Tetrahedron Letters, Vol.32, No 5, pp 663-666, 1991
Printed in Great Britain

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

# HYDROGEN AZIDE–AMINE SYSTEMS AS AN AZIDE NUCLEOPHILE FOR SUBSTITUTIONS OF SULFONATES, HALIDES, AND VICINAL DISULFONATES

Seiki Saito,* Hajime Yokoyama, Teruhiko Ishikawa, Nobuko Niwa, and Toshio Moriwake*

*Department of Applied Chemistry, Faculty of Engineering, Okayama University*

*Tsushima-naka, 3-1-1, Okayama , Japan 700*

*Summary:* Hydrogen azide–alkylamine combination turned out to ensure the displacement of simple primary or secondary sulfonates, halides, and vicinal disulfonates with an azido-group in which an enhanced reactivity is generally achieved as compared with a case of traditional alkali metal azides.

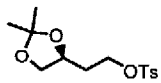
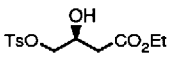
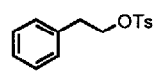
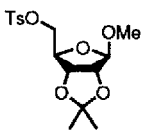
Nucleophilic substitutions of alkyl or alkenyl sulfonates and halides in acyclic or cyclic systems with alkali metal azides such as sodium or lithium azide ($NaN_3$ or $LiN_3$) are well-established basic organic reaction and play an important role in synthesizing primary amines Nevertheless, we have often encountered many hardships in doing these transformations mainly because of a low reactivity of these metallic azides. For instance, in some cases, which do not allow for those azides to attack sterically congested reaction centers, far more reactive trifluoromethanesulfonates coupled with tetraalkylammonium azide are required.[1] In addition, a vicinal-diazido introduction *via* an $S_N2$ process ($NaN_3$ in DMF) of acyclic secondary disulfonates strongly requires crown ether as a promoter, otherwise resulting in the decomposition of the substrates or the formation of deteriorated mixture.[2] Thus, a simple solution to these problems is a desirable goal of organic synthesis. In this communication, we provide our findings that hydrogen azide, when coupled with alkyl amines, becomes a useful azide nucleophile ($R_3NHN_3$) and applicable to azide substitution processes for a variety of sulfonates or halides including secondary vicinal disulfonates.

$R_3NHN_3$ reagents were prepared by simply mixing a solution of $HN_3$ in ether[3] with amines such as diethylamine (DEA) or diisopropylethylamine (DIPEA) and usually purified by sublimation to give the powders,[4] which was used as a solution in DMF. In general, $DEAHN_3$ reagent exhibited higher reactivity than $DIPEAHN_3$ reagent probably for steric reason. However, these may rapidly reach equilibrium consisted of the salt and the free counterparts This situation makes $DEAHN_3$ reagent more basic, in a kinetic sense, than $DIPEAHN_3$ reagent and attention should be paid when $DEAHN_3$ is applied to substrates having acidic hydrogens.

The reactions of $DEAHN_3$ reagent (2 – 2.5 eq) with several primary sulfonates in DMF at 60°C were conducted and the results were listed in Table 1. Every run provided the corresponding azides with high yields and purity.[5]

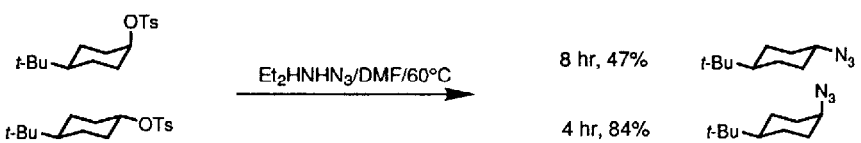
Table 1 Primary tosylate substitution with $Et_2HNHN_3$ at 60°C in DMF

$RCH_2OTs \longrightarrow RCH_2N_3$ ($Et_2HNHN_3$: 2 –2.5 eq)

| Substrate | Time | azide yield | Substrate | Time | azide yield |
|---|---|---|---|---|---|
|  | 0.5 hr | 73% |  | 6 hr | 76% |
|  | 0.5 hr | 90% |  | 16 hr | 86% |

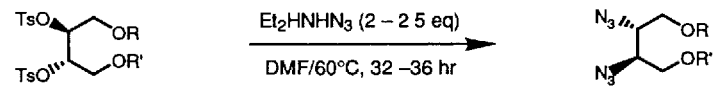
In order to confirm that $DEAHN_3$ attacks sulfonates with 100% inversion, stereochemically defined substrates such as *cis*- and *trans*-4-*t*-butylcyclohexyl tosylates were submitted to the reaction with $DEAHN_3$ in DMF at 60°C. The stereochemistry of the corresponding azides were ascertained on the basis of NMR spectroscopy to be quantitatively inverted (Scheme 1).

**Scheme 1.**



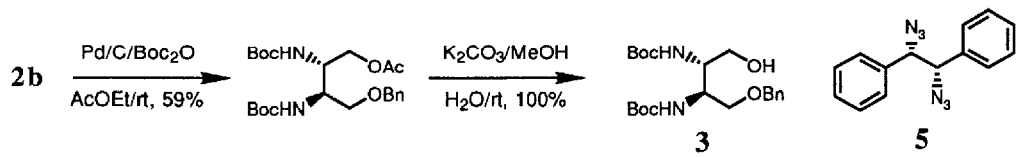

Keeping above important information in mind, we examined the applicability of $DEAHN_3$ reagent to vicinal azide substitution for optically pure 2,3-ditosylates of L-tartaric acid-based protected butanetetraol **1a–c** (Scheme 2). Although the rate of an $S_N2$ process was somewhat low, the desired vicinal diazides **2a–c** were given in good yields. The stereochemical outcome of **2a**, readily confirmed as 100% inversion at both stereogenic centers by an NMR spectroscopy because of its $C_2$ nature, should certainly be extrapolated to the cases of unsymmetrical products. A series of routine reactions[6] from, for instance, **2b**, led to protected vicinal diaminobutane-1,4-diols (**3**), which may serve as a potent chiral synthon for a variety of synthetic purposes. Recently developed chiral controller system by Corey[7] features 1,2-diamino-1,2-diphenylethane as the key ingredient, an immediate precursor (**5**) of which now became available in 79% yield from (*R**,*R**)-1,2-diphenylethylene dimesylate by the present simple chemistry. As already mentioned above,[2] $NaN_3$ required 18-crown-6 in order to effect the above vicinal diazide substitutions, otherwise no diazide being furnished.

**Scheme 2.**




**1a**: R = R' = Bn
**1b**: R = Ac, R' = Bn
**1c**: R = Ac, R' = PMBn

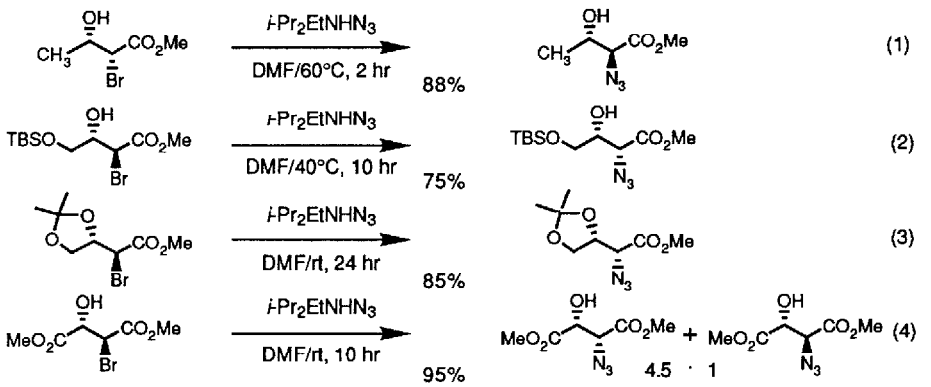
**2a**: R = R' = Bn
**2b**: R = Ac; R' = Bn
**2c**' R = Ac; R' = PMBn




**3** **5**

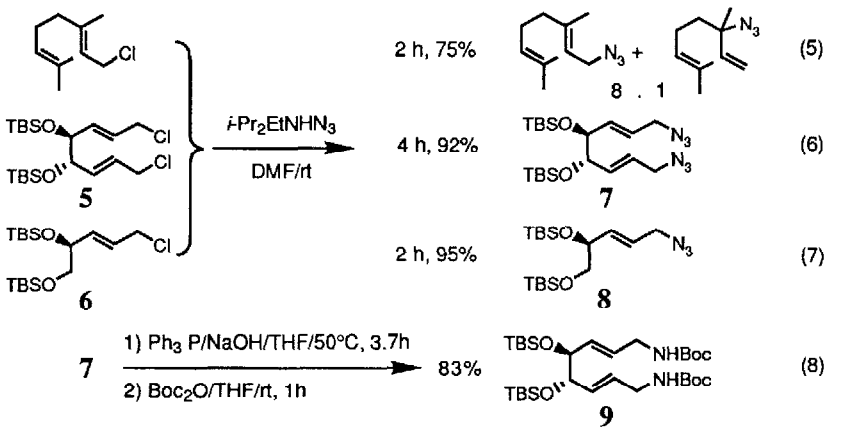
If the $S_N2$ process of $\alpha$-haloesters with the present "$N_3^-$" nucleophile takes place, the reaction should afford $\alpha$-azidoesters as precursors for $\alpha$-amino acids . In this case DEA must be replaced with DIPEA to prevent $\alpha$-azidoesters from epimerizing at the stereogenic center under the conditions. Thus, DIPEAHN3 reagent effected the desired transformations (Scheme 3). While bromobutanoates (Eqs 1 – 3) left no problem at all, succinate version suffered from considerable epimerization at the $\alpha$-position (Eq 4) even if DIPEAHN3 reagent was employed.

**Scheme 3.**




Finally, we tested the feasibility of the $S_N2$ reaction of primary allylic halides with the present reagents. It has generally been believed that an terminal allylic azide can rearrange in a thermodynamically controlled manner to give an equilibrated mixture consisted of the internal and terminal azides.[8] Hence, even if a clean $S_N2$ process is realized, the product would be a mixture of two types of azides. Indeed, the reaction of geranyl chloride with DIPEAHN3 (2 eq) in DMF proceeded at rt and was completed within 1.5 hr to give such a mixture in a ratio 8:1 (Eq 5), which, however, is delightfully much larger in favor of the primary azide than that of previously reported

(4:1).[8d] We also found that the allylic substrates bearing oxygen-linked setereocenter adjacent to the C=C bond such as **5** or **6** (Eqs 6 and 7) exclusively afforded clean $S_N2$ product **7** or **8** in very high yield, respectively. The protected 1,8-diaminooctadiene (**9**), given by reduction[9] and ensuing *N*–protection should be an interesting chiral synthon (Eq 8). The successful application of the present "$N_3^-$" nucleophiles to the regioselective azide cleavage of 2,3-epoxyesters will be a subject of a subsequent paper.




**Acknowledgment**: We are grateful to "The SC-NMR Laboratory of Okayama University" for high field NMR experiments.

## References and notes

(1) S. J Danishefsky, M. P. DeNinno, and S.-H. Chen, *J. Am. Chem Soc.*, **110**, 3929 (1988).

(2) Private communication through the courtesy of Prof. S. Torii and Dr. H. Okumoto (Okayama University): the reaction of methanesulfonate version of **1** (R = R' = Bn) with $NaN_3$ (2.2 eq ) in DMF at 80°C (20 hr) in the presence of 18-crown-6 (10 mol%) gave the corresponding diazide in 85% yield. Without crown ether, however, the reaction resulted in the formation of a complex mixture.

(3) H. Wolff, *Org. React.*, **3**, 307 (1946).

(4) *All the experiments, involving $HN_3$ generation, the preparation of the $HN_3$ ether solution, the sublimation of $HN_3$–amine salts, weighing or transfer of the salts, and not only the reactions employing the salts but also a workup should be executed in a well-ventilated hood because of their high toxicity.*

(5) All the new compounds obtained in this work showed satisfactory physical data (IR, NMR, mass, $[\alpha]_D$).

(6) S. Saito, H. Nakajima, M. Inaba, and T. Moriwake, *Tetrahedron lett.*, **30**, 5239 (1989).

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(8) (a) A. Gagneux, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **82**, 5956 (1960); (b) C. A. Vanderwerf and V. L. Heasley, *J. Org. Chem.*, **31**, 3534 (1966); (c) M Arimoto, H. Yamaguchi, E. Fujita, M. Ochiai, Y. Nagao, *Tetrahedron Lett.*, **28**, 6289 (1987); (d) S. Murahashi, Y. Taniguchi, Y. Imada, and Y. Tanigawa, *J. Org. Chem.*, **54**, 3292 (1989).

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(Received in Japan 15 October 1990)