Preparation of Polyfunctional Amines by the Addition of Functionalized Organomagnesium Reagents to Nitrosoarenes

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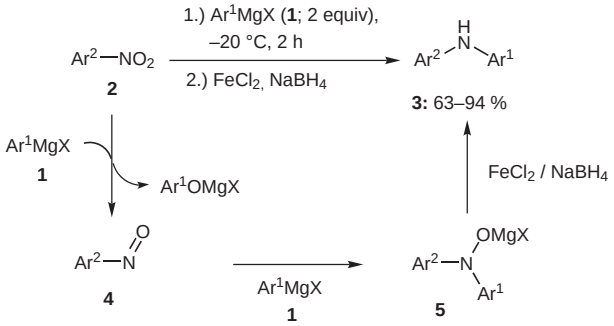
Abstract: The addition of functionalized arylmagnesium reagents to nitrosoarenes at –20 °C in THF furnishes after a reductive workup polyfunctional diarylamines in 43–74% yield.

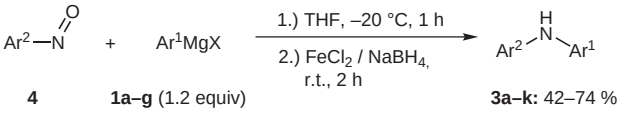
Key words: diarylamines, nitrosoarenes, organomagnesium reagents, arylation of amines, amination reaction

The amination of aryl halides is an important reaction.[1] Recently, several Pd(0)[2] and Cu(I)[3] catalyzed reactions between aromatic halides and various amines have been reported.[4] We found that this synthetic transformation can also be realized by reacting various polyfunctional arylmagnesium species **1** with nitroarenes **2** leading after a reductive workup procedure to polyfunctional amines of type **3** (Scheme 1).[5] This reaction requires two equivalents of the arylmagnesium reagent **1** since a first equivalent is wasted for the generation of the reactive nitrosoarene **4**, which reacts in a second step with Ar^1MgX **1** providing the magnesiated hydroxylamine **5**.[6] After reduction with $FeCl_2/NaBH_4$ the amines **3** are produced in good yields. Since a wide range of polyfunctional arylmagnesium reagents **1**[7] can be used for this amination, the waste of one equivalent of Ar^1MgX (converted to Ar^1OH) is disturbing. This could now be avoided by using directly the nitrosoarene[8] **4** for the amination reaction. Herein, we wish to report an efficient method allowing the direct addition of various arylmagnesium compounds **1** to various nitrosoarenes **4** leading after reductive workup to the polyfunctional diarylamines **3a**–**k** (Scheme 2 and Table 1).



Scheme 1

The reaction mixture of PhMgCl (**1a**; 1.2 equiv) with nitrosobenzene (**4a**; 1 equiv) in THF at –20 °C was stirred for 1 h and treated with $FeCl_2/NaBH_4$ at 25 °C for 2 h affording diphenylamine (**3a**) in 68% yield (entry 1 of Table 1). Several functionalized arylmagnesium compounds (**1b**–**f**) bearing either electron-withdrawing or electron-donating groups add to nitrosobenzene **4a** in satisfactory yields (entries 2–6). Functionalized or substituted nitrosobenzenes like **4b**–**c** undergo the addition reaction furnishing the polyfunctional diarylamines **3g**–**k** in 42–74% yield (entries 7–11). This new procedure allows the preparation of polyfunctional diarylamines **3** bearing various functional groups with an optimum atom economy, since only 1.2 equivalents of the Grignard reagent are used compared to 2.3 equivalents, which are required in the reaction with nitroarenes.



Scheme 2

In summary, we have developed a new synthesis of polyfunctional diarylamines by the addition of arylmagnesium halides to nitrosoarenes. The study of the extension of this reaction is currently underway in our laboratories.

Preparation of 4-Iodophenyl-phenylamine (3d); Typical Procedure

A dry, argon-flushed Schlenk-flask equipped with a septum and a magnetic stirring bar was charged with 1,4-diiodobenzene (791 mg, 2.40 mmol, 1.2 equiv) in anhydrous THF (8 mL) and cooled to –20 °C. *i*-PrMgCl (3.30 mL, 2.64 mmol, 1.3 equiv; 0.8 M in THF) was added dropwise via a cannula. The resulting mixture was stirred 0.5 h at –20 °C. When the iodine-magnesium-exchange was complete (as indicated by GC-MS-analysis of a reaction aliquot), nitrosobenzene (**4a**; 214 mg, 2.00 mmol) was added neat as one portion and the mixture was stirred for another 1.5 h at –20 °C. After quenching the reaction mixture by addition of ethanol (1 mL), it was allowed to warm up to room temperature. Iron(II)chloride (507 mg, 4.00 mmol, 2.0 equiv) and sodium borohydride (76 mg, 2.00 mmol, 1.0 equiv) were added. The reaction mixture was stirred for 2 h at

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room temperature and poured into brine (30 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL), the combined organic extracts were washed with brine (50 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by flash chromatography (silica gel, pentane/CH_2Cl_2, 7:1). After chromatographical purification, the product was dried in high vacuum, dissolved again in ether and filtered over cotton wool. Removal of solvent afforded the product (**3d**) as pale yellow, crystalline solid (419 mg, 1.42 mmol, 71% yield).[9]

Table 1 Polyfunctional Diarylamines of Type **3** Obtained by the Reaction of Arylnitroso Compounds **4** with Functionalized Arylmagnesium Reagents **1**

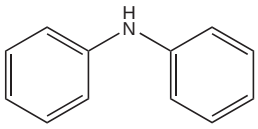
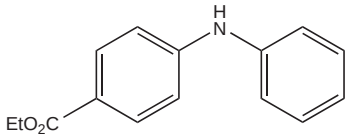
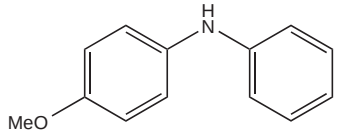
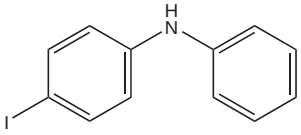
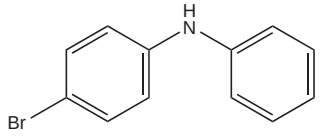
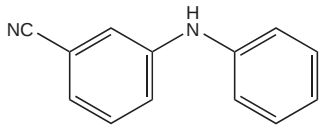
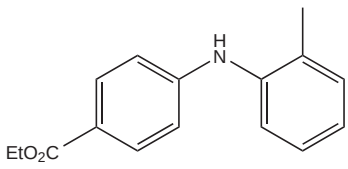
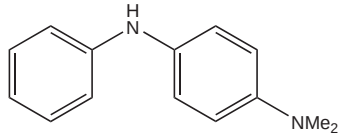
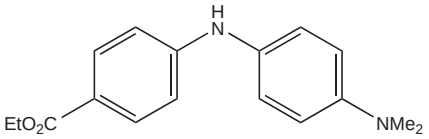
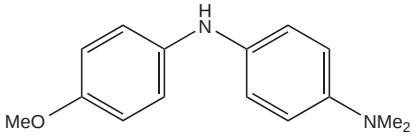
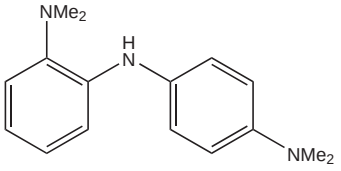
Entry	Ar^2NO **4**	Ar^1MgX **1**	Diarylamines **3**	Yield (%)[a]
1	PhNO **4a**	PhMgCl **1a**	 **3a**	68
2	PhNO **4a**	*p*-EtO_2C-C_6H_4-MgCl **1b**	 **3b**	73
3	PhNO **4a**	*p*-MeO-C_6H_4-MgBr **1c**	 **3c**	50
4	PhNO **4a**	*p*-I-C_6H_4-MgCl **1d**	 **3d**	71
5	PhNO **4a**	*p*-Br-C_6H_4-MgCl **1e**	 **3e**	43
6	PhNO **4a**	*m*-CN-C_6H_4-MgCl **1f**	 **3f**	58
7	*o*-Me-C_6H_4-NO **4b**	*p*-COOEt-C_6H_4-MgCl **1b**	 **3g**	42
8	*p*- Me_2N-C_6H_4NO **4c**	PhMgCl **1a**	 **3h**	73

Table 1 Polyfunctional Diarylamines of Type **3** Obtained by the Reaction of Arylnitroso Compounds **4** with Functionalized Arylmagnesium Reagents **1** (continued)

Entry	Ar^2NO **4**	Ar^1MgX **1**	Diarylamines **3**	Yield (%)[a]
9	*p*-Me_2N-C_6H_4-NO **4c**	*p*-EtO_2C-C_6H_4-MgCl **1b**	 **3i**	72
10	*p*-Me_2N-C_6H_4-NO **4c**	*p*-MeO-C_6H_4-MgBr **1c**	 **3j**	74
11	*p*-Me_2N-C_6H_4-NO **4c**	*o*-Me_2N-C_6H_4-MgCl **1g**	 **3k**	60

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(9) Analytical data of **3d**: Mp: 103–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 5.59 (br s, 1 H, NH), 6.73–6.76 (d, ^3J = 8.48 Hz, 2 H, $CH_{arom.}$), 6.87–6.99 (m, 3 H, $CH_{arom.}$), 7.18–7.23 (m, 2 H, $CH_{arom.}$), 7.42–7.45 (d, ^3J = 8.48 Hz, 2 H, $CH_{arom.}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 82.07, 118.53, 119.25, 121.80, 129.42, 138.06, 142.16, 143.13; IR (KBr): [cm^{-1}] = 3399 (s), 3054 (w), 3028 (w), 1932 (w), 1603 (s), 1581(vs), 1503(vs), 1482(vs), 1441 (m), 1387 (m), 1338 (w), 1315(vs), 1282 (m), 1238 (m), 1175 (m), 1154 (w), 1106 (w), 1078 (w), 1058 (w), 1027 (w), 1000 (w), 932 (w), 873 (w), 836 (m), 826 (m), 806 (m), 749 (s), 702 (m), 691 (s), 670 (w), 650 (w), 626 (w), 588 (w), 502 (m), 488 (w); MS (EI): *m/z* (*I*): 295 (100, M^+), 167 (31), 139 (2), 84 (8), 77 (2); HRMS: calcd: 294.9858; found: 294.9856; $C_{12}H_{10}IN$: calcd: C: 48.84; H: 3.42; N: 4.75; I: 43.00; found: C: 48.93; H: 3.40; N: 4.74; I: 42.99.