Palladium-Catalyzed Reaction of Aryl Bromides with Dialkylacetylenes to Produce Allenic Compounds

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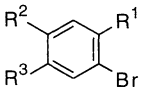
(Received May 13, 1997; CL-970358)

It has been found that aryl bromides, especially *ortho*-substituted ones, effectively react with dialkylacetylenes in the presence of a palladium catalyst and an appropriate base to give the corresponding aryl-substituted allenes as the predominant products.

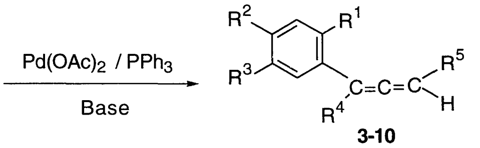
Palladium-catalyzed coupling of aryl halides and their synthetic equivalents such as aryl triflates with alkenes and alkynes as well as a number of nucleophilic reagents is now recognized to be a highly useful tool for the preparation of substituted aromatic compounds.[1,2] The reaction with alkenes (the Heck reaction) involves insertion of them to intermediary arylpalladium(II) complexes followed by elimination of hydridopalladium species to give styrene derivatives as products. In the reaction with alkynes, similar insertion may take place to give relatively stable styrylpalladium intermediates which are capable of undergoing further alkene- or alkyne-insertion or reaction with nucleophiles, while with terminal alkynes, the substitution of alkynic hydrogen often takes place to give arylalkynes. In other words, β-hydrogen elimination in the vinylic palladium intermediates has been considered to be an energetically unfavorable process.[2,3] By contrast, we observed that aryl-substituted allenes can be produced as the principal products in the palladium-catalyzed coupling of aryl bromides with dialkylacetylenes under appropriate conditions (Eq. 1). This is, to our knowledge, the first example of formation of allenic compounds with synthetically reasonable efficiency from the reaction of aryl halides with alkynes under the influence of palladium catalysis.[4]



+ $R^4C{\equiv}CCH_2R^5$

1a: $R^1 = R^3 = Me$, $R^2 = H$
1b: $R^1 = Et$, $R^2 = R^3 = H$
1c: $R^1 = R^3 = H$, $R^2 = Me$
1d: $R^1 = R^3 = H$, $R^2 = OMe$
1e: $R^1 = OMe$, $R^2 = R^3 = H$
1f: $R^1 = R^2 = R^3 = H$

2a: $R^4 = Pr$, $R^5 = Et$
2b: $R^4 = Bu$, $R^5 = Pr$
2c: $R^4 = Pr^i(CH_2)_2$, $R^5 = Pr^iCH_2$



(1)

3-10

When a mixture of 2,5-dimethylbromobenzene (**1a**) (2 mmol) and 4-octyne (**2a**) (2 mmol) was stirred in the presence of $Pd(OAc)_2$ (0.05 mmol, 2.5 mol%), PPh_3 (0.2 mmol), and Cs_2CO_3 (3 mmol) in DMF (5 cm^3) under nitrogen at 130 °C for 3 h, 5-(2,5-dimethylphenyl)-3,4-octadiene (**3**) was formed in a yield of 51% (Entry 1 in Table 1). The structure of **3** was unambiguously determined by its ^1H NMR spectrum which indicated the existence of isolated ethyl and propyl groups and a long-range coupling between the vinylic proton and the α-methylene hydrogen in the propyl substituent.[4] The IR spectrum of **3** also showed a characteristic peak at 1960 cm^{-1}. Increase in the amount of **2a** enhanced the product yield (Entries 2 and 3). Thus, **3** was obtained in a yield of 80% (71% after purification by Kugelrohr distillation) based on **1a** used.[5] The ratio of $PPh_3/Pd(OAc)_2$ was also affected the reaction (Entries 3-5); a maximum yield of **3** was obtained at a ratio of 4. While another carbonate base, K_2CO_3, could also be used as well as Cs_2CO_3,[6] the yield of **3** was very low when Na_2CO_3 or a tertiary amine, Bu_3N, was employed (Entries 6-8), suggesting that the identity of base is one of the most significant factors determining the reaction efficiency.

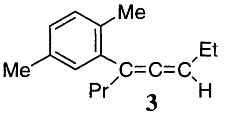
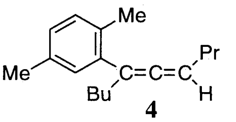
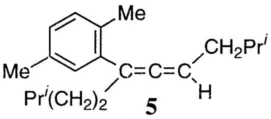
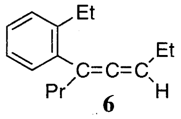
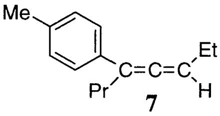
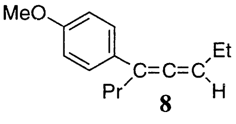
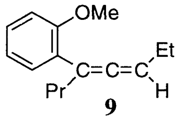
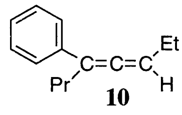
Table 1. Cross-coupling of 2,5-dimethylbromobenzene (**1a**) with 4-octyne (**2a**)[a]

Entry	**2a** / mmol	PPh_3 / mmol	Base	Yield of **3** / %[b]
1	2	0.2	Cs_2CO_3	51
2	3	0.2	Cs_2CO_3	64
3	4	0.2	Cs_2CO_3	80
4	4	0.1	Cs_2CO_3	50
5	4	0.3	Cs_2CO_3	39
6	4	0.2	K_2CO_3	81
7	4	0.2	Na_2CO_3	9
8	4	0.2	Bu_3N	3

[a]Reaction conditions: **1a** (2 mmol), $Pd(OAc)_2$ (0.05 mmol), Base (3 mmol), in DMF (5 cm^3) under N_2 at 130 °C for 3 h. [b]GLC yield based on amount of **1a** used.

Table 2 summarizes the results for the reaction of aryl bromides **1a-f** with **2a** and **1a** with 5-decyne (**2b**) and 2,9-dimethyl-5-decyne (**2c**). It can be seen that the reactions of **1** having an *ortho*-substituent can afford good product yields. While the reaction using 4-substituted aryl bromides gave relatively low product yields, the allenes formed could be readily isolated by distillation or column chromatography on silica gel. It is noted that analysis of each reaction mixture by GC-MS suggested that a number of by-products were formed and they were di- and tri-arylated compounds of **2**, although their isolation and structural determination have not yet been made. Thus, an *ortho*-substituent on **1** seems to prevent further reaction of allenes once formed. The use of relatively more reactive aryl iodides in place of aryl bromides were also found to tend to produce the by-products with higher yields. Treatment of **1a** with

Table 2. Cross-coupling of aryl bromides **1** with dialkylacetylenes **2**[a]

1	2	Time / h	Product[b]	Yield / %[c]
1a	**2a**	3	 **3**	80 (71)
1a	**2b**	1	 **4**	75 (68)
1a	**2c**	1	 **5**	83 (70)
1b	**2a**	2	 **6**	75 (62)
1c	**2a**	1	 **7**	37 (30)
1d	**2a**	1	 **8**	38 (27)
1e	**2a**	1	 **9**	72 (67)
1f	**2a**	1	 **10**	19

[a]Reaction conditions: **1** (2 mmol), **2** (4 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), Cs_2CO_3 (3 mmol) in DMF (5 cm^3) at 130 °C under N_2. [b]Satisfactory spectra were obtained in measurements of ^1H NMR, IR, and MS. [c]GLC yield based on amount of **1** used. Value in parentheses indicates yield after isolation.

ethyl 2-heptynoate gave a complex product mixture. From the reaction of **1a** with 1-trimethylsilyl-1-octyne, 1-(2,5-dimethylphenyl)-1-octyne (78%) was obtained as the product.[7]

In summary, we have presented herein that aryl bromides, especially *ortho*-substituted ones, effectively react with dialkylacetylenes by means of palladium catalysis, which may provide a convenient route to prepare some allenic compounds.

This work was partly supported by a Grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

References and Notes

1 R. F. Heck, "Palladium Reagents in Organic Syntheses," Academic Press, New York (1985).

2 J. Tsuji, "Palladium Reagents and Catalysts," Wiley, Chichester (1995), pp. 125-188.

3 E. Negishi, C. Coperet, S. Ma, and F. Liu, *Chem. Rev.*, **96**, 365 (1996).

4 Only an example of formation of an allenic product in 4% yield in the palladium-catalyzed reaction of methyl 2-iodobenzoate with 3-hexyne using triethylamine as base, to our knowledge, has been to date reported. W. Tao, L. J. Silverberg, A. L. Rheingold, and R. F. Heck, *Organometallics*, **8**, 2550 (1989).

5 Typical experimental procedure: In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (978 mg, 3 mmol) which was then dried at 150 °C *in vacuo* for 2 h. Then, **1a** (370 mg, 2 mmol), **2a** (440 mg, 4 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), PPh_3 (52.4 mg, 0.2 mmol), and DMF (5 cm^3) were added and the resulting mixture was stirred under nitrogen at 130 °C for 3 h. After cooling, the reaction mixture was extracted with diethyl ether, and dried over sodium sulfate. Product **3** (303 mg, 71%) was isolated by Kugelrohr distillation at 110 °C/2 mmHg. Anal. Found: C, 89.28; H, 10.32%. Calcd for $C_{16}H_{22}$: C, 89.66; H, 10.34%. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 0.95$ (3H, t, $J = 7.3$ Hz), 1.04 (3H, t, $J = 7.3$ Hz), 1.43-1.52 (2H, m), 2.01-2.08 (2H, m), 2.22-2.27 (2H, m), 2.29 (3H, s), 2.30 (3H, s), 5.20-5.24 (1H, m), 6.94 (1H, d, $J = 7.8$ Hz), 7.00 (1H, s), 7.05 (1H, d, $J = 7.3$ Hz). IR (neat) 1960 cm^{-1}. HRMS m/z (M^+) Found: 214.1726. Calcd for $C_{16}H_{22}$: 214.1721.

6 In the reaction with K_2CO_3, however, the product **3** was accompanied by small amounts of its two unidentified isomers (ca. 2% yield of each, confirmed by GC-MS), whereas formation of them was negligible in the case with Cs_2CO_3, which allowed to isolate **3** cleanly.

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