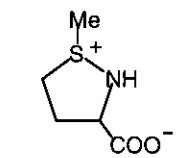
AN EFFICIENT SYNTHESIS AND SELECTIVE REACTION OF *N*-SUBSTITUTED ISOTHIAZOLIDINIUM SALTS

Okiko Miyata, Sachiko Yamakawa, Kanami Muroya, and Takeaki Naito*
Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

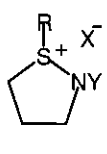
Abstract - The first example of the preparation of *N*-acylated isothiazolidinium salts is described, and the stability and reactivity of the isothiazolidinium salts are found to be highly dependent upon the substituent at the nitrogen atom.

Dehydromethionine (**1**)[1-3] having an isothiazolidinium structure was prepared by oxidative cyclization of an amino acid, methionine, and has been received considerable attention because of its important physiological responses.[4,5] As the related compounds, simple *N*-benzyl- and *N*-phenylisothiazolidinium salts (**2**) were also prepared by the reaction of the corresponding γ-amino sulfides with an oxidizing agent such as iodine and *N*-chlorosuccinimide.[6-8] On the other hand, there has been no example of the preparation of *N*-acylated isothiazolidinium salts by the known methods. *N*-Acylated isothiazolidinium salts remain to be investigated in view of not only their crucial biological roles in peptide systems involving methionine-enkephalin[5] but also exploration of a new practical synthetic method. We have assumed that a more powerful leaving group (X= $OCOCF_3$ in **3**) than halogen at the sulfur atom would provide the successful preparation of *N*-acylated isothiazolidinium salts due to the less basic and nucleophilic nitrogen atom of the *N*-acyl groups. We have chosen a trifluoroacetoxy group as a leaving group at the sulfur atom and succeeded in the first synthesis of *N*-acylated isothiazolidinium salts (**5a, b**) *via* a route involving acylation of γ-amino sulfoxides (**4a, b**) with trifluoroacetic anhydride (TFAA). Additionally, we have investigated the substituent effect on the nitrogen atom and disclosed that the cyclizability, stability and reactivity are highly dependent upon the substituent at the nitrogen atom.



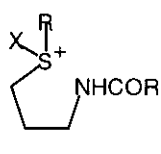
dehydromethionine

1



Y= benzyl, phenyl

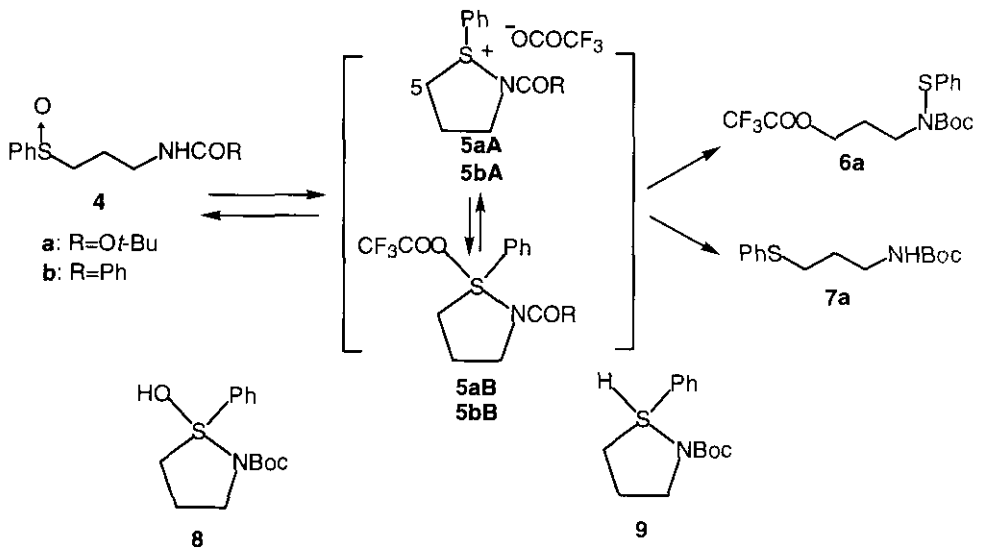
2



3

We initially investigated the reaction of *N*-Boc-γ-amino sulfoxide (**4a**) with TFAA (Scheme 1). Treatment of **4a** with 2 equiv. of TFAA in acetonitrile at 0 ℃ gave the cyclized product (**5a**) in quantitative yield which was characterized by the following spectral data. **5a** showed a molecular ion peak at m/z 266 (M^+)

($C_{14}H_{20}NO_2S$). In the ^1H NMR spectrum of **5a,** signals due to the hydrogens in the *S*-phenyl group and the isothiazolidinium ring appeared in lower field than those of the parent sulfoxide (**4a**).[9] Similar findings on the structures of known isothiazolidinium salts[5-7] were already reported. On the sulfonium structure of **5aA**, we cannot exclude another covalent sulfurane structure (**5aB**) as a possible structure. Upon treatment with TFAA, *N*-benzoylamino sulfoxide (**4b**) underwent similar cyclization to afford the *N*-benzoylisothiazolidinium salt (**5b**) in 99% yield. Thus, the newly-found reaction condition using TFAA has provided the first convenient route for the preparation of *N*-acylated isothiazolidinium salts. The formation of cyclic *N*-acylamino sulfonium salt has been previously[10,11] reported as a speculative intermediate in an abnormal Pummerer rearrangement despite the lack of chemical and spectral evidence.

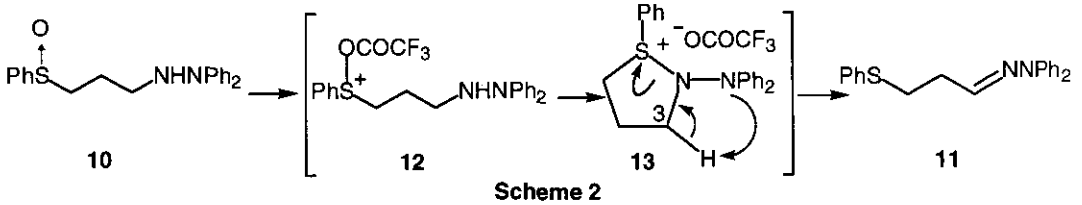


Scheme 1

N-Acylated isothiazolidinium salts (**5a, b**) prepared as above are relatively stable in acetonitrile. However, when a solution of **5a** in chloroform was allowed to stand at room temperature for 15 h, the CH_2-*S* bond cleaved trifluoroacetate (**6a**) was obtained in 96% yield. Furthermore, isothiazolidinium salt (**5a**) is labile to both hydrolysis under a basic conditions (NaOH)[6] and reduction with $NaBH_4$. Treatment of **5a** with either aqueous 5% NaOH or $NaBH_4$ gave the *N*-*S* bond cleaved sulfoxide (**4a**) in quantitative yield or the *N*-*S* bond cleaved sulfide (**7a**) in 93% yield, respectively. These regioselective reactions of **5a** giving three types of ring-opened products (**6a**, **4a**, and **7a**) can be explained as follows.[12] Trifluoroacetate (**6a**) is formed *via* either the ligand coupling of the sulfurane (**5aB**) or the attack of trifluoroacetate ion on C-5 position of the isothiazolizinium salt (**5aA**) leading to the CH_2-*S* bond cleavage. Sulfoxide (**4a**) is formed *via* two possible routes: one involves the basic hydrolysis of sulfurane (**5aB**) and the *N*-*S* bond cleavage of the resulting sulfurane (**8**); the other involves SN2 type of reaction on the sulfur atom of the isothiazolidinium salt (**5aA**). Sulfide (**7a**) is formed *via* a hydride attack to **5aA** from $NaBH_4$ and the ligand interconversion and ligand coupling of the resulting sulfurane (**9**).[12b]

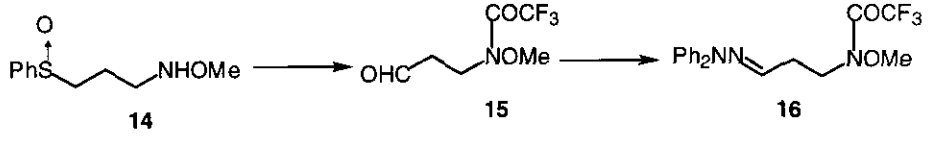
Next, we investigated the reaction of *N,N*-diphenylhydrazine (**10**) with TFAA in order to compare the substituent effect on the nitrogen atom of γ-amino sulfoxides (Scheme 2). Under the same conditions,

reaction of **10** with TFAA gave not the isothiazolidinium salt (**13**) but the hydrazone (**11**) in 85% yield as a result of intramolecular Swern-type of oxidation, which would be explained as follows. First, the sulfoxide (**10**) is acylated to give the acyloxysulfonium (**12**) which then cyclizes to form the isothiazolidinium intermediate (**13**).[13] The diphenylamino group in **13** abstracts intramolecularly a proton at the C-3 carbon to produce the oxidized hydrazone (**11**). The isothiazolidinium salt (**13**) is too reactive to be isolated as clearly shown in the short reaction time (5 min) even at -20 ℃.



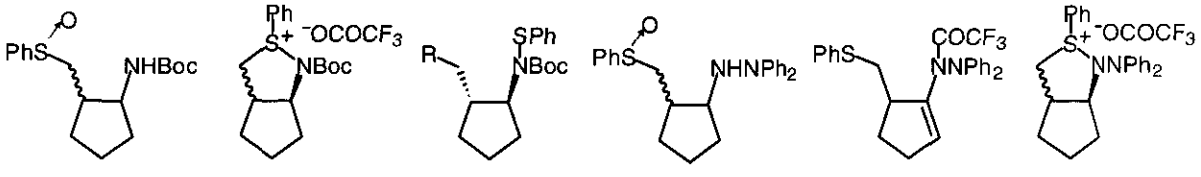
Scheme 2

Next, we investigated the reaction of *N*-methoxyamino sulfoxide (**14**) (Scheme 3). Under the same conditions, **14** gave the unstable aldehyde (**15**) which was characterized as the the corresponding hydrazone (**16**) by using 2 equiv. of TFAA. Thus, *N*-methoxyamino sulfoxide (**14**) undergoes the normal Pummerer rearrangement by treatment with TFAA.



Scheme 3

The regioselective reaction of acyclic γ-amino sulfoxides was extended to the cyclic *N*-Boc-amino and *N*,*N*-diphenylhydrazino sulfoxides (**17**)[14] and (**20**).[14]



17a: *cis* **17b**: *trans* | **18a**: *cis* **18b**: *trans* | **19** R=OCOCF3 | **20a**: *cis* **20b**: *trans* | **21** | **22**

Interestingly, in the case of cyclic *N*-Boc sulfoxides, *cis*- and *trans*-stereochemistries of the substrates (**17a,b**) were found to influence strongly the reaction course of isothiazolidinium salts. Treatment of *trans*-*N*-Boc-amino sulfoxide (**17b**) with TFAA gave the CH_2-*S* bond cleaved trifluoroacetate (**19**) though a possible intermediary, *trans*-isothiazolidinium salt (**18b**),[13] is sterically too unstable to be isolated. On the other hand, upon treatment with TFAA, *cis*-*N*-Boc-amino sulfoxide (**17a**) gave *cis*-isothiazolidinium salt (**18a**)[13] in 98% yield which afforded the starting *cis*-**17a** by treatment with aqueous 5% NaOH. Reaction of *cis*-*N*,*N*-diphenylhydrazino sulfoxide (**20a**) with TFAA gave the enamide (**21**) in 61% yield, which was also obtained

by the same reaction of the *trans*-isomer (**20b**) with TFAA. The reaction pathways from **20a, b** to **21** would involve the formation of isothiazolidinium salt (**22**)[13] as an intermediate, followed by Swern-type of oxidative *N-S* bond cleavage and finally acylation.

In conclusion, we have succeeded in the first synthesis of *N*-acylated isothiazolidinium salts *via* acylation of the *N*-acyl-γ-amino sulfoxides with TFAA and established that the isothiazolidinium salts undergo regioselective reactions depending upon the substituent at the nitrogen atom.

ACKNOWLEDGMENTS

This work was partly supported in part by Grant-in-Aid for scientific research (No. 09672293) from the Ministry of Education, Science, Sports and Culture, Japan and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for a research grants.

REFERENCES AND NOTES

1. T. F. Lavin, *J. Biol. Chem.*, 1943, **151**, 281.
2. R. S. Glass and J. R. Duchek, *J. Am. Chem. Soc.*, 1976, **98**, 965.
3. D. O. Lambeth, *J. Am. Chem. Soc.*, 1978, **100**, 4808.
4. R. F. Chapman and B. J. Peart, 'Comprehensive Heterocyclic Chemistry II,' Vol. 3, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Inc., Oxford, 1996, pp. 319-372.
5. R. Fruttero, G. Amiconi, F. Ascoli, M. Bolognesi, and P. Ascenzi, *Biochem. Mol. Biol. Int.*, 1995, **35**, 861.
6. D. W. Swank and D. O. Lambeth, *J. Heterocycl. Chem.*, 1982, **19**, 1515.
7. D. W. Swank and D. O. Lambeth, *J. Heterocycl. Chem.*, 1983, **20**, 1713.
8. D. O. Lambeth and D. W. Swank, *J. Org. Chem.*, 1979, **44**, 2632.
9. **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (9H, s), 1.78 (2H, m), 2.86 (2H, m), 3.25 (2H, t, *J*=7 Hz), 7.55 (5H, m). **5a**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.46 (9H, s), 2.63 and 2.78 (each 1H, m), 3.99 (2H, m), 4.22 (1H, ddd, *J*=10, 8, 2.5 Hz), 4.52 (1H, ddd, *J*=13, 12, 6 Hz), 7.72 (5H, m).
10. T. Kaneko, *J. Am. Chem. Soc.*, 1985, **107**, 5470.
11. A. Arnone, P. Bravo, S. Capelli, G. Fronza, S. V. Meille, and M. Zanda, *J. Org. Chem.*, 1996, **61**, 3375.
12. a) J. Drabowicz, P. Lyzwa, and M. Mikolajczyk, 'The Chemistry of Sulfur-containing Functional Groups,' ed. by S. Patai and Z. Rappoport, John Wiley and Sons, Inc., Chichester, 1993, pp. 799-956. b) K. S. Kim, I. B. Jung, Y. H.Kim, and S. Oae, *Tetrahedron Lett.*, 1989, **30**, 1087. c) P. R. Young and L.-S. Hsieh, *J. Am. Chem. Soc.*, 1978, **100**, 7121.
13. The corresponding sulfurane structures of **13**, **18a,b**, and **22** cannot be excluded.
14. O. Miyata, K. Muroya, J. Koide, and T. Naito, *Synlett*, 1998, 271.

Received, 15th April, 1999