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# Synthesis of N,N-Dimethylamines via Barbier–Grignard-Type Electrophilic Amination

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**Abstract:** Aryl Grignard reagents react with N,N-dimethyl O-(mesitylenesulfonyl)-hydroxylamine in THF under Barbier conditions at room temperature and give N,N-dimethylanilines with high yields in a 2-h reaction. The amination yield of in situ Grignard reagents were not lower than those of preformed aryl Grignard reagents. In situ cycloalkyl-, allyl-, and benzylmagnesium bromides did not react with N,N-dimethyl O-(mesitylenesulfonyl)hydroxylamine, except that amination of in situ n-hexylmagnesium bromide resulted in a medium yield. Grignard–Barbier-type amination of aryl bromides with N,N-dimethyl O-(mesitylenesulfonyl)hydroxylamine provides a new alternative route for the synthesis of N,N-dimethylanilines.

**Keywords:** Barbier–Grignard reaction, electrophilic amination, N,N-dimethylanilines, tertiary amines

Amines constitute an important class of compounds in organic synthesis.[1] In particular, arylamines have attracted much attention because of their subunit character in the structure of various natural products and biologically active compounds. Amines are generally prepared by nucleophilic amination, that is, coupling of an electrophilic carbon with a nucleophilic aminating reagent, $NH_2^{\oplus}$.[2] Recently, Cu-catalyzed or mediated Ullman-type

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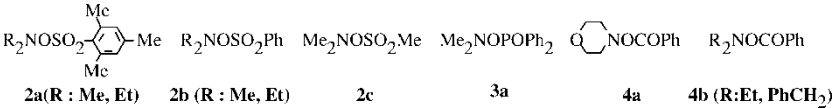
amination,[3] Pd-catalyzed Hartwig–Buchwald-type amination,[4,5] and Ni-catalyzed amination[6] of aryl halides with amines provide convenient and practical methods for the synthesis of arylamines. Another important strategy is electrophilic amination, that is, coupling of carbanions with an electrophilic aminating reagent, $NH_2^{\oplus}$.[2,7–9] This type of *umpolung* amination constitutes a potentially valuable method for transfer of an amino group to carbanions[10–12] and enolates[13,14] to give amines and $\alpha$-aminocarbonyl compounds, respectively. In addition, a successful asymmetric version of electrophilic amination provides the most important and general methods for the formation of chiral C—N bonds in stereomeric $\alpha$-aminoacids.[13,14]

As $NH_2^{\oplus}$ synthons, a number of $sp^3N$ or $sp^2$-containing reagents have been extensively used for electrophilic amination. $sp^3$-N-Type aminating reagents react with carbanions directly (Scheme 1) to give primary amines[7–12] and N-protected primary amines.[7–12,15] However, to date there have been a limited number of reagents and methods to prepare secondary and tertiary amines by electrophilic amination of carbanions.

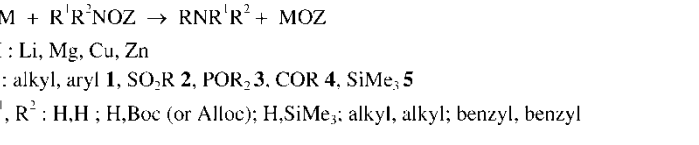
Boche et al. used N,N-dialkyl O-(arenesulfonyl)hydroxylamines **2a,b** successfully for the amination of organolithiums and phenyl and $\alpha$-naphthyl Grignard reagents under mild conditions.[16] They also carried out amination of cyclopentadienyllithium with **2c**[17] and amination of lithium 1-alkynylcuprates with **3a** with good yields.[18] Amination of diazapentalene was also successful using **2a** (R: Et).[19]



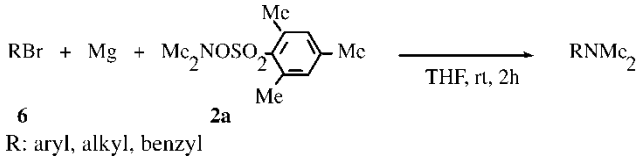

**2a(R : Me, Et)** **2b (R : Me, Et)** **2c** **3a** **4a** **4b (R:Et, $PhCH_2$)**

Johnson and Berman recently reported a general, convenient, and high-yield method for the synthesis of tertiary amines by copper-catalyzed amination of diorganozincs[20] and functionalized diarylzincs[21] and also nickel-catalyzed amination of organozinc halides[22] with N,N-dialkyl O-(benzoyl)hydroxylamines **4a,b.**

We have previously shown Barbier conditions to be applicable to electrophilic amination of Grignard reagents,[23] that is, we successfully carried out the amination of in situ prepared arylmagnesium bromides with acetone O-(2,4,6-trimethylphenylsulfonyl)oxime.[24]




***Scheme 1.*** Electrophilic amination of organometallics with $sp^3N$-type aminating reagents.




***Scheme 2.*** Synthesis of N,N-dimethylamines by Barbier–Grignard-type amination.

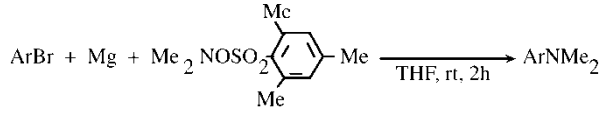


Encouraged by these results, we examined **2a** (R:Me) as aminating reagent in our in situ protocol, which gives expeditious access to the synthesis of tertiary amines. N,N-dialkyl O-(2,4,6-trimethylphenylsulfonyl)-hydroxylamines **2a,b** are easily prepared aminating reagents,[16] and prepre-pared organolithiums and unsubstituted aryl Grignard reagents were reported to have no practical problems in their amination with **2a** or **2b**. However, amination of in situ prepared Grignard reagents is, by all means, a less time-consuming procedure leading to fewer by-products.

Herein, we report a novel and efficient method for synthesis of N,N-dimethylanilines by Barbier–Grignard-type electrophilic amination (Scheme 2).

We carried out a series of reactions to establish the optimum conditions required for C–N coupling of in situ Grignard reagents with the $Me_2N^{\oplus}$ synthon. High yields of N,N-dimethylanilines were obtained by simultaneous

***Table 1.*** Amination of aryl Grignard reagents with N,N-dimethyl O-(2,4,6-trimethylphenyl-sulfonyl) hydroxylamine **2a** (R:Me) under Barbier conditions[a]




**2a**

| Entry | Ar | Yield (%)[b–d] |
|---|---|---|
| 1 | $C_6H_5$ **6a** | 81 (82) |
| 2 | 4-$MeC_6H_4$- **6b** | 79 (86) |
| 3 | 3-$MeC_6H_4$- **6c** | 83 (87) |
| 4 | 2-$MeC_6H_4$- **6d** | 60 |
| 5 | 4-$MeOC_6H_4$- **6e** | 80 (86) |
| 6 | 3-$MeOC_6H_4$- **6f** | 78 (91) |

[a]In situ prepared ArMgBr reagent (3 equiv.) was aminated with **2a** (1 equiv.) at room temperature.

[b]Yield of amine isolated after hydrolytic workup. The purity of amines are at least 95% as judged by GC analysis.

[c]GC yields are given in parentheses.

[d]Isolated yields and GC yields are averages of at least two reactions.

addition of 3 equiv. of aryl bromide and a THF solution of 1 equiv. of **2a** (R:Me) to 3.6 equiv. of Mg at room temperature and stirring the mixture at this temperature for 2 h.

Phenyl- and a number of substituted phenylmagnesium bromides were successfully aminated under Barbier conditions (Table 1). The yields are not lower than those obtained with preprepared aryl Grignard reagents. For example, amination of preprepared phenylmagnesium bromide with **2a** (R:Me) at room temperature gave 71% yield. (The reported[16] yield is 42%.) In comparison, amination of in situ prepared phenylmagnesium bromide gave the product in 81% yield. However, trying to aminate in situ prepared 3-bromophenylmagnesium bromide gave a mixture of products, and amination of in situ prepared 4-(trifluoromethyl)phenylmagnesium bromide resulted in 26% yield of product.

In our attempt to extend the Barbier–Grignard-type amination, n-hexylmagnesium bromide and benzylmagnesium bromide were reacted with **2a** (R:Me) using the in situ protocol. However, the results were less satisfactory because we could get N,N-dimethyl n-hexylamine and N,N–dimethyl benzylamine in only 54% and 10% isolated yields, respectively.

## EXPERIMENTAL

Under a nitrogen atmosphere, an oven-dried three-necked flask equipped with a reflux condenser, an addition funnel, and a magnetic stirring bar was charged with magnesium (0.0864 g, 3.6 mmol). The reaction flask and magnesium was flame dried, and the addition funnel was charged with **2a** (R:Me) (0.2430 g, 1 mmol in 4 mL of THF). At room temperature, the reaction was started by adding a few drops of aryl bromide (3 mmol) in a syringe. If necessary, the flask was heated for a short time. While stirring, aryl bromide and a solution of **2a** were added simultaneously at a rate that does not stop the reaction. (The use of aryl bromide without THF gave better results for the in situ formation of arylmagnesium bromide.) Following the disappaerence of magnesium, the reaction mixture was stirred at room temperature for 2 h. For quantitative GC analysis of the reaction products, the reaction mixture was hydrolyzed with a saturated $NaHCO_3$ solution (10 mL) and the aqueous layer was extracted with $Et_2O$ (2 × 10 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated. For the isolation of an N,N-dimethylaaniline, the ethereal solution of the product was washed with 1 M conc. HCl solution (2 × 10 mL). The aqueous phase was basified with 10% NaOH solution and extracted with $Et_2O$ (3 × 10 mL). The ethereal solution was dried over $Na_2SO_4$ and concentrated to give N,N-dimethyl anilines.

The purity of oily N,N-dimethylanilines was found to be ≥95% by GC analysis. Solid N,N-dimethylanilines were recrystallized. Melting points of solid N,N-dimethylanilines and $^1H$ NMR spectra of all ter-amines were

found to match spectra of authentic compounds and/or spectral data reported in the literature.

In conclusion, we demonstrated that Barbier–Grignard-type amination with N,N-dimethyl O-(2,4,6-trimethylphenylsulfonyl)hydroxylamine in THF at room temperature is a practical method to transfer the $Me_2N^{\oplus}$ moiety directly to aryl carbanions. Further investigations on the extensions of in situ protocol for electrophilic amination and the reaction mechanism are currently in progress in our laboratory.



## ACKNOWLEDGMENTS

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