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A New Synthesis of 4-Substituted Indoles *via* Tricarbonylarenechromium(0) Complexes

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Tricarbonyl-(η^6 -1-tri-isopropylsilylindole)chromium(0), lithiated selectively at C-4 by n-butyl-lithium– *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA), can be substituted in good yield by a range of electrophiles; the method has been used to synthesise 4-prenylindole.

We have recently reported¹ that the lithiation² of tricarbonyl-(η^{6} -N-protected indole)chromium(0) complexes occurs initially at C-2. If this position was trimethylsilylated, subsequent lithiation was predominantly at C-7 with minor amounts of C-4 attack. The well established importance of 4-substituted indoles³ led us to examine methods to achieve exclusive or predominant 4-lithiation and hence develop a general route to 4-substituted indoles. We now report such a method.

Since lithiation of tricarbonyl-(η^{6} -1-methyl-2-trimethyl-silylindole)chromium(0) (1, R¹ = Me, R² = SiMe₃) gave a

4:1 mixture of 7- and 4-lithiation,¹ the selectivity of attack is finely balanced. It was reasoned, therefore, that a bulky *N*substituent could provide sufficient lateral protection to favour 4-deprotonation. Accordingly, the *N*-t-butyldimethylsilyl complex[†] (2, $R^1 = SiMe_2Bu^t$, $R^2 = H$) [m.p. 143 °C (decomp.)] was prepared in 91% yield from the indole complex⁴ with

[†] All new compounds had correct microanalyses and spectroscopic data.

Table	1.	Synthesis	of	4-substituted	indoles.
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(CO)₂Cr

		4-Substituted indole complex (2, $R^1 = SiPr_{3}^i$) Isolated			4-Substituted indole (3, $R^1 = H$)		
Run	Electrophile	\mathbb{R}^2	yield (%)	M.p. (°C)	R^2	yield (%)	M.p. (°C)
1 2 3 4 5	Me ₃ SiCl EtO2CCl MeO2CCl PhSCl Me2C=CHCH2Br	SiMe ₃ CO ₂ Et CO ₂ Me SPh CH ₂ CH=CMe ₂	56 60 59 _e 36 g	145 (decomp.) 134—136 100—101 112—113.5	SiMe ₃ CO ₂ Et CO ₂ Me SPh CH ₂ CH=CMe ₂	86 a 84 b 81 a 26 f, g 95 g	6566 7071° 6869 d oil oil

^a Deprotection sequence: i, TBAF–THF, 0 °C, 10 min; ii, heat, pyridine, 2 h.¹¹ ^b Deprotection sequence: i, hv, air; ii, TBAF–THF, 0 °C, 10 min. ° Lit.¹² m.p. 70–71 °C. ^d Lit.¹² m.p. 64 °C. ° The complex was too unstable to be isolated. ^t Overall yield. ^g Deprotection sequence: i, TBAF–THF, 0 °C, 10 min; ii, hv, air, MeCN. ^b Estimated total yield 70%.

(3)potassium hydride and the silyl chloride in tetrahydrofuran (THF). However, lithiation of this complex with t-butyllithium-N, N, N', N'-tetramethylethylenediamine (TMEDA) in THF and quenching with ethyl chloroformate gave a mixture of products in low yield.

(CO)3Cr

R1

(2)

 R^1

(1)

The bulk of this protecting group lies principally in the tbutyl residue and in order to provide more spatially complete protection, we synthesised the N-tri-isopropylsilyl analogue^{5,6} $(2, R^1 = SiPr^{i_{3}}, R^2 = H)$ [m.p. 138–140 °C (decomp.)] in a similar manner (90%). Alternatively, indole can be N-triisopropylsilylated7 (100%) and the product complexed with hexacarbonylchromium(0) (85%) as previously described.^{1,8}

Lithiation of this complex (2, $R^1 = SiPr_{3}^i, R^2 = H$) required two equivalents of n-butyl-lithium-TMEDA at -78 °C for 3 h. The product was quenched with trimethylsilyl chloride to give a single product (56%) after crystallisation of the crude material. The n.m.r. spectrum of this product indicated it to be a 4- or 7-silylated indole complex. Thus, H-2 (δ 7.35) and H-3 (δ 6.4) were both present and the protons of the carbocyclic ring appeared as a simple ABC system. Decomplexation of the product (hv, tungsten lamp, air⁹) gave the substituted indole (3, $R^1 = \text{SiPr}^i_3$, $R^2 = \text{SiMe}_3$) (93%). A nuclear Overhauser effect (n.O.e.) difference spectrum of this at 250 MHz established the precise structure. Thus, irradiation of the methyls of the trimethylsilyl group produced enhancement of two protons (H-3 and H-5). Irradiation of the tri-isopropylsilyl protons also produced enhancement of two protons (H-2 and H-7). These observations are consistent only with 4-substitution.

N.m.r. analysis of the decomplexed mother liquors from the initial work-up procedure showed the presence of predominantly 4-silylated material together with small amounts of two isomers which are tentatively assigned as the 5- and 6-silylated

species (ratio 4-: 5-: 6- ca. 3: 1: 1). In particular, no product of attack at C-2 and C-7 was detected. The total yield of 4silvlated product was thus estimated as 70%, with ca. 5% of each of the 5- and 6-isomers.

The lithiation-quench procedure was repeated with a series of electrophiles (Table 1) and the products were isolated in fair to good yield.

The prenylated material (2, $R^1 = SiPr_{3}^i$, $R^2 = Me_2C=$ CHCH₂) (Table 1, run 5) was deprotected with tetrabutylammonium fluoride (TBAF) in THF (0 °C, 10 min)⁶ and decomplexed in acetonitrile (hv, tungsten lamp, air) to give 4prenylindole¹⁰ (3, $R^1 = H$, $R^2 = Me_2C=CHCH_2$) in 95% yield (28% overall from indole).

This method offers a rapid and apparently general route to 4-substituted indoles and further development in natural product synthesis is in hand.

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