Tetrahedron Letters, Vol.32, No 5, pp 667-670, 1991
Printed in Great Britain

0040-4039/91 $3 00 + (
Pergamon Press plc

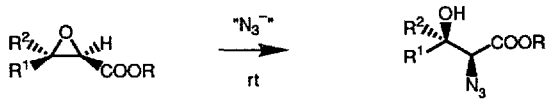
SELECTIVE C-2 OPENING OF 2,3-EPOXYESTERS WITH HN_3–AMINE SYSTEM: A VIABLE ROUTE TO β-HYDROXY-α-AMINO ACIDS

Seiki Saito,* Nobuyosi Takahashi, Teruhiko Ishikawa, and Toshio Moriwake*
Department of Applied Chemistry, Faculty of Engineering, Okayama University
Tsushima, Okayama, Japan 700

Summary: The combination of hydrogen azide with amines has proven to effect the C-2 opening of 2,3-epoxyester with high regioselectivity uniformly for *trans*-epoxyesters and depending on their structures for *cis*-2,3-epoxyesters .

An important breakthrough has recently been achieved by Sharpless with regard to a very strong preference for nucleophilic attack on C-3 of 2,3-epoxy alcohols, acids, and amides by the aid of Ti(O-*i*-Pr)$_4$-mediated epoxide activation.[1] He has also reported that diethylamine attacks the C-2 position of 2,3-epoxy acids,[1b] which can provide β-hydroxy-α-amino acids, albeit limiting to an *N,N*-disubstituted type. While cognizant of these encouraging developments, we have perceived a need for a general method for C-2 opening of the related structures, in particular, with respect to an introduction of azido-group into C-2 of 2,3-epoxyesters (Scheme I) because it can apparently appeal prospect for a straightforward access to β-hydroxy-α-amino acids of biological interests.[2]

Scheme I.



$HN_3 + R_3N \longrightarrow R_3NHN_3$ (1)

$Me_3SiN_3 + ROH + R_3N \longrightarrow R_3NHN_3 + Me_3SiOR$ (2)

$NaN_3 + R_3NHCl \longrightarrow R_3NHN_3 + NaCl$ (3)

R_3N : diethylamine (DEA), diisopropylamine (DIPA), diisopropylethylamine (DIPEA)

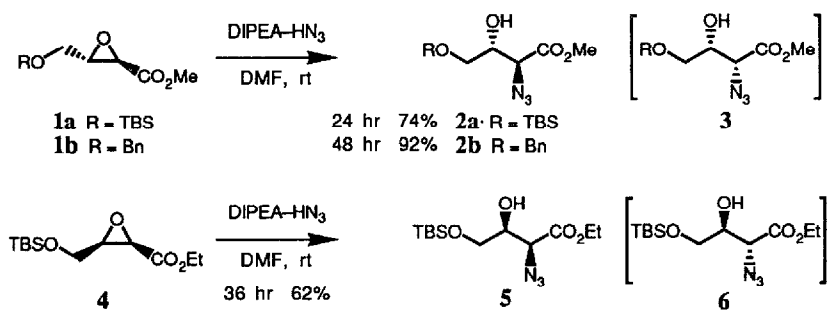
It was our mere conjecture that one of factors responsible for the C-2 ring cleavage of epoxy acids witnessed by Sharpless[1b] might be increasing nucleophilicity of the secondary amine which may emerge through the reasonable formation of ammonium carboxylate under the conditions. Thus, our attention was directed toward how to amplify "N_3^-" nucleophilicity and we reached to a piece of conclusion to use R_3NHN_3 type reagent as a new "N_3^-" nucleophile. The reagents were able to be conventionally prepared (Eq 1) as sublimable crystals by mixing a solution of known concentration of hydrogen azide with amine in ether, and as a solution or suspension in DMF by mixing azidotrimethylsilane, ROH (R = H or Me), and the amine in DMF (Eq 2) or the corresponding amine-hydrochloride with sodium azide in DMF (Eq 3).[3]

The representative outcomes shown in Scheme II delineate the power of the method. For instance, *trans*-2,3-epoxyesters (**1a** or **1b**)[4] led to β-hydroxy-α-azido esters (**2a** or **2b**)[5] in 74% or 92% yield, respectively, on treating **1** with DIPEA-HN_3 (Eq 1) in DMF at room temperature without any detectable amount of the C-3 opening product or epimerization at C-2 (**3**). It was also to be the

case for *cis*-2,3-epoxyester (**4**),[4] resulting in the exclusive formation of syn product (**5**),[6] none of **6** being detected.

The *O*-TBS-group was partly deprotected under the conditions which is responsible for the moderate yield of **2a** or **5**, and much higher yield of **2b** accordingly . This is probably because DIPEA-HN_3 rapidly reaches a state of equilibrium consisted of the salt and the free counterparts, HN_3 and DIPEA, the former acting as an acid. This situation, on the other hand, provides an opportunity for less hindered amines, such as DEA or DIPA, and HN_3 system to play a role of a base. Thus, these gave the epimerized product (**3**) in the ratio **2** : **3** = 3 : 1 or 5.5 : 1, respectively. It should be pointed out that the reactions of **1** with azidotrimethylsilane/MeOH in DMF[7] (60 °C), NaN_3/DIPEA in DMF, or NaN_3 in DMF at room temperature resulted in near quantitative recovery of **1**. Other attempts employing $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$[1c] in THF (60 °C) or NaN_3/NH_4Cl in ethylene glycol monomethyl ether–H_2O (8 : 1)[8] were unsuccessful to result in simple transesterification or the formation of a complex mixture, respectively.

Scheme II.

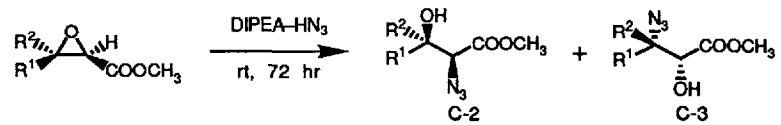


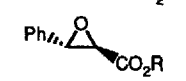
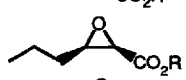
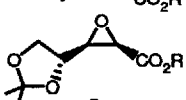
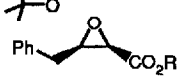
A number of *trans*- and *cis*-epoxyesters was synthesized[9] and their reactions with DIPEA-HN_3 reagent were examined under the identical conditions (3 eq reagent at rt for 72 hr) in order to know their reactivity trends for the structure variations. For the determination of regioselectivity the products were led to the corresponding acetates (Ac_2O/DMAP/CH_2Cl_2), which served to analyze the C-2 and C-3 ratio by NMR (500 MHz) unambiguously based on the chemical shifts and, for the *trans* series, $J_{2,3}$–values as well.[10] The results are shown in Table 1.

The following features are clearly indicated from these results coupled with those shown in the Scheme II: (a) the *trans*-isomers promise uniformly high C-2 selectivity except for one which bears a benzylic epoxy array (Entry 6), (b) the degree of regioselectivity reflects apparent steric bulk of the C-3 substituent and, in addition, the electronic effect of itself judging from the exceptionally high C-2 opening observed for **1** or **4**, (c) the reactivity and C-2 selectivity for the *cis*-isomers, although C-2 > C-3 is maintained, are generally low, which, however, become an acceptable level in some cases depending on the structure (**4** and Entry 8).

Although C-2 selection for *cis*-2,3-epoxyesters remains unsatisfactory, the present method for the azide cleavage of *trans*-2,3-epoxyesters with strong C-2 preference constitutes a straightforward access to β-hydroxy-α-azidoesters which are direct precursors for β-hydroxy-α-amino acids because the conversion of the azido groups to the corresponding *N*-Boc-amino groups had been established.[11] An exact reason why the HN_3-amine system realizes such a strong tendency of C-2 cleavage for *trans*-2,3-epoxyesters must await future study. However, one possible explanation can be provided by invoking acyl activation stemming from a protonation to its carbonyl group. The proton may be delivered from the HN_3-amine reagent to this functionality at the presumed

Table 1. Azide cleavage of 2,3-epoxyesters with DIPEA–HN_3 in DMF[a]

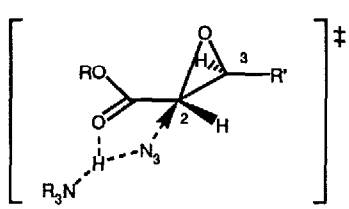


Entry	Epoxyester (R = CH_3)[b]	α-Azido-β-hydroxyester					
		Yield/%[c]:	C-2	C-3	$J_{2,3}$[d]/Hz:	C-2	C-3
1		52 (91)	12	1		4.3	3.5
2		52 (91)	10	1		4.3	3.5
3		68 (100)	29	1		4.9	4.4
4		66 (87)	73	1		5.9	2.3
5		93 (93)	43	1		4.0	3.4
6		64 (85)	1.5	1		6.5	5.5
7		27 (68)	1.3	1		3.1	3.4
8		56 (76)	57	1		4.0	2.7
9		23 (70)	5.8	1		2.4	3.0

(a) Conducted under the identical conditions for every entry (rt/72 hr/reagent : substrate ratio (3:1). (b) Prepared from the corresponding allylic alcohols through AE (Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765), RuO_4 oxidation (Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936), and esterification (CsF/MeI/DMF) for the entries 1–5, and others from the corresponding α,β-unsaturated ester through MCPBA epoxidation although resulting in low yields. (c) The yields in parenthesis, corrected for recovered substrate. (d) For the corresponding acetates.

transition state (9). This situation may also result in the enhanced nucleophilicity of "N_3^-", which, at the same time, can arrange in close proximity to the C-2 position of the oxirane ring for an S_N2 attack via a five-membered structure as depicted (9).

The HN_3–amine reagents are obviously a novel type of "N_3^-" nucleophile which has been demonstrated for S_N2 substitutions of various sulfonates and halides as reported



9

in the preceding paper[12] and presently for oxirane cleavages. Nonetheless, reactivity is still not so high, in particular, for oxirane cleavage. How to remedy this point is currently our major concern.

Acknowledgment: We thank to "Okayama Foundation of Science and Technology" for the financial support and to "The SC-NMR Laboratory of Okayama University" for 500 MHz NMR experiments.

References and notes

(1) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560. (b) Chong, J. M.; Sharpless, K. B. *ibid.* **1985**, *50*, 1563. (c) Caron, M.; Carlier, P. R.; Sharpless, K. B. *ibid.* **1988**, *53*, 5185.

(2) Novales-Li, P.; Watanabe, K.; Takeuchi, H.; Ohfune, Y.; Kurokawa, N.; Kurono, M. *Europ. J. Pharmac.* **1987**, *143*, 415 and literatures cited therein.

(3) ***Caution!*** *Hydrogen azide is extremely explosive and toxic. All the reaction employing this should be carried out in a well-ventilated hood. Never handled it as a neat liquid but as a solution in ether or water! For human toxicity, see The Merck Index, 9th Ed.; 1976, p 631 and Kagaku to Kogyo,* **1989**, *42*, 2072. Among the Eqs 1–3, the first procedure is the most reliable to give a crystalline reagent after sublimation which can be dissolved in DMF, CH_2Cl_2, or $CHCl_3$. *However, a very high sublimable property of the reagent prepared by this procedure should be exaggerated because of its acute toxicity such as a chest pain encountered even during weighing operations. The other procedures (Eqs 2 – 3) left no problems at all in this context.* The reactivity exhibited by the reagents prepared by these procedures was almost the same as that obtained by the first procedure only if the salts were treated under vacuum prior to use.

(4) Saito, S.; Nagao, Y.; Miyazaki, M.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1986**, *27*, 5249.

(5) **2a**: $[\alpha]^{32}_D$ –18.2° (c 1.59, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.067 (s, 3H, Si-Me), 0.071 (s, 3H, SiMe), 0.88 (s, 9H, Si-*t*-Bu), 2.7 (1H, OH), 3.72 (dd, J = 3.8, 10.4 Hz, 1H, C(OSi)*H*H), 3.75 (dd, J = 4.0,10.4 Hz, 1H, C(OSi)H*H*), 3.81 (s, 3H, OMe), 3.93–3.99 (m, 2H, CH(O) and CHN_3); ^{13}C-NMR (126 MHz, $CDCl_3$) δ –5.53. –5.48, 18.3, 25.8, 52.7, 62.7, 62.9, 71.7, 169.4. **2b**: $[\alpha]^{32}_D$ –24.8° (c 2.22, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.62 (dd, J = 2.8, 7.0 Hz, 1H, C(OSi)*H*H), 3.64 (dd, J = 3.4,7.0 Hz, 1H, C(OSi)H*H*), 3.77 (s, 3H, OMe), 4.05 (d, J = 6.2 Hz, 1H, CHN_3), 4.07 (m, 1H, CHO), 4.46 –4.49 (ABq, J = 11.7 Hz, 2H, $PhCH_2O$), 7.3–7.4 (m, 5H, ArH); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 52.7, 63.2, 69.8, 70.8, 73.6, 127.9, 128.0, 128.5, 137.4, 169.2.

(6) **5**: $[\alpha]^{32}_D$ –39.8° (c 1.13, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6H, Si-Me_2), 0.91 (s, 9H, Si-*t*-Bu), 1.34 (t, J = 7.2 Hz, 3H, CMe), 2.45 (1H, OH), 3.66 (dd, J = 6.4, 10.1 Hz, 1H, C(OSi)*H*H), 3.73 (dd, J = 6.1, 10.1 Hz, 1H, C(OSi)H*H*), 4.02 (d, J = 3.2 Hz, 1H, $CH(N_3)$), 4.17 (m, 1H, CH(OH)), 4.31(q, 2H, J = 7.2 Hz, OCH_2); ^{13}C-NMR (126 MHz, $CDCl_3$) δ –5.50, –5.46, 14.1, 18.2, 25.8, 62.2, 62.7, 63.4, 72.3, 169.2.

(7) Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309.

(8) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696.

(9) See the footnote (c) in Table 1.

(10) The multiplicity of the signal which shifts to the lower field by ca. 1 ppm on acetylation is used for a diagnosis with regard to the regioselectivity. We have also found that the $J_{2,3}$-values of the C-2 isomers (acetates) is larger than that of the C-3 isomers for the *trans*-epoxide series.

(11) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837.

(12) Saito, S.; Yokoyama, H.; Ishikawa, T.; Niwa, N.; Moriwake, T. submitted for publication in this Journal.

(Received in Japan 15 October 1990)