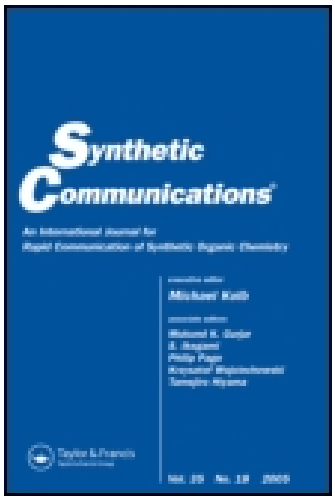

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A DIRECT LITHIATION ROUTE TO 2-ACYL-1-(PHENYLSULFONYL)INDOLES

Jun Jiang [a] & Gordon W. Gribble [b]

[a] Department of Chemistry , Dartmouth College , Hanover, NH, 03755, U.S.A.

[b] Department of Chemistry , Dartmouth College , Hanover, NH, 03755, U.S.A.

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A DIRECT LITHIATION ROUTE TO 2-ACYL-1-(PHENYLSULFONYL)INDOLES

Jun Jiang and Gordon W. Gribble*

Department of Chemistry,
Dartmouth College, Hanover, NH 03755, USA

ABSTRACT

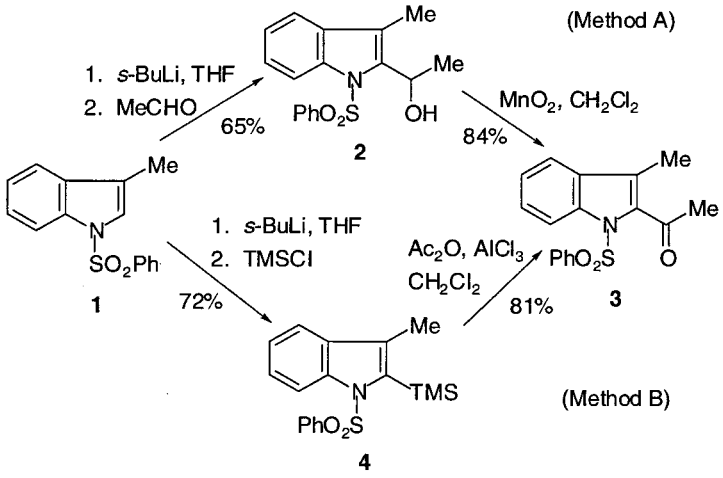
2-Acyl-1-(phenylsulfonyl)indoles (**3, 7–9**) are prepared in 75–84% yield from 1-(phenylsulfonyl)indoles (**1, 5**) in one operation by treatment of the latter with *s*-butyllithium followed by inverse quenching of the C-2 lithioindoles with carboxylic acid anhydrides (**6**).

Key Words: 2-Acylindoles; 2-Lithioindoles; Acylation; Lithiation; Carboxylic acid anhydrides

2-Acylindoles are important intermediates in the synthesis of various fused indoles such as furo[3,4-*b*]indoles[1] and pyrrolo[3,4-*b*]indoles,[2] and they are alkaloids in their own right.[3] In our previous work in this area we have prepared these ketones by the C-2 lithiation of a 1-(phenylsulfonyl)indole, quenching with an aldehyde, and oxidation with active manganese dioxide.[1a–e,2b,4] Alternatively, the 2-lithioindole can be treated with trimethylsilyl chloride and the resulting C-2 silylated indole subjected to an *ipso*-desilylation Friedel–Crafts acylation reaction with an acid chloride or anhydride to furnish the C-2 ketone.[5] For example, as summarized in

*Corresponding author. E-mail: grib@dartmouth.edu

Scheme 1 both methods afford the C-2 ketone **3** in 55–58% yield from 3-methyl-1-(phenylsulfonyl)indole (**1**).



Scheme 1.

Although these methods are often satisfactory, they do involve two steps and occasionally the oxidation with manganese dioxide is erratic and proceeds poorly if at all. We now describe a one-pot method that affords the 2-acylindoles usually in higher yields. Thus, lithiation of 1-(phenylsulfonyl)-indoles **1** and **5** with *s*-BuLi followed by inverse quenching with excess carboxylic acid anhydride **6** affords the desired ketones **3** and **7–9** in very good yield as shown in Scheme 2. Our results are summarized in Table 1 in comparison with the two-step methods depicted in Scheme 1 (Methods A and B, respectively).

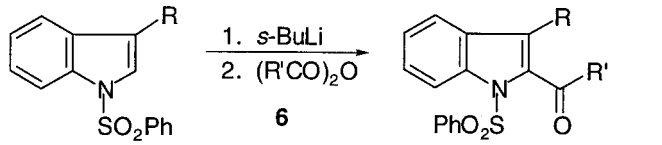
Table 1. Preparation of 2-Acylindoles **3, 7–9** from **1** and **5**

Indole	**6**, R′	Product	Yield, % Method A[a]	Method B[b]	Method C[c]
1	Me	**3**	55%	58%	81%
1	Ph	**7**	47%	–	84%
1	n-C_5H_{11}	**8**	–	57%	75%
5	Me	**9**	81%	–	76%

[a]Method A: 1) *s*-BuLi; 2) RCHO; 3) MnO_2.
[b]Method B: 1) *s*-BuLi; 2) TMSCl; 3) $(RCO)_2O$, $AlCl_3$.
[c]Method C: (Present method; Scheme 2) 1) *s*-BuLi; 2) $(RCO)_2O$.

Inverse quenching of the C-2 lithioindole with 5–10 equivalents of carboxylic acid anhydride was superior to either quenching with lesser quantities of acid anhydride or with acid chlorides, and better than a direct quenching (normal addition) with acid anhydrides. Thus, reaction of **1** with *s*-BuLi followed by inverse quenching with acetyl chloride (10 equivalents) gave only recovered starting material, presumably resulting from rapid enolization of the acid chloride. Direct quenching of the C-2 lithio species from **1** with acetic anhydride gave **3** in only 38% yield. A similar reaction with hexanoic anhydride gave **8** in 48% yield, whereas the inverse quenching procedure afforded **8** in 75% yield.

The availability of acid anhydrides makes this one-step procedure an attractive alternative to the two-step methods for the synthesis of 2-acyl-1-(phenylsulfonyl)indoles shown in Scheme 1.



1 R = Me
5 R = H

3 R = Me, R' = Me
7 R = Me, R' = Ph
8 R = Me, R' = *n*-C_5H_{11}
9 R = H, R' = Me

Scheme 2.

EXPERIMENTAL

Melting points were determined with a Mel-Temp Laboratory Device apparatus, and are uncorrected. Elemental analyses were done by Atlantic Microlab Inc. High resolution mass spectra (HRMS) were carried out at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana Champaign. Infrared spectra were recorded on a BioRad FT-IR Infrared Spectrophotometer, and ^{13}C and ^{1}H NMR spectra were recorded on a Varian XL-300 Fourier-transform NMR spectrometer. Tetrahydrofuran (THF) was distilled from sodium/benzophenone.

3-Methyl-1-(phenylsulfonyl)-2-(trimethylsilyl)indole (4): To a $-70^{\circ}C$ stirred solution of 3-methyl-1-(phenylsulfonyl)indole (**1**) (3.26 g, 12.0 mmol) in dry THF (100 mL) was added a solution of *s*-butyllithium (1.3 M in

cyclohexane, 14.0 mmol) dropwise via syringe. The reaction mixture was stirred at $-70^{\circ}C$ for 2 h and allowed to warm to r.t. for 4 h. The dark brown reaction mixture was recooled to $-70^{\circ}C$ and treated with freshly distilled trimethylsilyl chloride (1.47 g, 13.5 mmol) and stirred overnight. The mixture was quenched by aqueous ammonium chloride (250 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL) and the combined organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The resulting oil was purified by flash chromatography (10% ethyl acetate in hexanes) and the desired product **4** was obtained as a white solid (3.0 g, 8.8 mmol, 73%). Recrystallization (MeOH) gave **4** as colorless crystals which was identical (TLC, ^{13}C NMR, ^{1}H NMR) to what was obtained by us before:[6] m.p. 94–94.5°C (Lit.[6] m.p. 93–94°C; IR (KBr) ν_{max} 2944, 1444, 1385, 1174, 1106, 837, 725 cm^{-1}; UV (EtOH) λ_{max} 216, 220, 224, 284, 296 (sh) nm: ^{1}H NMR ($CDCl_3$) δ 7.95–7.98 (m, 1H), 7.55–7.58 (m, 2H), 7.16–7.43 (m, 6H), 2.35 (s, 3H), 0.54 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 139.5, 138.2, 138.0, 133.7, 133.6, 133.2, 128.7, 126.6, 125.5, 123.7, 119.2, 115.6, 12.1, 2.6; MS m/z 343 (M^+), 328 (100%), 264, 236, 202, 186, 160, 125, 73. Anal. Calcd for $C_{18}H_{22}NO_2SSi$: C, 62.94; H, 6.16; N, 4.08; S, 9.33. Found: C, 62.88; H, 6.19; N, 4.06; S, 9.38.

2-Hexanoyl-3-methyl-1-(phenylsulfonyl)indole (8). (General Procedure): To a $-70^{\circ}C$ stirred solution of 3-methyl-1-(phenylsulfonyl) indole (**1**) (1.09 g, 4.0 mmol) dissolved in dry THF (25 mL) was added a solution of *s*-butyllithium (1.3 M in cyclohexane, 4.5 mmol) dropwise via syringe. The reaction mixture was stirred at $-70^{\circ}C$ for 2 h and allowed to warm to r.t. for 4 h. The dark brown reaction mixture was recooled to $-70^{\circ}C$ and then was added to a stirred solution of hexanoic anhydride (4.2 mL, 20.0 mmol) in dry THF (25 mL) at $-70^{\circ}C$ via a cannula. And the mixture was stirred overnight. The mixture was quenched by aqueous sodium bicarbonate (250 mL) and the mixture was refluxed for 3 h to remove the excessive anhydride. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The resulting oil was purified by flash chromatography (10% ethyl acetate in hexanes) to give an oil (1.25 g, 88% pure, 75% yield) which contains 12% starting material according to ^{1}H NMR. The analytical sample was obtained as white crystals by recrystallization (ethyl acetate/hexanes) which was identical (TLC, ^{13}C NMR, ^{1}H NMR) to what was obtained by us before:[6] m.p. 75–77°C (Lit.[6] m.p. 76–77°C; IR (KBr) ν_{max} 2945, 2862, 1675 (C=O), 1560, 1449, 1369, 1171, 1100, 944, 577 cm^{-1}; UV (EtOH) λ_{max} 214, 244, 271 (sh), 276, 288 nm: ^{1}H NMR ($CDCl_3$) δ 8.04–8.07 (m, 1H), 7.45–7.64 (m, 2H), 7.23–7.46 (m, 6H), 3.02 (t, 2H, $J = 7.5$ Hz), 2.20 (d, 3H, $J = 1.8$ Hz),

1.68–1.77 (m, 2H), 1.33–1.40 (m, 4H), 0.87–0.94 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 199.2, 137.3, 136.5, 135.5, 134.0, 132.0, 128.9, 127.4, 126.2, 125.0, 120.9, 116.3, 115.3, 45.1, 31.6, 24.6, 22.7, 14.2, 9.5; MS *m*/*z* 370 (M^++1), 369 (M^+), 298, 271, 228, 172, 158 (100%), 130, 102, 77. Anal. Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79; S, 8.68. Found: C, 68.35; H, 6.37; N, 3.81; S, 8.84.

2-Acetyl-3-methyl-1-(phenylsulfonyl)indole (3): This was prepared from **1** in 81% yield by the general method, using 10 equivalents of acetic anhydride. The product was obtained as white needles, m.p. 115–117°C (Lit.[1a] m.p. 115.5–117°C). The spectra characteristics matched literature data;[1a] ^{13}C NMR($CDCl_3$) δ 195.8, 137.6, 136.9, 135.4, 134.1, 132.1, 128.9, 127.8, 127.4, 125.2, 121.1, 116.5, 32.4, 9.7.

2-Benzoyl-3-methyl-1-(phenylsulfonyl)indole (7): This was prepared from **1** in 84% yield by the general method, using 5 equivalents of benzoic anhydride. The product was obtained as a white solid, m.p. 139–140°C (Lit.[1a] m.p. 140.5–141°C). The spectra characteristics matched literature data.[1a]

2-Acetyl-1-(phenylsulfonyl)indole (9): This was prepared from **5** in 76% yield by the general method, using 10 equivalents of acetic anhydride. The product was obtained as white needles, m.p. 90–91°C (Lit.[4] m.p. 89–90°C). The spectra characteristics matched literature data.[4]

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