Pergamon

Tetrahedron Letters 43 (2002) 4487–4490

TETRAHEDRON
LETTERS

Stereospecific isomerization of 3-substituted-3-bromo-1,2-epoxypropanes using magnesium bromide

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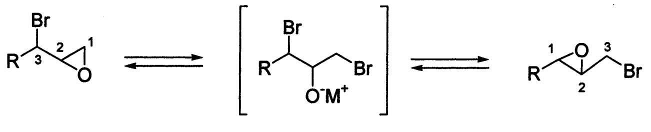
Received 13 February 2002; revised 22 April 2002; accepted 26 April 2002

Abstract—A novel stereospecific isomerization reaction of 3-substituted-3-bromo-1,2-epoxypropane derivatives into 1-substituted-3-bromo-1,2-epoxypropane derivatives is described. The choice of the solvent crucially influences the isomerization. The tendency of this isomerization could be predicted by comparison of the free energies calculation using ab initio and DFT methods. © 2002 Elsevier Science Ltd. All rights reserved.

3-Halo-1,2-epoxypropanes, which are represented as epichlorohydrin or epibromohydrin, are known as versatile substrates. They react with a variety of nucleophiles to facilitate the construction of many natural products,[1] polymers,[2] liquid crystals[3] and specific functionalities, such as allylalcohols,[4] halohydrins,[5] heterocycles,[6] and so on.

The synthesis of 3-halo-1,2-epoxypropanes has been reported by several stereoselective[7] or enantioselective[8] methods. Isomerization of 3-halo-1,2-epoxypropanes is an alternative strategy to access the regioisomeric 3-halo-1,2-epoxypropanes. Herein we report the first example of a regiospecific isomerization of the 3-substituted-3-bromo-1,2-epoxypropanes **1** into the 1-substituted-3-bromo-1,2-epoxypropanes **2** (Scheme 1).

Nucleophilic ring-opening by metal bromide salts or other brominating agent has been accepted as an appropriate route to the synthesis of bromohydrins.[5b]



1 **2**

Scheme 1.

We found the reaction of 3-substituted-3-bromo-1,2-epoxypropanes **1** and magnesium bromide gave regioisomeric 1-substituted-3-bromo-1,2-epoxypropane **2** in a highly stereoselective manner.

Initially, we investigated the isomerization of **1a** into **2a**. The reaction of **1a** with 1.2 equiv. of $MgBr_2$ as brominating agent in MeOH at 50°C provided **2** (**2a**/**2b**$=84/16$ (Table 1, entry 2)). When the reaction was conducted under reflux in MeOH, a considerable amount of the methoxy derivatives was obtained as side products. Thus, the reaction was carried out around 50°C. Unfortunately, this reaction is not applicable for the catalytic process, because using 0.05 equiv. of $MgBr_2$ did not give a satisfactory result (entry 1). We found that the choice of the solvent is crucially important for this reaction. For example, in the cases of MeCN, THF, ^{t}BuOH, and ^{i}PrOH, only a diastereomeric mixture of dibromo intermediate **3a** and **3b** was obtained in 48, 65, 55, and 73% combined yields, respectively. On the other hand, in the case of DMF, the undesired diastereoisomer **2b** was obtained in 46% combined yield (**2a**/**2b**$=9/91$, Scheme 2).

The reaction of **1a** with $MgBr_2$ in CF_3CH_2OH, which is known as a protic solvent, gave only a complex mixture. Thus, among the solvents examined, MeOH led to the best results compared to MeCN, DMF, THF, ^{t}BuOH, and CF_3CH_2OH. Table 1 summarizes the results of the isomerization of 3-phenyl-3-bromo-1,2-epoxypropane **1a** into 1-phenyl-3-bromo-1,2-epoxypropane **2a** in MeOH at 50°C. We examined the effect of several metal bromides as brominating agent

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Keywords: epoxides; isomerization; magnesium bromides; ab initio; DFT.

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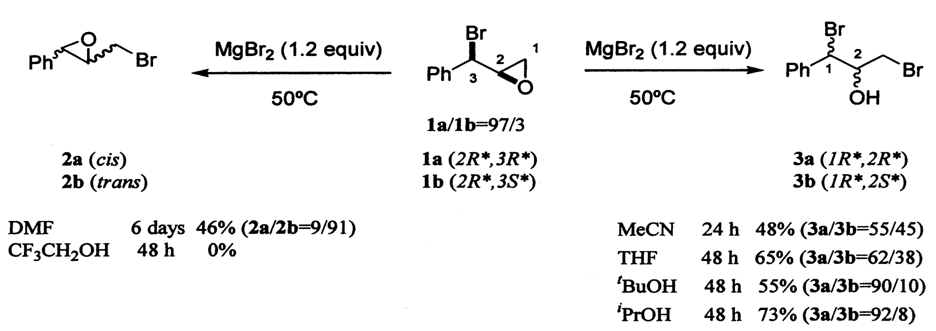
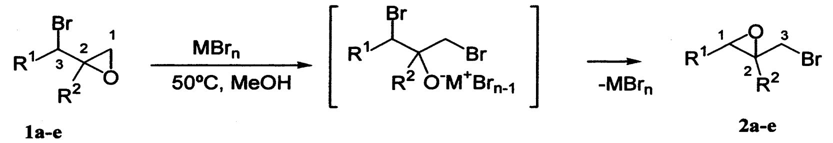
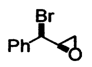
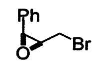
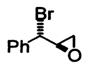
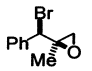
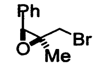
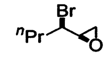
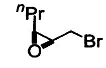
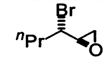
PII: S0040-4039(02)00830-4



Scheme 2.

Table 1. Isomerization of 3-substituted-3-bromo-1,2-epoxypropane into 1-substituted-3-bromo-1,2-epoxypropane in MeOH



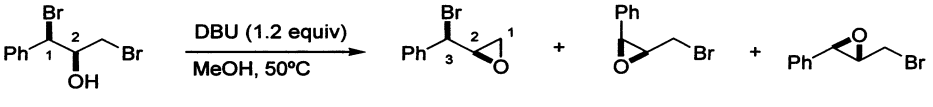
entry	substrate	((2R*,3R*)/(2R*,3S*))^b	MBr$_n$ (equiv.)	time h	product	yield^a (cis/trans)^b
1	 **1a**	(97/3)	$MgBr_2$ (0.05)	192	 **2a**	14 (87/13)
2		(97/3)	$MgBr_2$ (1.2)	48		77 (84/16)
3		(97/3)	LiBr (1.2)	96		62 (78/22)
4		(97/3)	LiBr (10)	68		63 (93/7)
5		(97/3)	NaBr (1.0)	72		52 (83/17)
6		(97/3)	KBr (1.0)	66		32 (86/14)
7		(97/3)	^{n}Bu$_4$NBr (1.2)	96		61 (83/17)
8	 **1b**	(8/92)	$MgBr_2$ (1.2)	48	 **2b**	75 (14/86)
9		(8/92)	LiBr (1.2)	96		56 (8/92)
10	 **1c**	(>98/2)	$MgBr_2$ (1.2)	48	 **2c**	68 (89/11)
11		(>98/2)	LiBr (1.2)	69		41 (65/35)
12	 **1d**	(>98/2)	$MgBr_2$ (1.2)	144	 **2d**	93^c (>98/2)
13		(>98/2)	LiBr (1.2)	144		85^c (>98/2)
14	 **1e**	(3/97)	$MgBr_2$ (1.2)	96	 **2e**	80 (2/>98)
15		(3/97)	LiBr (1.2)	120		84 (2/>98)

^{a}Combined yield. ^{b}Ratio was determined by ^{1}H NMR. The indication of >98/2 and 2/>98 means that a single diastereoisomer was observed. ^{c}Containing ca. 10% of starting **1d** as equilibrated product.

on the stereoselectivity and yield. Formation of the regioisomer **2a** was observed in all cases (Table 1, entries 1–6). Tetrabutylammonium bromide was also effective (entry 7).

We next turned our attention to exploring the scope and generality of this method for the synthesis of several 1-substituted-3-bromo-1,2-epoxypropanes **2b**–**e**. The results indicated the following tendency (entries 8–15). The reaction of diastereomeric **1b** with 1.2 equiv. of $MgBr_2$ or LiBr gave *trans*-epoxy compounds **2b** (entries 8, 9). The methyl-substituted **1c** gave the corresponding trisubstituted-epoxy compound **2c** predominantly (entries 10, 11). Remarkably, the alkyl-substituted substrates isomerized in higher yield and diastereoselectivity (entries 12–15). The relatively lower diastereoselectivity in the cases of phenyl-substituted derivatives **2a**–**c** could be due to the participation of an S_N1 mechanism on the bromination step caused by a stable benzylic cation.[9]

We assumed there is equilibrium between **1** and **2** based on the following evidence. (i) When **2a** was heated in MeOH at 50°C in the presence of 1.2 equiv. of $MgBr_2$ for 48 h, the formation of **1a** was not observed. However, when the reaction was conducted in ^{t}BuOH, the



3 (*1R*,2R**) **1a** (*2R*,3R**) **2a** (*cis*) **2b**(*trans*)

(3a/3b=>98/2)
(3a/3b=90/10)

24 h 65 % (1a/2a/2b=trace/97/3)
1 h 79 % (1a/2a/2b=50/38/11)

Scheme 3.

Table 2. pBP86/DN** and RHF/3-21G$^{(*)}$ energies (kcal mol^{-1}) at 'gaseous' and 'aqueous' phases

	RHF/3-21G$^{(*)}$		pBP86/DN**	
	Gaseous	Aqueous	Gaseous	Aqueous
1d	−1798944.24	−1798949.67	−1810292.39	−1810299.20
2d	−1798945.79	−1798951.25	−1810295.11	−1810300.48
Δ*G* (**1d**–**2d**)	(1.55)	(1.58)	(2.72)	(1.28)
1e	−1798945.06	−1798949.81	−1810293.84	−1810298.76
2e	−1798947.32	−1798952.53	−1810296.23	−1810301.17
Δ*G* (**1e**–**2e**)	(2.26)	(2.72)	(2.39)	(2.41)

dibromo-intermediate **3** was obtained. Thus, these results indirectly suggested a reverse reaction from **2a** to **3** would proceed in MeOH. (ii) Reaction of the dibromo-intermediate (**3a**/**3b**=90/10) with DBU (1.2 equiv.) for 1 h gave an isomeric mixture in 79% combined yield (**1a**/**2a**/**2b**=50/38/11). On the other hand, when reaction of the dibromo-intermediate (**3a**/**3b**= >98/2) with DBU (1.2 equiv.) was conducted for 24 h, only a trace of **1a** was observed (**1a**/**2a**/**2b**=trace/97/3). Therefore, the formation of **1a** was kinetically controlled, that is, a reverse reaction from **3** to **1a** might be feasible (Scheme 3). (iii) The propyl-substituted **1d** was transformed to **2d** in 93 and 85% yield along with recovery of **1d** in ca. 10%. The ratio of **1d** and **2d** did not change despite the prolonged (144 h) reaction (entries 12, 13). On the other hand, in the case of isomerization into **2e**, only a trace of the starting **1e** was observed (entries 14, 15).[10]

In effect, the isomerization reaction proceeds to afford the energetically more stable isomer. Computational studies were performed to understand the tendency by means of comparison of the total energies of the most stable conformers. Electronic structure calculations (HF and DFT) were carried out[11] on these materials **1d**, **1e**, **2d**, and **2e** at both gaseous and aqueous[12] phases. These results are listed in Table 2. In all cases the energy minima of produced **2d**, **2e** were predicted to be approximately 1.28–2.72 kcal mol^{-1} lower than that of the starting **1d**, **1e** at both RHF/3-21G$^{(*)}$ and pBP86/DN** levels. Thus, the relatively small basis set can be reproduced in the trend of this isomerization.

In conclusion, we have demonstrated the first example of isomerization of 3-substituted-3-bromo-1,2-epoxypropane derivatives into 1-substituted-3-bromo-1,2-epoxypropane derivatives. The tendency of this isomerization could be predicted by comparison of the free energies calculation using ab initio and DFT methods.

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9. Introduction of some electron-withdrawing groups at the phenyl group of **1a** would make it possible to suppress the S_N1 reaction. However, we could not synthesize these derivatives by a similar procedure to that described in Ref. 7b.
10. A typical procedure is as follows; To a solution of epoxides **1e** (269 mg, 1.5 mmol) in MeOH (7.5 mL) was added $MgBr_2$ (331 mg, 1.8 mmol), and the reaction mixture was stirred at 50°C. After completion of the reaction (144 h, TLC monitoring), the mixture was diluted with water, then extracted by pentane. The organic layer was dried (Na_2SO_4) and evaporated. The residue was distilled by Kugelrohr apparatus to afford **2e** (bp 170°C/30 mmHg, 214 mg, 80%).
11. PC Spartan Pro, VERSION. 1.0, Wavefanction Inc. 18401, Von Karaman, Suite 370, Irvine, CA 92612, USA.
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