.53, H 9.31, N 6.16: Found C 84.40, H 9.60, N 6.30.

3-(3-Chloropropyl)-2,3-dimethyl-3H-indole : Isolated as a pale yellow oil : bp 138°C / 0.05 mm Hg; ^{1}H nmr (90 MHz) δ : 1.15 (m, 2H), 1.3 (s, 3H), 2.0 (t, J=10Hz, 2H), 2.25 (s, 3H), 3.3 (t, J=6.4Hz, 2H), 7.1-7.6 (m, 4H). ^{13}C nmr (22.5 MHz) δ : 15.6, 22.7, 27.1, 34.1, 44.8, 57.2, 119.9, 121.4, 125.2, 127.7, 143.1, 154.3, 186.4. Ir υ : 2960, 1575, 1450, 1375, 1300, 1250, 1200, 860, 755, 645. Ms: 221 (M+31

%), 186 (54), 158 (100), 144 (98), 128 (17), 115 (34), 104 (16), 91 (23), 77(35). Accurate mass . Calcd for $C_{13}H_{16}ClN$ 221.0971: Found 221.0975.

1-Ethoxycarbonyl-2,3-dimethylindole: Isolated as a colourless oil: bp 91°C / 0.02 mm Hg; ^1H nmr (90 MHz) δ: 1.4 (t, J=8Hz, 3H), 2.1 (s, 3H), 2.5 (s, 3H), 4.4 (q, J=8Hz, 2H), 7.1-7.5 (m, 3H), 8.1 (m, 1H). ^{13}C nmr (22.5 MHz) δ: 9, 12.1, 13.1, 63, 116, 117.1, 119, 122, 123.1, 131, 133, 136.2, 153. Ir υ: 2980, 2940, 1730, 1460, 1400, 1340, 1220, 1150, 750. Ms: 217 (M^+ 50 %), 189 (5), 172 (70), 158 (40), 144 (100), 130 (28), 77 (32). Anal. Calcd for $C_{13}H_{15}NO_2$ C 71.89, H 6.91, N 6.45: Found C 71.75, H 7.15, N 6.40.

2,3-Dimethyl-1-trimethylsilylindole: Isolated as a pale yellow oil: bp 93°C / 0.5 mm Hg; ^1H nmr (90 MHz) δ: 0.5 (s, 9H), 2.2 (s, 3H), 2.4 (s, 3H), 7.1 (m, 2H), 7.5 (m, 2H). ^{13}C nmr (22.5 MHz) δ: 3.0, 9.1, 14, 111.2, 113, 118, 119.4, 120.6, 132.1, 136.4, 140.6. Ir υ: 3410, 3020, 2950, 2920, 1450, 1275, 1250, 1160, 1000, 940, 840, 730, 630. Ms: 217 (M^+ 100 %), 202 (42), 145 (18), 73 (55). Anal. Calcd for $C_{13}H_{19}NSi$ *C 71.82, H 8.81, N 6.44:* Found *C 72.00, H 8.70, N 6.70.*

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