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Palladium-Catalyzed Coupling Reaction of 4-Alkylnitrobenzenes with Aryl Bromides at Their Benzylic Position

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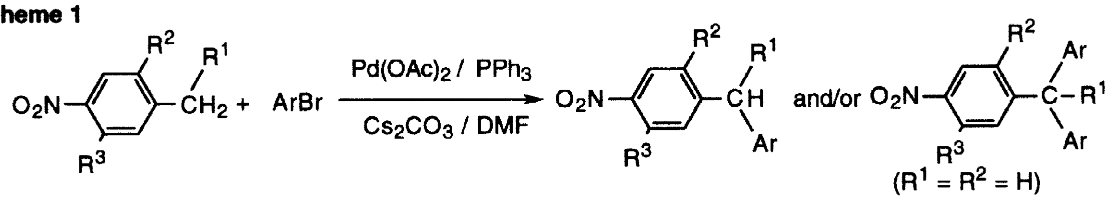
Abstract

4-Alkylnitrobenzenes effectively undergo coupling with aryl bromides at their benzylic position in the presence of a palladium catalyst and a base to give the corresponding mono- and/or di-arylated products in good yields.

Keywords: Arylation; Catalysis; Nitro compounds; Palladium and compounds

Palladium-catalyzed substitution reaction of aryl halides is now recognized to be of genuine synthetic utility [1-3]. For example, the Heck reaction with alkenes and the Suzuki and Stille coupling reactions with organoboronates and organostannanes, respectively, are often employed for the preparation of substituted aromatic compounds. Meanwhile, we have recently reported that the intermolecular cross-coupling of 2-hydroxybenzaldehydes [4], 2-phenylphenols [5], and azole compounds, including 2-substituted imidazoles, thiazoles, and oxazoles [6], with aryl halides can efficiently proceed in the presence of a palladium catalyst and an appropriate base without stoichiometric metalation to produce 2-aroylphenols, 2-(2'-arylphenyl)phenols, and 5-arylazoles [7,8], respectively. In the course of our study of arylation of aromatic substrates, we have found that 4-alkylnitrobenzenes can effectively react with aryl bromides at their benzylic position in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3, and with Cs_2CO_3 as a base, to give the corresponding mono- and/or di-

Scheme 1



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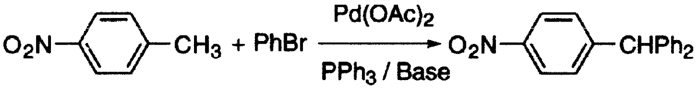
arylated products (Scheme 1). This is, to our knowledge, the first example of direct substitutive arylation on the side chain of alkylarenes under palladium catalysis, while the arylation of ketones, including benzylic ones, has been recently reported to be capable of proceeding at their α-position [5,9,10].

Table 1

Reaction of 4-nitrotoluene **1a** with bromobenzene **2a**[a]



1a **2a** **3**

Entry	**2a** / mmol	Base (mmol)	Temp / °C	Time / h	Yield of 3 / %[b]
1	1.2	Cs_2CO_3 (1.2)	140	1	18[c]
2	2.4	Cs_2CO_3 (2.4)	140	0.5	70
3	2.4	Cs_2CO_3 (2.4)	120	2	32
4	3	Cs_2CO_3 (3)	140	0.5	49
5	2	K_2CO_3 (2)	140	2	5

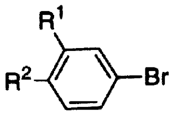
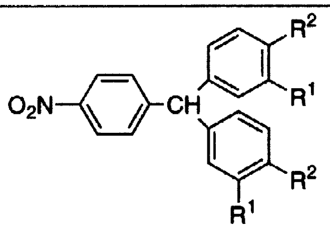
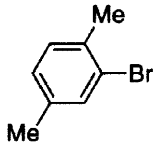
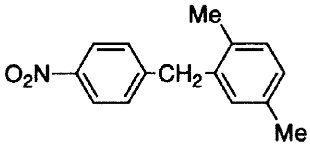
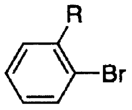
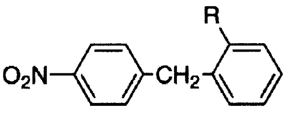
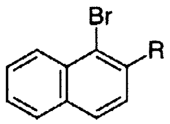
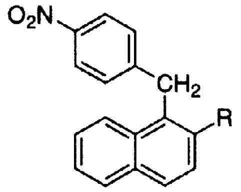
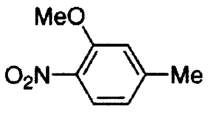
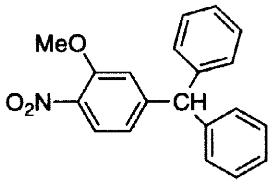
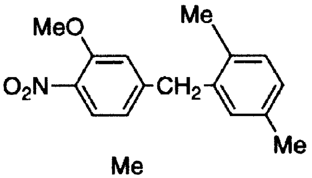
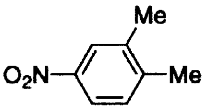
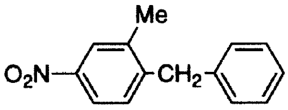
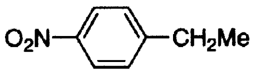
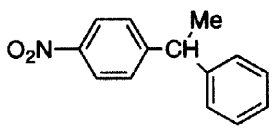
[a]Reaction conditions: **1a** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), in DMF (5 cm^3) under N_2. [b]GLC yield based on amount of **1a** used. [c]4-Benzylnitrobenzene (34%) was also formed.

When 4-nitrotoluene **1a** (1 mmol) was treated with bromobenzene **2a** (1.2 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), and Cs_2CO_3 (1.2 mmol) at 140 °C for 0.5 h under nitrogen, a mixture of 4-benzylnitrobenzene (34%) and diphenyl(4-nitrophenyl)methane **3** (18%), was produced (Entry 1 in Table 1). By using 2.4 mmol each of **2a** and Cs_2CO_3, the diphenylated product **3** was selectively obtained in a yield of 70%, formation of the mono- and tri-phenylated compounds not being detected (Entry 2). Decreasing the temperature to 120 °C or increasing the amount of **2a** to 3 mmol reduced the product yield (Entries 3 and 4). Another carbonate base, K_2CO_3, in place of Cs_2CO_3 was far less effective (Entry 5).

Table 2 summarizes the results for the reactions using a number of nitro compounds **1a-d** and aryl bromides **2a-h**.[#] The reactions of **1a** with 3- and 4-bromotoluenes **2b,c** afforded diarylated products **4** and **5**, respectively, as in the case with **2a**. In contrast, the reactions of **1a** with 2-substituted bromobenzenes **2d-f** and 1-bromonaphthalenes **2g,h** gave mono-arylated compounds **6-10** as the single major products, in spite of the fact that 2 equiv. of aryl bromides were used. From the reactions of 2-methoxy-4-methylnitrobenzene **1b** with **2a** and **2d** were obtained di- and mono-arylated compounds **11** and **12**, respectively, as expected. The reactions of 3,4-dimethyl- and 4-ethylnitrobenzenes **1c,d** with **2a** selectively gave mono-arylated products **13** and **14**. These results suggest that the present reaction is sensitive to steric factors and the second arylation is prevented by the presence of a neighboring substituent in either **1** or **2**, while it proceeds smoothly when these factors do not intervene.

[#] Typical procedure: In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (652 mg, 2 mmol) which was dried at 150 °C *in vacuo* for 2 h. Then, **1a** (137 mg, 1 mmol), **2h** (474 mg, 2 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 140 °C for 1 h. After cooling, the reaction mixture was extracted with diethyl ether, and dried over sodium sulfate. Product **10** (232mg, 79%) was isolated by column chromatography on silica gel using hexane-ether (99.5:0.5, v/v): M.p. 106-108 °C; Anal. Found: C, 73.58; H, 5.22; N, 4.96%. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78%. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 3.95$ (s, 3H), 4.55 (s, 2H), 7.30-7.54 (m, 4H), 7.43 (t, $J = 7.1$ Hz, 1H), 7.78-7.86 (m, 3H), 8.06 (d, $J = 8.8$Hz, 2H); ^{13}C NMR $\delta = 30.8$, 56.5, 113.1, 119.6, 122.9, 123.4, 123.4, 126.7, 128.5, 128.8, 128.9, 129.1, 132.9, 146.0, 149.1, 154.6; MS *m/z* 293 (M^+).

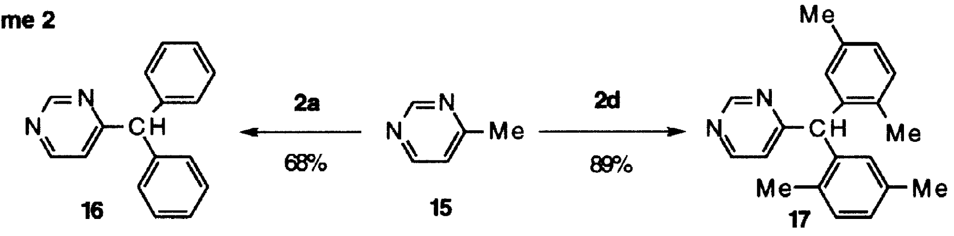
Table 2
Reaction of 4-alkylnitrobenzenes **1** with aryl bromides **2**[a]

1	2 (mmol)	Product[b]	Yield / %[c]
1a	 **2b** (2.4): R^1 = Me, R^2 = H **2c** (2.4): R^1 = H, R^2 = Me	 **4**: R^1 = Me, R^2 = H **5**: R^1 = H, R^2 = Me	54 (44) 51 (35)
1a	 **2d** (2)	 **6**	80 (73)
1a	 **2e** (2): R = Et **2f** (2): R = OMe	 **7**: R = Et **8**: R = OMe	71 (52) 63 (56)
1a	 **2g** (2): R = H **2h** (2): R = OMe	 **9**: R = H **10**: R = OMe	75 (58) 98 (79)
 **1b**	**2a** (2)	 **11**	74 (67)
1b	**2d** (2)	 **12**	96 (76)
 **1c**	**2a** (1.2)	 **13**	90 (70)
 **1d**	**2a** (2)	 **14**	91 (78)

[a]Reaction conditions: **1** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), Cs_2CO_3 (1.2-2.4 mmol) in DMF (5 cm^3) at 140 °C for 0.5-1 h under N_2. [b]Satisfactory spectra were obtained in measurements of ^1H and ^{13}C NMR and MS. [c]GLC yield based on amount of **1** used. Value in parentheses indicates yield after isolation. M.p. (°C) of **6-11** and **13** were 38-40, 62-64, 59-62, 82-83, 106-108, 140-141, and 43-44, respectively. Compounds **4**, **5**, **12**, and **14** were obtained as oils.

It may be reasonable to consider that the present coupling proceeds via the reaction of an intermediary arylpalladium species, which is formed from **2** and a Pd(0) species, with benzylic anions generated from **1** which has relatively acidic benzylic hydrogens to give an arylbenzylpalladium species and the subsequent reductive elimination affords products. The carbonate, Cs_2CO_3, which has relatively high solubility in DMF, appears to act as a good base for the abstraction of the proton from **1**. Thus, certain other alkylarenes having relatively strong electron-withdrawing substituents or alkyl-substituted heteroaromatic compounds are expected to be similarly arylated. In the preliminary examinations to confirm this consideration, 4-cyanotoluene, 4-methylbenzotrifluoride, and 3-nitrotoluene were observed to be unreactive; their benzylic hydrogens seem to be less acidic than that of **1**, as judged from the Hammett σ values of the substituents [11]. However, it was found that 4-methylpyrimidine **15** can efficiently undergo arylation under the present conditions as depicted in Scheme 2 (isolated yields are given). The exclusive formation of diarylated product **17** from the reaction with **2d** (2.4 equiv.) may be due to the fact that the methyl group of **15** is sterically less crowded than that of **1a**. It is worth noting that 2-nitrotoluene reacted with **2a** to give 2-benzoylaniline (26%) as the single coupling product; however, the mechanism for its formation is unclear at the present stage.

Scheme 2



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