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High-Pressure Promoted and Silica Gel Catalyzed Aminolysis of Epoxides with Glycine Esters[1)]

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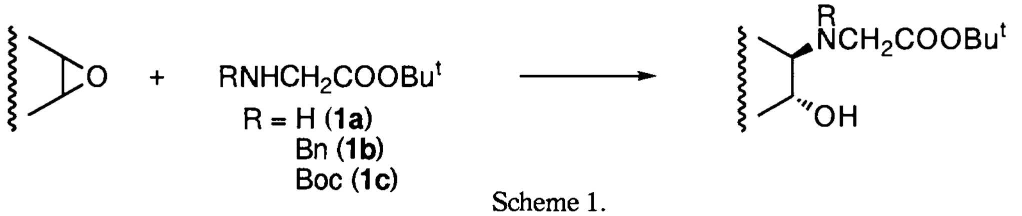
A variety of epoxides are efficiently reacted with *tert*-butyl glycinates under high pressure conditions or by supporting on silica gel to afford the corresponding *N*-(β-hydroxyalkyl)glycine esters.

The 1,2-aminoalcohol derivatives are an important class of intermediates in synthetic as well as in pharmaceutical chemistry and a variety of methods for the preparation of these compounds have been reported. Among these methods, the simplest approach relies on a direct ring opening reaction of epoxides with nitrogen nucleophiles, typically, aminolysis with aliphatic and aromatic amines.[2)] Unfortunately, this method is often carried out under drastic conditions using excess amines at elevated temperatures and is not always compatible with other functionalities. To overcome these difficulties, recently, newer techniques employing metal amides,[3)] catalysts,[4)] and enzymes[5)] have been developed.

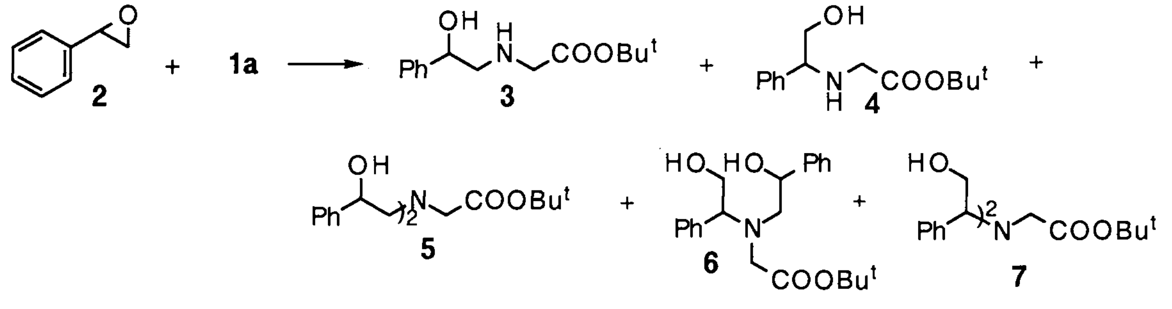
In our separate work directed toward a novel synthesis of kainoids via Michael addition reactions,[6)] we required an efficient method permitting aminolysis of epoxides with glycine esters (**1**) as an amine component (Scheme 1).[7)] However, our initial attempts to perform the reaction of *tert*-butyl glycinate (**1a**) with styrene oxide (**2**) in refluxing acetonitrile were completely failed due to largely decomposition of the substrates. Previous investigations from our laboratory have shown that this kind of reaction should be accelerated at high pressure in the absence of catalysts.[8)] Herein, we report that this expectation has been realized.



Scheme 1.

When a 1 : 1 mixture of **1a** and **2** in acetonitrile was conducted at 10 kbar and 65 °C for 24 h, a rather complex mixture of products was obtained. Careful separation by preparative TLC at 0 °C revealed the presence of **3** (33%), mp 65.0-65.5 °C, and **4** (19%), mp 84.5-85 °C, along with the 1 : 2 adduct **5** (13%) (Scheme 2).[9)] As minor byproducts it can be assumed that a diastereomeric mixture of **6** and **7** was formed, although we could not clarify their structures. Interestingly, we also found that the similar reaction occurred by exposure of both substrates on silica gel (500 mg/mmol; 6 days at room temperature),[10)] giving **3** (23%), **4** (32%), and **5**

(9%).[11] Apparently, in this case silica gel acted as an acid catalyst providing the S_N1-type adduct **4** preferentially, whereas at high pressure the S_N2-type **3** was a major product.

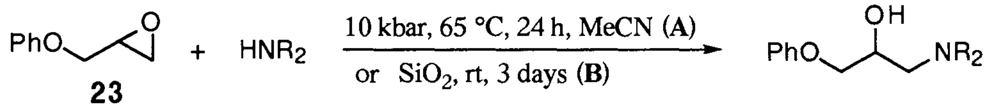


Scheme 2.

To establish the synthetic utility of these procedures, we then examined the reaction of *tert*-butyl *N*-benzylglycinate (**1b**).[12] As summarized in Table 1, **1b** reacts efficiently with a variety of epoxides to afford the corresponding *N*-(β-hydroxyalkyl)glycine esters.[9]

The excellent regioselectivities observed for **8**, **10**, and **11** reflect a critical feature of the steric hindrance in these reactions. Cyclohexene oxide (**9**) was less reactive than others (Runs 9-13) and only reacted smoothly with **1a** to give **18**, mp 96.5-97.5 °C, in 84% yield (Run 9). Evidently, epoxides are susceptible to aminolysis rather than esters as shown in Runs 14 and 15. As expected, the prolonged reactions produced a considerable amount of lactones through intramolecular transesterification (Runs 2, 6 and 11). As noted in Scheme 2, the product distribution for **12**, mp 75.0-76.5 °C, and **13**, mp 64.5-67.0 °C, was affected by the reaction conditions used (Runs 1 and 4). Thus, at high pressure **12** was obtained as a major product, while the formation of **13** was slightly favored on silica gel. The combination of both techniques is highly effective for deriving **13** (Run 3), implying the enhancement of acidic nature of silica gel at elevated pressures.[13] This is also the case for Runs 7 and 12. Particularly noteworthy is the optically active bis-epoxide **11** and on treatment with 2 equiv. of **1b** the desired diol **22**, $[\alpha]_D^{27}$ +39.2° (*c* 0.5, $CHCl_3$), was obtained in high yields (Runs 16 and 17).

The general feasibility of the present methods for some normal alkylamines was also briefly examined. Thus, high pressure-promoted and silica gel-assisted reactions of **23** with an equimolar amount of piperidine and *N,N*-diisopropylamine provided the corresponding aminoalcohols **24** and **25**, respectively, in good yields (Scheme 3).



R = $-(CH_2)_5-$ **24**: 72% (**A**); 77% (**B**)
R = i-Pr **25**: 74% (**A**); 61% (**B**)

Scheme 3.

In conclusion, a variety of epoxides can react with a stoichiometric amount of glycine esters (**1a** or **1b**) under high pressure or silica gel catalyzed conditions to produce *N*-(β-hydroxyalkyl)glycine esters in high yields. Since these reactions can be conducted under fairly mild conditions, the method exhibits a considerable utility in organic synthesis. By utilizing the key intermediate **22** further synthetic works on kainoids are now in progress.

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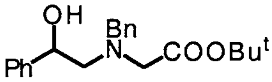
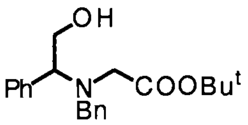
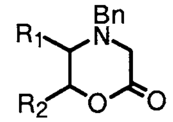
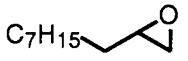
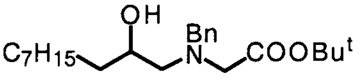
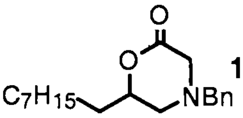
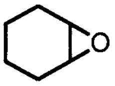
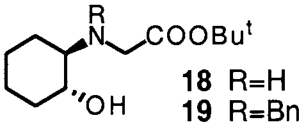
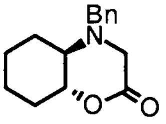
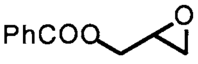
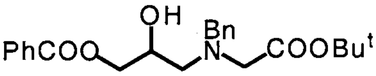
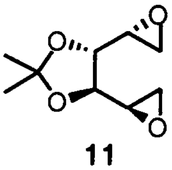
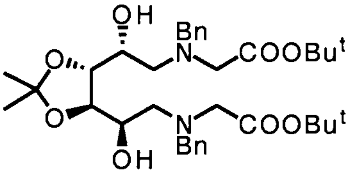
Table 1. High Pressure-Promoted, Silica Gel-Assisted Aminolysis of Epoxides with Glycine Esters[a]

Run	Epoxide	1	Method[b]	Reaction Conditions	Product yields, %[c]		
	2	1b			 **12**  **13**		 **14** R_1=H, R_2=Ph **15** R_1=Ph, R_2=H
1			A	65 °C, 24 h	**12**: 52		**13**: 22 (26)
2			A	65 °C, 48 h[d]	**12**: 6	**14**: 45	**15**: 20
3			B	65 °C, 36 h	**12**: 19		**13**: 71
4			C	rt, 3 days	**12**: 46		**13**: 51
	 **8**	1b			 **16**		 **17**
5			A	65 °C, 24 h	47		2 (46)
6			A	65 °C, 2 days	26		65 (6)
7			B	65 °C, 24 h	60		18 (20)
8			C	rt, 7 days	97		2
	 **9**				 **18** R=H **19** R=Bn		 **20**
9		1a	A	65 °C, 24 h	**18**: 84		
10			A	65 °C, 24 h	**19**: 11 (88)		
11		1b	A	80 °C, 3 days	**19**: 3		**20**: 56 (40)
12			B	rt, 24 h	**19**: 31 (55)		
13			C	rt, 6 days	**19**: 50 (50)		
	 **10**	1b			 **21**		
14			A	65 °C, 24 h	82		
15			C	rt, 6 days	87		
	 **11**	1b			 **22**		
16			A	rt, 24 h	82		
17			C	rt, 24 h	91		

a) Stoichiometric amounts of the starting materials were used for all reactions. b) **Method A**: at 10 kbar in MeCN; **Method B**: at 10 kbar in CH_2Cl_2 in the presence of silica gel (500 mg/mmol); **Method C**: adsorbed on silica gel (500 mg/mmol). c) Isolated yields. Yields in parentheses are recovery of **1**. d) Considerable amounts of polymeric substances were obtained.

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10) Wakogel C-300 was employed in this study. Other type of silica gel gave also comparable results.

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12) To avoid the concomitant formation of the lactone derivatives such as **15**, we did not use the corresponding ethyl ester. No desired reaction was occurred between **1c** and epoxide.

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