Convenient Synthesis of 4-Alkyl, Alkenyl, and Alkynyl Substituted N-(Phenylsulfonyl)indoles

Hiroyuki ISHIBASHI, Susumu AKAMATSU, Hiroko IRIYAMA, and Masazumi IKEDA

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan.
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The indole 1 reacted with organomagnesium or lithium reagents to give the carbinols 6 and 10, which, upon treatment under appropriate acidic conditions or neutral thermal conditions, gave the 1-phenylsulfonylindoles 8 and 11 bearing various kinds of alkyl, alkenyl, and alkynyl substituents at the 4-position. The indole 1 was also converted to the 4-cyanindole 14 via the cyanohydrin O-trimethylsilyl ether 13.

Keywords 4-alkylindole; 4-alkenylindole; 4-alkynylindole; Grignard reagent; organolithium compound; cupric chloride

The synthesis of indoles bearing a carbon-substituent at the 4-position is of particular interest in organic synthesis, because of the utility of this class of compounds as precursors for many therapeutically useful materials related to the ergot alkaloids, such as lysergic acid. Previous reports from our laboratory have shown that the acid-catalyzed reactions of the 7-aryltio-4,5,6,7-tetrahydroidindol-4-one with alcohols or thiols provide ready access to 4-alkoxy and 4-alkylthioindoles. Formation of 3 from 1 can be rationalized in terms of a ready aromatization of the intermediate vinyl ether 2 with elimination of p-chlorobenzenethiol. Our interest has now been focused on the synthesis of 4-alkylindoles by using 1 as a common intermediate, as an extension of the method. The attack of carbon nucleophiles such as Grignard reagents on the carbonyl carbon atom of 1 would provide the carbinols 6, and subsequent dehydrogenation under appropriate conditions might give the 4-alkylindoles through the intermediacy of 6,7-dihydroindoles. In the present paper, we wish to describe an application of this methodology to the synthesis of indoles bearing various carbon-substituents at the 4-position.

Grignard coupling of 1 with methylmagnesium bromide (4a) took place smoothly at room temperature to give the carbinol 6a in nearly quantitative yield. The 1H-NMR spectrum of 6a exhibited signals due to the methyl protons at C4 and the proton at C7 as a singlet (δ 1.33) and triplet (δ 4.80, J = 2 Hz), respectively. This indicates that compound 6a is a single stereoisomer, though the relative stereochemistry between C4 and C7 is unknown. The carbinol 6a was then treated with TsOH in refluxing benzene to give the 4-methyldienole 8a in 87% yield, with elimination of p-chlorobenzenethiol.

Similarly, compound 6b gave the 4-ethyldienole 8b in 70% yield. The carbinol 6c derived from 1 and 2-(1,3-dioxolan-2-yl)methylmagnesium bromide (4e), however, gave a complex mixture of products when heated with TsOH. It was assumed that the acetal function of the desired 8c or of the starting material 6c might be partially changed to the corresponding thioacetal by reaction with p-chlorobenzenethiol generated during the course of formation of 8c from 6c. In fact, a similar reaction in the presence of cupric chloride (CuCl2) as a thiol scavenger gave 8c in 74% yield. The vinyl derivative 6d also gave a complex mixture of products when treated with TsOH, probably due to the lability of the resulting vinylindole 8d under the acidic conditions employed. We found, however, that 8d was obtained in good yield (69%) just by heating 6d in refluxing toluene. This may be a result of ready formation of the intermediate conjugated diene 7d (R = CH = CH2).

Reactions of the indole 1 with organolithium reagents 5e-g gave the carbinols 6e-g, respectively. The aromatization of 6e was performed by treatment with TsOH in refluxing benzene to give the 4-(phenylsulfonylmethyl)indole 8e in 91% yield. The carbinol 6f derived from the lithio derivative of formaldehyde dimethyl mercaptan S-oxide (FAMSO) was converted to the aldehyde 8h by treatment with CuCl2 in aqueous acetone. Heating 6g in 10% H2SO4 in methanol gave the indol-4-ylacetic ester 8i in 88% yield.

Reactions of 1 with alkynyllithiums 9a-e also pro-
Experimental

4-Methyl-1-phenylsulfonyl-1H-indole (8a) Methylmagnesium bromide (4a) in tetrahydrofuran (THF) (1.92 ml, 1.92 mmol) was added to a solution of 1 (200 mg, 0.48 mmol) in THF (5 ml), and the mixture was stirred at room temperature for 4 h. A saturated NH₄Cl solution (20 ml) was added to the reaction mixture, and the whole was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄, and the solvent was evaporated off to give quantitatively the carbinal 6a [¹H-NMR (CDCl₃)] δ: 1.33 (3H, s), 4.80 (1H, t, J = 2 Hz), 6.33 (1H, d, J = 3.5 Hz)]. Compound 6a was then dissolved in benzene (10 ml), and the mixture was passed under reflux for 1 h in the presence of TsOH·H₂O (91 mg, 0.48 mmol). The reaction mixture was washed with a saturated NaHCO₃ solution and dried over MgSO₄. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 20:1) to give 8a (113 mg, 87%), mp 92–92.5 °C (from MeOH). IR (CCl₄) 1600, 1375 cm⁻¹. [¹H-NMR (CDCl₃)] δ: 2.40 (3H, s), 6.62 (1H, d, J = 3.5 Hz), 6.8–7.45 (5H, m), 7.52 (1H, d, J = 3.5 Hz), 7.7–8.0 (3H, m). Anal. Calc'd for C₂₃H₁₉NO₂S: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.19; H, 4.85; N, 5.10.

4-Ethyl-1-phenylsulfonyl-1H-indole (8b) According to a procedure similar to that described above for 6a, the indolone 1 (200 mg, 0.48 mmol) was allowed to react with ethylmagnesium bromide (0.96 mmol), and the resulting crude carbinal 6b was heated in benzene in the presence of TsOH 1 h. After work-up as described above for 8a, the crude material was chromatographed on silica gel (hexane–AcOEt, 20:1) to give 8b (96 mg, 70%), mp 72–73.5 °C (from hexane–AcOEt). [¹H-NMR (CDCl₃)] δ: 1.26 (3H, t, J = 7 Hz), 2.83 (2H, q, J = 7 Hz), 6.70 (1H, d, J = 4 Hz), 6.8–7.5 (5H, m), 7.50 (1H, d, J = 4 Hz), 7.7–8.0 (3H, m). Anal. Calc'd for C₂₃H₂₀NO₂S: C, 67.35; H, 5.30; N, 4.91. Found: C, 67.02; H, 5.24; N, 5.24.

4-[2-(1,3-Dioxolan-2-yl)ethyl]-1-phenylsulfonyl-1H-indole (8c) 2-(2-Bromoethyl)-1,3-dioxolane (1.3 g, 7.2 mmol) was added dropwise to a stirred suspension of magnesium turnings (108 mg, 4.5 mmol) in dry THF (5 ml), and the mixture was stirred at room temperature for 30 min to give a solution of 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide (20%). This solution was then added to a solution of 1 (450 mg, 1.08 mmol) in THF (20 ml) at −20 °C, and the mixture was stirred at the same temperature for 1 h. After work-up as described above for 6a, the crude material was chromatographed on silica gel (hexane–AcOEt, 2:1) to give 8c (539 mg, 96%). Compound 8c (44 mg, 0.03 mmol) was then dissolved in benzene (7 ml), and the mixture was heated under reflux for 5 min in the presence of a catalytic amount of TsOH·H₂O and CuCl₂·2H₂O (159 mg, 0.93 mmol). After work-up as described above for 8a, the crude material was chromatographed on silica gel (hexane–AcOEt, 5:1) to give 8d (246 mg, 74%) as an oil. [¹H-NMR (CDCl₃)] δ: 1.8–2.2 (2H, m), 2.75–3.1 (2H, m), 3.6–4.1 (4H, m), 4.90 (1H, t, J = 5 Hz), 6.82 (1H, d, J = 4 Hz), 7.0–7.55 (5H, m), 7.63 (1H, d, J = 4 Hz), 7.8–8.05 (3H, m). 4-Ethyl-1-phenylsulfonyl-1H-indole (8d) According to a procedure similar to that described above for 6a, the indolone 1 (127 mg, 0.30 mmol) was allowed to react with vinylmagnesium bromide (4d) (1.2 mmol) at room temperature for 1 h. After work-up as described above for 6a, the crude carbinal 6d was dissolved in toluene (5 ml), and the mixture was heated under reflux for 1.5 h. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 10:1) to give 8d (59 mg, 69%) as an oil. [¹H-NMR (CDCl₃)] δ: 5.37 (1H, dd, J = 10.5, 1.5 Hz), 5.77 (1H, dd, J = 17, 1.5 Hz), 5.86 (1H, d, J = 7.0 Hz, 7.0–10.5 Hz), 7.3–7.6 (5H, m), 7.65 (1H, d, J = 4 Hz), 7.8–8.1 (3H, m). Anal. Calc'd for C₂₃H₂₀NO₂S: C, 67.82; H, 4.62; N, 4.93. Found: C, 67.40, H, 4.85; N, 4.60.

1-Phenylsulfonyl-4-phenylsulfonylmethyl-1H-indole (8e) BuLi (15% hexane solution) (0.68 ml, 1.07 mmol) was added to a solution of methyl phenyl sulfoxide (168 mg, 1.07 mmol) in dry THF (5 ml) at −78 °C, and the mixture was stirred at the same temperature for 5 min. A solution of 1 (150 mg, 0.35 mmol) in THF (5 ml) was added to the above solution containing phenylsulfonylmethylthiium (5e), and the mixture was stirred at −78 °C for 15 min. After work-up as described above for 6a, the crude material was chromatographed on silica gel (hexane–AcOEt, 8:1) to give quantitatively 6e [¹H-NMR (CDCl₃)] δ: 3.42 (2H, s), 4.18 (1H, s), 4.87 (1H, brs), 6.36 (1H, d, J = 3.5 Hz)]. Compound 6e was then dissolved in benzene (3 ml), and the mixture was heated under reflux for 1 h in the presence of TsOH·H₂O (66 mg, 0.35 mmol). After work-up as described above for 8a, the crude material was chromatographed on silica gel (hexane–AcOEt, 3:1) to give 8e (133 mg, 91%), mp 142–143 °C (from hexane–AcOEt) (lit. 95° mp...
146—147°C. 1H-NMR (CDCl3) δ: 4.52 (2H, s), 6.46 (1H, d, J = 4 Hz), 6.9—7.1 (11H, m), 7.7—8.2 (3H, m).

1-Phenylsulfonyl-1H-indole-4-carboxaldehyde (8b) BuLi (15% hexane solution 1.15 ml, 1.8 mmol) was added to a solution of FAMS (228 mg, 1.8 mmol) in dry THF (5 ml) at —20°C, and the mixture was stirred at the same temperature for 30 min. A solution of 1 (150 mg, 0.36 mmol) in dry THF (1 ml) was added to the above solution containing the lithium derivative 5f at —78°C, and the mixture was stirred at the same temperature for 25 min. After work-up as described above for 8a, the crude material containing 6f was dissolved in acetonitrile (9 ml), a solution of CuCl2·2H2O (612 mg, 3.6 mmol) in water (1 ml) was added, and the mixture was heated under reflux for 30 min. Acetone was removed by evaporation, water (10 ml) was added to the residue, and the whole was extracted with AcOEt. The organic phase was dried over MgSO4, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane-AcOEt: 4:1) to give 9b (86 mg, 84%), mp 95—100°C (from hexane-AcOEt) (lit.9 mp 101.5—102°C). IR (CCl4): 1695 cm−1.

1H-NMR (CDCl3) δ: 7.2—8.0 (9H, m), 8.20 (1H, d, J = 8 Hz), 10.07 (1H, s).

Methyl 1-Phenylsulfonyl-1H-indole-4-acetate (8c) A solution of tert-butyl acetate (209 mg, 1.8 mmol) in THF (5 ml) was added to a solution of lithium diisopropylamine (1.0) (LDA) 1.8 mmol in THF (7 ml) at —78°C, and the mixture was stirred at the same temperature for 5 min. A solution of 1 (150 mg, 0.36 mmol) in THF (1 ml) was added to the above solution containing the lithioacetylide 5g, and the mixture was stirred at —78°C for 1 h. After work-up as described above for 6a, the crude material containing 9c was dissolved in MeOH (4.5 ml) and concentrated H2SO4 (0.5 ml), and the mixture was heated under reflux for 7 h. Water (15 ml) was added to the reaction mixture and the whole was extracted with CH2Cl2. The organic phase was dried over MgSO4, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane-AcOEt: 1:5) to give 10c (144 mg, 84%), 2.54 (2H, s), 4.66 (1H, s), 4.83 (1H, brs), 6.33 (1H, d, J = 3.5 Hz) was dissolved in a mixture of MeOH (4.5 ml) and concentrated H2SO4 (0.5 ml), and the mixture was heated under reflux for 3 h. The mixture was added to the above solution containing the lithium acetylide 9e at —78°C, and the mixture was stirred at the same temperature for 30 min. After work-up as described above for 10d, the crude material was chromatographed on silica gel (hexane-AcOEt: 5:1) to give 11d (112.2 mg, 61%), Compound 11d (112 mg, 0.21 mmol) was then dissolved in benzene (10 ml) containing TsOH·H2O (0.01 mmol) and CuCl2·2H2O (35 mg, 0.21 mmol), and the mixture was heated under reflux for 1 h. Water (10 ml) was added to the reaction mixture, and the organic layer was separated, then dried over MgSO4. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt: 15:1) to give 11e (84 mg, 57%) as an oil. IR (CCl4): 1751 cm−1. 1H-NMR (CDCl3) δ: 1.33 (3H, d, J = 7 Hz), 1.73 (3H, s), 2.75—3.13 (6H, m), 4.88 (1H, d, J = 3.5 Hz). Elemental analysis: Found: C, 68.62; H, 5.56; N, 3.48. Anal. Calc for C16H11NO5S: C, 68.82; H, 5.56; N, 3.48. 4-Ethyl-1-(1-phenylsulfonyl-1H-indolyl-4-yl)propionic acid (11f) According to a procedure similar to that described above for 9d, tert-butyl propionate (362 mg, 2.87 mmol) was lithiated with LDA (2.87 mmoles of 1 (300 mg, 0.72 mmol) in THF (1 ml) was added to the above solution containing the lithium acetylide 9d at —78°C, and the mixture was stirred at the same temperature for 30 min. After work-up as described above for 10d, the crude material was chromatographed on silica gel (hexane-AcOEt: 5:1) to give 11f (114 mg, 57%) as an oil. IR (CCl4): 1769 cm−1. 1H-NMR (CDCl3) δ: 1.33 (3H, d, J = 7 Hz), 1.73 (3H, s), 2.75—3.13 (6H, m), 4.88 (1H, d, J = 3.5 Hz). Elemental analysis: Found: C, 68.62; H, 5.56; N, 3.48. Anal. Calc for C16H11NO5S: C, 68.82; H, 5.56; N, 3.48. 4-(1-Phenylsulfonyl-1H-indolyl-4-yl)-3-butyronitrile (12) Acetyl acridine (246 mg, 2.4 mmol) was added to a stirred suspension of AlCl3 (643 mg, 4.8 mmol) in CH2Cl2 (10 ml), and the mixture was stirred at room temperature for 30 min, during which time it became orange. A solution of silylalkyne 11e (284 mg, 0.8 mmol) in CH2Cl2 (1 ml) was added to the above solution at —40°C, and the mixture was stirred at the same temperature for 15 min. Water (10 ml) was added to the reaction mixture and the organic layer was separated. The aqueous layer was further extracted with CH2Cl2, and the combined organic phases were washed with a saturated NaHCO3 solution, dried over MgSO4. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 7:1) to give 12 (277 mg, 89%), mp 105—106°C (from hexane-AcOEt). IR (CCl4): 2180, 1670 cm−1. 1H-NMR (CDCl3) δ: 2.47 (3H, s), 6.85 (1H, d, J = 3.5 Hz), 7.0—7.8 (5H, m), 7.67 (1H, d, J = 3.5 Hz), 7.7—8.2 (3H, m). Analytical data: Found: C, 66.77; H, 4.25; N, 4.33. Calc for C16H11NO5S: C, 66.99; H, 4.05; N, 4.33.

1-Phenylsulfonyl-1H-indole-4-carboxonitrile (14) Trimethylsilylnitrile (106 mg, 1.7 mmol) was added to a mixture of 1 (200 mg, 0.47 mmol) and Zn(0) (5 mg, 0.016 mmol) in dry CH2Cl2 (10 ml) at 0°C, and the mixture was stirred at room temperature overnight. Water (10 ml) was added to the reaction mixture, and the organic layer was separated, then dried over MgSO4. The solvent was evaporated off to give quantitatively the cyanohydrin O-trimethylsilyl ether 13i [1H-NMR (CDCl3) δ: 0.30 (9H, s), 4.83 (1H, brs), 6.40 (1H, d, J = 3.5 Hz)]. POCI3 (0.09 ml, 1 mmol) was added to a solution of 13 (175 mg, 0.34 mmol) in pyridine (1 ml), and the mixture was heated at 110°C for 5 h and then at 80°C for 1 h. A 10% HCl solution (10 ml) was added to the reaction mixture at 0°C, and the whole was extracted with diethyl ether. The organic phase was washed with brine, and dried over MgSO4. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give 14 (61 mg, 63%), mp 175—176°C (from hexane-AcOEt). IR (CHCl3): 2220 cm−1. 1H-NMR (CDCl3) δ: 0.90 (1H, d, J = 4 Hz), 7.3—8.1 (8H, m), 8.30 (1H, d, J = 8 Hz). Anal. Calc for C16H11NO5S:
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References and Notes


8) Methylmagnesium bromide (4a), ethylmagnesium bromide (4b), and vinylmagnesium bromide (4d) were purchased from Kanto Chemical Co., Inc. as 1 M solutions in THF. $^1$H-NMR spectra were measured on a JEOL JNM-PMX 60 (60 MHz) spectrometer using tetramethylsilane as an internal standard. For other general experimental details, see ref. 2b.