Novel One-Pot Synthesis of *N*-Alkyl Arylamines from Oxime Ethers Using Organometallic Reagents

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Abstract: A novel one-pot synthesis of α,α-disubstituted secondary arylamines from oxime ethers has been developed by two separate additions of organometallic reagents. As a related arylamine construction, very efficient synthesis of *N*-(diallyl)methyl arylamines is achieved via domino reactions involving addition–eliminative rearrangement–addition reactions of acyclic and cyclic oxime ethers with allylmagnesium bromide.

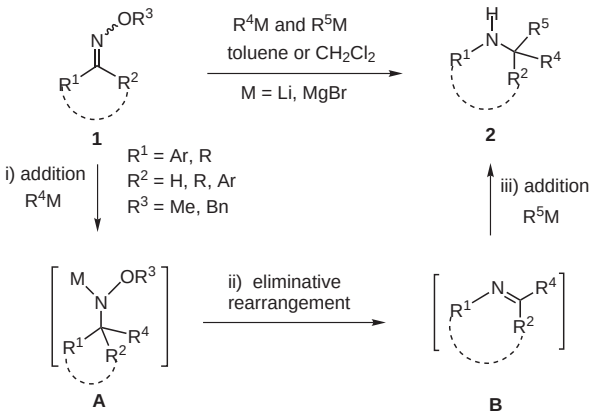
Key words: one-pot synthesis, arylamine, oxime ether, Grignard reagent, organolithium reagent, rearrangement

One-pot reactions are always challenging but interesting tasks for organic chemists, particularly in cases where the substrate shows complex behaviors with the reagents. Compared with imines, the reaction of oxime ethers with organometallic reagents is limited[1] due to its less electrophilic character, ease of α-deprotonation and aziridine formation.[2] Thus the addition reaction of organometallics to oxime ethers is sometimes problematic and can give rise to a variety of other products in addition to the desired product. However, oxime ethers are attractive starting materials in the synthesis of amino compounds[3] as cleavage of the N–O bond of alkoxy amines is easier than the cleavage of the amine C–N bond. *N*-Alkyl arylamines are important organic compounds that are widely used as precursors in the synthesis of important pharmaceutical[4] and polymeric products.[5] Oxime ethers are easily synthesized from readily available carbonyl compounds and easily converted into amines or alkoxy amines via addition reactions using a variety of reagents and catalysts.[6] In contrast, very little is known[7] about the direct transformation of oxime ethers to α,α-disubstituted secondary arylamines, taking advantage of the easily cleaved N–O bond.

Recently, we have reported the domino elimination–rearrangement–addition reaction of *N*-alkoxy(arylmethyl)amines to *N*-alkyl arylamines.[8] Based on our previous work, we have designed a one-pot synthesis of *N*-alkyl arylamines from oxime ethers by combining three crucial reactions (Scheme 1). These are the addition of a carbon nucleophile to an oxime ether (**1**→**A**), eliminative rearrangement of the alkoxyamino group (**A**→**B**) and addition of a carbon nucleophile to the resulting imine group (**B**→**2**). Thus, we have succeeded in the first and an efficient one-pot synthesis of α,α-disubstituted secondary arylamines from oxime ethers.

Initially, we investigated the one-pot reaction of *p*-methoxybenzaldehyde oxime ether **3a** as a model compound because in our previous report, the presence of a *p*-methoxy group in the substrate promoted the reaction to afford amines in good yields (Table 1).[8] After formation of the lithiated *N*-methoxy diarylamine from oxime ether **3a** (PhLi, $BF_3{\cdot}Et_2O$, toluene, –78 °C), three equivalents of PhLi were added to the same reaction flask at –20 °C. The reaction gave the desired product **4a** (33%) and also adduct **6a** (22%), the latter was formed by addition of only PhLi to the oxime ether (Table 1, entry 1).[9] In order to obtain **4a** exclusively, it was necessary to add four equivalents of PhLi in the second step.[10]

To establish this reaction as a potential method in the preparation of *N*-alkyl arylamines from oxime ethers, we used a variety of organometallic reagents with the substrate **3a** and obtained the desired products **4a**–**f** in moderate to good yields (Table 1, entries 2–7). When DIBAL-H was used as the hydrogen nucleophile in the second step, six equivalents of the reagent were required in order for the reaction to go to completion (Table 1, entry 7). An aliphatic *n*-BuLi reacted to afford the desired compound **4g** in low yield (Table 1, entry 8).



Scheme 1

We then examined the substituent effect on the substrate arylaldoxime ethers **3**. One-pot reactions using both *m*-methoxy aldoxime ether **3b** and *o*-methoxy aldoxime ether **3c** proceeded to give two types of products **4h**–**k** and **5h**–**k** (Table 1, entries 9–12) as a mixture of two regio-

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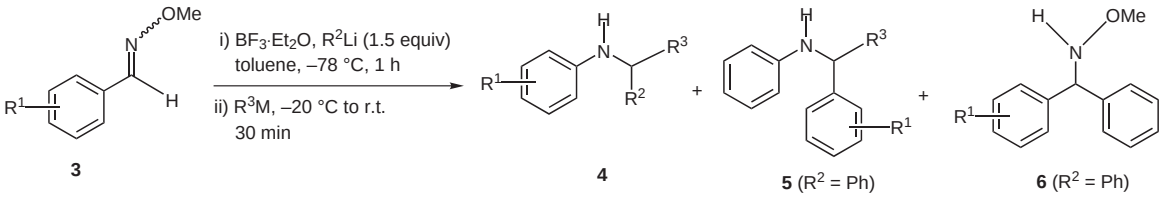
Table 1 One-Pot Reaction of Oxime Ethers **3** with Organometallic Reagents

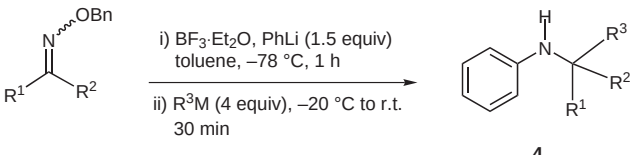


3 **4** **5** (R^2 = Ph) **6** (R^2 = Ph)

Entry	Oxime ether	R^1	R^2Li	R^3M (equiv)	Yield of **4** (%)		Yield of **5** (%)		Yield of **6** (%)	
1	**3a**	*p*-OMe	PhLi	PhLi (3)	**4a**	33	**5a**	–	**6a**	22
2	**3a**	*p*-OMe	PhLi	PhLi (4)	**4a**	63	**5a**	–	**6a**	–
3	**3a**	*p*-OMe	PhLi	*n*-BuLi (4)	**4b**	68	**5b**	–	**6b**	–
4	**3a**	*p*-OMe	PhLi	MeLi (4)	**4c**	67	**5c**	–	**6c**	–
5	**3a**	*p*-OMe	PhLi	EtLi (4)	**4d**	56	**5d**	–	**6d**	–
6	**3a**	*p*-OMe	PhLi	AllylMgBr (4)	**4e**	53	**5e**	–	**6e**	–
7	**3a**	*p*-OMe	PhLi	DIBAL-H (6)	**4f**	63	**5f**	–	**6f**	–
8	**3a**	*p*-OMe	*n*-BuLi	*n*-BuLi (4)	**4g**	27	**5g**	–	**6g**	–
9	**3b**	*m*-OMe	PhLi	PhLi (4)	**4h**	19	**5h**	37	**6h**	–
10	**3b**	*m*-OMe	PhLi	*n*-BuLi (4)	**4i**	12	**5i**	26	**6i**	–
11	**3c**	*o*-OMe	PhLi	PhLi (4)	**4j**	42	**5j**	18	**6j**	–
12	**3c**	*o*-OMe	PhLi	*n*-BuLi (4)	**4k**	39	**5k**	14	**6k**	–
13	**3d**	*p*-Me	PhLi	PhLi (4)	**4l**	59	**5l**	–	**6l**	–
14	**3d**	*p*-Me	PhLi	*n*-BuLi (4)	**4m**	54	**5m**	–	**6m**	–
15	**3d**	*p*-Me	PhLi	AllylMgBr (4)	**4n**	51	**5n**	–	**6n**	–
16	**3e**	H	PhLi	PhLi (4)	**4o**	32	**5o**	–	**6o**	–
17	**3e**	H	PhLi	*n*-BuLi (4)	**4p**	24	**5p**	–	**6p**	–

isomers formed by rearrangement of the parent aryl group and the newly added phenyl group, respectively. When we used *p*-methyl substituted and unsubstituted arylaldoxime ethers **3d** and **3e** as substrate, the corresponding amines **4l**–**p** were isolated in moderate to low yields (Table 1, entries 13–17).

Table 2 One-Pot Reaction of Enolizable Oxime Ethers **7** with Organometallic Reagents



4

7a: $R^1 = R^2$ = Me
7b: R^1 = Ph$(CH_2)_2$; R^2 = H

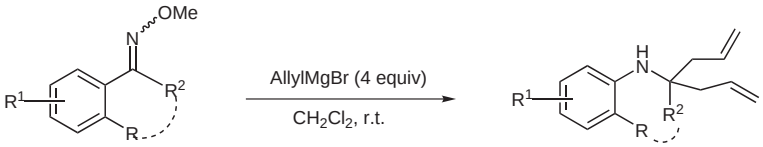
Entry	Oxime ether	R^3M	Yield (%)
1	**7a**	PhLi	**4q** 42
2	**7a**	AllylMgBr	**4r** 42
3	**7b**	PhLi	**4s** 33

In order to check the generality of our one-pot procedure, we next employed the enolizable oxime ethers **7** which gave the corresponding amines **4q**–**s** in moderate yields (Table 2). Since enolizable oxime ethers and their related imines sometimes do not tolerate nucleophilic addition reactions, our newly found one-pot synthesis is a promising approach in the synthesis of *N*-alkyl arylamines.

We then investigated the reaction of aryl oxime ethers **3** with allylmagnesium bromide as the nucleophile and found an efficient domino-type reaction involving nucleophilic addition, eliminative rearrangement and nucleophilic addition (Table 3).

According to the related reaction of aldoxime ether reported by the Pornet group,[11] we investigated the same reaction procedure using ketoxime ether **3f** as substrate and diethyl ether as solvent. The reaction at room temperature for 12 hours gave *N*-(diallyl)methyl arylamine **8b** in only 50% yield and also gave polymeric products. In order to develop efficient domino-type reactions applicable to both aldoxime and ketoxime ethers, we first investigated the solvent effect in the reaction of aldoxime ether **3a** with

Table 3 Preparation of Dihomoallylic Secondary Amines and Azepines Using a Domino-Type Reaction with Allylmagnesium Bromide



3 **8**

Entry	Oxime ether	R^1	R	R^2	Solvent	Time (min)	Yield (%)	
1[a]	**3a**	*p*-OMe	H	H	toluene	20	**8a**	83
2[a]	**3a**	*p*-OMe	H	H	hexane	30	**8a**	49[b]
3	**3a**	*p*-OMe	H	H	THF	180	**8a**	89
4[a]	**3a**	*p*-OMe	H	H	CH_2Cl_2	1	**8a**	98
5	**3f**	*p*-OMe	H	Ph	CH_2Cl_2	45	**8b**	quant
6	**3g**	*p*-Me	H	Me	CH_2Cl_2	45	**8c**	98
7	**3h**	*p*-Br	H	Me	CH_2Cl_2	45	**8d**	quant
8	**3i**	H	H	Ph	CH_2Cl_2	45	**8e**	98
9	**3j**	*o*-OMe	H	Me	CH_2Cl_2	45	**8f**	99
10	**3k**	*m*-Me	H	Me	CH_2Cl_2	45	**8g**	99
11[c]	**3l**	–	–	–	CH_2Cl_2	45	**8h**	63
12	**3m**	H	$-OCH_2CH_2-$		CH_2Cl_2	90	**8I**	98
13	**3n**	H	$-SCH_2CH_2-$		CH_2Cl_2	90	**8j**	91
14	**3o**	H	$-CH_2CH_2CH_2-$		CH_2Cl_2	90	**8k**	96
15	**3p**	*p*-OMe	$-CH_2CH_2CH_2-$		CH_2Cl_2	90	**8l**	quant

[a] These reactions were performed using 2.5 equivalents of allylmagnesium bromide at –78 °C.
[b] Compound **3a** (24%) was recovered.
[c] Methyl (3-pyridyl)ketoxime ether was used as substrate.

allylmagnesium bromide. Although toluene and tetrahydrofuran were effective solvents, hexane gave a low yield of our desired (diallyl)methylamine **8a** probably due to the low solubility (Table 3, entries 1–3). Using dichloromethane as a non-coordinating solvent gave us an excellent result as follows. Reaction of aldoxime ether **3a** with allylmagnesium bromide (2.5 equiv) in dry CH_2Cl_2 at –78 °C resulted in the production of (diallyl)methylamine **8a** within one minute and in 98% yield (Table 3, entry 4). Even when 1.2 equivalents of allylmagnesium bromide was used, the only product was the amine **8a** (46%) and also recovered substrate **3a** (38%). This result shows that the domino-type reaction involving nucleophilic addition, eliminative rearrangement and nucleophilic addition takes place very efficiently to form arylamines in CH_2Cl_2. With this encouraging result in hand, we further investigated the reaction of ketoxime ether **3f** with allylmagnesium bromide. The reaction required four equivalents of allylmagnesium bromide to proceed smoothly, but the expected product **8b** was produced in quantitative yield (Table 3, entry 5) within 45 minutes at room temperature.[12] Similarly, other ketoxime ethers **3g–l** afforded (diallyl)methylamines **8c–h** under the optimized conditions (Table 3, entries 6–11).

The efficiency of our procedure is highlighted by the short syntheses of diallylazepines **8i–l** in excellent yields at room temperature in 90 minutes (Table 3, entries 12–15). These compounds are core structures in pharmaceuticals because of their proven biological activity.[13]

In conclusion, we have developed a one-pot synthesis of *N*-alkyl arylamines from readily available oxime ethers and organometallic reagents. Additionally, *N*-(diallyl)methyl arylamines were effectively prepared by domino-type reactions of oxime ethers with allylmagnesium bromide.

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(9) The addition product **6a** was the only product isolated (63%) when the first reaction was continued for one hour without the second addition.

(10) **Typical procedure for the one-pot synthesis of amine 4m (Table 1, entry 14)**: The oxime ether **3d** (100 mg, 0.67 mmol) was dissolved in dry toluene (5 mL) under N_2 and cooled to –78 °C. $BF_3{\cdot}Et_2O$ (0.1 mL, 0.80 mmol) was added and the mixture was stirred for 15 min. PhLi (1.92 mol/L in *n*-butyl ether, 0.42 mL, 0.80 mmol) was added dropwise over 15 min. After 1 h, the reaction mixture was allowed to warm up to –20 °C. Then *n*-BuLi (1.6 mol/L in *n*-hexane, 1.7 mL, 2.7 mmol) was added at –20 °C and the mixture was stirred at r.t. for 0.5 h. The reaction mixture was quenched at 0 °C with aq sat. NH_4Cl solution (0.5 mL) and extracted with $CHCl_3$ (3 × 10 mL). The extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane–EtOAc, 8: 1) to give the amine **4m** (92 mg, 54%) as a pale yellow oil. IR (neat): 3413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 5 H), 6.88 (br d, *J* = 8.5 Hz, 2 H), 6.42 (br d, *J* = 8.5 Hz, 2 H), 4.25 (t, *J* = 6.5 Hz, 1 H), 3.93 (br s, 1 H), 2.17 (s, 3 H), 1.81–1.73 (m, 2 H), 1.41–1.24 (m, 4 H), 0.88 (br t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 145.2, 144.5, 129.5, 128.5, 126.7, 126.4, 126.2, 113.3, 58.5, 38.7, 28.5, 22.6, 20.3, 13.9; HRMS (ESI^+): *m*/*z* calcd for $C_{18}H_{23}N$: 253.1830; found: 253.1828.

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(12) **Typical procedure for the domino-type reaction in the synthesis of(diallyl)methylamine 8b (Table 3, entry 5)**: Allylmagnesium bromide (1 mol/L in Et_2O, 1.8 mL, 1.8 mmol) was added to a r.t. solution of oxime ether **3f** (110 mg, 0.46 mmol) in dry CH_2Cl_2 (2.3 mL). After being stirred at the same temperature for 45 min, the mixture was quenched with aq sat. NH_4Cl solution (1 mL) at 0 °C, extracted with $CHCl_3$ (4 × 10 mL) and washed with brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The oily mass was filtered through a short column of silica gel to give compound **8b** (133.3 mg) in quantitative yield, as a colorless oil. IR (neat): 3376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46 (br d, *J* = 8.0 Hz, 2 H), 7.34 (br t, *J* = 8.0 Hz, 2 H), 7.24 (br t, *J* = 7.5 Hz, 1 H), 6.59 (br d, *J* = 8.5 Hz, 2 H), 6.28 (br d, *J* = 8.5 Hz, 2 H), 5.66–5.52 (m, 2 H), 5.08–4.99 (m, 4 H), 3.66 (s, 3 H), 2.79 (dd, *J* = 6.5, 13.5 Hz, 2 H), 2.63 (dd, *J* = 8.0, 13.5 Hz, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.8, 145.2, 139.7, 133.4, 128.3, 126.6, 126.5, 118.7, 116.6, 114.3, 59.9, 55.5, 42.5; HRMS (ESI^+): *m*/*z* calcd for $C_{20}H_{23}NO$: 293.1779; found: 293.1782.

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