

Preparation of Primary Amines by the Copper(I) Catalyzed Reaction of 4,4'-Bis(trifluoromethyl)benzophenone *O*-Methylsulfonyloxime and Alkyl Grignard Reagents

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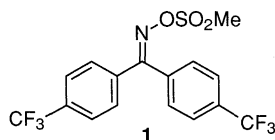
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Primary amines are prepared by the reaction of 4,4'-bis-(trifluoromethyl)benzophenone *O*-methylsulfonyloxime and alkyl Grignard reagents in the presence of a catalytic amount of $\text{CuCN}\cdot 2\text{LiCl}$ and the successive acid hydrolysis of the resulting *N*-alkylimine derivatives.

Preparation of aliphatic primary amines is an important process for the synthesis of biologically active nitrogen-containing compounds, and are generally prepared by the alkylation of nitrogen nucleophiles.¹ In addition, there have been reported the reactions of aliphatic organometallic reagents with nitrogen electrophiles, such as chloramine and hydroxylamine derivatives, in which excess organometallic reagents are required.^{2,3}

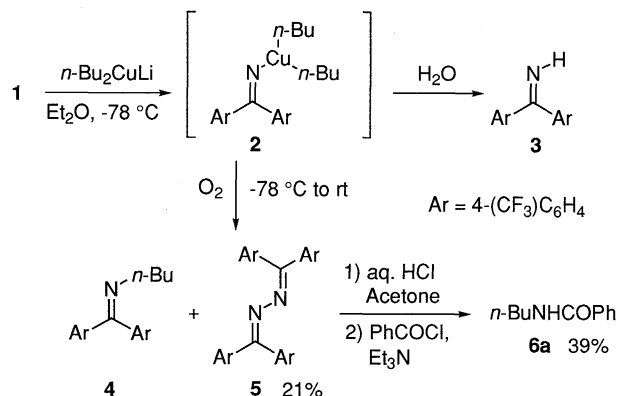
Substitution of hydroxyl group of oximes with alkyl group provides one of the efficient methods to prepare primary amines, because the resulting *N*-alkylimino compounds are readily hydrolyzed to primary amines. In fact, *O*-sulfonyloximes react with excess aryl metallic reagents to give aniline derivatives, while the reaction with aliphatic organometallic reagents affords primary amines in poor yield because of the side reactions such as the additional nucleophilic addition reaction of organometallic reagents to the intermediate imines.^{3a,b} In this paper, we will disclose the preparation of aliphatic primary amines from 4,4'-bis(trifluoromethyl)benzophenone *O*-methylsulfonyloxime (**1**) and alkyl Grignard reagents.

We chose 4,4'-bis(trifluoromethyl)benzophenone *O*-methylsulfonyloxime (**1**) as an oxime derivative to prevent the Neber reaction⁴ and the Beckmann rearrangement,⁵ which are susceptible side reactions of oxime derivatives. The *O*-sulfonyloxime **1** was prepared from 4,4'-bis(trifluoromethyl)benzophenone⁶ by treatment with hydroxylamine hydrochloride in pyridine and with methanesulfonyl chloride and triethylamine in dichloromethane successively.⁷



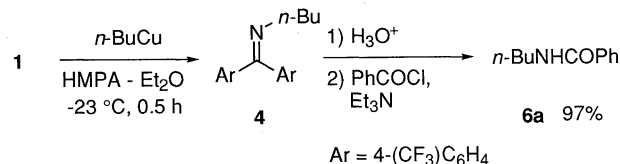
Although the *N*-alkylation of the *O*-methylsulfonyloxime **1** hardly proceeded by the reaction with butyllithium and butyl Grignard reagent in THF at 0 °C, lithium dibutylcuprate reacted with **1** at -78 °C. After quenching with pH 9 buffer, however, only a trace amount of the desired *N*-butylimine **4** was isolated and 4,4'-bis(trifluoromethylphenyl)methylideneimine (**3**)⁸ was obtained as a major product. This indicates that the oxidative addition of **1** to the cuprate occurs to give an imidocopper intermediate **2**, which hardly cleaves into the *N*-butylimine **4**. To facilitate the transformation of the imidocopper intermediate **2**

Scheme 1.



to the *N*-butylimine **4**, molecular oxygen was bubbled into the reaction mixture.⁹ Because the imine **4** was easily hydrolyzed during the purification and the resulting butylamine is volatile, **4** was converted to *N*-butylbenzamide (**6a**) by the hydrolysis with aq. HCl in acetone and the successive acylation with benzoyl chloride and triethylamine. The yield of the benzamide **6a** was, however, 39% and 4,4'-bis(trifluoromethyl)benzophenone azine (**5**) was obtained as a side product. The reaction in the presence of hexamethylphosphoramide (HMPA) improved the yield of **6a** to 61% (Scheme 1).

In contrast to the method using the cuprate, the alkylation of **1** with butylcopper was found to proceed smoothly without the oxidation with molecular oxygen. When the *O*-sulfonyloxime **1** was treated with 1.7 molar amounts of butylcopper (generated from butyllithium and CuI) in the presence of 8.5 molar amounts of HMPA in Et_2O at -23 °C, *N*-butylbenzamide (**6a**) was obtained almost quantitatively (97%), after hydrolysis and acylation. In the absence of HMPA, **6a** was obtained only in 46% yield. Butylcopper generated from butylmagnesium chloride and $\text{CuBr}\cdot\text{LiBr}$ also reacted with **1** in HMPA - THF, giving **6a** in 92% yield.



A catalytic process has been developed by improving the above alkylation method as shown in Table 1. That is, to a mixture of **1**, a 0.2 molar amount of $\text{CuCN}\cdot 2\text{LiCl}$, and 8.5 molar amounts of HMPA in THF, 1.2 molar amounts of

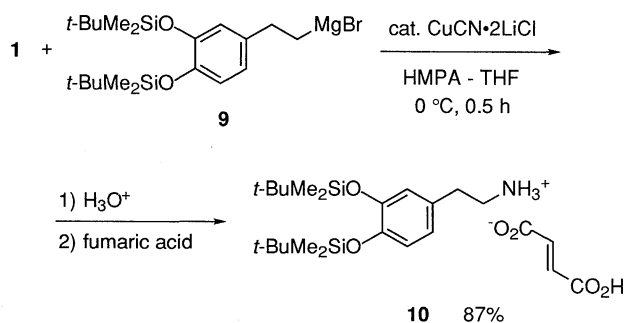
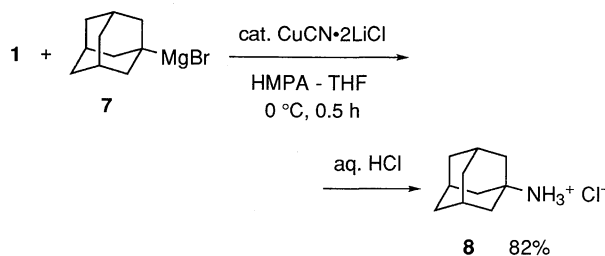
Table 1. Reaction of *O*-sulfonyloxime **1** with Grignard reagents in the presence of cat. CuCN·2LiCl

1	RMgX cat. CuCN·2LiCl HMPA - THF 0 °C, 0.5 h		1) H ₃ O ⁺ 2) PhCOCl, Et ₃ N		RNHCOPh 6
	RMgX			Yield / %	
	<i>n</i> -BuMgCl	6a	96		
	<i>i</i> -PrMgBr	6b	93		
	 -MgCl	6c	80		
	<i>t</i> -BuMgCl ^a	6d	61		

^a The reaction was carried out by using 1.5 molar amounts of *t*-BuMgCl and 0.5 molar amount of CuCN·2LiCl.

butylmagnesium chloride in THF was added dropwise at 0 °C over 30 min. After hydrolysis and acylation, the benzamide **6a** was obtained in 96% yield with 97% recovery of the 4,4'-bis(trifluoromethyl)benzophenone. In this reaction, the azine **5** was not detected. Furthermore, by the reactions with secondary and tertiary alkyl Grignard reagents, the corresponding benzamides **6b**, **6c**, and **6d** were obtained in good yield.

This catalytic amination reaction was further applied to the



preparation of 1-adamantylamine hydrochloride (**8**) and a precursor of dopamine **10**.¹⁰ 1-Adamantylmagnesium bromide (**7**)¹¹ and Grignard reagent **9** were treated with the *O*-sulfonyloxime **1** under the above reaction conditions. The crude imines thus produced were hydrolyzed to give 1-adamantylamine hydrochloride (**8**) and a dopamine derivative **10** in 82% and 87% yield, respectively.

In conclusion, primary amines are prepared not only from primary and secondary alkyl Grignard reagents, but also from tertiary ones. In the present method, the use of slight excess of Grignard reagents are sufficient to prepare the primary amines in good yield. 4,4'-Bis(trifluoromethyl)benzophenone, the starting material of 4,4'-bis(trifluoromethyl)benzophenone *O*-methylsulfonyloxime (**1**), is also recovered quantitatively after the reaction.

References and Notes

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- 7 The *O*-sulfonyloxime **1** is isolated as stable crystals; mp 93–94 °C (recrystallized from hexane-ethyl acetate).
- 8 The structure of the imine **3** was determined by transformation to benzamide and 4,4'-bis(trifluoromethyl)benzophenone by acid hydrolysis and the successive treatment with benzoyl chloride and triethylamine.
- 9 There have been reported that amidocuprates provide alkylated amines upon exposure to oxygen, see; a) A. Alberti, F. Canè, P. Dembech, D. Lazzari, A. Ricci, and G. Seconi, *J. Org. Chem.*, **61**, 1677 (1996); b) H. Yamamoto and K. Maruoka, *J. Org. Chem.*, **45**, 2739 (1980).
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