Novel Domino Elimination–Rearrangement–Addition Reaction of *N*-Alkoxy(arylmethyl)amines to *N*-Alkyl Arylamines

Okiko Miyata, Tatsuya Ishikawa, Masafumi Ueda, Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan
Fax +81(78)4417556; E-mail: taknaito@kobepharma-u.ac.jp

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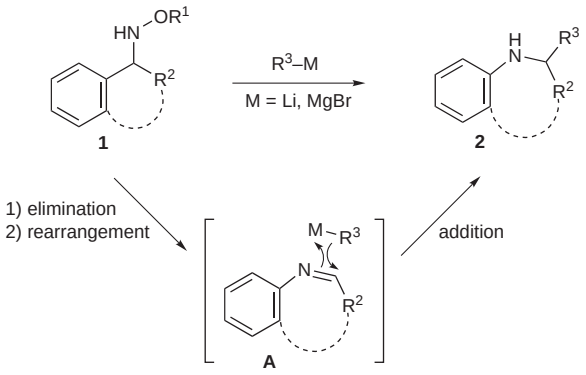
Abstract: A new domino reaction of *N*-alkoxy(arylmethyl)amines to *N*-alkyl arylamines, consisting of three types of reactions: elimination of alcohol, rearrangement of the aryl group, and addition of an organolithium or a magnesium reagent, has been developed for the first time.

Key words: domino reaction, *N*-alkoxyamine, Grignard reagent, organolithium reagent, rearrangement

Domino processes consist of several bond-forming reactions and allow highly efficient synthesis[1] of complex molecules starting from simple substrates because domino reactions increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. We have now developed a highly potential synthetic method for *N*-alkyl arylamines via a route involving domino elimination–rearrangement–alkylation of readily available alkoxyamines.

The alkoxyamines **1** have recently received much attention as a tin-free radical initiator[2] and an important precursor of amines, which are of fundamental interest in many fields of chemistry. Generally, the alkoxyamines are mainly prepared by alkylation of hydroxylamines,[3] cycloaddition of either nitroso compounds or nitrones to alkenes,[4] and the addition of either nucleophiles or radicals to oxime ethers.[5] The alkoxyamines can be easily converted to amines by either reductive or alkylative N–OC bond cleavage. Furthermore, it is known that the reaction of alkoxyamines with a reducing reagent such as Red-Al, $LiAlH_4$, and DIBAL-H gives rise to reductive rearrangement which results in the formation of the secondary amines.[6,7] In contrast, little is known about the transformation of alkoxy(arylmethyl)amines to N-substituted arylamines carrying a branched substituent by a domino process including rearrangement and alkylation. As only one related work, Yamamoto's group has reported alkylative rearrangement of *O*-acylhydroxylamine carrying the ethoxycarbonyl moiety, which acts as a good leaving group, by the treatment with trialkylaluminums.[8] However, they had reported the reactions with only trialkylaluminum and not with more common and commercially available organolithium and organomagnesium reagents.

We now report the first example of domino elimination–rearrangement–addition of alkoxy(arylmethyl)amines **1** using organolithium and organomagnesium reagents (Scheme 1). This newly found domino reaction consists of consecutive elimination–rearrangement–addition reaction of alkoxy(arylmethyl)amines. The α-branched *sec*-arylamines **2** readily prepared by this domino reaction are widely found as a core structure in pharmaceuticals, agrochemicals, and other important materials.[9]



Scheme 1

We first investigated the domino reaction of *N*-methoxy(phenylethyl)amine (**3a**) (Scheme 2, Table 1). Treatment of phenethylamine **3a** with two equivalents of *n*-BuLi in Et_2O at room temperature gave *N*-(1-methylbutyl)aniline (**4a**) in 39% yield.[10] In order to improve the yield of **4a**, we next employed 3 equivalents of *n*-BuLi in Et_2O and obtained *N*-alkylaniline **4a** in moderate yield (entry 2). The reaction of **3a** with PhLi gave **4b** in 57% yield (entry 3). Existence of either a *p*-methoxy group on the benzene ring or a phenyl group at the R^2 position in the substrates promoted this domino reaction. The reaction of **3b** with *n*-BuLi and PhLi gave the desired products **4c** and **4d**, respectively, in both 85% yields (entries 4 and 5). Furthermore, upon treatment with *n*-BuLi and PhLi, *N*-methoxydiphenyl methyl amine (**3c**) gave the desired products **4e** and **4f** both in high yields (entries 6 and 7). It is interesting to note that all of the reactions proceeded quickly and completed in only 15 minutes.[12] Additionally, an aryl group migrated selectively to give arylamines **4** and we could not detect the product formed by migration of an alkyl group. Corresponding *N*-cyclopenyl derivative of **3b** did not undergo the domino reaction under the same reac-

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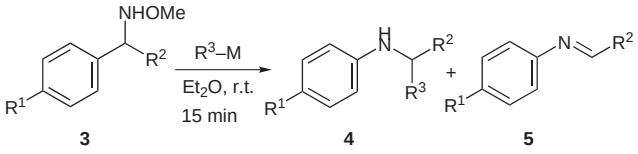
Table 1 Reaction of *N*-Methoxybenzylamines **3** with RLi or RMgBr

Entry	Substrate	R^1	R^2	R^3–M (equiv)	Yield of **4** (%)	Yield of **5** (%)
1	**3a**	H	Me	*n*-BuLi (2)	**4a**, 39	**5a**, –
2	**3a**	H	Me	*n*-BuLi (3)	**4a**, 48	**5a**, –
3	**3a**	H	Me	PhLi (3)	**4b**, 57	**5a**, –
4	**3b**	MeO	Me	*n*-BuLi (3)	**4c**, 85	**5b**, –
5	**3b**	MeO	Me	PhLi (3)	**4d**, 85	**5b**, –
6	**3c**	H	Ph	*n*-BuLi (3)	**4e**, 85	**5c**, –
7	**3c**	H	Ph	PhLi (3)	**4f**, 85	**5c**, –
8	**3b**	MeO	Me	PhMgBr (3)	**4d**, 26	**5b**, –
9	**3c**	H	Ph	EtMgBr (3)	**4g**, 26	**5c**, 54
10	**3c**	H	Ph	PhMgBr (3)	**4f**, –	**5c**, 19

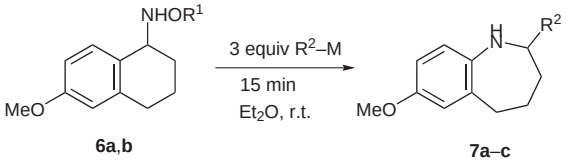


Scheme 2

tion conditions and was recovered completely. It suggests that the secondary amino moiety in substrate is necessary for this domino reaction.

We next examined the domino reaction with the Grignard reagent, which is a weaker nucleophile than alkyl lithium. When methoxyamine **3b** was treated with PhMgBr, the desired *N*-alkyl arylamine **4d** and *p*-methoxyaniline were obtained in 26% and 15% yields, respectively (entry 8). The reaction of unsubstituted **3c** with EtMgBr gave *N*-alkyl arylamine **4g** and imine **5c** in 26% and 54% yields, respectively, while the use of PhMgBr did not give N-substituted aniline **4f** (entries 9 and 10). The fact that imine **5c** was isolated in the domino reaction suggests strongly that *N*-alkyl arylamine **4** would be formed through the alkylation of **5**. We attempted the domino reaction of **3a** with Me_3Al and Et_2Zn but the desired product was not obtained.

To the best of our knowledge, this reaction represents the first example of N–OC bond cleavage of alkoxyamine using Grignard reagents. It is known that upon treatment with the Grignard reagent, *O*-tosyloximes undergo the N–OC bond cleavage to afford amines.[13]

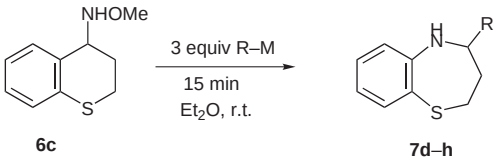


Scheme 3

Table 2 Domino Reaction of **6a**,**b**

Entry	Substrate	R^1	R^2-M	Yield (%)
1	**6a**	Me	*n*-BuLi	**7a**, 66
2	**6a**	Me	PhLi	**7b**, 63
3	**6a**	Me	EtMgBr	**7c**, 61
4	**6a**	Me	PhMgBr	**7b**, 65
5	**6b**	Bn	EtMgBr	**7c**, 66

To demonstrate the generality of the newly found domino reaction of methoxyamines, we next investigated the reaction of readily available cyclic alkoxyamines **6** and **8** with organolithium and magnesium reagents. The expected products of azepines **7** and **9** are known as the core structure in pharmaceuticals due to their unique biological activities.[14]



Scheme 4

At first, the reactions of bicyclic alkoxyamines **6a**,**b** with organometallic compounds were examined (Scheme 3, Table 2).

The treatment of 1-alkoxyaminotetraline **6a** with *n*-BuLi and PhLi in Et_2O gave the 2-butyl- and 2-phenylbenzazepines **7a** and **7b** in 66 and 63% yields, respectively (entries 1 and 2). Similarly, the reaction of **6a** with Grignard reagents proceeded smoothly to give **7c** and **7b** (entries 3 and 4). When the cyclic alkoxyamine **6b** bearing a benzyloxy group was used as a substrate, the yield of benzazepine **7c** was similar to that shown in entry 3 (entry 5).

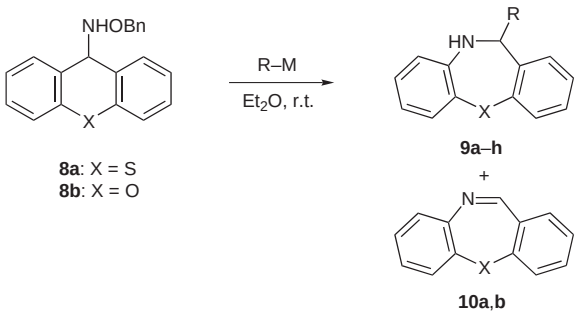
Table 3 Domino Reaction of **6c**

Entry	R-M	Yield (%)
1	*n*-BuLi	**7d**, 81
2	PhLi	**7e**, 79
3	EtMgBr	**7f**, 91
4	PhMgBr	**7e**, 90
5	AllylMgBr	**7g**, 87
6	VinylMgBr	**7h**, 75

In the case of 4-methoxyaminobenzothiopyran (**6c**), 1,5-benzothiazepines **7d**–**h** bearing alkyl and phenyl groups were obtained in better yields (Scheme 4, entries 1–4 in Table 3). Furthermore, the allyl- and vinyl magnesium bromides were also effective for this domino reaction (entries 5 and 6).

We next investigated the domino reaction of tricyclic alkoxyamines **8** with Grignard reagents (Scheme 5, Table 4).

When three equivalents of EtMgBr was used in the reaction of **8a**, ethylated dibenzo[*b*,*f*][1,4]thiazepine **9a** was obtained in addition to a minor product of dibenzo[*b*,*f*][1,4]thiazepine **10a** (entry 1). However, reaction of **8a** with four equivalents of EtMgBr proceeded smoothly to give **9a** in 89% yield as the sole product (entry 2). As shown in Table 4, the desired products **9b**–**d** were obtained in high yield in the reaction of **8a** with various types of Grignard reagents (entries 3–5). Under the same reaction conditions, dibenzopyran **8b** gave dibenz[*b*,*f*][1,4]oxazepines **9e**–**h** in more than 80% yield (entries 6–9).

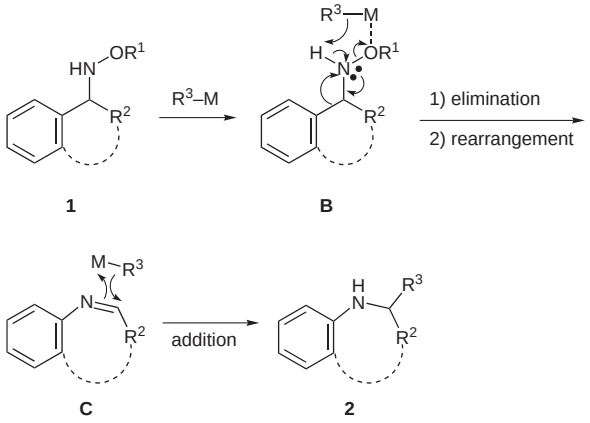


Scheme 5

We propose a possible reaction pathway for the formation of *N*-alkyl arylamine **2** as shown in Scheme 6. At first, *N*-alkoxy(arylmethyl)amine **1** would be chelated with organolithium or Grignard reagent to generate the intermediate **B** which is converted to the imine **C** via α-elimination of both proton on the nitrogen atom of the oxime ether and the alkoxide anion and subsequent rearrangement of a phenyl group to nitrogen atom. Finally, the addition of organolithium and magnesium reagents to the imine **C** proceeds smoothly to give *N*-alkyl arylamines **2**.

Table 4 Domino Reaction of **8**

Entry	Substrate	R-M (equiv)	Yield of **9** (%)	Yield **10** (%)
1	**8a**	EtMgBr (3)	**9a**, 69	**10a**, 23
2	**8a**	EtMgBe (4)	**9a**, 89	**10a**, –
3	**8a**	PhMgBr (4)	**9b**, 92	**10a**, –
4	**8a**	Allyl MgBr (4)	**9c**, 94	**10a**, –
5	**8a**	Vinyl MgBr (4)	**9d**, 87	**10a**, –
6	**8b**	EtMgBr (4)	**9e**, 84	**10b**, –
7	**8b**	PhMgBr (4)	**9f**, 86	**10b**, –
8	**8b**	Allyl MgBr (4)	**9g**, 82	**10b**, –
9	**8b**	Vinyl MgBr (4)	**9h**, 81	**10b**, –



Scheme 6

Possibility of the nitrenoid[11] would not be excluded as an intermediate in conversion of **B** to **C**.[15]

In conclusion, we have shown for the first time that the domino elimination–rearrangement–addition reaction of *N*-alkoxy(arylmethyl)amines proceeds smoothly in the presence of organometal reagent to give the N-substituted arylamines. Furthermore, we have succeeded in the synthesis of cyclic compounds carrying an azepine ring widely found in biologically active compounds.

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(10) *N*-Butyl-1-phenylethylamine was also obtained in 11% yield as a minor product. This product would be formed by substitution of the methoxy group with an *n*-butyl group. P. Beak[11] and co-workers reported nucleophilic displacement of alkoxide by the alkyl group at the nitrogen atom in the alkoxyamines.

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(12) **Typical Procedure for Domino Elimination–Rearrangement–Addition Reaction of 4,*N*-Dimethoxy-α-methyl Benzenemethanamine(3b) with *n*-BuLi (entry 4 in Table 1).**
To a stirred solution of **3b** (45 mg, 0.25 mmol) in Et_2O (1.7 mL) was added *n*-BuLi (1.6 mol/L in *n*-hexane; 0.47 mL, 0.75 mmol) under a nitrogen atmosphere at r.t. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with H_2O at 0 °C and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by PTLC (*n*-hexane–EtOAc, 6: 1) afforded **4c** (44 mg, 85%) as a pale yellow oil. IR: ν_{max} = 3393 cm^{-1}. ^1H NMR (200 MHz): δ = 6.77 (2 H, br d, *J* = 9.0 Hz), 6.55 (2 H, br d, *J* = 9.0 Hz), 3.74 (3 H, s), 3.36 (1 H, sext, *J* = 6.0 Hz), 1.60–1.27 (6 H, m), 1.14 (3 H, d, *J* = 6.0 Hz), 0.90 (3 H, t, *J* = 6.0 Hz). ^{13}C NMR (50 MHz): δ = 152.2, 144.0, 115.3, 114.9, 55.7, 50.0, 36.6, 28.3, 22.7, 20.5, 14.0. HRMS: *m/z* calcd for $C_{13}H_{21}NO$ [M^+]: 207.1624; found: 207.1626.

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(15) Yamamoto[8] group has employed *O*-ethoxycarbonyl-*N*-benzyl-*N*-cycloalkylhydroxylamines as substrates, which have no hydrogen atom on a nitrogen atom. Substrates of our newly found reaction need the secondary amino moiety. Thus reaction pathway of our domino reaction using organolithium and organomagnesium reagents would be completely different from Yamamoto's reaction.[8]