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Preparation of diarylamines by the addition of 4-(*N*,*N*-dimethylamino)phenyllithium to nitroarenes

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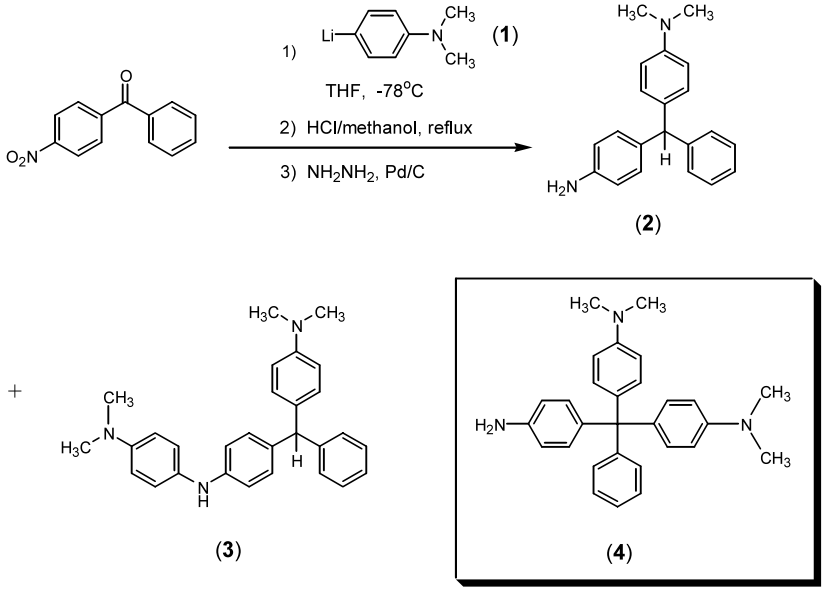
Abstract—The addition of 4-(*N*,*N*-dimethylamino)phenyllithium to nitroarenes in THF (−78°C) affords the corresponding diarylamines in one-pot and the reaction appears to be general in scope. A 'nitroso'-based mechanism is proposed for this novel nitroreductive *N*-arylation reaction.

We have recently developed[1] a general method for the preparation of *N*-desmethylated metabolites of malachite green, a potentially genotoxic dye.[2] We envisioned[1] that an addition of 4-(*N*,*N*-dimethylamino)phenyllithium (**1**) to 4-nitrobenzophenone should give the didesmethyl leuco derivative **2** after the usual acid-catalyzed dehydration and reduction (Scheme 1). Interestingly, however, the sequence afforded a 1:7 ratio of the desired **2** and a tandem addition adduct **3**, whose structures have been thoroughly characterized.[1] The major product was initially thought to be the isomeric adduct **4**; however, the identity of **3** was confirmed by NMR.[3] Clearly, the formation of the diarylamine **3** can be rationalized in terms of simultaneous addition of **1** to both the ketone and nitro groups of 4-nitrobenzophenone.



Scheme 1.

Keywords: aryllithium; diarylamine; nitroarene.
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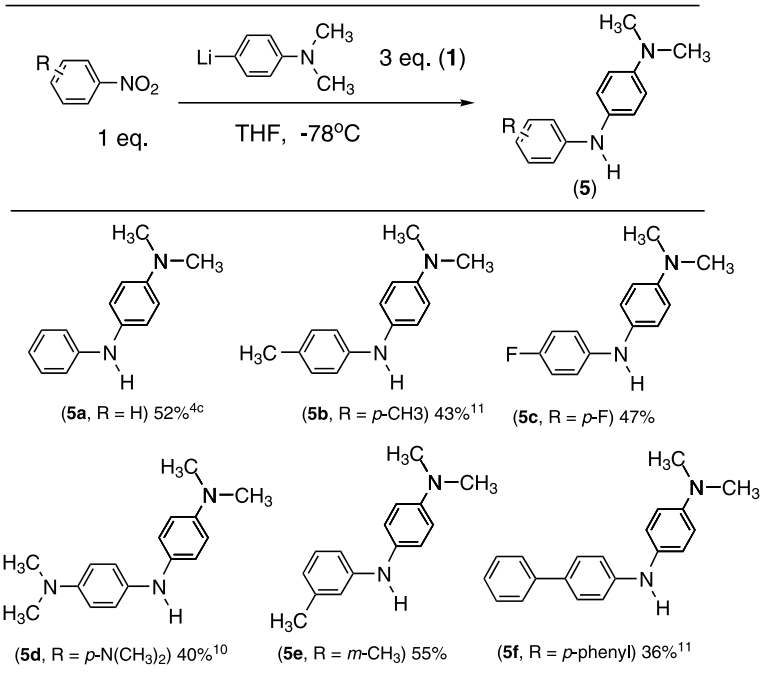
Diarylamines belong to an important class of functional groups that are accessible mostly via metal-catalyzed cross-coupling reactions using aromatic amines (collectively known as Buchwald–Hartwig reaction) as precursors.[4] While the reaction of nitroarenes with Grignard reagents has been studied extensively,[5] surprisingly little is known about analogous reactions with organolithium agents. Buck and Kobrich[6] have reported that nitrobenzene, or nitrosobenzene, reacts with excess phenyllithium to give diphenylamine and azobenzene as well as phenol. The phenol formation reaction, which utilizes nitrobenzene as a novel aromatic hydroxylating agent, has been employed for the preparation of certain phenolic substances that are otherwise difficult to obtain.[7] However, the use of nitroarenes as precursors for the preparation of diarylamines has not been explored. We have investigated the reactions of various nitroarenes with **1** and found that the corresponding diarylamines[8] can be prepared in a simple, one-step process.

A series of nitroarenes have been employed to give the *N*,*N*-dimethylated diarylamines in moderate yields (Table 1).[9] The use of excess (at least 3 equiv.) aryllithium is required to complete the nitroreductive *N*-arylation (Scheme 2). All the reactions were conducted under nitrogen with exclusion of oxygen. Although yields are generally lower than the existing Grignard-based[5b] and metal-catalyzed reactions,[4] the new reaction is simple and is complementary to existing procedures. It offers a valuable alternative of using nitroarenes as a starting material for aromatic carbon–nitrogen bond formation.

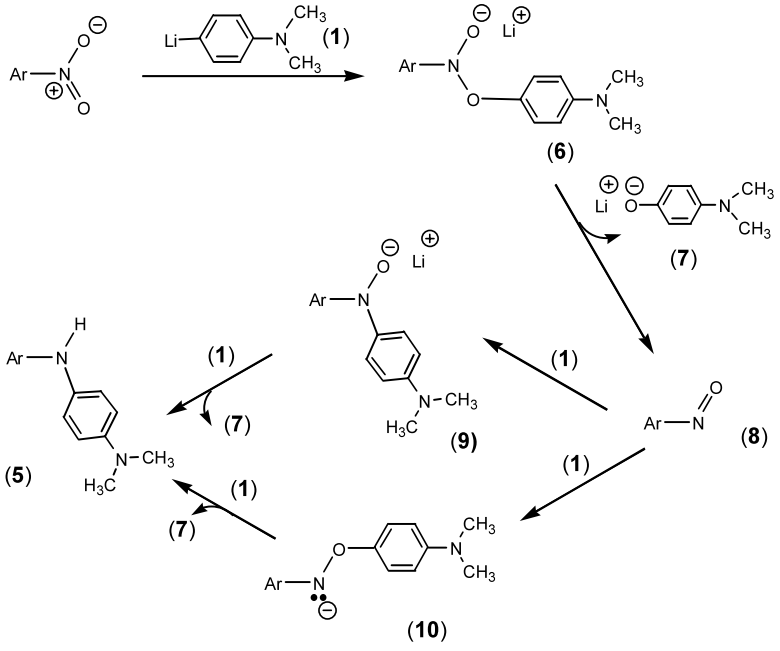
While the mechanisms of the nitroreductive *N*-arylation with Grignard reagents have been studied,[5] little is known regarding the reactions with aryllithium. Reaction of nitroarenes with aryl Grignard reagents is shown to produce a coupled product diaryl hydroxylamine via a nitroso intermediate. The resulting hydroxylamine could be further reduced to diarylamine by an additional Grignard reagent,[5d,e] but Sapountzis and Knochel[5b] have reported that a reductive workup procedure ($NaBH_4/FeCl_2$ or Zn) is required for its preparative application. The general validity of this mechanism had been substantiated by isolation of the highly air sensitive hydroxylamine intermediate and the corresponding phenol.

A similar mechanism can be applied for reactions with aryllithium. Thus, the first equivalent of **1** attacks the oxygen atom of the nitro group via either a radical or a polar mechanism to produce an adduct **6** (Scheme 2). Decomposition of **6** furnishes **8** and 4-(*N*,*N*-dimethylamino)phenol (**7**).[12] Like the Grignard case, the nitroso intermediate **8** may react with the second equivalent of **1** to form a 'hydroxylamine' intermediate (**9**). Alternatively, a novel 'nitrenoid' (**10**) intermediate can be formed if addition occurs at the oxygen atom of the nitroso group of **8**.[6a,13] These species can then react with the third equivalent of **1** to produce diarylamine **5** and **7** upon protonation. Support for these mechanisms comes from the fact that the phenol **7** is isolated as a main product and that reaction yields increase with the use of 3 equivalents of **1** (Table 1). We have shown that nitrosobenzene reacts with 3 equivalents of **1** to give **5a**

Table 1. Reactions of 4-(*N*,*N*-dimethylamino)phenyllithium (**1**) with nitroarenes[a]



[a]all new compounds were characterized by NMR, MS, and elemental analyes and showed typical AX NMR spectral patterns for para substitution.[9]



Scheme 2.

as the sole product (44%). This is contrasted with the analogous reaction with arylmagnesium chloride, which required a reductive work up. It appears that the hardness of aryllithium reagent is an important factor in determining the relative propensity for phenol formation. Also, it may be that the lithiated **5** is sufficiently electron-rich to compete with **1** for reducing the hydroxylamine **9**, thereby decreasing the overall yield. Colored reaction mixtures indicate that some byproducts might be formed from the radical, $Me_2NC_6H_4^{\bullet}$, produced in reactions involving single electron transfers via charge transfer complexes.

In summary, we have described a novel aryl carbon–nitrogen bond formation involving nitroarenes and aryllithium. The reaction of aryllithium **1** with nitroarenes provides direct access to *N*,*N*-dimethylated diarylamines in one-pot without any additional reduction steps and appears to be general in scope. Efforts to elucidate the reaction mechanism and to expand nitroarenes to prepare a variety of diarylamines including arylamine-nucleoside adducts are currently underway.

Acknowledgements

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3. **3**: mp 155–156°C (ethylacetate:hexane): TLC R_f 0.31 (benzene:hexane:ether:triethylamine = 10:15:3:0.5), R_f 0.75 ($CHCl_3$:MeOH = 95:5); HPLC t_R 23.7 min (acetonitrile in 0.1 mM pH 4.50 ammonium acetate 10–90%, a 30 min gradient); $UV_{\lambda max}$ 297 nm (log 4.60), 263 nm (log 4.57): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55 (s, NH, 1H, H_{13}, D_2O exchangeable), 7.26 (dd, 2H, H_4, J = 7.53, 7.60 Hz), 7.15 (dd, 1H, H_5, J = 7.32, 7.34 Hz), 7.08 (d, 2H, H_3, J = 7.22 Hz), 6.94 (d, 2H, H_8, J = 8.91 Hz), 6.90 (d, 2H, H_2, J = 8.71 Hz), 6.84 (d, 2H, H_6, J = 8.59 Hz), 6.77 (d, 2H, H_7, J = 8.61 Hz), 6.67 (d, 2H, H_9, J = 8.95 Hz), 6.64 (d, 2H, H_1, J = 8.75 Hz), 5.29 (s, 1H, H_{10}), 2.83 (s, 6H, H_{12}), 2.80 (s, 6H, H_{11}); ^{13}C NMR (126 MHz, DMSO-d_6) δ 148.74 (q), 145.86 (q), 145.27 (q), 143.89 (q), 133.64 (q), 133.03 (q), 132.11 (q), 129.47 (C6), 129.38 (C2), 128.84 (C4 or C3), 128.04 (C3 or C4), 125.71 (C5), 120.87 (C8), 114.10 (C7), 113.85 (C9), 112.35 (C1), 54.40 (C10), 40.85 (C11), 40.22 (C12); ESI-MS m/z 422 (M+1); HRMS calcd for $C_{29}H_{31}N_3$, 421.2510. Found 421.2518. Anal. calcd for $C_{29}H_{31}N_3$, C, 82.62; H, 7.41; N, 9.97%. Found C, 82.70; H, 7.66; N, 9.89.
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9. **Typical procedure for the synthesis of 5a–f**: Butyllithium (5.6 mL, 1.6 M in hexane, 9.0 mmol) was added via a syringe to a solution of *N*,*N*-dimethyl-4-bromoaniline (1.8 g, 9.0 mmol) in dry THF (50 mL) at −78°C under a nitrogen atmosphere. The resulting turbid solution was stirred at the same temperature for 2 h. A solution of nitroarene (2.5 mmol, Table 1) in dry THF (50 mL) was added dropwise to the mixture, which turned to orange initially and then dark brown. The reaction mixture was warmed slowly to room temperature and stirred overnight. The reaction was quenched by addition of H_2O and the residual THF was evaporated. The aqueous residue was then extracted with ether and the combined ether extracts were washed with H_2O and dried over anhydrous $MgSO_4$. The purification by column chromatography on silica (ethyl acetate and hexane), followed by recrystallization from ethyl acetate and hexane, afforded pure products (**5a–f**, Table 1). **5a**: mp 130–131°C;[4c] ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (s, 1H, D_2O exchangeable), 7.11 (dd, $J=7.91$ Hz, 2H), 6.99 (d, $J=8.83$ Hz, 2H), 6.84 (d, $J=7.72$ Hz, 2H), 6.72 (d, $J=9.19$ Hz, 2H), 6.64 (dd, $J=7.54$ Hz, 1H), 2.82 (s, 6H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 148.06, 147.71, 134.08, 129.93, 123.35, 118.96, 115.57, 114.91, 41.42; LRMS (70 eV) m/z (%) 212.1 (100, M^+), 197.1 (41), 167.1 (14). **5b**: mp 91–92°C;[11] ^{1}H NMR (300 MHz, DMSO-d_6), δ 7.50 (s, 1H, D_2O exchangeable), 6.94 (d, $J=8.83$ Hz, 4H), 6.77 (d, $J=8.09$ Hz, 2H), 6.70 (d, $J=8.83$ Hz, 2H), 2.81 (s, 6H), 2.17 (s, 3H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 147.71, 145.06, 135.06, 130.43, 128.19, 122.46, 116.33, 115.10, 41.55, 20.66; LRMS (70 eV) m/z (%) 226.2 (100, M^+), 211.1 (39), 112.9 (12), 83.9 (13). **5c**: mp 105–107°C, ^{1}H NMR (300 MHz, acetone-d_6 with D_2O): δ 6.98 (d, $J=8.45$ Hz, 1H), 6.88 (m, 4H), 6.72 (d, $J=8.46$ Hz, 2H), 2.80 (s, 6H); ^{13}C NMR (75.5 MHz, acetone-d_6): δ 157.21 (d, $^1J_{C\text{-}F}=234.4$ Hz), 148.06, 144.15, 134.65, 122.91, 117.12 (d, $^3J_{C\text{-}F}=7.32$ Hz), 116.33 (d, $^2J_{C\text{-}F}=21.97$ Hz), 115.05, 41.46; LRMS (70 eV) m/z (%) 230.1 (100, M^+), 215.1 (41), 185.1 (13), 114.8 (16); HRMS calcd for $C_{14}H_{15}N_2F$: 230.1219. Found: 230.1219; Anal. calcd for $C_{14}H_{15}N_2F$ C, 73.02; H, 6.57; N, 12.16; F, 8.25. Found: C, 73.26; H, 6.53; N, 11.91; F, 8.03. **5d**: mp 120.7–121.4°C;[10] ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.18 (s, 1H), 6.84 (d, $J=8.83$ Hz, 4H), 6.66 (d, $J=8.82$ Hz, 4H), 2.77 (s, 12H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 146.69, 137.56, 119.89, 115.57, 41.86; LRMS (70 eV) m/z (%) 255.1 (100, M^+), 240.1 (35), 126.8 (23). **5e**: mp 92.5–93.5°C; ^{1}H NMR (300 MHz, acetone-d_6 with D_2O) δ 6.99 (m, 3H), 6.71 (m, 4H), 6.48 (d, $J=6.98$ Hz, 1H), 2.83 (s, 6H), 2.17 (s, 3H); ^{13}C NMR (75.5 Hz, acetone-d_6) δ 148.01, 147.67, 139.38, 134.28, 129.82, 123.36, 119.94, 116.35, 114.93, 112.94, 41.46, 21.78; LRMS (70 eV) m/z (%) 226.2 (100, M^+), 211.1 (44); HRMS calcd for $C_{15}H_{18}N_2$: 226.1470. Found: 226.1467; Anal. calcd for $C_{15}H_{18}N_2$ C, 79.61; H, 8.02; N, 12.38; F, 8.25. Found: C, 79.76; H, 7.91; N, 12.41. **5f**: mp 124–126°C;[11] ^{1}H NMR (300 MHz, acetone-d_6 with D_2O) δ 7.55 (dd, $J=7.36$ Hz, 2H), 7.44 (d, $J=8.46$ Hz, 2H), 7.36 (dd, $J=7.91$ Hz, 2H), 7.22 (dd, $J=7.36$ Hz, 1H), 7.06 (d, $J=8.82$ Hz, 2H), 6.98 (d, $^3J=8.83$ Hz, 2H), 6.76 (d, $J=9.19$ Hz, 2H), 2.84 (s, 6H); ^{13}C NMR (75.5 MHz, acetone-d_6) δ 148.27, 147.34, 142.24, 133.74, 131.58, 129.67, 128.46, 126.96, 126.89, 123.66, 115.81, 114.91, 41.41. LRMS (70 eV) m/z (%) 288.2 (100, M^+), 273.2 (30), 143.9 (17).
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