New Imino-Wittig Rearrangement of Benzyl and Allyl Hydroximates

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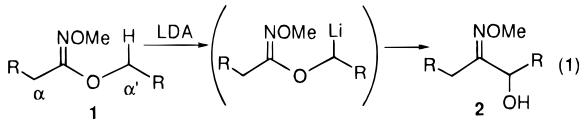
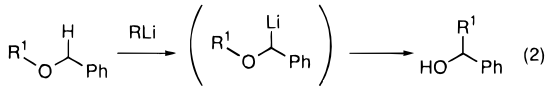
We now report the first example of an imino-Wittig rearrangement of benzyl and allyl hydroximates by treatment of benzyl and allyl hydroximates **1** with a base, where the *N*-alkoxy imino group migrates from an oxygen to a carbon atom (eq 1). The 1,2-rearrangement of



(1)

1 **2**

α-lithio ethers to the corresponding alcohols is the Wittig rearrangement (eq 2),[1] where R^1 is generally an alkyl group such as a benzyl or *tert*-alkyl.[2] However, migration

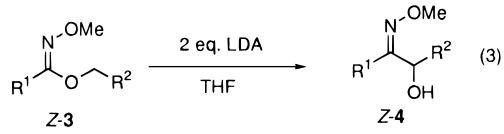


(2)

of an imino group (R^1: RC═NR) to a negatively charged carbon has not been reported so far. We have now found that 1,2-Wittig rearrangement of benzyl and allyl (*Z*)-hydroximates **3** proceeds smoothly to give 2-hydroxy oxime ethers **4** (eq 3) and provides a new entry to carbon−carbon bond formation.

We first investigated the rearrangement of hydroximates **3**[3] having the *Z*-geometry at the C═N bond. The results of those studies are summarized in Table 1. Treatment of benzyl (*Z*)-benzohydroximate (**3a**) with 2 equiv of LDA in THF at −23 °C afforded the 2-hydroxy oxime ether having the *Z*-geometry **4a**[4] as the sole product in 89% yield (Table 1, entry 1). This result shows that the rearrangement occurs with retention of configuration at the *N*-methoxy imino group. In the rearrangement of allyl (*Z*)-hydroximate **3b**, lowering the temperature (−40 °C) improved the yield from 45% to 60% (Table 1, entries 2 and 3). When R^2 is a methoxycarbonyl group, many spots are observed on TLC due to

Table 1. 1,2-Wittig Rearrangement of (Z)-Hydroximates 3



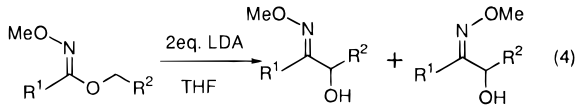
(3)

Z-**3** *Z*-**4**

entry	substrate	R^1	R^2	*T* (°C)	yield (%)
1	**3a**	Ph	Ph	−23	89
2	**3b**	Ph	CH═CH_2	−23	45
3	**3b**	Ph	CH═CH_2	−40	60 (82)[a]
4	**3c**	Ph	COOMe	−50 → 0	*b*
5	**3d**	*p*-tolyl	Ph	−23	76
6	**3e**	styryl	Ph	−23	79
7	**3f**	Et	Ph	−23	64
8	**3g**	$PhCH_2CH_2$	Ph	−23	75 (89)[a]
9	**3h**	$PhCH_2CH_2$	CH═CH_2	−40	64
10	**3i**	CH_2═$CH(CH_2)_3$	Ph	−23	70

[a] Based on recovery of the starting material. [b] Complex mixture observed on TLC.

Table 2. 1,2-Wittig Rearrangement of (*E*)-Hydroximates 5



(4)

E-**5** *E*-**6** *Z*-**4**

entry	substrate	R^1	R^2	*T* (°C)	yield (%)	ratio (*E*)-**6**:(*Z*)-**4**
1	**5a**	Ph	Ph	−23	41 (51)[a]	3:1
2	**5b**	Ph	CH═CH_2	−40	19 (34)[a]	1.7:1
3	**5e**	styryl	Ph	−23	58 (71)[a]	1:1

[a] Based on recovery of the starting material.

the formation of a complex reaction mixture (Table 1, entry 4). The rearrangements of *p*-toluo- and cinnamohydroximates **3d** and **3e** proceeded smoothly to give the rearranged products **4d**[4] and **4e**[4], respectively (Table 1, entries 5 and 6).

In order to compare the acidity of the two methylene groups at the α- and α′-positions (eq 1), we next investigated the reaction of the hydroximates **3f**−**i** having active methylene groups at the α-position of the *N*-methoxyimino group with LDA. Although the presence of two active methylene groups in these substrates was expected to complicate the reaction, the rearrangements of the hydroximates **3f**, **3g**, **3h**, and **3i** proceeded cleanly to give the rearranged products **4f**−**i**[4] as the sole isolated product under similar conditions (Table 1, entries 7−10).

This rearrangement was then applied to the (*E*)-hydroximate **5a**[3] under the same reaction conditions (eq 4, Table 2). However, the yield decreased markedly, giving a 3:1 mixture of (*E*)-**6a**[4] and (*Z*)-**4a** with recovery of starting material (Table 2, entry 1). Since the equilibration between (*E*)-**6a**[4] and (*Z*)-**4a** was not observed under the reaction conditions, (*E*)-**6a** and (*Z*)-**4a** would be the kinetic products. Similarly, the rearrangements of (*E*)-hydroximates **5b,e**[3] gave a mixture of (*E*)-**6b,e**[4] and (*Z*)-**4b,e**[4] (Table 2, entries 2 and 3).

In order to clarify the reaction pathway, we investigated the cross reaction. The fact that a mixture of **3d** and **3b** that was treated with LDA gave only a mixture of two products **4d** and **4b** suggests that the newly found rearrangement of hydroximates proceeds *via* an intramolecular process. From the above results, we propose two

(1) Reviews on the 1,2-Wittig rearrangement: (a) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763. (b) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 975−1014.

(2) A few papers have been published on the migration of alkenyl, carbonyl, and thiocarbonyl groups. (a) Rautenstrauch, V.; Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 2576−2580. (b) Hayashi, T.; Baba, H. *J. Am. Chem. Soc.* **1975**, *97*, 1608−1609. (c) Crooks, P. A.; Galt, R. H. B.; Matusiak, Z. S. *Chem. Ind.* **1976**, 693−694. (d) Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.* **1984**, *25*, 3399−3402.

(3) The substrates **3a**−**i** and **5a,b,e** were prepared according to the reported procedure. Johnson, J. E.; Springfield, J. R.; Hwang, J. S.; Hayes, L. J.; Cunningham, W. C.; McClaugherty, D. L. *J. Org. Chem.* **1971**, *36*, 284−294.

(4) **4a** and **6a** were identical with the authentic samples[5a] that were prepared by treatment of benzoin with methoxyamine hydrochloride. The stereochemistries of other rearranged products **4b,d**−**i** and **6b,e** were deduced by comparison of the chemical shifts of the α′-methine protons in ^{1}H-NMR spectra according to ref 5b, which states that signals due to α′-methine protons of *cis*-*O*-methyloxime appear at appreciably lower fields than those of *trans*-isomers.

(5) (a) Creary, X.; Wang, Y.-X.; Jiang, Z. *J. Am. Chem. Soc.* **1995**, *117*, 3044−3053. (b) Karabatsos, G. J.; Hsi, N. *Tetrahedron* **1967**, *23*, 1079−1095.

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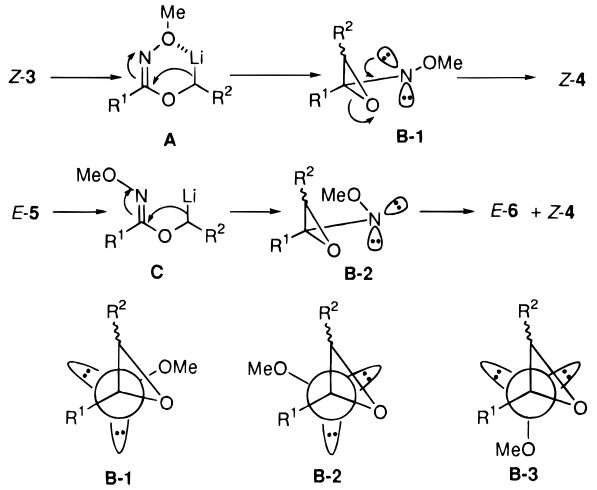
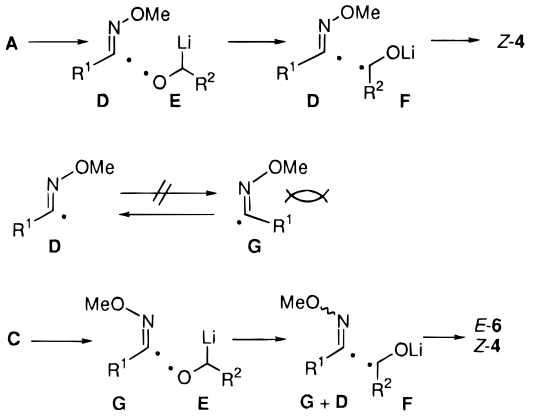
Scheme 1



possible reaction pathways for this rearrangement. The first pathway proceeds by an ionic addition−elimination process as proposed for the related 1,2-rearrangements (Scheme 1).[2a,d,6] Grovenstein[6] suggested that in the 1,2-Wittig rearrangement of benzyl propenyl ether initial cyclization of the lithio ether, generated from the benzyl propenyl ether, proceeds by *anti*-addition to give the epoxide, and subsequent ring opening of the epoxide occurs by *syn*-elimination to give the product with the same configuration at the trisubstituted olefin. According to this mechanism, we propose a possible reaction pathway of the imino-Wittig rearrangement as shown in Scheme 1. Treatment of (*Z*)-**3** with LDA gives the lithio ether **A**, which would be stabilized by chelation with a methoxy group. Intramolecular addition of the resulting carbanion **A** to the imino double bond then proceeds in an *anti*-fashion to give the epoxide **B-1** as shown in the Newman projection. Finally, the epoxide **B-1** undergoes ring-opening reaction in *anti*-periplanar manner involving the nitrogen lone pair and C−O bond to afford the rearranged product (*Z*)-**4** with retention of configuration at the methoxy imino group.

On the other hand, rearrangement of (*E*)-hydroximate **5** proceeded slowly and nonstereoselectively to give a mixture of (*E*)-**6** and (*Z*)-**4**. As in the case of (*Z*)-**3**, treatment of (*E*)-**5** with LDA gives the lithio ether **C**, which would not be stabilized by chelation with the methoxy group and then undergoes *anti*-addition to the imino group to give the epoxide **B-2**. The Newman projection shows that in the conformation **B-2** the C−O bond and lone pair are not situated *anti*-periplanar suitable for the E2 type of the final ring-opening reaction. Therefore, there would be two possible reaction pathways. One is E1cB-type elimination from the conformation **B-2**, which gives a mixture of (*E*)-**6** and (*Z*)-**4** products. The other is E2-type elimination from the conformational isomers **B-1** and **B-3**, both of which gave the rearranged products (*Z*)-**4** and (*E*)-**6**, respectively.

Scheme 2



The alternative is a radical mechanism as shown in Scheme 2. It is known that 1,2-Wittig rearrangement of the ethers proceeds not in a concerted fashion but *via* the radical dissociation−recombination mechanism.[7−9] The cyclic intermediate **A**, formed from (*Z*)-**3**, dissociates to the radical pair of the imidoyl radical **D**[10] and the oxygen radical **E**, whereupon the oxygen radical **E** isomerizes to carbon radical **F**. Recombination of the resulting radical pair of imidoyl radical **D** and carbon radical **F** occurs more rapidly than inversion of the imidoyl radical center **D** to the geometrical isomer **G**, judging from the high degree of retention at the oxime ether group. On the rearrangement of (*E*)-hydroximate **5**, it is suggested that the isomerization of the imidoyl radical center **G**, formed from intermediate **C**, isomerizes partially to the isomer **D** due to steric hindrance between the R^1 group and the methoxy group in **G** during the course of the reaction. Elucidation of the precise mechanism involving stereoselectivity of the imino group requires further detailed investigation.

In conclusion, we have shown for the first time that benzyl and allyl (*Z*)-hydroximates smoothly rearrange to give 2-hydroxy oxime ethers, which would serve as precursors of diols and amino alcohols widely found in biologically active natural products. The application of the imino-Wittig rearrangement to the synthesis of biologically active natural products is now under study.

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Supporting Information Available: Experimental procedure and compound characterization data (5 pages).

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(6) Grovenstein, E., Jr.; Black, K. W.; Goel, S. C.; Hughes, R. L.; Northrop, J. H.; Streeter, D. L.; VanDerveer, D. *J. Org. Chem.* **1989**, *54*, 1671−1679. Grovenstein, *et al.* have discussed the reaction mechanism of the 1,2-rearrangement of the benzyl and methallyl propenyl ethers leading to the formation of the carbinols with retention of stereochemistry in the propenyl group, which was previously reported by Büchi's group.[2a]

(7) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron* **1994**, *50*, 5927−5932 and references cited therein.

(8) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375−377.

(9) Lansbury, P. T.; Pattison, V. A.; Sidler, J. D.; Bieber J. B. *J. Am. Chem. Soc.* **1966**, *88*, 78−84.

(10) We could not isolate cyclopentanone *O*-methyloxime as a product that is expected to be formed *via* radical cyclization of an intermediary imidoyl radical **D** in the reaction of **3i**.