Chem. Pharm. Bull.
36(4)1305—1308(1988)

Condensed Heteroaromatic Ring Systems. XIII.[1] One-Step Synthesis of 2-Substituted 1-Methylsulfonylindoles from *N*-(2-Halophenyl)methanesulfonamides

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(Received September 9, 1987)

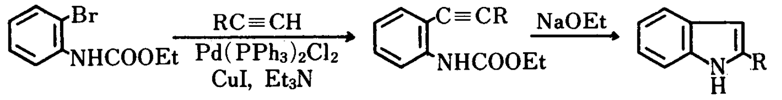
The reaction of *N*-(2-bromophenyl)- and *N*-(2-iodophenyl)methanesulfonamide with terminal acetylenes in the presence of dichlorobis(triphenylphosphine)palladium yielded 1-methylsulfonylindoles having carbon-functional groups at the 2-position, such as hydroxymethyl, 2-hydroxyethyl, diethoxymethyl, 2-ethoxycarbonylethyl, *etc.*, in one step.

Keywords——palladium-catalyzed reaction; dichlorobis(triphenylphosphine)palladium; *N*-(2-halophenyl)methanesulfonamide; acetylene; 2-substituted 1-methylsulfonylindole

In the preceding paper of this series,[1] we have reported that ethyl 2-(trimethylsilylethynyl)carbanilates derived from ethyl 2-halocarbanilates underwent an indole-cyclization and that the method was applicable conveniently for the synthesis of pyrrolopyridines from the corresponding aminohalopyridines. The method, however, is insufficient for the synthesis of indole derivatives containing a carbon-functional group at the 2-position. The present paper deals with a palladium-catalyzed reaction of *N*-(2-halophenyl)methanesulfonamides with terminal acetylenes, which provides a facile method for the synthesis of such indole derivatives.

When ethyl 2-bromocarbanilate (**1**) was heated with phenylacetylene in triethylamine in the presence of catalytic amounts of dichlorobis(triphenylphosphine)palladium and cuprous iodide, the cross-coupling reaction proceeded to give ethyl 2-(phenylethynyl)carbanilate (**2a**). On treatment of the crude **2a** with sodium ethoxide, 2-phenylindole (**3a**) was isolated in 63% overall yield from **1**. Similarly, 2-butylindole (**3b**) was obtained in 48% yield by the reaction of **1** with 1-hexyne followed by the indole-cyclization of the resulting crude intermediate (**2b**), but the reaction of **1** with ethynyl compounds having a functional group, such as propargyl alcohol, 3,3-diethoxyl-1-propyne, 3-butyn-1-ol, and ethyl 4-pentynoate, failed to give any indoles.

Then, *N*-(2-bromophenyl)methanesulfonamide (**4**) and *N*-(2-iodophenyl)methanesulfonamide (**5**) were employed as starting materials instead of **1**. When **4** or **5** was treated with



1 **2a,b** **3a,b**

a : R=Ph
b : R=Bu

Chart 1

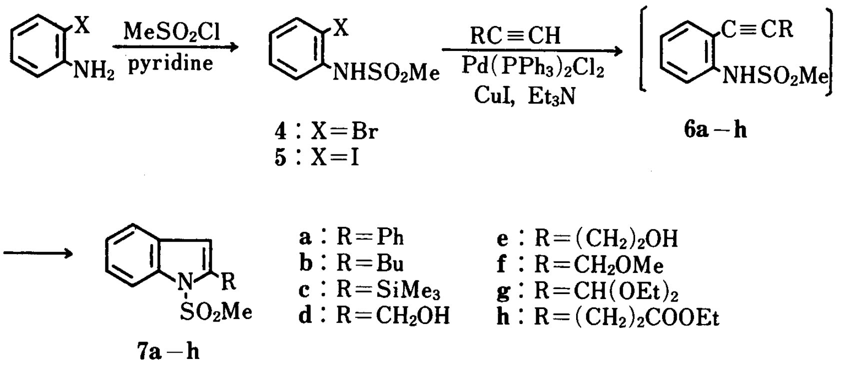


Chart 2

Table I. 2-Substituted 1-Methylsulfonylindoles from *N*-(2-Halophenyl)methanesulfonamides

No.	Yield (%)[a] from **5**	mp (°C) [bp/mmHg]	IR cm^{-1} (CHCl$_3$)	^{1}H-NMR δ (ppm) (CDCl$_3$)[b]
7a	66 (20)	116—117	—	2.59 (3H, s), 6.62 (1H, s), 7.2—7.7 (8H, m), 8.0—8.2 (1H, m)
7b	64 (43)	81—82	—	0.8—2.1 (7H, m), 2.7—3.2 (2H, m), 2.87 (3H, s), 6.35 (1H, s), 7.1—7.5 (3H, m), 7.8—8.1 (1H, m)
7c	31 (58)	[125/3]	—	0.36 (9H, s), 2.92 (3H, s), 6.88 (1H, s), 7.1—7.7 (3H, m), 7.8—8.1 (1H, m)
7d	53 (0)	93—94	3580 (OH)	2.7—3.2 (1H, br), 3.11 (3H, s), 4.88 (2H, d, *J*=7), 6.65 (1H, s), 7.2—7.7 (3H, m), 7.8—8.1 (1H, m)
7e	59 (47)	80—81	3630 (OH)	1.6—2.1 (1H, br), 3.02 (3H, s), 3.24 (2H, t, *J*=6), 3.8—4.2 (2H, br), 6.58 (1H, s), 7.2—7.7 (3H, m), 7.8—8.2 (1H, m)
7f	71 (12)	73.5—74	—	3.18 (3H, s), 3.42 (3H, s), 4.67 (2H, s), 6.63 (1H, s), 7.2—7.7 (3H, m), 7.9—8.2 (1H, m)
7g	63 (0)	83—84	—	1.32 (6H, t, *J*=7), 3.23 (3H, s), 3.75 (4H, q, *J*=7), 5.90 (1H, s), 6.90 (1H, s), 7.1—8.2 (4H, m)
7h	43 (49)	112—113	1730 (CO)	1.26 (3H, t, *J*=7), 2.5—3.6 (4H, m), 3.02 (3H, m), 4.29 (2H, q, *J*=7), 6.45 (1H, s), 7.2—7.6 (3H, m), 7.8—8.1 (1H, m)

a) Yields in parentheses are from **4**. *b*) ^{1}H-NMR spectra of **7a**—**c** were taken in CCl$_4$.

terminal acetylenes in the presence of the same catalysts, the ethynyl intermediates (**6**) spontaneously cyclized to give the corresponding 1-methylsulfonylindoles (**7**).

Based on the results of this reaction listed in Table I, **5** appears to be a more favorable substrate than **4**, except for the reaction with trimethylsilylacetylene.

In addition, what reagents contribute to the cyclization of **6** to **7** was investigated by using alternatively synthesized **6c**. Namely, the palladium-catalyzed reaction of 2-bromonitrobenzene (**8**) with trimethylsilylacetylene followed by the reduction of the nitro group with iron powder and ferrous sulfate under acidic conditions gave 2-(trimethylsilylethynyl)aniline (**9**). The aniline (**9**) was allowed to react with methanesulfonyl chloride in pyridine to give **6c**. When **6c** was heated in the presence of cuprous iodide[2)] without addition of dichlorobis(triphenylphosphine)palladium for 3 h, **7c** was isolated in 78% yield together with 15% of 1-methylsulfonylindole (**10**). On the other hand, no indole derivative was obtained by heating **6c** in triethylamine and dimethylformamide (DMF) for 10 h, and on heating of **6c** in the presence of dichlorobis(triphenylphosphine)palladium without addition of cuprous iodide, **7c** was isolated as a sole product, although the yield of **7c** was only 20%. In contrast, treatment of **6c** in the presence of the palladium catalyst and cuprous iodide gave only **7c** in 45% yield.

Based on these results, it is likely that the cyclization of **6c** to **7c** is caused by co-operative

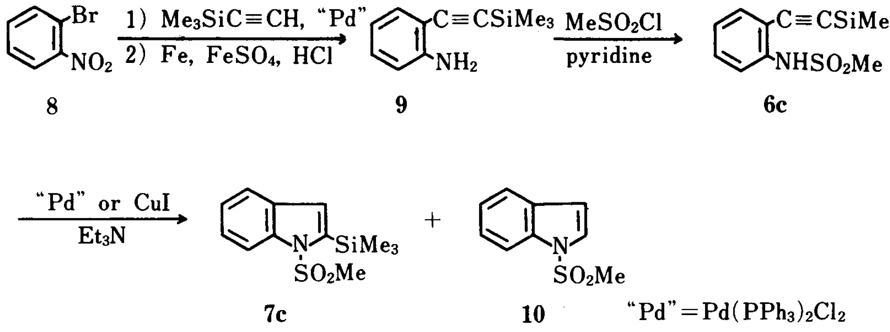


Chart 3

action of cuprous iodide and dichlorobis(triphenylphosphine)palladium. Although the mechanism of the spontaneous cyclization of **6** to **7** is not fully revealed at present, the reaction of *N*-(2-iodophenyl)methanesulfonamide with acetylenes in the presence of cuprous iodide and dichlorobis(triphenylphosphine)palladium provides a facile one-step synthesis of 2-substituted 1-methylsulfonylindoles (**7**).

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad.

Ethyl 2-bromocarbanilate was prepared by the literature method.[1]

General Procedure for the Preparation of 2-Substituted Indoles (3a, b) from Ethyl 2-Bromocarbanilate (1)——A mixture of **1** (5 mmol), an acetylene (7.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.25 mmol), CuI (0.4 mmol), and Et_3N (8 mmol) was heated in a sealed tube for 3—5 h at 100—110 °C. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using hexane–C_6H_6 (2 : 1, v/v) as an eluent. The crude product obtained from the hexane–C_6H_6 (2 : 1, v/v) eluate was added to ethanolic EtONa [prepared from Na (20 mmol) and dry EtOH (50 ml)], and the mixture was refluxed for 12—24 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography followed by recrystallization or distillation.

2-Phenylindole (3a)——According to the general procedure, colorless scales (cyclohexane), mp 187—188 °C (lit.[2] mp 187—188 °C), were obtained. Yield 0.61 g (63%). IR ($CHCl_3$) cm^{-1}: 3440. ^{1}H-NMR ($CDCl_3$): 6.80 (1H, d, J=2), 7.0—7.8 (9H, m), 8.30 (1H, br s).

2-Butylindole (3b)——According to the general procedure, a pale yellow liquid, bp 155—160 °C, was obtained. Yield 420 mg (48%). IR ($CHCl_3$) cm^{-1}: 3450. ^{1}H-NMR (CCl_4): 0.6—1.9 (7H, m), 2.4—2.8 (2H, m), 6.10 (1H, s), 6.9—7.6 (5H, m). Picrate, mp 115—116 °C (brown needles from ether–hexane). *Anal.* Calcd for $C_{18}H_{17}N_4O_7$ (picrate): C, 53.73; H, 4.51; N, 13.92. Found: C, 53.69; H, 4.37; N, 13.71.

General Procedure for the Preparation of *N*-(2-Halophenyl)methanesulfonamides (4 and 5)——Methanesulfonyl chloride (45 mmol) was added to a solution of a 2-haloaniline (30 mmol) in pyridine (40 ml) at room temperature with stirring, and the mixture was stirred for 3 h. After removal of the pyridine, the residue was diluted with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with 3 N HCl and 1 N $NaHCO_3$. The residue obtained from the CH_2Cl_2 extract, was recrystallized from hexane–CH_2Cl_2.

***N*-(2-Bromophenyl)methanesulfonamide (4)**——According to the general procedure, colorless prisms, mp 76—77 °C, were obtained from 2-bromoaniline. Yield 7.13 g (95%). IR ($CHCl_3$) cm^{-1}: 3340. ^{1}H-NMR ($CDCl_3$): 2.99 (3H, s), 6.6—7.9 (5H, m). *Anal.* Calcd for $C_7H_8BrNO_2S$: C, 33.62; H, 3.22; N, 5.60. Found: C, 33.71; H, 3.18; N, 5.58.

***N*-(2-Iodophenyl)methanesulfonamide (5)**——According to the general procedure, colorless needles, mp 93—94 °C, were obtained from 2-iodoaniline. Yield 8.74 g (98%). IR ($CHCl_3$) cm^{-1}: 3325. ^{1}H-NMR ($CDCl_3$): 3.01 (3H, s), 6.4—8.0 (5H, m). *Anal.* Calcd for $C_7H_8INO_2S$: C, 28.30; H, 2.71; N, 4.71. Found: C, 28.48; H, 2.61; N, 4.77.

General Procedure for the Preparation of 2-Substituted 1-Methylsulfonylindoles (7)——A mixture of a *N*-(2-halophenyl)methanesulfonamide (**4** and **5**) (5 mmol), an acetylene (7.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.25 mmol), CuI (0.4 mmol), Et_3N (2 ml), and DMF (1 ml) was heated in a sealed tube for 24 h at 120 °C for **4** or at 80 °C for **5**. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography followed by distillation or recrystallization.

TABLE II. Analytical Data for 2-Substituted 1-Methylsulfonylindoles

No.	Formula	Analysis (%)					
		Calcd			Found		
		C	H	N	C	H	N
7a	$C_{15}H_{13}NO_2S$	66.40	4.83	5.16	66.65	4.88	5.11
7b	$C_{13}H_{17}NO_2S$	62.12	6.82	5.57	61.98	6.96	5.48
7c	$C_{12}H_{17}NO_2SSi$	53.90	6.41	5.24	53.67	6.41	5.01
7d	$C_{10}H_{11}NO_3S$	53.32	4.92	6.22	53.02	4.84	6.09
7e	$C_{11}H_{13}NO_3S$	55.21	5.48	5.85	54.93	5.49	5.77
7f	$C_{11}H_{13}NO_3S$	55.21	5.48	5.85	55.18	5.57	5.80
7g	$C_{14}H_{19}NO_4S$	56.55	6.44	4.71	56.49	6.26	4.79
7h	$C_{14}H_{17}NO_4S$	56.93	5.80	4.74	56.69	5.97	4.66

2-(Trimethylsilylethynyl)aniline (9)——A mixture of 2-bromonitrobenzene (**8**) (5.05 g, 25 mmol), trimethylsilylacetylene (3.50 g, 35 mmol), $Pd(PPh_3)_2Cl_2$ (500 mg, 0.78 mmol), CuI (250 mg, 1.25 mmol), and Et_3N (25 ml) was stirred at room temperature for 14 h. After evaporation of the Et_3N, the residue was diluted with H_2O and extracted with ether. The crude product obtained from the ethereal extract was added to a mixture of 0.1 N HCl (100 ml), C_6H_6 (25 ml), and MeOH (5 ml), and then Fe (12.5 g, 0.22 mol) and $FeSO_4 \cdot 2H_2O$ (1.0 g, 5.3 mmol) were added with vigorous stirring, and the whole was refluxed for 4 h. The mixture was extracted with C_6H_6, and the C_6H_6 extract was purified by SiO_2 column chromatography using hexane–C_6H_6 (2 : 1, v/v) as an eluent, followed by distillation to give a colorless liquid, bp 110—115 °C/3 mmHg. Yield 2.75 g (58%). IR ($CHCl_3$) cm^{-1}: 3490, 3400, 2160. ^1H-NMR (CCl_4): 0.23 (9H, s), 3.5—4.6 (2H, br), 6.3—7.3 (4H, m). *Anal.* Calcd for $C_{11}H_{15}NSi$: C, 69.78; H, 7.99; N, 7.40. Found: C, 69.60; H, 8.04; N, 7.33.

***N*-(2-Trimethylsilylethynylphenyl)methanesulfonamide (6c)**——Methanesulfonyl chloride (700 mg, 6.1 mmol) was added to a solution of **9** (1.0 g, 5.3 mmol) in pyridine (4 ml), and the mixture was stirred for 3 h at room temperature. After removal of the pyridine, the residue was diluted with H_2O and extracted with ether. The ethereal extract was washed with 3 N HCl and 1 N $NaHCO_3$. The residue obtained from the ethereal extract was recrystallized from hexane to give colorless prisms, mp 137—138 °C. Yield 1.30 g (92%). IR ($CHCl_3$) cm^{-1}: 3330, 2160. ^1H-NMR ($CDCl_3$): 0.27 (9H, s), 2.99 (3H, s), 6.0—6.6 (1H, br), 6.9—7.7 (4H, m). *Anal.* Calcd for $C_{12}H_{17}NO_2SSi$: C, 53.90; H, 6.41; N, 5.24. Found: C, 53.62; H, 6.47; N, 5.21.

Cyclization of 6c without Catalysts——A mixture of **6c** (200 mg, 0.75 mmol) in Et_3N (0.3 ml) and DMF (0.15 ml) was heated at 80 °C for 10 h. The reaction mixture was treated according to the general procedure for the preparation of 2-substituted 1-methylsulfonylindoles to recover **6c** (171 mg, 86%).

Cyclization of 6c in the Presence of Cuprous Iodide——A mixture of **6c** (200 mg, 0.75 mmol), CuI (12 mg, 0.06 mmol), Et_3N (0.3 ml), and DMF (0.15 ml) was heated at 80 °C for 3 h. The reaction mixture was treated as above, and the crude product was purified by SiO_2 column chromatography using hexane–C_6H_6 (3 : 1, v/v) as an eluent. The first eluate gave **7c** (156 mg, 78%). The second eluate afforded 1-methylsulfonylindole (**10**), bp 140 °C/0.5 mmHg (lit.[4] bp 125 °C/0.2 mmHg). Yield 21 mg (15%). ^1H-NMR (CCl_4): 2.90 (3H, s), 6.60 (1H, d, $J=5$), 6.9—8.0 (4H, m).

Cyclization of 6c in the Presence of Dichlorobis(triphenylphosphine)palladium——A mixture of **6c** (200 mg, 0.75 mmol), $Pd(PPh_3)_2Cl_2$ (24 mg), Et_3N (0.3 ml), and DMF (0.15 ml) was heated at 80 °C for 7 h. The reaction mixture was treated as above to give **7c** (40 mg, 20%).

Cyclization of 6c in the Presence of Dichlorobis(triphenylphosphine)palladium and Cuprous Iodide——A mixture of **6c** (100 mg, 0.37 mmol), $Pd(PPh_3)_2Cl_2$ (12 mg, 0.019 mmol), CuI (6 mg, 0.03 mmol), Et_3N (0.15 ml), and DMF (0.075 ml) was heated at 80 °C for 3 h. The mixture was treated as above to give **7c** (45 mg, 45%).

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