

The Direct C-4 Substitution of Indole; An X-Ray Crystal Structure Analysis of 4-(Trimethylsilyl)indole

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Indole was converted into the 1,4-diacetyl and 1-acetyl-4-(3-chloropropanoyl) derivatives by direct C-4 electrophilic substitution *via* 4-(trimethylsilyl)indole (**3c**); the structure of (**3c**) was confirmed by a single crystal X-ray analysis.

Concise strategies for the total synthesis of lysergic acid from indole derivatives including tryptophan are thwarted by the low nucleophilicity at C-4 of indole.¹ Herein we report a direct

method to effect the Friedel–Craft acylation of indole. This reaction is directly relevant to ergot alkaloid synthesis.

The Birch reduction of indole (**1**) has been shown to provide

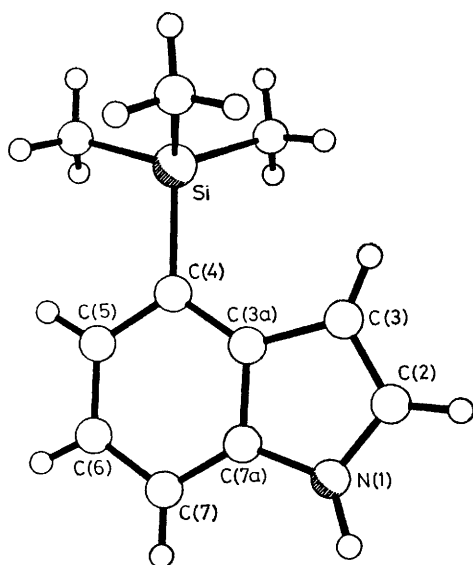
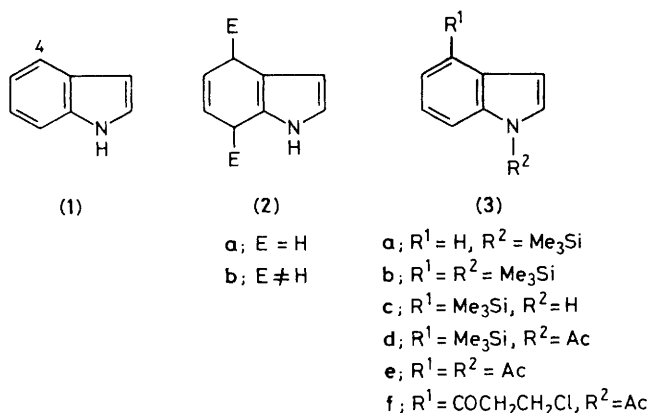


Figure 1. The crystal structure of (3c). Bond distances: (the two values in each case refer to the two independent molecules) N(1)–C(2) 1.360(6), 1.353(6); C(2)–C(3) 1.349(5), 1.348(5); C(3)–C(3a) 1.471(5), 1.445(5); C(7a)–N(1) 1.383(4), 1.377(4); C(4)–Si 1.890(3), 1.874(2); Si–Me (range of values) 1.852(4) to 1.866(4) Å.

4,7-dihydroindole (2a).² This reduction, which must proceed *via* anion and radical anion intermediates at C-4 and C-7, presents the opportunity to prepare substituted 4,7-dihydroindole derivatives (2b) by dissolving metal reduction in the presence of an electrophile (E⁺). Indole (1), on reduction using lithium metal (4 equiv.) and chlorotrimethylsilane (4 equiv.) in tetrahydrofuran (THF) at 5–45 °C gave a very air-labile product which was not isolated. Oxidation *in situ* using *p*-benzoquinone (2 equiv.) in dichloromethane at 0 °C gave 1,4-bis(trimethylsilyl)indole (3b) and 1-(trimethylsilyl)indole (3a) (3:1, 84%). Chromatography gave pure (3b) (50%). In the same way reduction (Li, Me₃SiCl, THF) of (3a) with oxidative (*p*-benzoquinone) work-up gave (3b) (55%). On brief warming in methanol and recrystallisation from aqueous methanol, (3b) gave 4-(trimethylsilyl)indole (3c) (94%). In these transformations the selective formation of the mono-(trimethylsilyl)benzene ring is in contrast to the reaction of benzene itself. It has been reported³ that reduction of benzene

(Li, Me₃SiCl, THF) and subsequent oxidation (*p*-benzoquinone) gave 1,4-bis(trimethylsilyl)benzene. With indole (1) the highly selective C-4 substitution probably resulted from release of steric congestion⁴ (*N*-1-SiMe₃ and *C*-7-SiMe₃) in the oxidation step. Although mechanistically curious, this selective silylation is preparatively useful.

4-(Trimethylsilyl)indole (3c) was treated with sodium hydride (1.5 equiv.) and then acetyl chloride (1.5 equiv.) in THF to give the 1-acetyl derivative (3d) (96%). This substituted indole (3d) reacted smoothly with acetyl chloride (5 equiv.) or 3-chloropropanoyl chloride (5 equiv.) and aluminium chloride (5 equiv.) in dichloromethane at room temperature to give 1,4-diacetylindole (3e) (95%) and 1-acetyl-4-(3-chloropropanoyl)indole (3f) (70%).

These results deserve substantiation. All new compounds were fully characterised by spectral data and microanalyses. In addition, the structure of 4-(trimethylsilyl)indole (3c) was proven by an X-ray crystallographic study.

Crystal data: (3c), C₁₁H₁₅NSi, *M* = 189.3, triclinic, *a* = 7.786(3), *b* = 12.459(5), *c* = 12.800(6) Å, α = 93.56(3), β = 104.40(3), γ = 102.77(3)°, *U* = 1164 Å³; space group *P*1̄, *Z* = 4. Of the 2397 independent reflections (θ ≤ 50°) measured on a diffractometer using Cu-K_α radiation 250 had |*F*₀| < 3σ (|*F*₀|) and were classified as unobserved. The structure was solved by direct methods and refined anisotropically to give *R* = 0.043.†

Distinguishing between 4- and 7-(trimethylsilyl)indole hinged on the assignment of the nitrogen atom position. The presence of two crystallographically independent molecules in the unit cell had the advantage that it provided an independent check on this assignment. In both molecules we see (Figure 1) the significantly shorter distance associated with the C–N bond [C(7a)–N(1)] compared with that of the opposite C–C bond [C(3)–C(3a)], thus unambiguously confirming the assignment.

The generation of indole derivatives functionalised at C-4 by carbon electrophiles is henceforth an easy operation. These reactions are inexpensive, simple, and amenable to multigram synthesis.

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† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.