[Chem. Pharm. Bull. 36(6)2248—2252(1988)]

Palladium-Catalyzed Coupling Reaction of 3-Iodoindoles and 3-Iodobenzo[*b*]thiophene with Terminal Acetylenes

TAKAO SAKAMOTO, TATSUO NAGANO, YOSHINORI KONDO, and HIROSHI YAMANAKA*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received November 13, 1987)

The palladium-catalyzed coupling reaction of 3-iodoindoles possessing an electron-withdrawing group at the 1- or 2-position with terminal acetylenes smoothly proceeded to yield 3-ethynylindoles. Similarly, the reaction of 3-iodobenzo[*b*]thiophene gave the expected products, but the reaction of 3-bromobenzo[*b*]furan provided resinous materials.

Keywords——palladium-catalyzed reaction; 3-iodoindole; 3-iodobenzo[*b*]thiophene; terminal acetylene; 3-ethynylindole; 3-ethynylbenzo[*b*]thiophene

Palladium-catalyzed cross-coupling reaction of aryl halides with terminal acetylenes has been regarded as one of the most effective methods for the introduction of ethynyl functions into aromatic nuclei.[1] The method, developed in benzene chemistry,[2] has been extended to π-electron-deficient N-heteroaromatics[3] and azoles.[4] Prior to our present study, however, little work has been done on this reaction of π-electron-sufficient heteroaryl halides with terminal acetylenes.[5]

From these points of view, we investigated the palladium-catalyzed reaction of 3-iodoindole derivatives, 3-iodobenzo[*b*]thiophene, and 3-bromobenzo[*b*]furan with terminal acetylenes, and obtained satisfactory results, except for 3-bromobenzo[*b*]furan. The present paper deals with the practical aspects of this reaction using trimethylsilylacetylene, phenylacetylene, 1-hexyne, and propargyl alcohol as representatives of terminal acetylenes.

Since 3-iodoindole (**2**) is unstable during purification,[6] **2** was treated with methanesulfonyl chloride in the presence of tetrabutylammonium bromide (TBAB) under basic conditions to give 1-methylsulfonyl-3-iodoindole (**3**), which is stable enough for purification and the subsequent palladium-catalyzed reaction. Thus, the coupling reaction of **3** with terminal acetylenes in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine or using a small amount of dimethylformamide (DMF) as a co-solvent, smoothly proceeded at room temperature, and the corresponding 3-ethynyl-1-methylsulfonylindoles (**4a**—**d**) were obtained in satisfactory yields.

As in the case of indole (**1**),[6] ethyl indole-2-carboxylate (**5**) was easily iodinated under the same conditions, and ethyl 3-iodoindole-2-carboxylate (**6**) was obtained in almost quantitative yield as a stable solid. Although the coupling reaction of **6** with 1-hexyne gave the product (**7c**) in poor yield (28%), the coupling reaction of **6** with trimethylsilylacetylene and with phenylacetylene at 60 °C gave the corresponding 3-ethynyl compounds (**7a** and **7b**) in satisfactory yields. In order to improve the yield, ethyl 3-iodo-1-methylsulfonylindole-2-carboxylate (**8**) was employed as a substrate, and it was found that the coupling reaction of 8 with 1-hexyne gave ethyl 3-(1-hexynyl)-1-methylsulfonylindole-2-carboxylate (**9c**) in 62% yield, as expected, while the coupling reaction of **8** with phenylacetylene afforded only 49% yield of ethyl 1-methylsulfonyl-3-phenylethynylindole-2-carboxylate (**9b**).

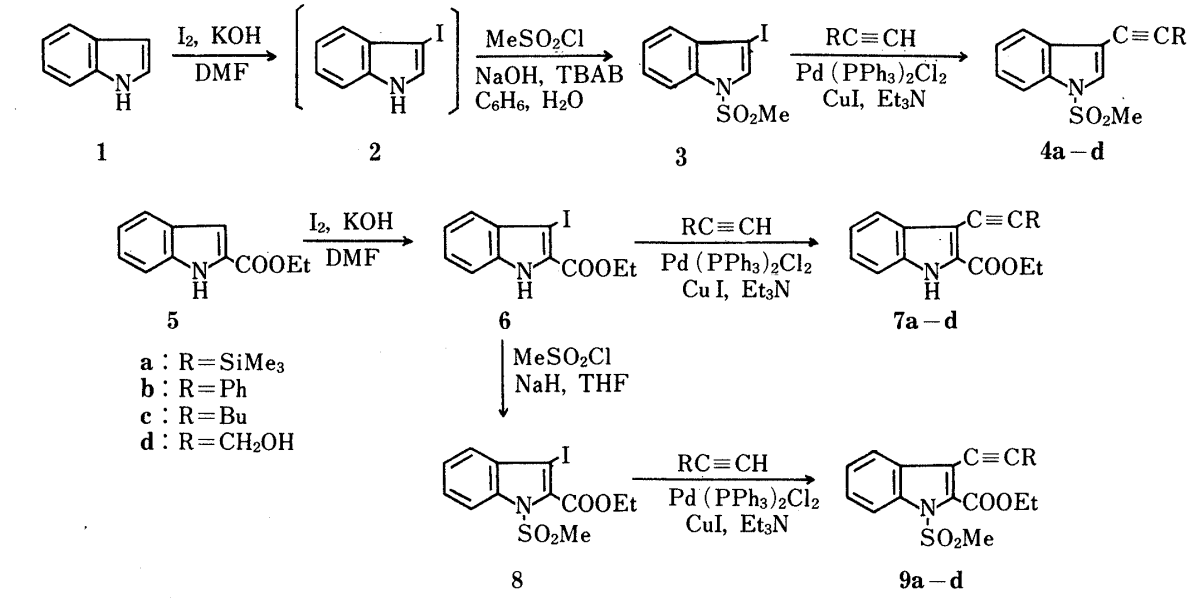

Chart 1

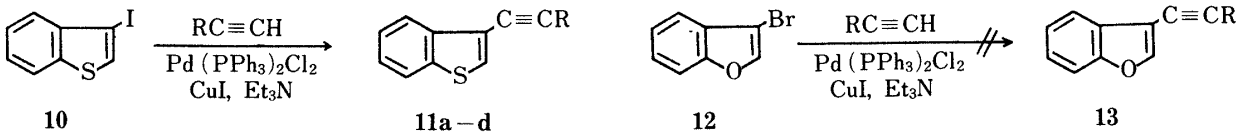

Chart 2

Despite the fact that the coupling reaction of *N*-(2-iodophenyl)methanesulfonamide with propargyl alcohol gave 1-methylsulfonylindole-2-methanol *via* *N*-[2-(3-hydroxyprop-1-yn-1-yl)phenyl]methanesulfonamide,[7] the coupling reaction of ethyl 3-iodoindole-2-carboxylate (**6**) and ethyl 3-iodo-1-methylsulfonylindole-2-carboxylate (**8**) with propargyl alcohol failed to give any detectable product, though the reason for this failure remains to be clarified.

Then, the coupling reaction of 3-iodobenzo[*b*]thiophene (**10**) and 3-bromobenzo[*b*]furan (**12**) was investigated. 3-Iodobenzo[*b*]thiophene (**10**)[8] easily reacted with the acetylenes including propargyl alcohol, and the corresponding 3-ethynyl derivatives (**11a—d**) were obtained in yields ranging from 58% to 96%. On the other hand, the coupling reaction of 3-bromobenzo[*b*]furan (**12**)[9] with the acetylenes under the same conditions gave resinous materials, and no desired product was isolated.

As is clear from the present investigation, the palladium-catalyzed coupling reaction of π-electron-sufficient heteroaryl halides with terminal acetylenes, like that of π-electron-deficient heteroaryl halides, provides an simple and practical method for the synthesis of ethynyl derivatives of these rings, although some restrictions still remain.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer and a IR-810 spectrometer. Mass spectra were taken with a JEOL JMS-O1SG-2 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 contants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, t=triplet, q=quartet, m=multiplet, and br=broad.

3-Iodo-1-methylsulfonylindole (3)——Potassium hydroxide (21.00 g, 380 mmol) was added to a solution of indole (**1**) (11.72 g, 100 mmol) in DMF (50 ml), and the mixture was stirred at room temperature for 5 min. Then, a solution of I_2 (25.38 g, 100 mmol) in DMF (50 ml) was added dropwise to the mixture at room temperature. The mixture was

stirred for 10 min, then was poured into a solution of $NaHSO_3$ (10 g) and 25% aqueous NH_3 (100 ml) in H_2O (1500 ml), and the resulting precipitate (3-iodoindole) was filtered off. A solution of methanesulfonyl chloride in C_6H_6 (150 ml) was added dropwise under vigorous stirring at room temperature to a mixture of the above precipitate, TBAB (3.22 g, 10 mmol), 50% (v/v) aqueous NaOH (100 ml), C_6H_6 (150 ml), and H_2O (150 ml). Stirring was continued for 1 h, the organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was column-chromatographed on silica gel using C_6H_6 as an eluent. The product was recrystallized from MeOH to give colorless needles, mp 112—114 °C. Yield 15.48 g (49%). ^{1}H-NMR ($CDCl_3$): 3.10 (3H, s), 7.2—8.0 (5H, m). *Anal.* Calcd for $C_9H_8INO_2S$: C, 33.66; H, 2.51; N, 4.36; S, 9.98. Found: C, 33.94; H, 2.52; N, 4.40; S, 9.93.

Ethyl 3-Iodoindole-2-carboxylate (6)——Potassium hydroxide (8.82 g, 160 mmol) was added to a solution of ethyl indole-2-carboxylate (**5**)[10] in DMF (100 ml), and the mixture was stirred at room temperature for 5 min. Then a solution of I_2 (11.42 g, 45 mmol) in DMF (50 ml) was added. After being stirred at room temperature for 30 min, the mixture was poured into a solution of $NaHSO_3$ (10 g) and 25% aqueous NH_3 (100 ml) in H_2O (1500 ml). The resulting precipitate was filtered off and recrystallized from EtOH to give yellow needles, mp 135—137 °C. Yield 14.04 g (99%). IR ($CHCl_3$) cm^{-1}: 1695. ^{1}H-NMR ($CDCl_3$): 1.48 (3H, t, J=7), 4.45 (2H, q, J=7), 7.0—7.7 (4H, m), 9.50 (1H, br s). *Anal.* Calcd for $C_{11}H_{10}INO_2$: C, 41.93; H, 3.20; N, 4.45. Found: C, 42.11; H, 3.16; N, 4.44.

Ethyl 3-Iodo-1-methylsulfonylindole-2-carboxylate (8)——Compound **6** (12.60 g, 40 mmol) was added to a stirred suspension of oil-free NaH (1.15 g, 48 mmol) in tetrahydrofuran (100 ml) at 0 °C, and the mixture was stirred for 20 min at this temperature. Then, methanesulfonyl chloride (6.88 g, 60 mmol) was added at 0 °C, and the whole was stirred at room temperature for 20 min. After removal of the solvent *in vacuo*, the residue was diluted with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O and 1 N $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was recrystallized from ether–hexane to give pale yellow scales, mp 107—109 °C. Yield 13.37 g (85%). IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$): 1.46 (3H, t, J=7), 3.50 (3H, s), 4.49 (2H, q, J=7), 7.2—8.1 (4H, m). *Anal.* Calcd for $C_{12}H_{12}INO_4S$: C, 36.66; H, 3.08; N, 3.56; S, 8.15. Found: C, 36.79; H, 3.56; N, 3.44; S, 8.23.

Ethyl 3-Ethynylindole-2-carboxylates (7a—d) (General Procedure A)——A mixture of an ethyl 3-iodoindole-2-carboxylate (**6**) (2 mmol), an acetylene (2.4 mmol), $Pd(PPh_3)_2Cl_2$ (64 mg), CuI (32 mg), and Et_3N (10 ml) was stirred at room temperature or at 60 °C under an argon atmosphere. The mixture was concentrated *in vacuo*, diluted with H_2O, and extracted with ether. The ethereal extract was washed with H_2O, dried over $MgSO_4$, and evaporated. The residue

TABLE I. Yields and Spectral Data for 3-Ethynylindoles and 3-Ethynylbenzo[*b*]thiophenes

No.	Yield (%)	Method	IR cm^{-1} ($CHCl_3$)	^{1}H-NMR δ (ppm) ($CDCl_3$)
4a	70	A[a]	2160	0.28 (9H, s), 3.13 (3H, s), 7.2—8.1 (5H, m)
	74	B		
4b	74	A[a]	—	3.08 (3H, s), 7.0—8.0 (10H, m)
	75	B		
4c	72	A[a]	—	0.90 (3H, t, J=7), 1.1—1.9 (4H, m), 2.40 (3H, t, J=7), 2.97 (3H, s),
	78	B		7.2—7.9 (5H, m)
4d	69	A[a]	3600	1.90 (1H, br s), 3.10 (3H, s), 4.57 (2H, s), 7.2—8.0 (5H, m)
	74	B		
7a	75	A[b]	2165	0.31 (9H, s), 1.50 (3H, t, J=7), 4.53 (2H, q, J=7), 7.0—7.9 (4H, m),
			1695	9.60 (1H, br s)
7b	89	A[b]	1690	1.48 (3H, t, J=7), 4.50 (2H, q, J=7), 7.1—8.1 (9H, m), 9.30 (1H, br s)
7c	28	A[b]	1700	1.00 (3H, t, J=7), 1.2—2.1 (4H, m), 1.45 (3H, t, J=7), 2.60 (2H, t, J=7),
				4.48 (2H, q, J=7), 7.0—8.0 (4H, m), 9.60 (1H, br s)
9a	64	A[b]	2160	0.30 (9H, s), 1.47 (3H, t, J=7), 3.60 (3H, s), 4.48 (2H, q, J=7),
	45[c]	B	1720	7.2—8.1 (4H, m)
9b	49	A[b]	1720	1.45 (3H, t, J=7), 3.61 (3H, s), 4.48 (2H, q, J=7), 7.2—8.1 (9H, m)
	64	B		
9c	62	A[b]	1715	0.95 (3H, t, J=7), 1.2—2.1 (4H, m), 1.45 (3H, t, J=7), 2.55 (2H, t, J=7),
				3.57 (3H, s), 4.50 (2H, q, J=7), 7.2—8.1 (4H, m)
11a	80	B	2150	0.30 (9H, s), 7.2—8.1 (5H, m)
11b	96	B	2210	7.1—8.2 (10H, m)
11c	91	B	2225	0.95 (3H, t, J=7), 1.2—2.0 (4H, m), 2.35 (2H, t, J=7), 7.1—8.2 (5H, m)
11d	58	B	3600	3.30 (1H, br s), 4.60 (2H, s), 7.1—8.1 (5H, m)
			2220	

a) At room temperature. *b*) At 60 °C. *c*) Starting material was recovered in 38% yield.

TABLE II. Physical Constants and Analytical Data for 3-Ethynylindoles and 3-Ethynylbenzo[*b*]thiophenes

No.	mp or bp/mmHg (°C)	Appearance (Recryst. solvent)	Formulae	Analysis (%) Calcd (Found)			
				C	H	N	S
4a	83—85	Colorless needles (Pentane)	$C_{14}H_{17}NO_2SSi$	57.70 (57.77	5.88 5.85	4.81 4.87	11.10 11.20)
4b	100—102	Colorless needles (Ether–hexane)	$C_{17}H_{13}NO_2S$	69.13 (69.42	4.44 4.33	4.74 4.76	10.85 10.71)
4c	190—195/2	Colorless liquid (Viscous oil)	$C_{15}H_{17}NO_2S$	65.43 (65.46	6.22 6.36	5.09 5.11	11.64 11.89)
4d	96—97	Pale yellow needles (Ether–hexane)	$C_{12}H_{11}NO_3S$	57.82 (57.96	4.45 4.54	5.62 5.52	12.86 12.60)
7a	149—151	Colorless needles (Hexane)	$C_{16}H_{19}NO_2Si$	67.33 (67.19	6.71 6.74	4.91 4.78)	
7b	184—186	Colorless needles (Ether–hexane)	$C_{19}H_{15}NO_2$	78.87 (79.06	5.23 5.06	4.84 4.84)	
7c	96—98	Colorless needles (Pentane)	$C_{17}H_{19}NO_2$	75.81 (75.55	7.11 7.07	5.20 5.20)	
9a	79—81	Pale yellow needles (Ether–hexane)	$C_{17}H_{21}NO_4SSi$	56.17 (56.06	5.82 5.79	3.85 3.83	8.82 9.02)
9b	146—148	Pale yellow scales (Ether–hexane)	$C_{20}H_{17}NO_4S$	65.38 (65.31	4.66 4.58	3.81 3.75	8.83 8.89)
9c	44—45	Pale yellow scales (Hexane)	$C_{18}H_{21}NO_4S$	62.23 (62.24	6.09 6.33	4.03 4.07	9.23 9.36)
11a	115—120/2	Colorless liquid	$C_{13}H_{14}SSi$	67.77 (67.81	6.12 6.19		13.91 13.62)
11b	170—175/2	Colorless liquid	$C_{16}H_{10}S$[a]				
11c	160—165/3	Colorless liquid	$C_{14}H_{14}S$	78.46 (78.54	6.58 6.74		14.96 14.71)
11d	205—210/3	Colorless liquid	$C_{11}H_8OS$	70.19 (70.13	4.28 4.25		17.03 16.84)

a) An analytically pure sample was not obtained because of comtamination with a trace of 1,4-diphenylbutadiyne. High-resolution mass spectrum Calcd for $C_{16}H_{10}S$: 234.0503. Found 234.0496.

was column-chromatographed on silica gel using hexane–Et_3N (9 : 1 v/v) as an eluent. The product was recrystallized from the solvent shown in Table II.

Ethyl 3-Ethynyl-1-methylsulfonylindole-2-carboxylate (9a—c)——The residue obtained according to general procedure A was column-chromatographed on silica gel using hexane–Et_3N (9 : 1 v/v) as an eluent. The product was recrystallized from the solvent shown in Table II.

3-Ethynyl-1-methylsulfonylindoles (4a—d) (General Procedure B)——A mixture of a 3-iodo-1-methylsulfonylindole (**3**) (2 mmol), an acetylene (2.4 mmol), $Pd(PPh_3)_2Cl_2$ (64 mg), CuI (32 mg), Et_3N (2.4 ml), and DMF (5 ml) was stirred at room temperature under an argon atmosphere. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was washed with H_2O, dried over $MgSO_4$, and evaporated, then the residue was column-chromatographed on silica gel using hexane–Et_3N (9 : 1 v/v) as an eluent. The product was recrystallized from the solvent shown in Table II or distilled *in vacuo*.

3-Ethynylbenzo[*b*]thiophene (11a—d)——The residue obtained according to general procedure B was column-chromatographed on silica gel using hexane as an eluent, and the product was distilled under reduced pressure.

References and Notes

1) R. F. Heck, "Palladium Reagents in Organic Syntheses," Academic Press, London, 1985, pp. 299—306.
2) *a*) L. Casser, *J. Organometal. Chem.*, **93**, 253 (1975); *b*) H. A. Dieck and R. F. Heck, *ibid.*, **93**, 259 (1975); *c*) K. Sonogashira, Y. Toda, and N. Hagihara, *Tetrahedron Lett.*, **1975**, 4467; *d*) S. Takahashi, Y. Kuroyama, K. Sonogashira, and N. Hagihara, *Synthesis*, **1980**, 627; *e*) W. B. Austin, N. Bilow, W. J. Kellegham, and K. S. Y. Lau, *J. Org. Chem.*, **46**, 2280 (1981).

3) *a*) K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **26**, 3843 (1978); *b*) K. Tanji, T. Sakamoto, and H. Yamanaka, *ibid.*, **30**, 1865 (1982); *c*) H. Yamanaka, M. Shiraiwa, K. Edo, and T. Sakamoto, *ibid.*, **27**, 270 (1979); *d*) T. Sakamoto, M. Shiraiwa, Y. Kondo, and H. Yamanaka, *Synthesis*, **1983**, 312; *e*) A. Ohsawa, Y. Abe, and H. Igeta, *Chem. Pharm. Bull.*, **28**, 3488 (1980); *f*) Y. Akita, A. Inoue, and A. Ohta, *ibid.*, **34**, 1447 (1986); *g*) E. C. Taylor and P. S. Ray, *J. Org. Chem.*, **52**, 3997 (1987).
4) *a*) H. Yamanaka, M. Shiraiwa, E. Yamamoto, and T. Sakamoto, *Chem. Pharm. Bull.*, **29**, 3543 (1981); *b*) T. Sakamoto, H. Nagata, Y. Kondo, M. Shiraiwa, and H. Yamanaka, *ibid.*, **35**, 823 (1987).
5) It has been reported that the palladium-catalyzed reaction of 2-bromothiophene with phenylacetylene gives 2-phenylethynylthiophene, and this is the only previously known example of the application of the reaction to π-electron-sufficient heteroaromatics.[2b)]
6) V. Bocchi and G. Palla, *Synthesis*, **1982**, 1096.
7) T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, and H. Yamanaka, *Chem. Pharm. Bull.*, **36**, 1305 (1988).
8) R. Garrtner, *J. Am. Chem. Soc.*, **74**, 4950 (1952).
9) *a*) T. Okuyama, K. Kunugiza, and T. Fueno, *Bull. Chem. Soc. Jpn.*, **47**, 1267 (1974); *b*) R. Stoermer and B. Kahlert, *Ber.*, **35**, 1633 (1902).
10) Y. Murakami, Y. Yokoyama, T. Miura, H. Hirasawa, Y. Kamimura, and M. Izaki, *Heterocycles*, **22**, 1211 (1984).