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O-TBS-*N*-tosylhydroxylamine: A Reagent for Facile Conversion of Alcohols to Oximes

Katsushi Kitahara, Tatsuya Toma, Jun Shimokawa, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

fukuyama@mol.f.u-tokyo.ac.jp

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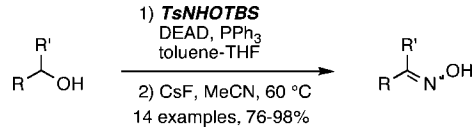
ABSTRACT

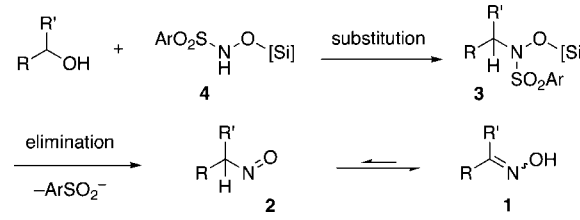


A variety of oximes were synthesized from the corresponding alcohols, alkyl halides, or alkyl sulfonates without using external oxidants. With this simple two-step procedure involving substitution with readily available TsNHOTBS and subsequent treatment with CsF, a range of oximes were prepared including the ones hardly preparable with conventional procedures.

Oxime is a frequently used functionality in organic synthesis. Its synthetic utility is prominent as the precursor for important functionalities such as amines, nitriles, amides, and nitrile oxides, to name a few.[1] Preparation of this versatile functionality has been dependent primarily on the reaction between hydroxylamine and the corresponding aldehydes or ketones. However, there are cases where the oxidative preparation of aldehydes or ketones is not desirable due to the presence of the other readily oxidizable functionalities. In addition, the highly reactive nature of some ketones and aldehydes would make them unsuitable for preparation of the corresponding oximes. Herein, we describe a novel two-step protocol for the preparation of a variety of oximes from the corresponding alcohols without going through ketones or aldehydes.

Our idea of preparing oximes stems from the fact that nitrosoalkane **2** readily tautomerizes to the corresponding oxime **1** (Scheme 1).[1,2] We envisaged that nitrosoalkane **2** would be obtained by the extrusion of sulfinate[3] from the *O*-silyl-*N*-arylsulfonylhydroxylamine **3** with the assistance of a fluoride ion. The hydroxylamine derivative **3** could be easily synthesized from the corresponding alcohols or alkyl halides by the Mitsunobu reaction[4] or by conventional substitution reactions with *O*-silyl-*N*-arylsulfonylhydroxylamine **4**.[5]

Scheme 1



We employed a tosyl group and a TBS group for N-activating and O-protecting hydroxylamine simply because

(1) For a review, see: Yamane, M.; Narasaka, K. In *Science of Synthesis*; Padwa, A., Ed.; Georg Thieme Verlag: Stuttgart, 2004; Vol. 27, pp 605−647.

(2) (a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E; Pecht, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640. (b) Touster, O. *Org. React.* **1953**, *7*, 327.

(3) Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 3195.

(4) Mitsunobu, O. *Synthesis* **1981**, 1.

(5) An *N*-arylsulfonyl hydroxylamine derivative is known as an excellent substrate for Mitsunobu reaction: Yamashita, T.; Kawai, N.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 15038. (a) Similar substitution reactions using hydroxylamine derivatives are known: Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 3096. (b) Hanessian, S.; Yang, R.-Y. *Synlett* **1995**, 633. (c) Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593.

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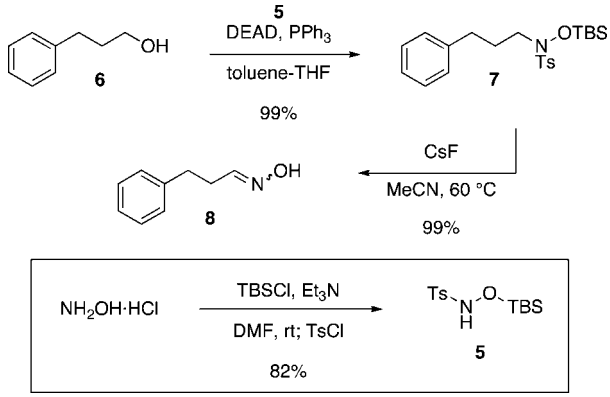
they are inexpensive and readily available. As this species was hitherto unknown in the literature,[6] we tried to prepare **5** by sulfonylation of *O*-TBS-hydroxylamine.[7] Since *O*-TBS-hydroxylamine could be synthesized easily by silylation of hydroxylamine, we could develop a facile one-pot synthesis of the reagent *O*-TBS-*N*-tosylhydroxylamine (TsNHOTBS **5**). Thus, hydroxylamine hydrochloride (1.1 equiv) was mixed with TBSCl (1.1 equiv) and Et_3N (5.0 equiv) in DMF (0.3 M) at room temeperature, and after completion of the silylation, *p*-toluenesulfonyl chloride (1.0 equiv) was added to the mixture. After crystallization from hexane, **5** was obtained in 82% yield as stable white crystals.[8] To test our working hypothesis, **5** was reacted with 3-phenylpropan-1-ol (**6**) under Mitsunobu conditions, and much to our delight, **7** was obtained in 99% yield (Scheme 2). Subsequent

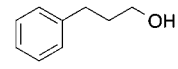
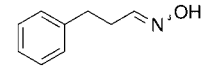
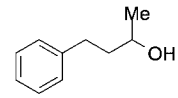
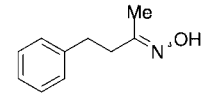
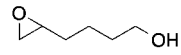
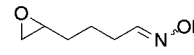
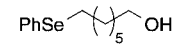
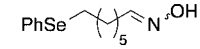
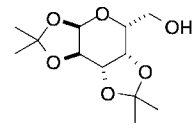
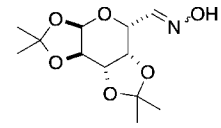
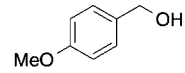
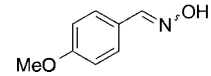
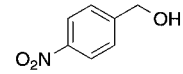
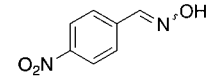
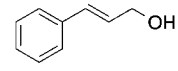
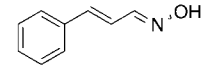
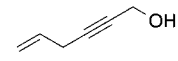
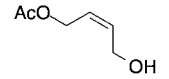
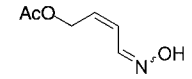
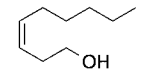
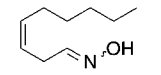
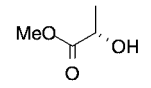
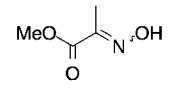
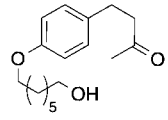
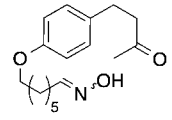
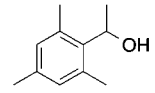
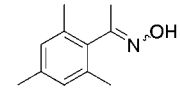
Scheme 2



desilylative elimination of *p*-toluenesulfinate by treatment with CsF[9] proceeded uneventfully, providing the desired oxime **8** in 99% yield as a mixture of *E*,*Z* isomers.

To investigate the scope and limitations of this novel transformation, a number of alcohols were subjected to the reaction conditions. As is evident from the results shown in Table 1, various oximes were obtained in high yields. Secondary alcohol led to ketoxime in the same manner as aldoxime (entry 2). Benzyl, allyl, and propargyl alcohols are also good substrates for this reaction (entries 6−9). While *cis*-α,*β*-unsaturated aldehyde tends to give a mixture of *cis*- and *trans*-α,*β*-unsaturated oximes under conventional conditions,[10] no such isomerization of the double bond was observed in entry 10. Similarly, avoidance of the intermediacy of a carbonyl intermediate makes our method reliable for the synthesis of *β*,*γ*-unsaturated oxime (entry 11). Equally noteworthy is the fact

Table 1. Two-Step Formation of Oximes from Alcohols[a]

entry	alcohol	oxime	yield[b]
1			99 / 99
2			91 / 92
3			100 / 82
4			97 / 98
5			84[c] / 90
6			91 / 99
7			97[d] / 91
8			99 / 94
9			100 / 92[e]
10			93 / 98
11			99 / 89
12			95 / 95[e]
13			85 / 99
14			99[f] / 94

[a] Standard conditions for Mitsunobu reaction: 1.1 equiv of alcohol,[13] 1.0 equiv of TsNHOTBS, 1.5 equiv of DEAD, 2.0 equiv of PPh_3, toluene−THF (3:1, 0.2 M), 0 °C. Standard conditions for oxime formation: 2.0 equiv of CsF, MeCN (0.1 M), 60 °C. [b] Isolated yields for Mitsunobu reaction/oxime formation reaction. [c] Mitsunobu reaction was conducted with 2.5 equiv of DEAD and 3.0 equiv of PPh_3. [d] A minimal amount (1.05 equiv) of DEAD was used because of the unstability of the product to the reagent. [e] 2.0 equiv of AcOH was added for buffering the basicity. [f] Mitsunobu reaction was conducted with 1.5 equiv of alcohol and 2.0 equiv of DEAD at 40 °C.

(6) For other reports of *O*-silyl-*N*-sulfonylhydroxylamines, see: (a) Bruynes, C. A.; Jurriens, T. K. *J. Org. Chem.* **1982**, *47*, 3966. (b) Pohlman, G.; Brink, K.; Bliefert, C. *Z. Naturforsch., B: Anorganische Chemie, Organische Chemie* **1980**, *35B*, 1494.

(7) West, R.; Boudjouk, P. *J. Am. Chem. Soc.* **1973**, *95*, 3983.

(8) For experimental details, see: Supporting Information.

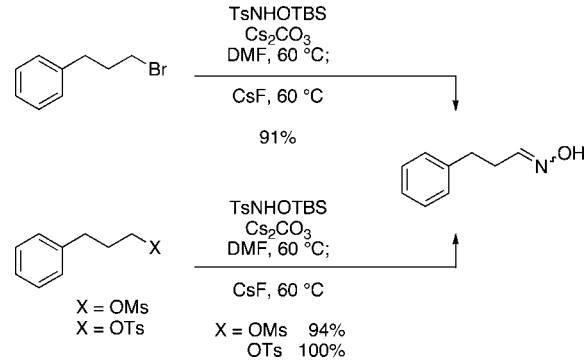
(9) While several fluoride sources including TBAF were examined, CsF gave the best result.

(10) Enev, V. S.; Drescher, M.; Kählig, H.; Mulzer, J. *Synlett* **2005**, 2227. According to the authors, this was the first example of a stereoselective synthesis of *cis*-α,*β*-unsaturated oxime.

that the presence of a ketone does not interfere with the Mitsunobu reaction and thus does not require protection during the oximation (entry 13).[11] Furthermore, this method proved to be applicable to the preparation of hindered oximes. There are cases where the very long reaction time is needed for the completion of the formation of oxime from the corresponding hindered ketones. One such example is the 2′,4′,6′-trimethylacetophenone oxime, which requires 32 days at room temperature in the strongly basic medium for completing the reaction.[12] The present method requires only 3 h to prepare the oxime (entry 14).

To further expand the scope of the reaction, we next examined the substitution reactions with alkyl bromide, mesylate, and tosylate using TsNHOTBS and Cs_2CO_3 (Scheme 3).[13,14] As expected, these substrates underwent smooth, one-pot conversion to give the corresponding oxime in excellent yields.[15]

Scheme 3



In conclusion, we have developed a general method for synthesizing oximes from the corresponding alcohols, alkyl bromides, and alkyl sulfonates by means of a substitution reaction with TsNHOTBS. Since the present method does not need to use carbonyl compounds for synthesizing oximes, it is likely to find a unique niche in synthetic organic chemistry.

Acknowledgment. We are grateful for the Grant-in-Aid (15109001 and 18890048) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL800677P

(11) Since aldehydes react with TsNHOTBS to give silylated hydroxamic acids presumably by the mechanism similar to Angeli-Rimini's reaction, they are not compatible with the present method. For Angeli-Rimini's reaction, see: (a) Hassner, A.; Wiederkehr, R.; Kascheres, A. J. *J. Org. Chem.* **1970**, *35*, 1962. (b) Porcheddu, A.; Giacomelli, G. *J. Org. Chem.* **2006**, *71*, 7057.

(12) (a) Pearson, D. E.; Keaton, O. D. *J. Org. Chem.* **1963**, *28*, 1557. (b) Greer, F.; Pearson, D. E. *J. Am. Chem. Soc.* **1955**, *77*, 6649.

(13) Excess alcohols were used in these cases because the hydroxylamine intermediates have similar polarity to **5** and could not be isolated in pure form. From the synthetic point of view, an excess amount of **5** could be used if it is not necessary to isolate the intermediate in pure form, because **5** decomposes upon treatment with CsF.

(14) Use of K_2CO_3 instead of Cs_2CO_3 substantialy decreases the efficiency of the elimination of toluenesulfinate, often resulting in incomplete reactions.

(15) A one-pot procedure was employed because partial desilylation was observed in the first step.