Synthesis of Isoxazolines and Isoxazoles *via* Generation of Nitrile Oxides from *O*-Stannyl Aldoximes

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The reactions of *O*-tributylstannyl aldoximes and active halogen compounds such as *tert*-butyl hypochlorite or *N*-bromosuccinimide, whereby nitrile oxides are generated effectively, are applied to the preparations of isoxazolines and isoxazoles *via* [3 + 2] dipolar cycloaddition.

Nitrile oxides have been utilized as an important class of synthetic intermediates for the preparation of isoxazolines and isoxazoles *via* [3 + 2] dipolar cycloaddition reactions.[1] In previous work, we have reported a novel procedure to generate nitrile oxides from hydroximoyl chlorides under neutral conditions by the use of organotin compounds such as bis(tributyltin) oxide and tetraphenyltin.[2] The usefulness of the former tin compound suggests that organotin compounds having Sn–O bonds will function analogously as the effective dehydrochlorination reagents. Furthermore, ω-haloalkoxytin compounds are known to afford cyclic ethers on heating with the elimination of organotin halide.[3] By considering this information, the *O*-stannylated derivative of hydroximoyl chloride seems to be a key intermediate in the formation of nitrile oxides. We now describe the results of our studies in which *O*-tributylstannyl aldoximes **1** are employed as the starting materials.

The stannylated aldoximes **1** were prepared in moderate yields by heating a mixture of tri-n-butyltin hydride (Bu_3SnH) and the aldoxime at 80 °C with a catalytic amount of triethylamine. The derivatives of aldoximes **1** were treated with *tert*-butyl hypochlorite (Bu^tOCl) at −20 °C in dichloromethane to generate the nitrile oxides; the formation of which was monitored by IR spectroscopy. With compound **1a**, the characteristic absorption of benzonitrile oxide was observed at 2250 cm^{-1} as reported previously.[4] When the reaction was carried out in the presence of unsaturated compounds, the corresponding isoxazolines **2** or isoxazoles **3** were obtained *via* [3 + 2] dipolar cycloaddition. A typical procedure is as follows: to a solution of *O*-tributylstannyl benzaldoxime **1a** (1.46 mmol) and butyl vinyl ether (7.3 mmol, 5 equiv.) in dichloromethane (3 ml), Bu^tOCl (1.50 mmol) was added dropwise keeping the reaction temperature below −20 °C. The solution was stirred for 5 h at ambient temperature and

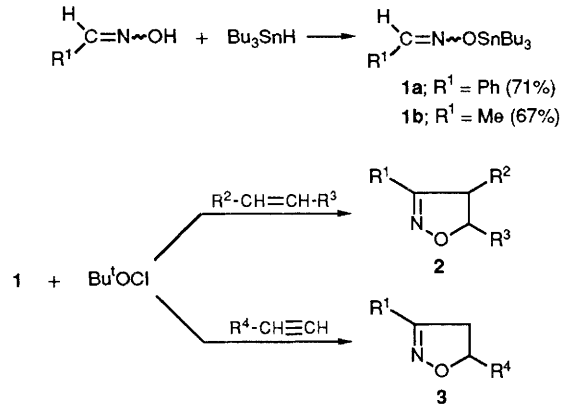

Table 1 Preparation of isoxazolines **2** and isoxazoles **3** from *O*-tributylstannyl aldoximes **1**

	1	Alkene		Alkyne	Molar ratio 1 : Alkene/	Yield (%)[a]	
Run	R^1	R^2	R^3	R^4	Alkyne	2	3
1	Ph	H	Ph		1:1	82	
2		H	$MeCO_2$		1:2	64	
3		H	BuO		1:5	69	
4		H	Me_3SiCH_2		1:8	62	
5		$-(CH_2)_4-$			1:20	51[b]	
6		H	MeCH(Cl)		1:5	54	
7	Me	H	Ph		1:2	60	
8		H	$BrCH_2$		1:5	55	
9		H	MeCO		1:3	35	
10	Ph			Ph	1:2		60
11				$BrCH_2$	1:5		55
12	Me			Ph	1:2		51
13				MeO_2C	1:4		66

[a] Yields are based on *O*-tributylstannyl aldoximes **1**. [b] The reaction was carried out without solvent.

then treated with aqueous potassium fluoride solution. After the usual work-up, 3-phenyl-5-butoxyisoxazoline was isolated in a 69% yield by silica gel chromatography with chloroform as eluent (run 3).

Various alkenes and alkynes were employed as dipolarophiles (Table 1). As with the previous procedure,[2] the use of butyl vinyl ether and vinyl acetate resulted in the production of the corresponding isoxazolines, in which the elimination of the butoxy and acetoxy groups was not observed (run 2 and 3).[5] This reaction system was also effective for the preparation of cyclic products having a halogenated substituent. As shown in the examples using allylic and propargylic halogen compounds, isoxazolines and isoxazoles were obtained, respectively, in moderate yields (runs 6, 8 and 11). These results indicated that the formation of nitrile oxides proceeded preferentially to the intermolecular dehalogenation of the halogen compounds.

Stannylated acetaldoxime **1b**, consisting of almost equal amounts of the *E*- and *Z*-isomer, afforded cyclic products in over 60% yields from the reactions with styrene and methyl propiolate (runs 7 and 13), *e.g.* the clear effects caused by these isomers on the halogenation and/or dehalogenation step were not observed. Accordingly, both geometrical isomers of **1** seemed to be applicable to the nitrile oxide formation. As to the halogenation reagents, other active halogen compounds such as *N*-chloro- and *N*-bromo-succinimide were also effective for the formation of nitrile oxides and the reactions using these reagents in dimethylformamide solution gave cyclic products in analogous yields to those obtained by the use of ButOCl.

The efficient generation of nitrile oxides from hydroximoyl chlorides and bis(tributyltin) oxide was shown in previous work.[2] This tin species is reported to afford alkoxides by treatment with alcohols under azeotropic conditions.[6] In addition, *O*-stannylated aldoximes **1** were shown here to be useful precursors of nitrile oxides. These observations support the assumption that *O*-stannylated hydroximoyl chloride is a possible intermediate in these reactions, although attempts to obtain evidence of its formation have been unsuccessful. Further, the elimination of the tributyltin halide from the assumed intermediate may occur much more readily compared to that from β-bromoalkoxytins,[3] which are regarded as the analogues of the intermediate.

Received, 13th August 1991; Com. 1/04246G

References

1 R. Huisgen, *Angew. Chem.*, 1963, **75**, 604; C. Grundmann, *Synthesis*, 1970, 344; A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; P. A. Harris, A. Jackson and J. A. Joule, *Tetrahedron Lett.*, 1989, **30**, 3193; S. Kanemasa, Y. Asai and J. Tanaka, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 375 and references cited therein.
2 O. Moriya, Y. Urata and T. Endo, *J. Chem. Soc., Chem. Commun.*, 1991, **17**.
3 B. Delmond, J. C. Pommier and J. Valade, *J. Organomet. Chem.*, 1972, **47**, 337.
4 R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, 1960, **26**, 546.
5 R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 1962, 2215.
6 A. G. Kleinschmidt, P. R. Palan and S. C. Vasishtha, *J. Chem. Soc. C*, 1971, 3972.