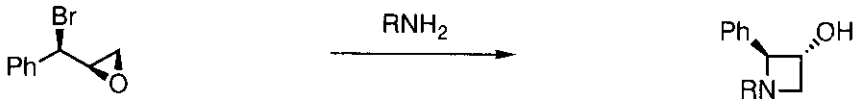
SYNTHESIS OF 1-ALKYL-3-HYDROXY-2-PHENYLAZETIDINES†

Takashi Toda,* Michinori Karikomi, Masabumi Ohshima, and Masaaki Yoshida

Department of Applied Chemistry, Faculty of Engineering, Utsunomiya University, Ishiicho, Utsunomiya 321, Japan

Abstract– Several (*R**, *S**)-1-alkyl-3-hydroxy-2-phenylazetidines (**1**) were synthesized by the reaction of (*R**, *R**)-2-(1-bromobenzyl)oxirane (**2a**) with aliphatic primary amines in good yields. By the reaction of (*R**, *S**)-2-(1-bromobenzyl)oxirane (**2b**), only (*R**, *R**)-2-aminomethyl-3-phenyloxirane (**3**) was obtained. Also, the reaction of (*R**, *R**)-2-(1-bromobenzyl)-2-methyloxirane (**2c**) gave a mixture of (*R**, *S**)-3-hydroxy-3-methyl-2-phenylazetidine (**4**) as the major product and (*R**, *S**)-2-aminomethyl-2-methyl-3-phenyloxirane (**5**) as the minor product.

Syntheses of four membered ring compounds are difficult tasks except for preparation of cyclobutanes and oxetanes of which syntheses have been achieved by cycloaddition reactions of allenes[1] or by photochemical reactions of ethylene derivatives for the former, and also photochemical cycloaddition between ethylenes and carbonyl compounds for the latter.[2] The other four membered ring systems such as azetidines, thietanes, etc are remained as challengable problems. Syntheses of azetidines have rarely reported and the yields reported were rather poor.[3,4] In this report, we wish to present an improved synthesis of azetidine derivatives in good yields. Since 2-(1-haloalkyl)oxiranes (**2**) possess three adjacent reactive sites and it is known that the first attack of nucleophiles usually takes place at a less hindered site of oxirane ring system, the attack of primary amines on 2-(1-bromobenzyl)oxiranes (**2a-c**) would take place at the C_3-position where is no substituent and thus the most reactive site. Since the next reactive site of **2a** is the benzyl position, the intermediate amine readily forms the azetidine ring by the intramolecular cyclization.



2a **1**

The starting 2-(1-bromobenzyl)oxiranes (**2a,b**) could be prepared from *E*- and *Z*-cinnamyl alcohols respectively by bromination and dehydrobromination, successively, as described in the preceding paper.[5] *E*-Cinnamyl alcohol is commercially available and could be lead to the (*R**, *R**)-diastereomer (**2a**) by the above procedure. The reactions of **2a** and aliphatic primary amines were carried out in methanol at room temperature. The results obtained are shown in Table 1.[6] All the products (**1**) shows *trans* configuration between 3-hydroxyl and 2-phenyl groups. The yields are usually good and satisfactory except for a few cases. Warming or refluxing of the reaction mixture made reaction time shorter, but also some other reactions took place to give unknown or intractable products and the yields become lower (see, runs 7 and 8).

Table 1. Synthesis of the Azetidines (**1**) from (*R**, *R**)-2-(1-bromobenzyl)oxirane (**2a**)

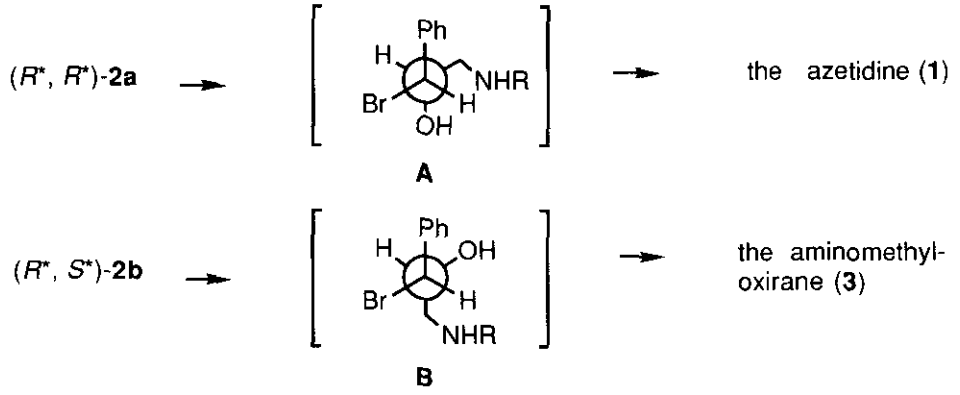
run	amine	temp	time / h	yield / %
1	*n*-Pr	room temperature	24	65
2	allyl	room temperature	24	72
3	*i*-Pr	room temperature	70	72
4	*t*-Bu	room temperature	72	79
5	*c*-C_6H_{11}	room temperature	67	79
6	*c*-C_6H_{11}	room temperature	112	50[a]
7	$PhCH_2$	room temperature	20	92
8	$PhCH_2$	reflux	5	87
9	$PhCH_2$	reflux	5	59[b]
10	*p*-Cl-$C_6H_4CH_2$	room temperature	30	93
11	$PhCH_2CH_2$	room temperature	20	83
12	$C_{16}H_{33}$	room temperature	50	69
13	CH_2COOEt	room temperature	30	85[c]

a) in MeCN, b) in THF, c) in EtOH

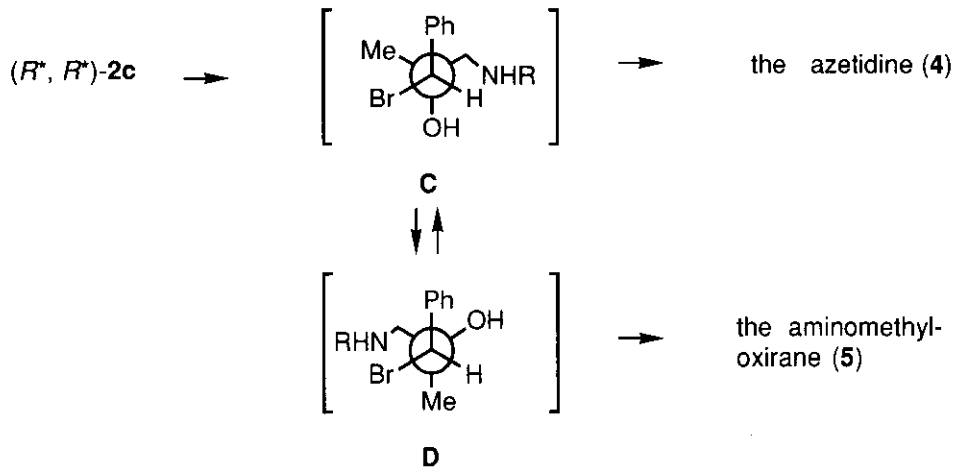
When we used the (*R**, *S**)-diastereomer (**2b**) prepared from *Z*-cinnamyl alcohol, only 2-aminomethyl-3-phenyloxirane (**3**) was obtained in 67% yield by the reaction with benzylamine under the same conditions. For investigation of steric interference at the 2-position, (*R**, *R**)-2-(1-bromobenzyl)-2-methyloxirane (**2c**) was

employed as the starting substance. The reaction of **2c** gave a mixture of 1-benzyl-3-hydroxy-3-methyl-2-phenylazetidine (**4**, 72%) and 2-(*N*-benzylaminomethyl)-2-methyl-3-phenyloxirane (**5**, 20%).

The difference of the reactivities of the oxiranes (**2a**-**c**) could be explained by the differences of their conformation of the reaction intermediates. Here, we briefly explain the difference between (*R**, *R**)-**2a** and (*R**, *S**)-**2b**. If we draw the intermediates attacked by an amine of the each oxirane, those could be written as **A** for the former and as **B** for the latter. These figures cleanly indicate why **2a** gave the azetidine (**1**) and the aminomethyloxirane (**3**) from **2b**. The reason for the subordinate selectivity in the azetidine formation by using (*R**, *R**)-**2c** is elucidated by equilibrium of two conformers **C** and **D**. These are not the most stable one, but **C** is more stable than **D**, even though four membered ring is more difficult to enclose than three membered one. These situations reflected to the formed ratio of the azetidine (**4**) and the amino methyl oxirane (**5**).



(*R**, *R**)-2-(1-Haloalkyl)oxiranes (**2a**,**c**) are readily obtainable active oxiranes as the starting substances for azetidine synthesis. The results shown above are encouraging for synthesis of this important and interesting heterocyclic system.



REFERENCES

† Dedicated to Dr. M. Hamana on the occasion of his 75th birthday.

1. H. Hopf, "[2+2] Cycloadditions of Allenes" in 'The Chemistry of The Allenes,' ed. by S. R. Landor, Academic Press, Inc., New York, 1982, pp. 525-562.
2. N. J. Turro, ' Modern Molecular Photochemistry,' The Benjamin / Cummings Inc., California, 1978, pp. 419~432; pp. 432~452.
3. K. Masuda, *Yuki Gosei Kagaku Kyokai Shi*, 1972, **30**, 271.
4. V. R. Gaertner, *J. Org. Chem.*, 1967, **32**, 2972; T. Okutani and K. Masuda, *Chem. Pharm. Bull.*, 1974, **22**, 1498; R. H. Higgins, M. R. Watson, W. J. Faircloth, Q. L. Eaton, and H. J. Jenkins, Jr., *J. Heterocycl. Chem.*, 1988, **25**, 383; N. H. Cromwell and B. Phillips, *Chem. Rev.*, 1979, **79**, 331.
5. M. Yoshida, T. Hide, M. Ohoshima, H. Sasaki, and T. Toda, *Heterocycles*, submitted for publication.
6. Spectral and analytical data of representative product is as follows: (2*R**, 3*S**)-1-benzyl-3-hydroxy-2-phenylazetidine; bp 148-150 °C / 0.09 mmHg; ^{1}H nmr ($CDCl_3$) δ 2.2 (1H, br s), 2.73 (1H, t, J = 6.9 Hz), 3.44 (1H, d, J = 12.9 Hz), 3.61 (1H, dd, J = 6.9, 1.2 Hz), 3.87 (1H, d, J = 5.4 Hz), 3.88 (1H, d, J = 12.9 Hz), 4.11 (1H, dt, J = 6.9, 5.4 Hz), 7.2-7.5 (5H, m); ^{13}C nmr ($CDCl_3$) δ 26.12, 60.10, 70.85, 78.25, 126.64, 126.95, 127.44, 128.11, 128.26, 128.70, 137.64, 140.33; ir (neat) 3350, 1600, 1500, 1450 cm^{-1}; ms (20 eV) m/z (rel. intensity) 239 (M^+, 21), 195 (42), and 91 (100).

Received, 6th November, 1991