Dehydrochlorination of Hydroximic Acid Chlorides by the Use of Organotin Compounds: An Application for Synthesis of Isoxazolines and Isoxazoles

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The reactions of hydroximic acid chlorides and organotin compounds such as bis(tributyltin) oxide or tetraphenyltin, whereby nitrile oxides are generated effectively, are applied to the preparations of isoxazolines and isoxazoles *via* [3 + 2] dipolar cycloaddition.

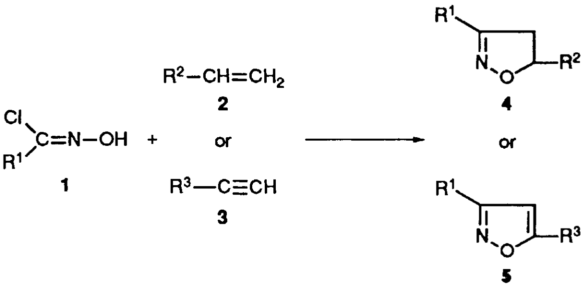
Nitrile oxides are known as the reactive intermediates for synthesis of a variety of heterocyclic compounds *via* [3 + 2] dipolar cycloaddition.[1] Several procedures for the preparation of these dipoles have been developed concurrently with the investigation into the synthetic application of the cycloaddition reactions.[2] The dehydrogenation of aldoximes, which seems to proceed through the formation of halogenated derivatives of aldoximes such as hydroximic acid chlorides or bromides, has been recognized as a useful procedure in these investigations. The transformations of hydroximic acid halides into nitrile oxides have usually been conducted in the presence of a basic reagent or by refluxing in a solvent in which evolved hydrogen halides are virtually insoluble, *e.g.* toluene.[3]

Organotin compounds have been reported to give organotin halides readily by the reaction with halogens and hydrogen halides,[4] as demonstrated elsewhere.[5] By considering the results of these previous investigations, the use of organotin derivatives in the dehydrohalogenation of hydroximic acid halides was examined, and seemed to provide a convenient technique for the preparation of nitrile oxides under mild and neutral conditions.

In this report, we describe the results of our approach to prepare title compounds **4** and **5** from hydroximic acid chlorides **1** and unsaturated compounds **2** and **3** *via* [3 + 2] dipolar cycloaddition in the presence of the organotin derivatives such as bis(tributyltin) oxide and tetraphenyltin.

The starting materials **1** were prepared according to the reported procedures.[6]† The procedure for the preparation of cyclization products **4** and **5** was simple to use. Thus, a solution of **1**, unsaturated compound **2** or **3** (2.0 equiv.) and bis(tributyltin) oxide (0.5 equiv.) in benzene was stirred at room temperature for 5 h. The products were isolated by silica gel chromatography eluting with chloroform (method A). Tetraphenyltin (1.0 equiv.) was also used instead of bis(tributyltin) oxide, (70 °C for 6 h) (method B, Scheme 1). These results are summarized in Table 1.

The reactions of **1** and alkenes **2** with bis(tributyltin) oxide proceeded efficiently to give isoxazolines **4** in moderate yields. The procedure was also effective in obtaining isoxazoles **5** from alkynes **3**. With allyltrimethylsilane **2b** as a dipolarophile, the corresponding isoxazoline **4b** was obtained without the elimination of a trimethylsilyl group. This result demonstrated that hydrogen chloride evolved by the generation of the nitrile oxide intermediate was trapped selectively by the organotin species. Interestingly, the successive transformation from the



Scheme 1 *Reagents and conditions*: method A, $(SnBu_3)_2O$; room temp.; method B, $SnPh_4$, 70 °C

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† Phenylchloroxime, which was obtained readily from benzaldoxime and t-butylhypochlorite, could be treated with organotin compounds and unsaturated compounds without isolation.

Table 1 Preparation of isoxazolines **4** and isoxazoles **5**

	1	**2**	**3**		Yield (%)	
	R^1	R^2	R^3	Method	**4**	**5**
a	Ph	Ph		A	90	
				B	84	
b	Ph	Me_3SiCH_2		A	83	
c	Ph	Br		A		74 (R^3 = H)
d	EtO_2C	$MeCO_2$		A	64	
e	EtO_2C	EtO		A	85	
f	EtO_2C	Ph		B	87	
g	Ph		MeO_2C	A		60
				B		53
h	Ph		Ph	A		68

isoxazoline to the isoxazole was not observed in the examples using vinyl acetate **2d** and ethyl vinyl ether **2e**. In the presence of a base or after heating, the cycloaddition of nitrile oxides to alkenes that contain potential leaving groups such as halogen, alkoxy or acetoxy group, is often accompanied by the elimination of these groups and results in the production of isoxazoles.[1b] Of the methods reported A proved favourable for the preparation of isoxazolines such as **4d** and **4e**. However, the halogen substituted isoxazoline was not obtainable from the vinylbromide **2c**.

The dehydrochlorination of **1** was effected by use of tetraphenyltin heated in benzene. The cyclization products **4** and **5** were obtained in reasonable yields compared to those using bis(tributyltin) oxide. The effectiveness of tetraphenyltin in these reactions suggests that organotin derivatives having four tin–carbon bonds can also be used for dehydrohalogenation.

Two types of organotin compounds can, thus be used in the formation of nitrile oxides, which could successively participate in [3 + 2] dipolar cycloaddition to unsaturated compounds.

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