Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 6163–6166
Tetrahedron Letters

A facile method for the stereoselective preparation of (1*E*,3*E*)-4-substituted-1-amino-1,3-dienes via 1,4-elimination

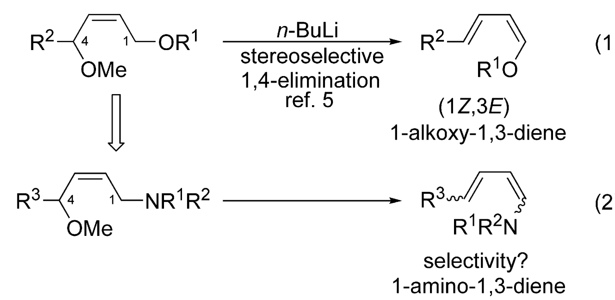
Eiji Tayama* and Sayaka Sugai

Graduate School of Science and Technology, Niigata University, Niigata 950-2181, Japan

Received 7 May 2007; revised 25 June 2007; accepted 26 June 2007
Available online 4 July 2007

Abstract—The 1,4-elimination reaction of 1-amino-4-methoxy-(2*Z*)-alkenes is shown to proceed with high (1*E*,3*E*)-stereoselectivities to afford the corresponding 4-substituted-1-amino-1,3-dienes in good yield. The scope and stereochemical features of the synthetic method are described.

1-Amino-1,3-dienes (1,3-dienamines or 1,3-dienamides) are very useful building blocks, which work as active diene components in the Diels–Alder reaction to afford nitrogen-containing fused-ring compounds.[1] The reactive 1,3-dienamines are usually prepared by condensation of α,β- or β,γ-unsaturated aldehydes or ketones with secondary amines.[2] The analogue, 1,3-dienamides, which are less reactive and easily handled, are prepared by N-acylation and isomerization of the *N*-acyliminium ions.[3] Overman has reported another preparative method of 1,3-dienamides from 2,4-dienoic acids via the Curtius rearrangement.[4] However, the stereoselective preparative methods of 4-substituted-1-amino-1,3-dienes has been limited. Recently, we reported an efficient and stereoselective synthetic method of 1,3-dienyl ethers (1-alkoxy-1,3-dienes) via the 1,4-elimination reaction (Scheme 1, Eq. 1).[5] With that method, we extended the 1,4-elimination reaction to 1-amino analogues, which would afford the corresponding 1-amino-1,3-dienes (Eq. 2). We now wish to report that treatment of 1-amino-4-methoxy-(2*Z*)-alkenes (**1**) with organic bases affords the 1,3-dienamines or dienamides in high (1*E*,3*E*)-stereoselectivities.



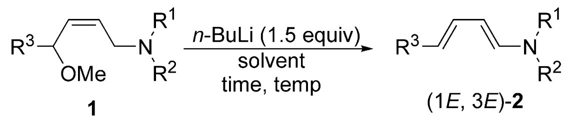
Scheme 1. Application of 1,4-elimination for 1-amino derivatives.

First, we carried out the reaction of (2*Z*)-*N*-(4-methoxyoct-2-en-1-yl)-*N*-methylaniline (**1a**)[6] with *n*-butyllithium in diethyl ether (Table 1, entry 1). The corresponding 1,4-elimination product, *N*-methyl-*N*-(oct-1,3-dien-1-yl)aniline (**2a**) was obtained in 96% yield with high stereoselectivity [(1*E*,3*E*):(1*Z*,3*E*) = 96:4].[7,8] The stereochemistry of **2a** was assigned by ^{1}H NMR [$J_{1H-2H} = 13.4$ Hz and $J_{3H-4H} = 15.0$ Hz for (1*E*,3*E*), and $J_{1H-2H} = 8.4$ Hz and $J_{3H-4H} = 15.3$ Hz for (1*Z*,3*E*)]. Equally high (1*E*,3*E*)-stereoselectivity was observed in the reaction in THF (entry 2). To define the scope and limitation of the present 1,3-dienamine forming reaction, we prepared a series of substrates **1b–i** and carried out their reactions with *n*-butyllithium. The corresponding 1,3-dienemines **2b–d** were obtained with good yield and excellent (1*E*,3*E*)-stereoselectivities (entries 3–5). However, the reaction of more electron-rich substrates such as *N*-(4-methylphenyl)-(**1e**) or *N*-(4-methoxyphenyl)-derivatives (**1f**) gave **2e** [(1*E*,3*E*):(1*Z*,3*E*) = 89:11] or **2f** [(1*E*,3*E*):(1*Z*,3*E*) = 74:26] with lower stereoselectivities (entries 6,7). The reaction of the 4-cyclohexyl derivative (**1g**) also afforded **2g** [(1*E*,3*E*):(1*Z*,3*E*) = 87:13] with lower selectivity (entry 8). However, the reaction of 4-phenyl derivative (**1h**) or *N*-methyl-*N*-(1-phenyethyl) derivative (**1i**) as an

Keywords: 1,4-Elimination; 1-Amino-1,3-dienes; Dienamines; Dienamides; Diels–Alder reaction.
* Corresponding author. Tel./fax: +81 25 262 7741; e-mail: tayama@gs.niigata-u.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.06.140

Table 1. 1,4-Elimination reaction of 4-methoxy-(2*Z*)-alkenylamine derivatives (**1**) with *n*-butyllithium



Entry	R^1	R^2	R^3		Solvent	Temp, time	Yield (%)[a]	(1*E*,3*E*):(1*Z*,3*E*)[b]
1	Ph	Me	*n*-Bu	**a**	Et_2O	0 °C, 3 h, then rt, 1 h	96	96:4
2	Ph	Me	*n*-Bu	**a**	THF	0 °C, 2 h	88[c]	97:3
3	Ph	$CH_2CH{=}CMe_2$	*n*-Bu	**b**	Et_2O	0 °C, 2 h, then rt, 1 h	89	95:5
4	4-Cl-Ph	Me	*n*-Bu	**c**	Et_2O	0 °C, 1 h, then rt, 2 h	79	95:5
5	4-CF_3-Ph	Me	*n*-Bu	**d**	Et_2O	0 °C, 1 h, then rt, 2 h	90	98:2
6	4-Me-Ph	Me	*n*-Bu	**e**	Et_2O	0 °C, 1 h, then rt, 2 h	86	89:11
7	4-MeO-Ph	Me	*n*-Bu	**f**	Et_2O	0 °C, 2 h, then rt, 1 h	68	74:26
8	Ph	Me	*c*-Hex	**g**	Et_2O	0 °C, 1 h, then rt, 2 h	93	87:13
9	Ph	Me	Ph	**h**	Et_2O	0 °C, 1 h, then rt, 2 h	0	—
10	CH(Me)Ph	Me	*n*-Bu	**i**	Et_2O	0 °C, 1 h, then rt, 3 h	0	—

[a] Isolated yield after purification by chromatography on pH-controlled silica gel (pH = 9.5). For more details, see Supplementary data.
[b] The ratios were determined by ^{1}H NMR assay.
[c] Include 7% of (1*E*,3*Z*)-isomer.

aliphatic amine substrate[9] gave a complex mixture of unidentified products (entries 9 and 10).

Though its exact origin is unclear, the high (1*E*,3*E*)-stereoselectivity of 1,4-elimination reaction of **1** may be rationalized as a result of the precoordination of *n*-butyllithium to the 4-ether oxygen to form complex **A**, which leads to the (1*E*,3*E*)-isomer (Fig. 1). This precoordination would accelerate the (1*E*,3*E*)-stereoselective 1,4-elimination reaction because the butyllithium is located at the position close to the 1-proton (H_1). Complex **B** which leads to the (1*E*,3*Z*)-isomer would be sterically less favorable than complex **A**. The formation of chelate complex **C**[10] would be suppressed by the steric repulsion between the 4-methoxy and 1-bulky amino substituent. However, the reaction of a more electron-rich substrate such as **1f** is accompanied by the 1,4-elimination via complex **C** leading to lowered (1*E*,3*E*)-selectivity (Table 1, entry 7).

In fact, the reaction with the 2*E*-isomer of **1a** gave a complex mixture of unidentified products and **2a** was hardly observed (Scheme 2); the interaction of butyllithium to the ether oxygen would not be expected at the transition state of the reaction because of the *E*-geometry of the double bond. This observation suggests that the butyllithium should be located at the position close to the 1-proton for the 1,4-elimination reaction.

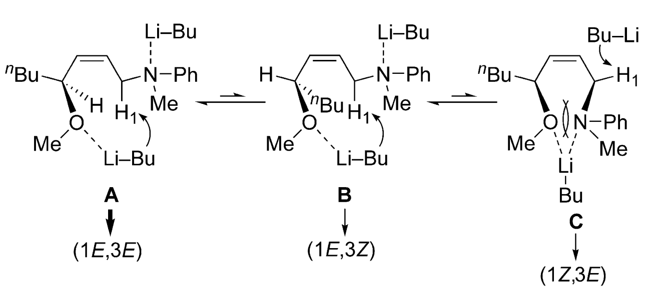
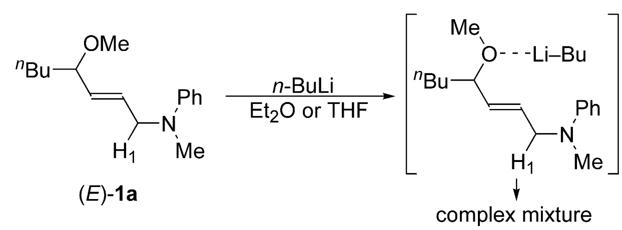


Figure 1. Proposed mechanism of the stereoselective 1,4-elimination reaction of **1a**.



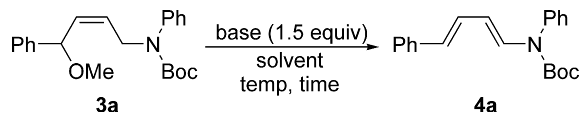
Scheme 2. The 1,4-elimination reaction of the 2*E*-isomer of **1a**.

Next, we applied our 1,4-elimination reaction to the *N*-*tert*-butoxycarbonyl (Boc) derivative **3a**,[11] which would afford *N*-Boc-1,3-dienamide **4a** (Table 2). The reaction of **3a** under the standard reaction condition (entry 1, *n*-butyllithium in diethyl ether) gave **4a** in lower yield with no stereoselectivity [(1*E*,3*E*):(1*E*,3*Z*) = 59:41]. Use of THF as a solvent (entry 2) or lithium diisopropylamide (LDA) as a base (entry 3) did not show any improvement of stereoselectivities. Interestingly however, use of lithium bis(trimethylsilyl)amide (LiHMDS) as a base dramatically improved the stereoselectivity; the ratio of (1*E*,3*E*):(1*Z*,3*E*) was 95:5 though the reaction proceeded slowly (entry 4), while use of sodium bis(trimethylsilyl)amide (NaHMDS) in THF gave a complex mixture (entry 5). When the reaction was carried out in diethyl ether–THF (4:1), the 1,4-elimination reaction proceeded smoothly to afford **4a** in 71% yield with high (1*E*,3*E*)-stereoselectivity (entry 6).[12]

To further expand the scope of the present stereoselective preparation of *N*-Boc-1,3-dienamides **4**, we prepared a series of *N*-Boc derivatives **3b–f** and carried out their reactions with NaHMDS in diethyl ether–THF (4:1). As shown in Table 3, various types of *N*-Boc-1,3-dienamides **4b–f** were obtained with good yield and high (1*E*,3*E*)-stereoselectivities.

At present, no reasonable explanation can be offered for the pronounced effect of the bases on the stereoselectivity, while the high (1*E*,3*E*)-selectivity observed may be explained as a result of the 1,4-elimination through com-

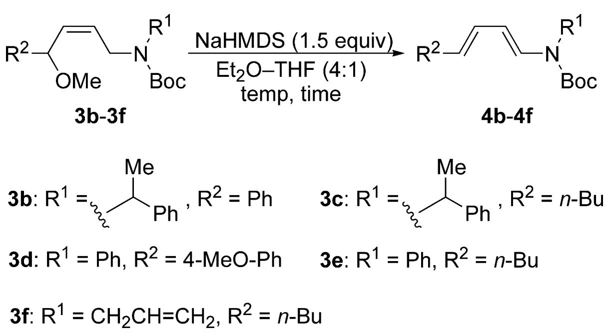
Table 2. Preparation of *N*-Boc-1,3-dienamide **4a** by the stereoselective 1,4-elimination reaction



Entry	Base	Solvent	Temp, time	Yield[a] (%)	dr[b]
1	*n*-BuLi	Et_2O	0 °C, 2 h	57	59:41[c]
2	*n*-BuLi	THF	0 °C, 2 h	58	54:46[c]
3	LDA	THF	0 °C, 2 h	90	64:36[c]
4	LiHMDS	THF	rt, 5 h, then reflux, 1 h	70	95:5[d]
5	NaHMDS	THF	0 °C, 2 h, then rt, 4 h	0	—
6	NaHMDS	Et_2O–THF (4:1)	rt, 3 h	71	94:6[d]

[a] Isolated yield.
[b] The ratios were determined by ^{1}H NMR assay.
[c] (1*E*,3*E*):(1*E*,3*Z*).
[d] (1*E*,3*E*):(1*Z*,3*E*).

Table 3. Preparation of various types of *N*-Boc-1,3-dienamides by the stereoselective 1,4-elimination reaction



Entry		Temp, time	Yield[a] (%)	(1*E*,3*E*):(1*Z*,3*E*)[b]
1	**b**	0 °C, 3 h, then rt, 1 h	98	>98:2
2	**c**	0 °C, 4 h, then rt, 7 h	83	>98:2
3	**d**	0 °C, 3 h, then rt, 1 h	99	96:4
4	**e**	rt, 3 h, then reflux, 3 h	72	94:6
5[c]	**f**	−20 °C, 15 h	77	>98:2

[a] Isolated yield.
[b] The ratios were determined by ^{1}H NMR assay.
[c] 2.0 equiv of NaHMDS was used.

plex **D** as depicted in Figure 2. It is interesting to note that a similar reaction of the (2*E*)-isomer of **3e** afforded a mixture (87:13) of the (1*Z*,3*E*)- and (1*Z*,3*Z*)-**4e** in a 70% combined yield (Scheme 3).[13] Again, the mechanistic origin of the (1*Z*)-selectivity observed here is unclear. Further mechanistic studies are awaited.

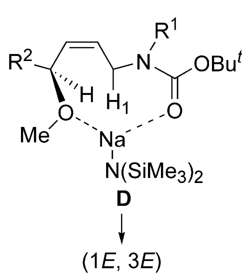
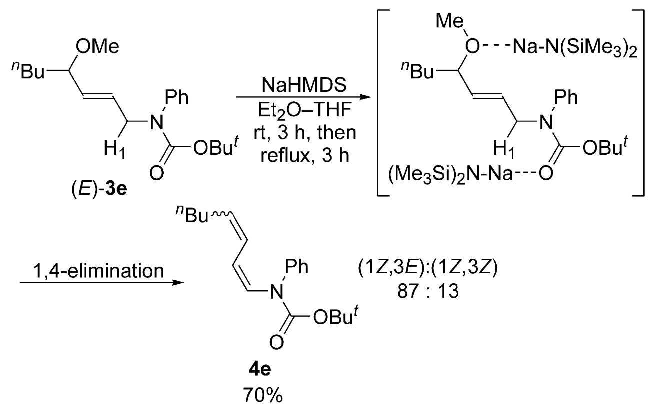
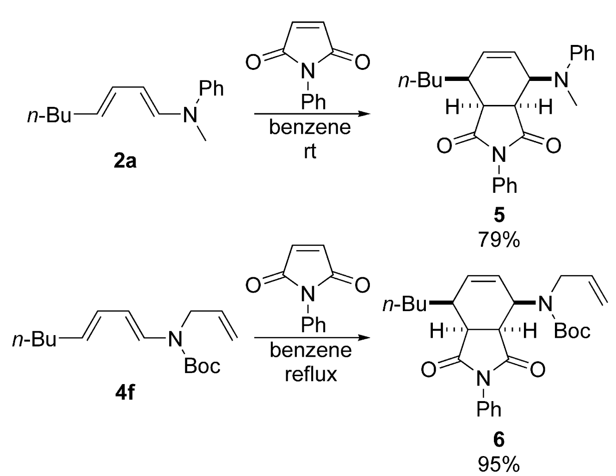


Figure 2. Proposed mechanism of the stereoselective 1,4-elimination reaction of **3**.



Scheme 3. The 1,4-elimination reaction of the 2*E*-isomer of **3e**.

Finally, the Diels–Alder reaction of the 4-substituted-1-amino-1,3-dienes obtained was performed (Scheme 4). The reactions of dienamine **2a** or dienamide **4f** with *N*-phenylmaleimide in benzene proceeded smoothly to give **5** or **6** with good yield.



Scheme 4. The Diels–Alder reaction of 4-substituted-1-amino-1,3-dienes.

In summary, we have demonstrated that the 1,4-elimination reaction of 1-amino-4-methoxy-(2*Z*)-alkenes with *n*-butyllithium or NaHMDS affords the corresponding 4-substituted-1-amino-1,3-dienes with good yield and excellent (1*E*,3*E*)-stereoselectivities. Our method is widely applicable for the preparation of different types of the 1,3-dienamines and 1,3-dienamides.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformations of Carbon Resources' from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.140.

References and notes

1. Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.1.3.2, pp 331–333.
2. For review: Hickmott, P. W. *Tetrahedron* **1984**, *40*, 2989–3051.
3. (a) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, *20*, 981–984; (b) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204–207; (c) Oppolzer, W.; Fröstl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593–595.
4. (a) Jessup, P. J.; Petty, C. B.; Roos, J.; Overman, L. E. *Org. Synth.* **1979**, *59*, 1–7; (b) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164–2167.
5. (a) Tayama, E.; Sugai, S.; Hara, M. *Tetrahedron Lett.* **2006**, *47*, 7533–7535; (b) Tayama, E.; Sugai, S. *Synlett* **2006**, 849–852.
6. Prepared from *N*-methylaniline in four steps (71% overall yield) [(i) propargyl bromide, K_2CO_3, acetonitrile, rt, then reflux; (ii) LDA, ^{n}BuCHO, THF, −78 °C, then rt; (iii) ^{n}Bu$_4$NI, $(MeO)_2SO_2$, benzene, 50% aq. NaOH, rt; (iv) H_2 (1 atm), Lindlar cat., quinoline, benzene, rt]. For more details, see Supplementary data.
7. *Reaction procedure*: A solution of **1a** (698 mg, 2.82 mmol) in ether (12 mL) was treated with a 1.6 M hexane solution of *n*-BuLi (2.6 mL, 4.2 mmol) at 0 °C and the mixture was stirred for 3 h at 0 °C and for 1 h at room temperature. The resulting mixture was quenched with water and extracted with ether. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on pH-controlled silica gel (hexane as eluent) to afford **2a** (582 mg, 96% yield) as a pale yellow oil.
8. Condensation of *N*-methylaniline and *trans*-oct-2-en-1-nal (benzene, reflux, 3 h) gave **1a** in 57% yield as a mixture of stereoisomers [(1*E*,3*E*):(1*E*,3*Z*) = 6:4].
9. The presence of aliphatic amines might suppress the favorable 1,4-elimination reaction. For example, the reaction of **1a** using LDA (THF, 0 °C, 2 h, then rt, 2 h), which affords diisopropylamine after reaction, gave **2a** in lower yield and stereoselectivity [70% yield, (1*E*,3*E*):(1*Z*,3*E*) = 84:16].
10. This type of intermediate has been claimed to give the (1*Z*,3*E*)-1,3-dienyl ethers. For more details, see Ref. 5.
11. Prepared from *N*-Boc-aniline by the similar procedures to those described for **1a**. For more details, see Supplementary data.
12. *Reaction procedure*: A solution of **3a** (147 mg, 0.416 mmol) in ether (2.5 mL) was treated with a 0.99 M THF solution of NaHMDS (0.63 mL, 0.62 mmol) at 0 °C. The mixture was stirred for 3 h at room temperature and quenched with water at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (hexane:ethyl acetate = 20:1 to 10:1 as eluent) gave **4a** (94.8 mg, 71% yield) as a colorless gum.
13. Assigned by ^{1}H NMR assay. (1*Z*,3*E*)-**4e**: $J_{1H–2H} = 8.4$ Hz, $J_{3H–4H}$ = not identifiable by multiplet peaks, (1*Z*,3*Z*)-**4e**: $J_{1H–2H} = 9.5$ Hz, $J_{3H–4H} = 11.2$ Hz. For more details, see Supplementary data.