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A new, simple, and mild azidolysis of vinylepoxides

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ABSTRACT

A new, simple, and mild regio-and stereocontrolled azidolysis of vinylepoxides with $TMSN_3/BF_3$ system is reported. The method appears of general value and works very well particularly in the presence of electron-poor olefins, regardless of the size of substituents on the heterocyclic ring.

Nucleophilic ring-opening of epoxides is a powerful tool in organic synthesis due to their highly functionalized nature and versatile reactivity. Among the variously functionalized epoxides, the vinylepoxides are a very interesting subclass having several positions for nucleophilic attack (Fig. 1) and a judicious choice of nucleophile directs the ring-opening in S_N2 and S_N2' (route A) modes.[1] Generally the vinylic moiety functions as a regiochemical directing element (route B) and the homoallylic attack (route C) is not normally observed.

The ring-opening reaction of vinylepoxides is a key step of total synthesis of many natural products as (−)-Balanol,[2] Hyacinthacine A_1,[3] (−)-Muricatacin,[4] (−)-LL-C10037α,[5] methyl β-D-vicenisaminide,[6] etc. Moreover, they are useful synthons for the synthesis of biologically active products as iminosugars,[7] inositol derivatives,[8] sphingosines,[9] macrolide antibiotics,[10] benzazepine skeletons.[11]

Despite the rich literature on the chemistry of epoxide opening, to the best of our knowledge there are few reports concerning a systematic study on the ring-opening of vinyloxiranes by azide.[12] The azide moiety is one of the most popular amine precursors in organic synthesis and the starting material for the Huisgen 1,3-dipolar cycloaddition reaction with alkynes to form stable aromatic 1,2,3-triazoles (click chemistry).[13]

As we are interested in synthetic methodologies to prepare highly functionalised chiral fragments by stereo-and regioselective ring opening of functionalised 3-membered heterocyclic rings,[14] we planned to extend our studies on the azidolysis of vinylepoxides.

In the light of the excellent results recently obtained on the Lewis acid-mediated regioselective opening of epoxy amines using $TMSN_3$ as source of azide group,[15] we decided to employ the $TMSN_3/BF_3{\cdot}OEt_2$ system[16] to attempt the regio-and stereocontrolled azidolysis of the vinylepoxides.

To study the reactivity of these substrates we prepared compounds with various R and R′ (Scheme 1) to investigate the influence of the steric hindrance of R on the oxirane ring and the electronic effects of R′ on the double bond.

Vinyloxiranes were easily prepared from the corresponding allylic alcohol in three efficient steps: epoxidation of the double bond (by *m*-CPBA for racemic compounds, by Sharpless AE for optically active compounds),[17] oxidation of the alcohol group and Wittig[18] or Horner–Emmons[19] olefination (Scheme 1).

All substrates were submitted to the reaction with $TMSN_3$ (1 equiv) and $BF_3{\cdot}OEt_2$ (2 equiv) in dry CH_2Cl_2 at room temperature.[20] Under these conditions, in a few hours (0.75–4.1 h) the starting material disappeared and the corresponding anti azido alcohol was generally obtained in a satisfactory yield. The allylic

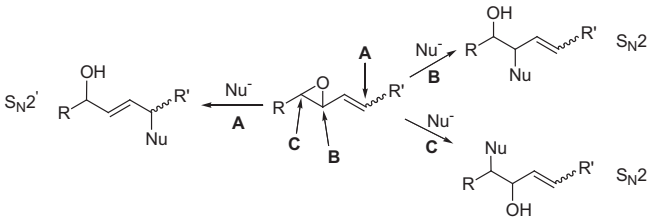

Figure 1. Position for nucleophilic attack on a vinylepoxide.

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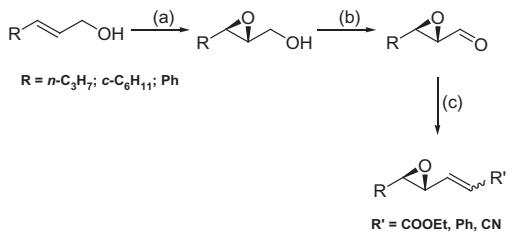
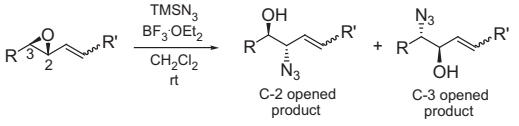


Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, rt, 90–95%; (b) TEMPO, IBDA, CH_2Cl_2, rt, 68–87%; (c) (i) for R′ = CO_2Et:TEPA, LiOH, THF, reflux, 89–92%; (ii) for R′ = Ph:Ph_3PCH_2PhBr, LiOH, *i*-PrOH, rt, 59–75%; (iii) for R′ = CN:$(EtO)_2POCH_2CN$, LiOH, THF, reflux, 63–86%.

Table 1
Azidolysis of vinylepoxides with $TMSN_3$ and $BF_3{\cdot}OEt_2$[19]



Entry	Substrate	R	R′	Isomer ratio C2:C3[a]	Product	Time (h)	Yield (%)
1	**1**	*n*-C_3H_7	CO_2Et	>95:5	**2**	1	96
2	**3**	*c*-C_6H_{11}	CO_2Et	>95:5	**4**	1.3	96
3	**5**	Ph	CO_2Et	40:60	**6:7**	3	78[b]
4	**8**	*n*-C_3H_7	CN	>95:5	**9**	1.2	87
5	**10**	*c*-C_6H_{11}	CN	>95:5	**11**	1	94
6	**12**	*n*-C_3H_7	Ph	>95:5	**13**	4	52
7	**14**	*c*-C_6H_{11}	Ph	>95:5	**15**	4.1	48
8	**16**	*n*-C_3H_7	*n*-C_5H_{11}	55:45	**17:18**	3.5	75[b]
9	**19**	*c*-C_6H_{11}	*n*-C_5H_{11}	52:48	**20:21**	4.3	68[b]

[a] Ratio determined by ^{1}H NMR of the crude product.
[b] Yields of the isomeric mixture.

position of the azide group was established by spin–spin decoupling experiments and the anti configuration was assigned based on a S_N2 mechanism, since only one diastereisomer was detected.

As shown in Table 1, the steric hindrance of R did not affect the regio-and stereoselectivity of the epoxide ring opening. Only with R = Ph (entry 3) the reaction proceeded with poor regioselectivity, as already noted for several other phenyl substituted epoxides,[20] due to the simultaneous presence of the activated benzylic position.

Regarding the effect of the R′ group, a complete regioselective nucleophilic attack in the allylic position was observed when an electron-withdrawing substituent on the double bond (R′ = COOEt, CN and Ph; entries 1, 2, 4–7), although for R′ = Ph the ring opening occurred in moderate yields and longer reaction time.

Finally, when a poor electron-withdrawing group was present on the double bond (R′ = Alk; entries 8 and 9), the azidolysis occurred without any regioselectivity.

In summary we have developed a new, simple, and mild regio- and stereocontrolled azidolysis of vinyl epoxides. The method appears of general value and works very well particularly in the presence of electron poor olefins, regardless of the size of substituents on the heterocyclic ring. Moreover, considering the versatility of azide group and the possibility to further functionalize the double bond, the obtained products are promising intermediates for the preparation of highly functionalized chiral fragments.

Further work is currently in progress in order to extend this methodology to vinyl aziridines.

Acknowledgments

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General procedure: To a stirred solution of the vinylepoxides (1 mmol) in dry CH_2Cl_2 (3 mL) were added $TMSN_3$ (1 mmol) and $BF_3{\cdot}OEt_2$ (2 mmol) dropwise and the solution was stirred at room temperature. Then, the reaction was diluted with CH_2Cl_2, the organic phase was washed with $NaHCO_3$ (3 mL), brine (3×3 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure. Often the crude product was characterized without further purification, unless otherwise stated. All reactions were carried out under nitrogen and were monitored by TLC.
NMR data for representative compounds: Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.25–1.47 (m, 4H), 2.95 (b s, 1H, OH), 3.68 (m, 1H), 4.01 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 6.01 (d, J = 15.9 Hz, 1H), 6.82 (dd, J = 6.6, 15.9 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.3; 13.6; 18.3; 34.2; 60.3; 66.9; 72.2; 124.7; 140.4; 165.1.
Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J = 7.0 Hz, 3H), 1.25–1.55 (m, 4H), 3.75 (q, J = 4.4 Hz, 1H), 4.06 (ddd, J = 1.4 4.4 6.4 Hz, 1H), 5.66 (dd, J = 1.4 16.3 Hz, 1H), 6.70 (dd, J = 6.4 16.3 Hz, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.7; 18.6; 34.7; 67.1; 72.6; 103.3; 116.7; 148.1.
Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 7.4 Hz, 3H), 1.57–1.87 (m, 4H), 3.90 (dd, J = 1.8, 7.1 Hz, 1H), 4.03 (dd, J = 6.8, 7.3 Hz, 1H), 5.82 (dd, J = 7.2, 11.4 Hz, 1H), 6.77 (d, J = 11.4 Hz, 1H), 7.22–7.47 (m, 5H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.5; 18.3; 36.5; 68.3; 71.7; 122.1;126.4; 127.3; 127.5; 131.9; 152.1.
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