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$HClO_4$·SiO_2-mediated Improved Isomerization of Glycidic Esters to α-Hydroxy-β,γ-unsaturated Esters: Application in the Formal Synthesis of (*R*)-Baclofen and β-Phenyl GABA Analogues

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An efficient isomerization of glycidic esters to corresponding allylic alcohols, viz. α-hydroxy-β,γ-unsaturated esters has been brought about using $HClO_4$·SiO_2. Five of these allylic alcohols underwent selective S_N2' nucleophilic substitution to generate γ-azido-α,β-unsaturated esters which were readily converted to an antispastic drug Baclofen and four other β-phenyl GABA analogues.

Synthesis of chiral and achiral vinyl epoxides from α-hydroxy-β,γ-unsaturated esters[1] was reported a few years ago. Conversion of α-hydroxy-β,γ-unsaturated esters into fluorinated vinyl epoxides has also been demonstrated by Olah et al.[2] Besides this, facile oxidation of α-hydroxy-β,γ-unsaturated esters into α-keto-β,γ-unsaturated esters which further undergo easily the Michael addition and the Diels–Alder reaction to form some useful intermediates has also been reported.[3] α-Hydroxy-β,γ-unsaturated esters can be derived from the corresponding glycidic esters by acid (or Lewis acid)-catalyzed regioselective isomerizations. These acidic catalysts include $LiClO_4$,[4] $Mg(ClO_4)_2$,[5] H_2SO_4–AcOH,[6] BF_3·Et_2O,[3] $ClSiMe_3$,[3] Zeolite H-ZSM 5,[7] Nafion-H,[2] HI,[8] Ph_3SiClO_4,[9] and $Yb(OTf)_3$.[10] However, some of these reagents are either hygroscopic or difficult to handle, while in some cases yields are relatively low and require longer reaction times along with formation of some side products. Moreover, there is no generalized reported method for isomerization of aromatic-based glycidic esters.

Recently, the utility of $HClO_4$·SiO_2 as a stable and solid acidic reagent for a variety of useful transformations has been reported.[11] It therefore occurred to us that such a catalyst could also be utilized for the conversion of glycidic esters into the corresponding α-hydroxy-β,γ-unsaturated esters. Further, we also realized that α-hydroxy-β,γ-unsaturated esters could serve as useful precursors for procuring γ-aminobutyric acid (GABA) derivatives, such as Baclofen **1** and Phenibut **2** (Figure 1), which are important inhibitory neurotransmitters involved in dispensing of several psychological and physiological responses in the biological systems.[12] Although the therapeutic effect of Baclofen is associated with the (−)-*R*-isomer, still it has been commercialized in its racemic form under the trade name Lioresal, Baclofen, etc.[12,13] In this paper we wish to report the use of $HClO_4$·SiO_2 as an efficient catalyst for the isomerization of glycidic esters into α-hydroxy-β,γ-unsaturated esters which, in turn, are converted into GABA derivatives, albeit in racemic form. We envisioned the preparation of Baclofen, 3-(4-chlorophenyl)-4-aminobutyric acid to be derived from allylic alcohol **B** (Scheme 1) via an S_N2' azide displacement and further chemical manipulation. The allylic alcohol in turn could be obtained from epoxide **C** (a glycidic ester) through an acid-catalyzed rearrangement. The epoxide **C** could be obtained by reaction between a ketone, especially acetophenone derivatives **D** and ethyl chloroacetate.

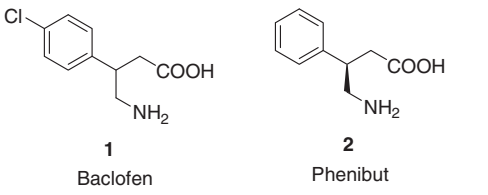
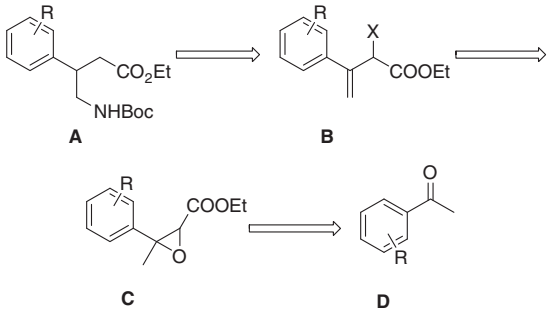


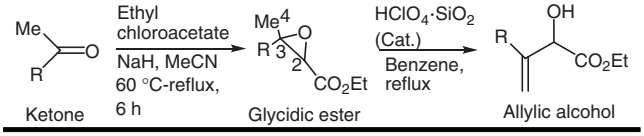
Figure 1. Structures of Baclofen and Phenibut.



Scheme 1. Retrosynthesis for the Baclofen synthesis.

Isomerization of the glycidic ester **3** (Table 1) was performed using 10% weight equivalent of $HClO_4$·SiO_2 in refluxing benzene which led to the isolation of the required allylic alcohol **4** in 93% yield. Reduction in the amount of the reagent led to longer reaction time and unreacted starting material was recovered, hence, we used minimum of 10% weight equivalent of the catalyst. The reaction was found to work with several glycidic esters which were derived from variously substituted aromatic ketones (Table 1) and nonaromatic ketones (Table 2). As we are interested in conversion to allylic alcohols, we prepared glycidic esters following the reported procedure[1f,1g] and are reporting the results of glycidic esters in Tables 1 and 2. The diastereomeric ratios are based on comparison of proton intensities of the corresponding protons. In this regard glycidic ester **17** was isolated as a single diastereomer and has been assigned trans configuration based on NOE experiments. Irradiation of H-2 and H-4 (methyl protons) showed negligible enhancement in the signals of one another, while showed 0.4% enhancement for phenyl protons. Thus the H-2 proton and methyl group are trans oriented with respect to one another. When the reactions were performed with glycidic esters having

Table 1. Isomerization of glycidic esters derived from acetophenones[a]

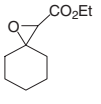
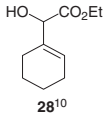
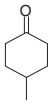
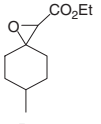
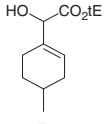
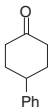
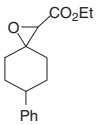
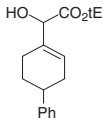
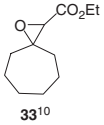
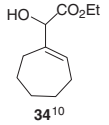
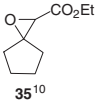
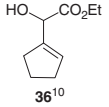


Ketone — Glycidic ester — Allylic alcohol

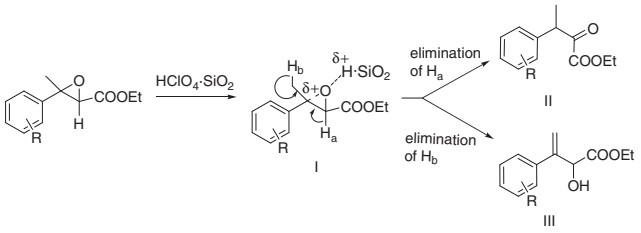
Sr. No.	Ketone R =	Glycidic ester/Yield (dr)	Allylic alcohol/ Yield	Cat. /mg	Time /min
1	Phenyl	**3**[2]/64% (3:1)	**4**[2]/93%	5	30
2	*o*-Tolyl	**5**/83% (1:1)	**6**/80%	5	30
3	*p*-Tolyl	**7**[10]/55% (6.7:1)	**8**[10]/94%	5	30
4	*m*-Methoxyphenyl	**9**/74% (6:1)	**10**/90%	5	30
5	*p*-Methoxyphenyl	**11**/48% (2:1)	**12**/62%	5	10
6	*o*-Chlorophenyl	**13**/90% (5:1)	**14**/66%	5	30
7	*m*-Chlorophenyl	**15**/90% (13:1)	**16**/76%	5	30
8	*p*-Chlorophenyl	**17**[b]/87%	**18**/85%	5	30
9	*o*-Fluorophenyl	**19**/76% (6:1)	**20**/74%	5	30
10	*p*-Fluorophenyl	**21**/86% (13:1)	**22**/78%	5	30
11	*m*-Nitrophenyl	**23**/88% (1.7:1)	**24**/86%	15	150
12	*p*-Nitrophenyl	**25**/89% (2:1)	**26**/88%	35	210

[a]Reactions were carried out at 50 mg scale in 1.5 mL of dry benzene. The compound solutions were preheated to reflux and catalyst was added at this temperature under N_2 atmosphere.[16] [b]Only single isomer isolated.

Table 2. Isomerization of glycidic esters derived from cyclic ketones[a]

Sr. No.	Ketone	Glycidic ester	Yield/%	Allylic alcohol	Time (mins)	Yield/%
1		 **27**[10]	71	 **28**[10]	30	82
2		 **29**[7] dr = 1:2.5	57	 **30**[7] dr = 1:1	30	79
3		 **31**[10] dr = 4:1	44	 **32**[10] dr = 2:3	30	72
4		 **33**[10]	32	 **34**[10]	30	83
5		 **35**[10]	41	 **36**[10]	15	91

[a]Reactions were carried out at 50 mg scale in 1.5 mL of dry benzene with 5 mg $HClO_4 \cdot SiO_2$. The compound solutions were preheated to reflux and catalyst was added at this temperature under N_2 atmosphere.[16]

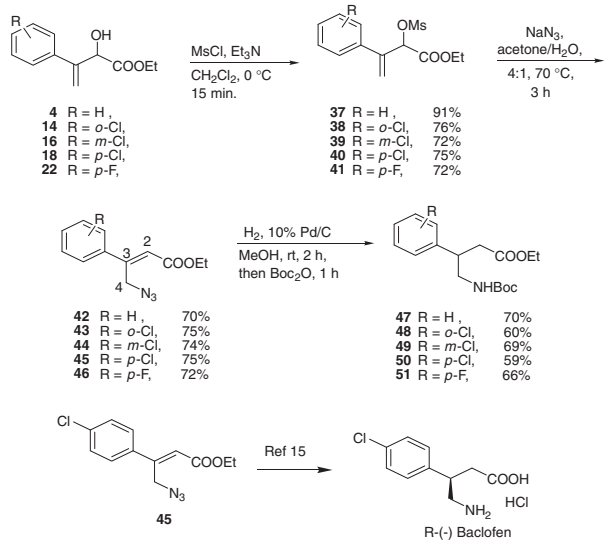


Scheme 2. Mechanism of the isomerization of glycidic esters.

electron-donating substituents on the phenyl ring, the yields of the allylic alcohols were found to be higher in general (Table 1, Entries 2–4). Strangely, when the electron-donating group was *m*-methoxy, the yield of allylic alcohol **10** was found to be 90% (Table 1, Entry 4), while *p*-methoxy-substituted phenyl glycidic ester **11** generated the corresponding allylic alcohol **12** in only 62% yield (Table 1, Entry 5) along with some polar intractable mixture of compounds. However, electron-withdrawing substituents yielded slightly lower yields of allylic alcohols in general (Table 1, Entries 6–10) as compared to electron-donating substituents. When the electron-withdrawing-group nitro functionality was used as a substituent, the yields of the corresponding allylic alcohols **24** and **26** were found to be at par (Table 1, Entries 11 and 12) with the yields obtained from electron-donating substituents. But, it required higher amount of the catalyst and longer time interval for the reaction to complete. Also it was found that the yields obtained for the isomerization of glycidic esters derived from nonaromatic ketones were a little lower in general as compared to isomerization yields of the aromatic ketone-based glycidic esters (Table 2).

A tentative mechanism for such an isomerization is shown in Scheme 2. It is expected that when glycidic ester reacts with the acidic catalyst, partial positive charge develops at the benzylic carbon leading to structure **I**. The elimination of the proton H_a or H_b would lead to either α-keto ester **II** or an allyl alcohol **III**, respectively. The ease of elimination of a particular proton i.e., H_a or H_b depends upon their respective acidities and antiperiplanarity with respect to the cleaving C–O bond. Although the acidity of H_a proton is much higher than that of H_b proton, but its fixed conformation at the tertiary carbon center makes its elimination difficult due to which the formation of α-keto esters is known to occur only under drastic conditions and with poor yields. However, the acidity of the H_b proton is very low, but as it can achieve antiperiplanarity, the elimination does not require drastic conditions like H_a proton.

Based upon the mechanism (Scheme 2), the low yield of allylic alcohol **12** (Table 1, Entry 5) can be rationalized. The partial positive charge developed at the benzylic carbon in the



Scheme 3. Conversion of isomerized allylic alcohols into Baclofen derivatives.[16]

glycidic ester **11** upon treatment with $HClO_4 \cdot SiO_2$ catalyst is resonance stabilized. This reactive center may undergo other low-energy reactions even before isomerization could take place. This resulted in the formation of a polar intractable mixture of compounds along with low yield of the allylic alcohol **12**. The high reactivity of this center is reflected in the reduced time required for completion of the reaction. Similarly, when reactions were performed on glycidic esters **23** and **25** (Table 1, Entries 11 and 12) at reflux temperature, the partial positive charge developed at the benzylic positions of the corresponding glycidic esters becomes difficult because of the deactivation due to the nitro functionality. Due to this, the C–O bond cleavage occurs at elevated temperatures. However, at reflux temperature, cleavage of C–O bond took place with facile elimination of proton to yield the allylic alcohol in very good yields. The reluctance of the C–O bond cleavage is reflected in the increased requirement of the amount of catalyst along with the extended time required for the completion of the reaction. The greater reactivity of the glycidic ester **35** to form allylic alcohol **36** amongst nonaromatic ketone-derived glycidic esters (Table 2, Entry 5) appears to be due to opening of the more strained epoxide on the cyclopentane ring compared to epoxide on a cyclohexane ring or cycloheptane ring.

The allylic alcohols **4**, **14**, **16**, **18**, and **22** were subjected to mesylation (Scheme 3) to yield the corresponding allylic mesylates **37**–**41** in moderate to good yields. These mesylates underwent selective S_N2' nucleophilic displacement with azide ion to yield allylic azides **42**–**46** in moderate yields. The geometry of the allylic azides has been determined through NOE experiments for two representative compounds **42** and **45**. Irradiation of the H-2 and H-4 protons led only to negligible enhancements in the signals of one another while for the phenyl protons showed enhancement of nearly 1.5%. Thus, the allylic and alkene protons are trans oriented with respect to each other. Under these reaction conditions, no trace of the product via an S_N2 displacement could be isolated. Further one-pot hydrogenation of the double bond and azide reduction with 10% Pd/C-catalyzed conditions followed by in situ Boc protection of the primary amine led to the protected β-phenyl-γ-aminobutyric acids (GABA) **47** (protected racemic phenibut), **48**, **49**, **50** (protected Baclofen), and **51**.[14]

Of the azido esters **42**–**46**, compound **45** has been converted into (*R*)-Baclofen upon sequential reductions with Ru(II)–(*S*)-BINAP, H_2 (200 psi),[15] and $NaBH_4$–$CoCl_2$, followed by hydrolysis, thus completing its formal synthesis.

In summary, a new reagent system has been introduced for the isomerization of various aromatic-based glycidic esters to the corresponding α-hydroxy-β,γ-unsaturated esters (allylic alcohols). The reagent works equally well with cyclic ketone derived glycidic esters. Five of these β-phenyl-derived allylic alcohols were readily converted to γ-aminobutyric acid ester analogues including Baclofen.

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