Tetrahedron Letters,Vol.30,No.30,pp 3987-3990,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

SYNTHESIS OF ISOXAZOLINES AND ISOXAZOLES FROM ALDOXIMES BY THE USE OF SODIUM BROMITE WITH ORGANOTIN HALIDE

Osamu Moriya,* Hideki Nakamura,† Toshifumi Kageyama,†
and Yoshikiya Urata

Department of Chemistry, The National Defense Academy, Hashirimizu, Yokosuka 239, Japan
†Department of Industrial Chemistry, Faculty of Engineering, Kanto-Gakuin University, Mutuura, Yokohama 236, Japan

Summary: The oxidizing system using sodium bromite with a catalytic amount of tri-butyltin chloride is applied for the preparations of isoxazolines and isoxazoles from aldoximes via dipolar cycloaddition.

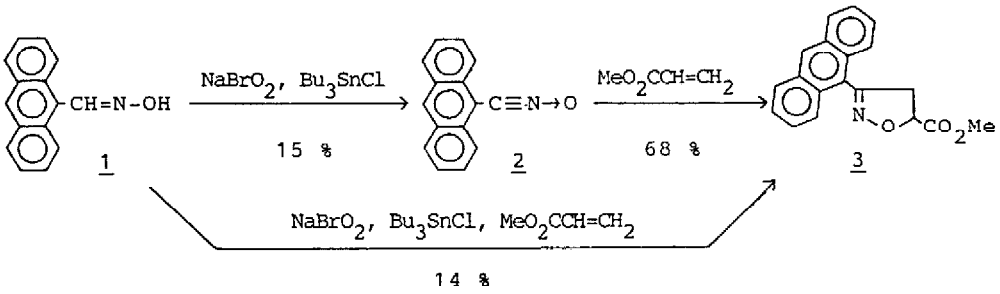
Isoxazolines and isoxazoles, which are readily converted into poly-functional derivatives such as enamino ketones, aminoketones, and 1,3-diketones, are receiving much attention as an important class of synthetic intermediates for the studies directed toward natural product synthesis.[1] The [3+2] dipolar cycloaddition reaction of nitrile oxide to olefins has been especially exploited for the preparations of these heterocyclic compounds over the years with the interests in the reactivities of the dipoles.[2] In the several studies for the formation of nitrile oxide intermediates and also isoxazolines from aldoximes, sodium hypochlorite and bromite have been reported to be the effective reagents.[3,4] On the other hand, sodium bromite ($NaBrO_2$), the related active bromine compounds to the hypohalite, has not been nominated as a usable reagent for those reactions. This oxidizing agent, synthetic utilities of which have been shown very recently,[5,6] is more stable than the hypohalites and now available in a high state of purity. From the view based on these properties of $NaBrO_2$, the use of it seemed to provide a convenient procedure for the synthesis of nitrile oxides and title compounds.

During the course of our investigations progressed on this line, we have found that the combination of $NaBrO_2$ and a catalytic amount of tri-n-butyltin chloride (Bu_3SnCl) showed a characteristic selectivity of oxidizing action. In this report, the results of an application of this new oxidizing system for the one-pot transformations of aldoximes into isoxazolines and isoxazoles via 1,3-dipolar cycloaddition reaction were described.

At first, the dehydrogenation of anthraldoxime (1) was conducted, which has been known to afford the sterically hindered stable nitrile oxide (2).[7] The expected product 2 was obtained in 15 % yield by treating 1 at room temperature with an excess amount of $NaBrO_2$ in the presence of Bu_3SnCl, whereas the dehydrogenation of 1 was not observed in the

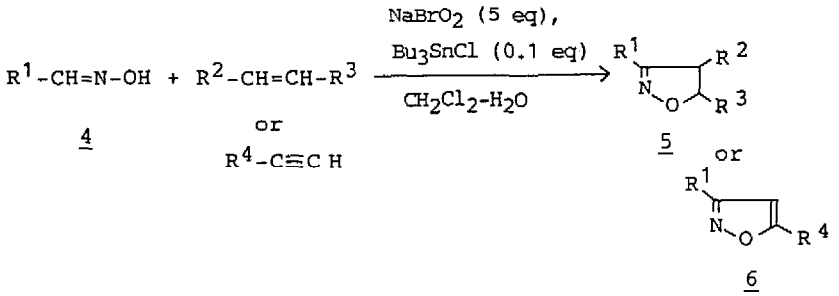
similar reaction without organotin catalyst. The resulting nitrile oxide 2 reacted readily with methyl acrylate as a dipolarophile to give the isoxazoline 3 in 68 % yield.

The oxidation of alkenes by $NaBrO_2$ in the presence of acetic acid has been presented by us to give α-bromoketones in high yields.[5] However, the alkenes such as styrene and cyclohexene were virtually inactive in the present catalytic system. By considering these results, the one-pot reaction to give isoxazole 3 was attempted. Thus, to the solution of anthralaldoxime (1), methyl acrylate(2 equivalent), Bu_3SnCl (0.1 equivalent), in dichloromethane, $NaBrO_2$ (5 equivalent) in H_2O was added dropwise at room temperature. The reaction mixture was stirred for about 1~2 h untill the yellow color of $NaBrO_2$ was disappeared. After the usual work-up, the product was purified by column chromatography (SiO_2, $CHCl_3$) to give the isoxazoline 3 in 14 % yield. The isolated yield observed in this one-pot process was in agreement with the overall yield in the former process, in which the dipole 2 was isolated as an intermediate for the cyclization reaction. In this manner the applicability of the present oxidizing system for the one-pot formation of isoxazolines was demonstrated.



Next, the oxidizing system was applied for the reactions starting from benz- and acetaldoxime with various alkenes and alkynes (Table 1). The alkenes and alkynes having terminal unsaturated bond reacted efficiently with induced nitrile oxides to give the corresponding isoxazolines (5) and isoxazoles (6) in high yields, respectively. These results indicated that a carbon-carbon triple bond was also stable to the organotin-catalyzed oxidation. Disubstituted alkenes such as cyclohexene and diethyl fumarate also afforded the cyclic products, but the yields were only moderate. Such decreases in yields are considered to be resulted from the steric effects in the cyclization step, which have been observed usually in 1,3-dipolar cycloaddition reactions.[2] The other case, which seemed to be affected by a steric hindrance, was given in the above scheme. In the reaction starting from anthraldoxime (1), the poor yield of cyclic product 3 appears to be due to the effects of big aromatic group in the dehydrogenation step. This assumption was supported by the facts that the cycloaddition of the dipole 2 to methyl

acrylate was not affected so strongly by the steric effects of 2 as described above and, further, the reaction of the same dipolarophile with smaller aromatic aldoxime such as benzaldoxime afforded the cyclic product in moderate yield. The additional feature of this method was that the successive transformations from isoxazoline stage to isoxazole did not proceed in the examples using butyl vinyl ether and β-bromostyrene. The cycloaddition reactions involving these alkenes, which have a potential leaving group such as alkoxy and halogen, often accompany the eliminations of such groups under usually



4 5 or 6

Table 1. Synthesis of Isoxazolines (5) and Isoxazoles (6) from Aldoximes (4)[a]

Aldoxime (4)	Alkene		Alkyne	Ratio of 4/Alkene or	Isoxazoline (5) or Isoxazole (6)
R^1	R^2	R^3	R^4	Alkyne	Yield (%)[b]
Ph	Ph	H		1/2	91
	Ph	Br		1/4	98
	OBu	H		1/2	72
	—(CH2)4—			1/20	23
	COMe	H		1/2	88
	CO2Me	H		1/2	68
	CO2Et	CO2Et		1/4	50
	CN	H		1/2	58
Me	Ph	H		1/2	82
	CO2Me	H		1/2	48
Ph			Ph	1/2	80
			OEt	1/3	45
Me			OEt	1/3	72

[a] All reactions were carried out at room temperature.
[b] Yields are based on starting aldoxime (4).

employed basic conditions.

The related specie, sodium chlorite, was applied instead of $NaBrO_2$ for the oxidations in a similar manner as above, but it was unsuccessful to get the cyclized products from aldoximes. With regard to the organometallic catalysts, dibutyltin dichloride and trimethylsilyl chloride were found to be also effective for those selective oxidative reactions. Recently, the combination of the later silyl compound with sodium dichromate or chromic anhydride has been used for the oxidations of various substrates, in which alkenes have been converted efficiently to α-chloroketones.[8] In contrast with such oxidizing system, the catalytic system employing $NaBrO_2$ is characterized by a low reactivity to carbon-carbon unsaturated bonds.

Although further investigations are required to clarify the actual oxidizing species in the reactions using $NaBrO_2$ with the organometallic catalyst,[9] the catalytic oxidizing system was shown to possess a suitable selectivity for the dehydrogenations of aldoximes leading to formations of isoxazolines and isoxazoles through nitrile oxide intermediates.

References

1) For review see: A. P. Kozikowski, ACC. Chem. Res., 17, 410 (1984).
2) For review see: C. Grundmann, Synthesis, 1970, 344.
3) C. Grundmann and J. M. Dean, J. Org. Chem., 30, 2809 (1965).
4) For recent application of the method see: A. Padwa, U. Chiacchio, D. C. Dean, A. M. Schffstall, A. Hassner, and K. S. K. Murthy, Tetrahedron. Lett., 1988, 4169.
5) T. Kageyama, S. Kawahara, K. Kitamura, Y. Ueno, and M. Okawara, Chem. Lett., 1983, 1097; T. Kageyama, Y. Ueno, and M. Okawara, Synthesis, 1983, 815; T. Kageyama, Y. Tobito, A. Katoh, Y. Ueno, and M. Okawara, Chem. Lett., 1983, 1481.
6) S. Kajigaeshi, T. Nakagawa, N. Nagasaki, and S. Fujisaki, Synthesis, 1985, 674 and references cited therein.
7) C. Grundmann and S. K. Datta, J. Org. Chem., 34, 2016 (1969).
8) J. G. Lee and D. S. Ha, Tetrahedron Lett., 1989, 193.
9) The organotin catalyst was revealed to accelerate the decomposition of sodium bromite and have no advantageous effect on the cyclization step. In addition, the dehydrogenation of aldoximes in our oxidizing system was more highly effected by a steric factor compared to that using sodium hypobromite as displayed in the reaction using anthraldoxime. These facts suggests that the activated oxidizing specie may involve a bulky trbutyltin moiety.

(Received in Japan 7 April 1989)