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Synthesis of Primary Amines by the Electrophilic Amination of Grignard Reagents with 1,3-Dioxolan-2-one *O*-Sulfonyloxime

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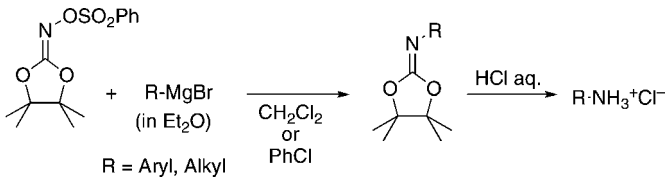
ABSTRACT



Primary amines are prepared by the electrophilic amination of Grignard reagents with 4,4,5,5-tetramethyl-1,3-dioxolan-2-one *O*-phenylsulfonyloxime and the acidic hydrolysis of the resulting imines.

Primary amines are an important class of compounds in organic synthesis, which provide various nitrogen-containing biologically active substances and fine chemicals. Generally, primary amines are prepared by the alkylation of nucleophilic amination reagents such as potassium phthalimidate[1] or the reduction of nitrogen-containing compounds having a nitro or cyano group.[2] Recently, transition-metal-mediated amination methods have been developed[3] and are also applied for the synthesis of primary amines.[4] While the reaction of organometallic reagents with electrophilic nitrogen reagents such as hydroxylamine derivatives has also been developed (electrophilic amination),[5] the method is less common compared with the former methods.

Previously, we found that the intramolecular nucleophilic substitution on the sp^2 nitrogen of oximes occurred easily in an S_N2 manner.[6,7] Based on this finding, we expected to prepare primary amines by the intermolecular substitution on oximes with organometallic reagents because the resulting *N*-alkylimines **A** would be easily hydrolyzed to give primary amines (Scheme 1).

Although some aminations with oxime derivatives for the synthesis of primary amines have been reported, these

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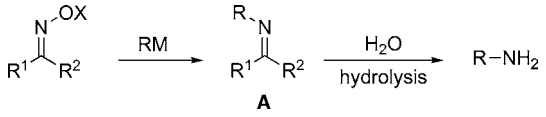
Scheme 1. Electrophilic Amination with Oximes

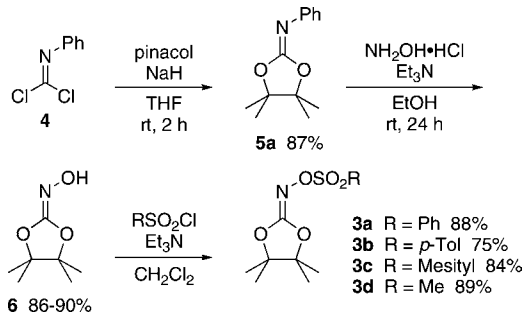


methods still remain practical due to the use of an excess amount of organometallic reagents, overalkylation, and low product yield.[8] We also examined the electrophilic amination of Grignard reagents with oxime derivatives such as bis-[3,5-bis(trifluoromethyl)phenyl]ketone *O*-tosyloxime (**1**)[9] and 1,3-dimethyl-2-imidazolidinone *O*-tosyloxime (**2**).[10] While primary amines are prepared in high yield with wide generality, it was desired to modify these oximes to realize more efficient synthetic processes. For example, bulky substituents of **1** like 3,5-bis(trifluoromethyl)phenyl groups are not appropriate for atom economy, and the hydrolysis of the resulting imines derived from **2** requires harsh basic conditions (CsOH, ethylene glycol, 150 °C).

Recently, we found that 4,4,5,5-tetramethyl-1,3-dioxolan-2-one *O*-phenylsulfonyloxime (**3a**) is definitely suitable for the amination of Grignard reagents. In this letter, we wish to describe the electrophilic amination with **3a**.

1,3-Dioxolan-2-one *O*-sulfonyloximes **3a**−**d** were prepared as shown in Scheme 2. Commercially available

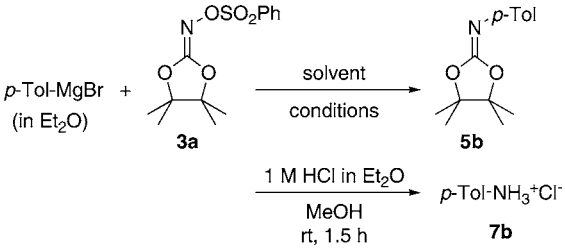
Scheme 2. Preparation of 1,3-dioxolan-2-one *O*-sulfonyloximes **3a**−**d**



phenylcarbonimidic dichloride (**4**) was treated with pinacol and NaH to give 2-phenylimino-1,3-dioxolane **5a** in 87% yield, which was transformed to 1,3-dioxolane oxime **6** with hydroxylamine in 90%. *O*-Sulfonylation of oxime **6** proceeded smoothly under the standard procedure to afford *O*-sulfonyloximes **3a**−**d** in high yields.

The amination of *p*-tolyl Grignard reagent prepared in Et_2O was examined with *O*-phenylsulfonyloxime **3a** in various solvents (Table 1).[11] The Grignard reagent reacted with

Table 1. Reaction of *O*-Phenylsulfonyloxime **3a** with *p*-Tolylmagnesium Bromide[a]



run	solvent	conditions	yield/%
1	CH_2Cl_2	0 °C, 30 min	90
2	PhCl	0 °C, 30 min	97
3[b]	PhCl	rt, 1 h	90
4	toluene	rt, 40 min	86
5	1,4-dioxane	rt, 6 h	85
6	THF	rt, 6 h	*c*

[a] **3a**: *p*-TolMgBr = 1:1.1. [b] *p*-TolMgBr in THF was used. [c] After the reaction of **3a** with *p*-TolMgBr, **5b** was obtained in 39% yield and 56% of **3a** was recovered. Further hydrolysis was not examined.

oxime **3a** smoothly in dichloromethane at 0 °C within 30 min (run 1). The obtained crude imine **5b** was successfully hydrolyzed to *p*-toluidine in high yield under HCl-acidic conditions by the contrast to the case of 2-imidazolidinone-oxime **2**.[12] Reaction of the Grignard reagent in chlorobenzene also proceeded efficiently to give **7b** in 97% yield after acid hydrolysis (run 2). Grignard reagent prepared in THF was less reactive to **3a**, and the amination was completed after 1 h at room temperature (run 3). Although **3a** was barely dissolved in toluene, the amination proceeded at room temperature (run 4). In polar solvents such as 1,4-dioxane and THF, the reaction became much slower (runs 5 and 6).

Several 1,3-dioxolan-2-one oximes **3b**−**d** were examined for amination with *p*-tolyl Grignard reagent ((i) **3**, *p*-TolMgBr in Et_2O, CH_2Cl_2; (ii) 1 M HCl in Et_2O, MeOH). Although the amination with *O*-tosyl oxime **3b** and *O*-mesitylsulfonyl oxime **3c** proceeded smoothly, the yields of **7b** were slightly decreased (90% and 80%, respectively). *O*-Methylsulfonyl oxime **3d** is hygroscopic and the amination was not reproducible, though freshly prepared one gave toluidine in 86% yield. In addition, 1,3-dioxolan-2-one *O*-tosyloxime (**8**),[8] having no methyl groups on the 1,3-dioxolane ring, was very moisture sensitive and was difficult to use as a common amination reagent. Tetramethyl groups are indispensable

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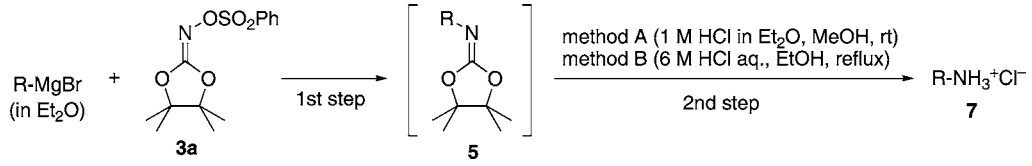
(11) Although **3a** reacted with various organometalic reagents such as PhZnCl, Ph_2Zn, PhCu, and Ph_2Cu, the yields of amination products were low.

(12) Prior to study amination with oxime **3**, the hydrolysis of 2-phenylimino-1,3-dioxolane **5a** was examined to check the difficulty of the hydrolysis of the aminated compounds and was found to be easily hydrolyzed under acidic conditions (1 M HCl in Et_2O, MeOH, rt) to give aniline hydrochloride in 96% yield. 1 M HCl in Et_2O was purchased from Aldrich.

Table 2. Amination of Various Grignard Reagents with Oxime **3a**[a]



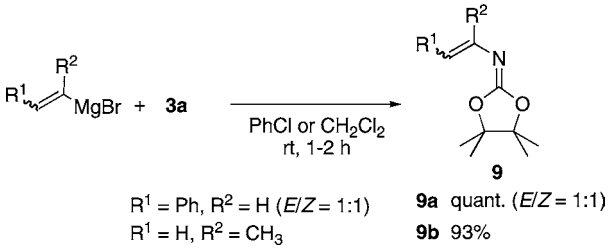
		first step			second step			
run	R	solvent	*T*/°C	time/h	method	time/h	product	yield/%
1	Ph	PhCl	0	0.5	A	1.5	**7a**	93
2	Ph	CH_2Cl_2	rt	1	A	1.5	**7a**	92
3	*p*-Tol	PhCl	0	0.5	A	1.5	**7b**	97
4	*o*-MeO-C_6H_4	CH_2Cl_2	rt	0.5	A	2	**7c**	96
5	*m*-MeO-C_6H_4	CH_2Cl_2	rt	0.5	A	2.5	**7d**	90
6	*p*-MeO-C_6H_4	PhCl	0	0.5	A	2.5	**7e**	96
7	*p*-MeO-C_6H_4	CH_2Cl_2	rt	0.5	A	2.5	**7e**	90
8	2,4-$(MeO)_2$-C_6H_3	CH_2Cl_2	rt	1	A	6.5	**7f**	91
9	*p*-F-C_6H_4	CH_2Cl_2	rt	1	A	1.5	**7g**	90
10	*p*-CF_3-C_6H_4	PhCl	0	1	A	0.5	**7h**	94
11	*p*-CF_3-C_6H_4	CH_2Cl_2	rt	1	A	0.5	**7h**	91
12	2,6-Me_2-C_6H_3	PhCl	0	1	B	3	**7i**	90
13	1-naphthyl	CH_2Cl_2	rt	0.5	A	1	**7j**	93
14	$PhCH_2CH_2$	CH_2Cl_2	rt	0.25	B	3	**7k**	90
15	$PhCH(CH_3)CH_2$	CH_2Cl_2	0	0.5	B	2	**7l**	92
16	$PhCH_2CH(CH_3)$	PhCl	0	1	B	6	**7m**	87
17	$PhCH_2CH(CH_3)$	CH_2Cl_2	0	1	B	6	**7m**	89
18	*c*-hexyl	CH_2Cl_2	0	0.5	B	6	**7n**	92[b] (92)[c]
19	1-adamantyl	CH_2Cl_2	0	0.5	B	10	**7o**	89
20[d,e]	1-norbornyl	CH_2Cl_2	rt	0.2	B	10	**7p**	64

[a] Oxime **3a**: 2.0 mmol; Grignard reagents: 2.2 mmol. [b] ^{1}H NMR yield (internal standard: anthracene). [c] Isolated yield of *N*-benzoyl derivative (PhCOCl, Et_3N, CH_2Cl_2, rt, 30 min). [d] Oxime **3a**: 1.0 mmol. Grignard reagent: 2.6 mmol. [e] Grignard reagent in THF−hexane was used.

substituents for oxime **3** as a treatable reagent. The amination of *p*-tolyl Grignard reagent proceeded efficiently with *O*-phenylsulfonyloxime **3a** in CH_2Cl_2 or chlorobenzene.

The amination with **3a** exhibited a wide generality for amination of various aryl and alkyl Grignard reagents as listed in Table 2. Regardless of the steric congestion and the electronic effect of the substituents on the aryl group, aryl Grignard reagents were smoothly aminated with **3a**, and thus-formed imine **5** was hydrolyzed under acidic conditions at room temperature giving anilines in high yield (runs 1−13). Alkyl Grignard reagents also reacted with **3a** to afford primary, secondary, and tertiary alkylamines **7** in high yields (runs 14−20) after the hydrolysis of the resulting *N*-alkylimines **5** under reflux in acidic EtOH.

Scheme 3. Amination of Alkenyl Grignard Reagents with **3a**



2-Aza-1,3-dienes are used for the synthesis of various heterocycles and are generally prepared by aza-Wittig reaction or enolization of *N*-acyl imines.[13] Azadienes **9** could be prepared by the reaction of alkenyl Grignard reagents such as styryl and isopropenyl Grignard reagents with **3a** in high yield (Scheme 3).

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Supporting Information Available: Typical experimental procedure, spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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