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A New General Preparation of Polyfunctional Diarylamines by the Addition of Functionalized Arylmagnesium Compounds to Nitroarenes

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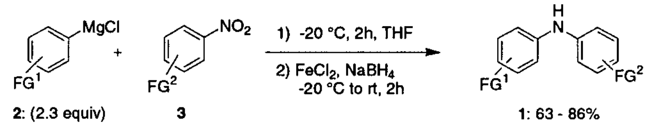
Received April 29, 2002

The arylation of amines is an important reaction since arylamines are commonly found in pharmaceuticals and materials with interesting electronic properties.[1] Recently, various diarylamines have been prepared by palladium-catalyzed cross-coupling reactions of amines with aryl halides.[2] Other transition metals such as copper[3] and nickel[4] have also allowed the performance of C−N bond-formation reactions. Oxidative coupling procedures between arylboronic acids and aromatic or heterocyclic amines mediated by Cu(II) salts are also effective.[5] In all these approaches, aromatic amines are used as precursors. We envisioned that the reaction of aromatic nitrogen compounds in a higher oxidation state with aryl organometallics should provide the desired diarylamines. The reaction of nitroarenes with aromatic Grignard reagents has been extensively studied[6] and is complicated by the sensitive nature of the resulting diarylhydroxylamines, which readily oxidize in air, leading to reactive diarylnitroxyl radicals.[7] No preparative application of diarylamines has resulted from these studies.

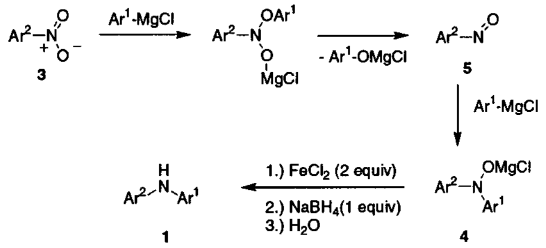
Herein, we wish to report a solution to this longstanding problem, resulting in a new general preparation of polyfunctional diarylamines of type **1**. Recently, we have developed a general preparation of functionalized arylmagnesium reagents by using a bromine− or iodine−magnesium exchange reaction.[8,9] We have now found that functionalized arylmagnesium species of type **2** react smoothly with various nitroarenes (**3**), providing after reductive workup polyfunctional diarylamines of type **1** in 63−86% yield. (Scheme 1 and Table 1).

Thus, the reaction of ethyl 4-iodobenzoate with *i*-PrMgCl in THF (−20 °C, 30 min) produces the corresponding functionalized Grignard reagent (2.3 equiv) (**2a**) to which 4-bromo-1-nitrobenzene (1 equiv) is added. After 2 h at −20 °C, the reaction is complete, and the reaction mixture is treated with EtOH (1 mL), $NaBH_4$ (1 equiv), and $FeCl_2$ (2 equiv)[10] (20 °C, 2 h), affording after chromatographical purification the diarylamine **1a** in 73% isolated yield (entry 1 of Table 1). This reaction can be applied to many functionalized arylmagnesium reagents bearing an ester, cyano, methoxy, or iodine substituent. Moreover, the nitroarene can bear either electron-withdrawing (CN, CO_2Et) or electron-donating groups (Br, OMe). The reductive workup is necessary since the intermediate diarylhydroxylamine **4** obtained is not stable in air and oxidizes rapidly, affording a diarylnitroxyl which decomposes within minutes into multiple products. We have observed that an excess (2 equiv) of the arylmagnesium reagent (Ar^1MgX) is necessary to obtain complete conversion. This can be readily explained by considering the mechanism [11] of this reaction (Scheme 2).

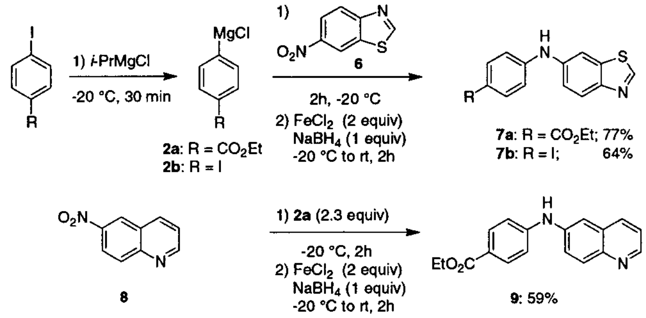
Scheme 1



Scheme 2



Scheme 3



The first Grignard equivalent adds at the oxygen of the nitro group of arene **3**, producing an intermediate arylnitroso derivative (**5**) after elimination of magnesium phenolate. Reaction of this intermediate with the second equivalent of the Grignard reagent leads to the formation of the C−N bond and produces the air-sensitive diarylhydroxylamine **4** which is converted under very mild conditions into the diarylamine **1**, by addition of $FeCl_2$ and $NaBH_4$.[10,12] We have also shown that nitrosobenzene reacts with arylmagnesium halides such as ethyl 4-iodobenzoate after iodine/magnesium exchange, furnishing the desired diarylamine after reductive treatment.[13] As indicated in Table 1, the reaction has a broad scope. Preliminary results indicate that heterocycles bearing a nitro group also undergo the arylation reaction. Thus, the reaction of 4-carbethoxyphenylmagnesium chloride (**2a**) or 4-iodophenylmagnesium chloride (**2b**) with 6-nitrobenzothiazole (**6**) leads under the usual reaction conditions to the desired arylated amines **7a,b** in 77 and 64% yield, respectively. Similarly, reaction of the nitroquinoline **8** with the arylmagnesium compound **2a** furnishes the desired aminoquinoline **9** in 59% yield (Scheme 3).

In summary, we have developed a new practical arylation of functionalized aromatic or heterocyclic nitro derivatives to amines.[14] The method complements existing procedures and appears to have a broad synthetic scope. Extensions of the reaction are currently underway.

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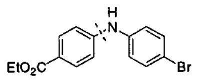
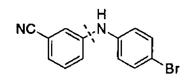
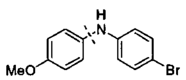
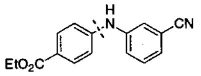
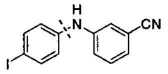
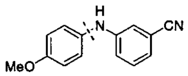
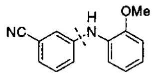
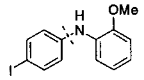
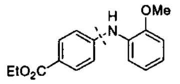
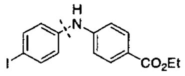
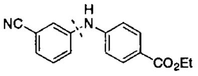
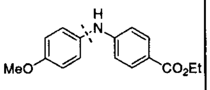
10.1021/ja026718r CCC: $22.00

Table 1. Polyfunctional Amines of Type 1 Obtained by the Reaction of Arylmagnesium Halides with Nitroarenes

Entry	Aryl Grignard **2** (FG^1)	Nitroarene **3** (FG^2)	Product of Type **1**^{a}	Yield (%)^b
1	*p*-CO$_2$Et	*p*-Br	 **1a**	73
2	*m*-CN	*p*-Br	 **1b**	78
3	*p*-MeO	*p*-Br	 **1c**	84
4	*p*-CO$_2$Et	*m*-CN	 **1d**	75
5	*p*-I	*m*-CN	 **1e**	71
6	*p*-MeO	*m*-CN	 **1f**	72
7	*m*-CN	*o*-OMe	 **1g**	74
8	*p*-I	*o*-OMe	 **1h**	86
9	*p*-CO$_2$Et	*o*-OMe	 **1i**	85
10	*p*-I	*p*-CO$_2$Et	 **1j**	71
11	*m*-CN	*p*-CO$_2$Et	 **1k**	63
12	*p*-MeO	*p*-CO$_2$Et	 **1l**	74

[a] The dotted line indicates the new C−N bond formed during the reaction. [b] Yield of analytically pure compound.

Acknowledgment. Dedicated to Professor Theodor Severin. We thank the Deutsche Forschungsgemeinschaft (Leibniz program) and I.S. thanks Aventis Pharma (Frankfurt a. M.) for a fellowship. We also thank Chemetall GmbH (Frankfurt a.M.) and BASF AG (Ludwigshafen) for generous gifts of chemicals.

Supporting Information Available: Detailed experimental procedures and characterization data of each compound (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Thomas, G. *Medicinal Chemistry*; Wiley-VCH: Weinheim, 2000. (b) Bellmann, E.; Shaheen, S.; Thayumanavan, S.; Barlow, S.; Grubbs, R.; Marder, S.; Kippelen, B.; Peyghambarian, N. *Chem. Mater.* **1998**, *10*, 1668−1676.

(2) (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.***1999**, *576*, 125−146. (b) Wolfe, J. P.; Wagan, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. Hartwig, J. F. In *Modern Amination Methods*; Ricci, A. Ed.; Wiley-VCH: Weinheim, 2000. For mechanistic studies, see: Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618−4630.

(3) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803−3805. (c) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333−1336. (d) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986−2987.

(4) (a) Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4492−4494. (b) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 247−250.

(5) (a) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077−2079. (b) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233−1236. (c) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415−3418. (d) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G.; *J. Am. Chem. Soc.* **2000**, *122*, 7600−7601.

(6) (a) Wieland, H. *Chem. Ber.* **1903**, *36*, 2315 (b) Gilman, H.; McCracken, R. *J. Am. Chem. Soc.* **1927**, *49*, 1052−1061. (c) Severin, T.; Schmitz, R. *Chem. Ber.* **1963**, *96*, 3081−3084. (d) Severin, T.; Adam, M. *Chem. Ber.* **1964**, *97*, 186−189. (e) For an excellent review, see: Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109−115. (f) Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R.; Ciminale, F. *J. Chem. Soc., Perkin Trans. 2* **1985**, 773−779.

(7) Berti, C. *Synthesis* **1983**, 793−794.

(8) For reviews, see: (a) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565−569. (b) Rottländer, M.; Boymond, L.; Berillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem.—Eur. J.* **2000**, *6*, 767−770. See also: (c) Varchi, G.; Jensen, A. E.; Dohle, W.; Ricci, A.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 477−480.

(9) (a) Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618−4634. (b) Dohle, W.; Lindsay, D. M.; Knochel, P. *Org. Lett.* 2001, 3, 2871−2873. (c) Sapountzis, I.; Dohle, W.; Knochel, P. *Chem. Commun.* **2001**, 2068−2069. see also (d) Lee, J.; Valende-Ortiz, R.; Guijairo, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428−5430. (e) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481−2483.

(10) Ono, A.; Sasaki, H.; Yaginuma, F. *Chem. Ind. (London)*, **1983**, 480.

(11) Koebrich, G.; Buck, P. *Chem. Ber.* **1970**, *103*, 1412−1419.

(12) There is good evidence for this mechanism, since no products of type Ar^1−NH−Ar^1 are detected. Such products should appear if C−N-bond formation takes place via a type of 1,2-addition to the nitroarene **1**. Yost, Y.; Gutmann, H. R.; Muscoplat, C. C. *J. Chem. Soc. C* **1971**, 2119−2122.

(13) The reaction of nitrosobenzene with 4-carbethoxyphenylmagnesium chloride (**2a**) (1.2 equiv) furnished under standard conditions ethyl 4-anilinobenzoate in 70% yield. See also: Bartoli, G.; Rosini, G.; *Synthesis* **1976**, 270−271.

(14) **Typical Experimental Procedure**. In a dry and argon-flushed 25-mL flask, equipped with a magnetic stirrer and a septum, the iodobenzene derivative (3.5 mmol) was dissolved in dry THF (8 mL) and cooled to −20 °C, and *i*-PrMgCl (3.6 mmol, 0.85 M in THF) was added dropwise. The I/Mg exchange was complete after 30 min, and functionalized nitrobenzene (1.5 mmol) was added. After 2 h of stirring at −20 °C, the reaction was quenched with ethanol (1 mL), and FeCl$_2$ (3 mmol) and NaBH$_4$ (1.5 mmol) were added. After 2 h stirring at room temperature, the reaction mixture was poured into water (25 mL). The aqueous phase was extracted with diethyl ether (3 × 40 mL). The organic fractions were washed with brine (30 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Chromatographical purification on silica gel furnished the product.

JA026718R