J. Org. Chem. **1996,** *61,* 6770−6771

Olefin Inversion: Stereospecific Olefin Synthesis from *Vicinal* Alkoxyiodoalkanes with Butyllithium by an E2 *Syn* Mechanism

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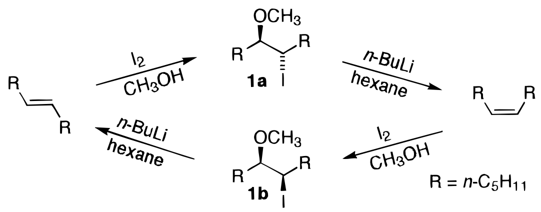
Received August 9, 1996

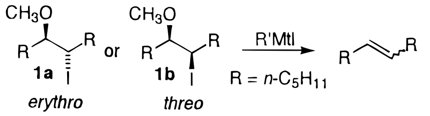
The carbon−carbon double bond is a basic structural unit in organic chemistry, and numerous reports have been published on the syntheses and chemical reactivities of alkenes.[1] Among many synthetic methods, the 1,2-elimination reaction is one of the most effective for forming alkenes.[2] The use of *vicinal* dihalogen compounds as a route to alkenes does have an advantage over most dehydrohalogenation reactions because the double bond forms at a specific position. However, the procedure cannot be applied to olefin inversion[3] since *anti* addition followed by *anti* elimination of dihalogen results in the recovery of the starting alkenes. In the E2 mechanism, *anti* elimination is generally favored,[4] and *syn* elimination has been found only in the cases where the molecule could not achieve an *anti*-periplanar transition state because of steric or conformational factors.[5] In this paper, we show that the reaction of *vicinal* alkoxyiodoalkanes with butyllithium proceeds in *syn* fashion to afford alkenes stereospecifically and that the interconversion of olefinic geometrical isomers has been performed by an *anti* addition of an iodine−alkoxy moiety to an alkene and subsequent *syn* elimination of these groups (Scheme 1).

Scheme 1



We examined a β elimination reaction[6,7] of methoxyiodoalkane[8] **1a** and **1b** with organometallic reagents (Table 1). Treatment of *erythro*-6-iodo-7-methoxydodecane (**1a**, *erythro/threo* = 97/3) with butyllithium in hexane−ether (1:1) at −78 °C for 30 min provided *(Z)*-6-dodecene (*E/Z* = 6/94) selectively in 77% yield.[9] Meanwhile, *threo*-isomer **1b** (*erythro/threo* = 3/97) afforded *(E)*-6-dodecene with high stereoselectivity (*E/Z* = 96/4) in 65% yield[9] under the same reaction conditions (Table 1, entry 5). These results showed us that the elimination with butyllithium in hexane−ether proceeded in *syn* fashion.[10] Thus, *(E)*-6-dodecene could be converted into *(Z)* isomer by sequential treatment with I_2/MeOH and butyllithium and *(Z)*-6-dodecene could be also transformed into the *(E)*-isomer in the same way. The use of *sec*-butyllithium or *tert*-butyllithium instead of butyllithium resulted in a decrease of selectivity especially for the transformation of *threo* alkoxyiodoalkane into *(E)*-6-dodecene (Table 1, entries 6 and 7).[11] Among the solvent systems examined (hexane, hexane−ether (3:1), hexane−ether (1:1), ether, DME), hexane−ether (1:1) proved to be the best in terms of the combination of yields and stereoselectivities. In ether, the yield was improved (2−7%) but stereoselectivities were decreased slightly (2−5%). DME also gave better yields of 6-dodecene, but in somewhat lower specificity with regard to stereochemistry (Table 1, entries 4 and 8).

Table 1. 1,2-Elimination of 6-Iodo-7-methoxydodecane 1 with Butyllithium[a]



entry	methoxyiodoalkane **1** *erythro/threo*	R′-Mtl/solvent	6-dodecene yield (%) *(E/Z)*
1	**1a** 97/3	*n*-BuLi/hex−Et$_2$O (1:1)	77 (6/94)
2	**1a** 97/3	*s*-BuLi/hex−Et$_2$O (1:1)	82 (4/96)
3	**1a** 97/3	*t*-BuLi/hex−Et$_2$O (1:1)	85 (11/89)
4	**1a** 97/3	*n*-BuLi/DME	79 (75/25)
5	**1b** 3/97	*n*-BuLi/hex−Et$_2$O (1:1)	65 (96/4)
6	**1b** 3/97	*s*-BuLi/hex−Et$_2$O (1:1)	83 (81/19)
7	**1b** 3/97	*t*-BuLi/hex−Et$_2$O (1:1)	83 (48/52)
8	**1b** 3/97	*n*-BuLi/DME	85 (11/89)

[a] The reactions were performed at −78 °C.

The reaction of other various *vicinal* methoxyiodoalkanes with butyllithium was studied (Table 2). Several comments are worth noting. (1) The regioisomeric mixture **2a** afforded *(Z)*-3-dodecene almost exclusively upon treatment with butyllithium in hexane−ether at −78 °C (Table 2, entry 1). On the other hand, treatment of a regioisomeric mixture of **2b** with butyllithium provided *(E)*-3-dodecene as a single product (Table 2, entry 2). Thus, the interconversion of olefinic geometrical

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(1) *The Chemistry of Alkenes*; Patai, S., Ed.; Interscience: New York, 1964. *The Chemistry of Alkenes*; Zabicky, J., Ed.; Interscience: New York, 1968; Vol. 2.

(2) Krebs, A.; Swienty-Busch, J. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 6, Chapter 5.1, pp 949−974. Kocienski, P. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 6, Chapter 5.2, pp 975−1010.

(3) Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557 and references cited therein. *cis*-Chlorotelluration−*trans*-dechlorotelluration: Bäckvall, J.-E.; Engman, L. *Tetrahedron Lett.* **1981**, *22*, 1919. *vic*-Bromohydrin trifluoroacetate with NaI: Sonnet, P. E. *J. Org. Chem.* **1980**, *45*, 154. *vic*-Bromochloride with NaI: Jie, M. S. F. L. K.; Chan, M. F. *J. Am. Oil Chem. Soc.* **1985**, *62*, 109.

(4) Bach, R. D.; Badger, R. C.; Lang, T. J. *J. Am. Chem. Soc.* **1979**, *101*, 2845. McLennan, D. J.; Lim, G. C. *Aust. J. Chem.* **1983**, *36*, 1821. Ogawa, S.; Takagaki, T. *J. Org. Chem.* **1985**, *50*, 2356.

(5) *Cis* E2 reaction of *trans*-2-arylcyclopentyl tosylate: Depuy, C. H.; Morris, G. F.; Smith, J. S.; Smat, R. J. *J. Am. Chem. Soc.* **1965**, *87*, 2421. *Cis*-1,2-elimination of 1,2-dibromo compounds with bis(trimethylsilyl)mercury: Bennett, S. W.; Eaborn, C.; Jackson, R. A.; Walsingham, R. W. *J. Organomet. Chem.* **1971**, *27*, 195.

(6) Nicolaou, K. C.; Duggan, M. E.; Ladduwahatty, T. *Tetrahedron Lett.* **1984**, *25*, 2069. Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390. Rao, A. V. R.; Reddy, E. R.; Joshi, B. V.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 6497. Ireland, R. E.; Häbich, D.; Norbech, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271. The stereochemical outcome has not been discussed in the foregoing literature.

(7) The stereoselective conversion of iodo acetals into alkenyl ethers has been reported. Maeda, K.; Shinokubo, H.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1996**, *61*, 2262.

(8) Cambie, R. C.; Noall, W. I.; Potter, G. J.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 226.

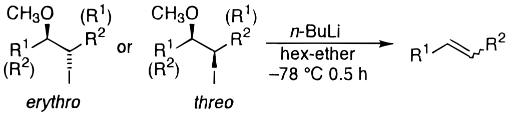
(9) S_N2 Reaction product *n*-$C_5H_{11}CH$(*n*-Bu)CH(OMe)-*n*-C_5H_{11} was also obtained in 5−10% yield.

(10) Stereospecific β-elimination of conformationally rigid bromo ethers with Na or Zn has been reported in the synthesis of natural products. Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. Kato, T.; Aoki, M.; Uyehara, T. *J. Org. Chem.* **1987**, *52*, 1803.

(11) Methyllithium and trimethylaluminum proved to be unreactive toward alkoxyiodoalkanes, and **1a** and **1b** were recovered unchanged. In contrast, treatment of **1a** and **1b** with Et_2Zn provided the same isomeric mixture of 6-dodecene (*E/Z* = 91/9).

S0022-3263(96)01543-5 CCC: $12.00

Table 2. 1,2-Elimination of Various Regioisomeric Mixtures of *Vicinal* Methoxyiodoalkanes with Butyllithium[a]



entry		methoxyiodoalkane[b] R^1	R^2	*erythro/threo*	alkene yield (%) (*E/Z*)
1	**2a**	*n*-C_8H_{17}	C_2H_5	99/1	70 (3/97)
2	**2b**	*n*-C_8H_{17}	C_2H_5	4/96	64 (96/4)
3	**3a**	*n*-C_8H_{17}	$(CH_2)_8OCH_3$	88/12	66 (13/87)
4	**3b**	*n*-C_8H_{17}	$(CH_2)_8OCH_3$	4/96	64 (96/4)
5	**4a**	*n*-C_5H_{11}	$CH_2CH_2CH_2OCH_3$	99/1	83 (25/75)
6	**4b**	*n*-C_5H_{11}	$CH_2CH_2CH_2OCH_3$	5/95	63 (91/9)
7	**5a**	*n*-C_5H_{11}	$CH_2CH_2CH_2Br$	98/2	76 (12/88)
8	**5b**	*n*-C_5H_{11}	$CH_2CH_2CH_2Br$	11/89	77 (89/11)
9	**6b**	$-(CH_2)_6-$		1/99	94[c] (95/5)

[a] The reactions were performed at −78 °C for 30 min. [b] 1:1 regioisomeric mixtures. [c] GC yield.

isomers has been also achieved for the unsymmetrical alkene. (2) Olefins having a methoxy group at the remote position such as *(E)*- and *(Z)*-1-methoxy-9-octadecene afforded the inverted alkenes stereospecifically by methoxyiodination and subsequent treatment with butyllithium (Table 2, entries 3 and 4). (3) Dimethoxyiodododecanes **4a** and **4b** having two methoxy groups at a closer position to each other could be also converted into the corresponding alkenes stereospecifically. However, the selectivities were slightly inferior to those for **3a** and **3b**. The loss of stereoselectivity for the transformation of *erythro* dimethoxyiodododecanes **4a** was larger than that for the *threo* regioisomeric mixture **4b**. (4) A similar decrease of stereochemical purity was also observed in the reaction of **5a** prepared from *(E)*-1-bromo-4-decene. (5) Iodoetherification of *cis*-cyclooctene followed by treatment with butyllithium gave *trans*-cyclooctene (*trans/cis* = 95/5) selectively in 94% yield.

In order to elucidate the reaction mechanism, the role of the alkoxy moiety was examined. Replacing the methoxy group of **1a** with the *tert*-butoxy moiety afforded 6-dodecene in only 43% yield. Nevertheless, the stereoselectivity of the product was still high (*E/Z* = 5/95). The use of a more bulky triisopropylsiloxy group resulted in the recovery of the starting material almost exclusively. It should be also mentioned that the reaction of *erythro*-6-chloro-7-iodododecane with butyllithium proceeded in *anti* fashion to provide *(E)*-6-dodecene exclusively (*E/Z* = 99/1).

On the basis of these facts, we are tempted to assume the following reaction mechanism (E2, *syn*-periplanar). (1) The oxygen atom of methyl ether coordinates to lithium of butyllithium to give **A**, (2) the conformation of alkoxyiodoalkane changes to **B**, and (3) *syn* elimination of iodine and the methoxy group provides alkene stereospecifically (Scheme 2).[12]

Scheme 2

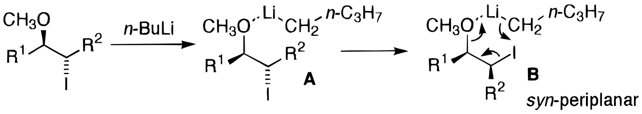
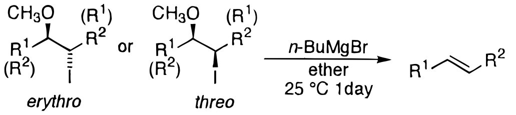
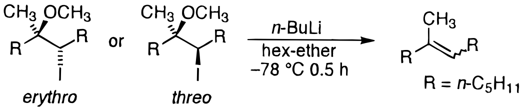


Table 3. 1,2-Elimination of Various *Vicinal* Methoxyiodoalkanes with Butylmagnesium Bromide



entry		alkoxyiodoalkane R^1	R^2	*erythro/threo*	alkene yield (%) (*E/Z*)
1	**1a**	*n*-C_5H_{11}	*n*-C_5H_{11}	97/3	92 (>99/1)
2	**2a**	*n*-C_8H_{17}	C_2H_5	99/1	94 (>99/1)
3	**4a**	*n*-C_5H_{11}	$CH_2CH_2CH_2OCH_3$	99/1	86 (>99/1)
4	**5a**	*n*-C_5H_{11}	$CH_2CH_2CH_2Br$	98/2	66 (>99/1)
5	**1b**	*n*-C_5H_{11}	*n*-C_5H_{11}	3/97	96 (>99/1)
6	**2b**	*n*-C_8H_{17}	C_2H_5	4/96	82 (>99/1)
7	**4b**	*n*-C_5H_{11}	$CH_2CH_2CH_2OCH_3$	5/95	94 (>99/1)
8	**5b**	*n*-C_5H_{11}	$CH_2CH_2CH_2Br$	11/89	97 (>99/1)

Table 4. Conversion of 7-Iodo-6-methyl-6-methoxydodecane into 6-Methyl-6-dodecane



entry		*erythro/threo*	R-Mtl/solvent	yield (%) (*E/Z*)
1	**7a**	95/5	*n*-BuLi/hex-Et_2O	74 (12/88)
2	**7b**	1/99	*n*-BuLi/hex-Et_2O	68 (95/5)
3	**7a**	95/5	*n*-BuMgBr/Et_2O	70 (75/25)
4	**7b**	1/99	*n*-BuMgBr/Et_2O	92 (76/24)

The use of butylmagnesium bromide instead of butyllithium changed the course of the reaction completely, and *(E)*-olefin was produced with high stereoselectivities irrespective of the stereochemistry of the starting alkoxyiodoalkane (Table 3). For instance, treatment of *erythro*-6-iodomethoxydodecane **(1a)** or *threo*-6-iodo-7-methoxydodecane **(1b)** with butylmagnesium bromide in ether at 25 °C gave the same *(E)*-6-dodecene exclusively in 92% or 96% yield, respectively (Table 3, entries 1 and 5).[13,14] The reaction of *trans*-1-iodo-2-methoxycyclooctane derived from *cis*-cyclooctene afforded a mixture of *cis*- and *trans*-cyclooctene (*cis/trans* = 90/10) in 86% yield.

The elimination reaction was then applied to the formation of trisubstituted alkenes (Table 4). An addition of butyllithium to **7a** in hexane−ether (1:1) at −78 °C gave *(Z)*-6-methyl-6-dodecene selectively. On the other hand, **7b** provided *(E)*-6-methyl-6-dodecene selectively upon treatment with butyllithium. The selectivities were slightly inferior to those in the formation of disubstituted alkenes. Treatment of **7a** and **7b** with butylmagnesium bromide afforded the same isomeric mixture consisting of *(E)*-6-methyl-6-dodecene and *(Z)*-isomer in 3:1 ratio.

Supporting Information Available: Experimental procedures and spectral data for all compounds (5 pages).

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(12) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. Stanetty, P.; Krumpak, B.; Rodler, I. K. *J. Chem. Res.*, Miniprint **1995**, 2110. Halogen−metal exchange followed by *syn* elimination of LiOMe might be an alternative mechanism. However, this proposed mechanism could be negated by the fact that the reaction of **1a** and **1b** with *s*-BuLi and *t*-BuLi gave stereochemical results different from those obtained in the reaction with *n*-BuLi.

(13) A radical intermediate might be involved in the course of the reaction. Single electron transfer from Grignard reagent into iodoalkanes followed by departure of iodide would produce the carbon radical. Second single electron transfer would provide a carbanion that collapses to alkene along with the elimination of the methoxide ion.

(14) A mixture of *(E)*- and *(Z)*-alkenes could be converted with *(E)*-pure alkene by sequential treatment with I_2/MeOH and butylmagnesium bromide. For instance, *trans*-cyclododecene (>99/<1) was obtained in 80% overall yield from a commercially available (Nacalai tesque, Inc.) *cis*- and *trans*-cyclododecene (34/66). Moreover, *trans*-cyclododecene could be converted into *cis*-isomer (*cis/trans* = >99/<1) in 75% overall yield by methoxyiodination and subsequent treatment with butyllithium in hexane−ether.