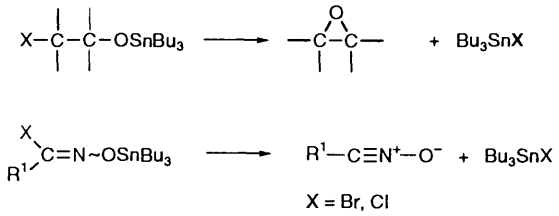
Generation of Nitrile Oxides *via O*-Tributylstannyl Aldoximes; Application to the Synthesis of Isoxazolines and Isoxazoles[1]

Osamu Moriya,*[a] Hideo Takenaka,[a] Masaichi Iyoda,[a] Yoshikiyo Urata[a] and Takeshi Endo[b]
[a] *Department of Chemistry, The National Defense Academy, Hashirimizu, Yokosuka 239, Japan*
[b] *Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan*

Nitrile oxides were generated readily by the reaction of aldoximes **1**, with *tert*-butyl hypochlorite and bis(tributyltin) oxide. The reaction proceeded efficiently under mild conditions, in which *O*-stannylated aldoximes **2** are thought to be key intermediates. This reaction system was applicable to the one-pot syntheses of isoxazole derivatives **4** and **5** in the presence of dipolarophiles *via* a [3 + 2] cycloaddition.

The synthetic and mechanistic aspects of the application of nitrile oxides in 1,3-dipolar cycloadditions, have been extensively studied.[2] Correspondingly, several procedures have been reported for the generation of nitrile oxides. The dehydrogenation of aldoximes *via* the formation of halogenated derivatives such as hydroximoyl chlorides and bromides, has been frequently employed as an effective procedure. The transformation of these halogenated derivatives into nitrile oxides is readily achieved in the presence of a basic reagent or by refluxing in a solvent where evolved hydrogen halides are virtually insoluble. Although these procedures have been applied to the synthesis of isoxazoles, an alternative process, whereby the nitrile oxide is generated *in situ* and is treated, without isolation, with a dipolarophile under mild and neutral conditions in the subsequent cycloaddition step, seems worth further study. Recent applications of 1,3-dipolar cycloadditions in organic synthesis have moved towards achieving finer chemo-, regio- and stereo-selectivity, and the reaction conditions mentioned above may be used to advantage in such applications.[3]

Various organotin compounds have been known to give organotin halides readily by their reaction with halogens and hydrogen halides.[4] Organotin derivatives having Sn–O bonds are especially useful as halogen trapping reagents. In fact, these organotin compounds have been employed for the oxidation of alcohols and the formation of cyclic ethers from 1, ω-halogenoalkoxy compounds.[5] By considering the results of these previous investigations, the use of alkoxytin compounds seemed to provide a convenient procedure for the generation of nitrile oxides from aldoximes under neutral conditions (Scheme 1). We now describe the results of our approach to prepare

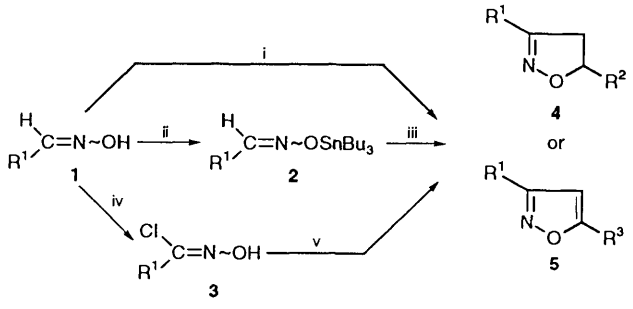


Scheme 1

isoxazole derivatives **4** and **5** from aldoximes **1** *via* a [3 + 2] dipolar cycloaddition, in which bis(tributyltin) oxide [$(Bu_3Sn)_2O$] and *tert*-butyl hypochlorite (Bu^{t}OCl) are employed as an organotin reagent and active halogen source, respectively, for the generation of nitrile oxide intermediates.

The stannylation of aldoximes **1** to give **2** was easily achieved by mixing **1** and a 0.5 equiv. of $(Bu_3Sn)_2O$ in an appropriate solvent such as dichloromethane or benzene at room temperature. After distillation under reduced pressure, compound **2** was isolated in high yield. The efficient formation of compound **2** was confirmed by ^1H NMR measurement of a mixture of **1** and $(Bu_3Sn)_2O$ in $CDCl_3$. For example, the signals at δ 8.20 and 8.15 assigned to the proton of the hydroxy group of **1a** and **1b**, respectively, disappeared rapidly within 5 min following the addition of $(Bu_3Sn)_2O$. These observations indicated that the aldoximes **1** were stannylated more readily than common alcohols[6] and that the one-pot synthesis of isoxazole derivatives **4** and **5** from **1** in the presence of a dipolarophile, without the isolation of **2**, was possible. The subsequent generation of nitrile oxides from *O*-stannylated aldoxime **2** was conducted by reaction with Bu^{t}OCl, at a temperature maintained below −20 °C in dichloromethane solution. Although no experimental attempt was made to isolate nitrile oxides, their formation was detected in the IR spectrum of the reaction mixture. For example, the characteristic absorption of benzonitrile oxide appeared at the reported region of 2250 cm^{-1} following the addition of Bu^{t}OCl in the case of **1a**.[7] On the basis of such fundamental information, a reaction system consisting of compound **1**, $(Bu_3Sn)_2O$ and the halogenating reagent was used for the synthesis of isoxazole derivatives **4** and **5** *via* a [3 + 2] dipolar cycloaddition.

The preparation of isoxazole derivatives **4** and **5** was carried out by the following Methods A–C to obtain information on the efficiency, and an insight into the nature, of the reactions (Scheme 2). In Method A, an equimolar amount of Bu^{t}OCl was added dropwise at −20 °C to a solution of the aldoxime **1**, 0.5 equiv. of $(Bu_3Sn)_2O$ and an excess of the dipolarophile. In



Scheme 2 *Reagents:* i, $(Bu_3Sn)_2O$, R^2–CH=CH_2 or R^3–C≡CH, Bu^{t}OCl (Method A); ii, $(Bu_3Sn)_2O$; iii, R^2–CH=CH_2 or R^3–C≡CH, Bu^{t}OCl (Method B); iv, Bu^{t}OCl; v, $(Bu_3Sn)_2O$, R^2–CH=CH_2 or R^3–C≡CH (Method C)

Table 1 Preparation of isoxazolines **4** from aldoximes **1**, *O*-stannylated **2** and chlorinated aldoximes **3**

Run	Aldoximes 1, 2 or 3 R[1]	Dipolarophiles R[2]	R[3]	Method[a]	Ratio of Dipolarophile/aldoxime (mol/mol)	Product yield[b](%) 4
1	**1a** Ph	Ph		A	2/1	73
2	**2a** Ph	Ph		B	3/1	77
3	**3a** Ph	Ph		C	2/1	87
4	**1a** Ph	$MeCO_2C$		A	2/1	62[c]
5	**2a** Ph	MeO_2C		B	2/1	67[c]
6	**3a** Ph	MeO_2C		C	2/1	91[c]
7	**1a** Ph	$MeCO_2$		A	2/1	56
8	**2a** Ph	$MeCO_2$		B	2/1	63
9	**2a** Ph	BuO		B	5/1	69
10	**1a** Ph	$HOCH_2$		A	5/1	72
11	**3a** Ph	Me_3SiCH_2		C	3/1	83
12	**2b** Me	Ph		B	2/1	60
13	**2b** Me	MeCH(Cl)		B	5/1	54
14	**2b** Me	Ph_3SnCH_2		B	2/1	63
15	**1b** Me	Ph_3Sn		A	2/1	37
16	**1c** CH_2=CH	Ph		A	3/1	53
17	**2c** CH_2=CH	Ph		B	3/1	71
18	**2c** CH_2=CH	MeO_2C		B	3/1	46[d]
19	**6** *p*-phenylene	MeO_2C		A	6/1	**7** 77

[a] For the Method A, B and C, see footnotes to Scheme 2. [b] Yields are based on **1** in Method A, **2** in Method B and **3** in Method C, respectively. [c] A small amount of 4-substituted regioisomer was contaminated. [d] This compound contained a small amount of polymeric impurities.

Table 2 Preparation of isoxazoles **5** from aldoximes **1**, *O*-stannylated **2** and chlorinated aldoximes **3**

Run	Aldoximes 1, 2 or 3 R[1]	Dipolarophiles R[3]	Method	Ratio of dipolarophile/aldoximes (mol/mol)	Product yield[b](%) 5
20	**1a** Ph	Ph	A	2/1	55
21	**2a** Ph	Ph	B	2/1	60
22	**3a** Ph	Ph	C	2/1	70
23	**1a** Ph	$HOCH_2$	A	5/1	73
24	**2a** Ph	$BrCH_2$	B	5/1	55
25	**2b** Me	Ph	B	4/1	69
26	**2b** Me	MeO_2C	B	4/1	64

[a] For the Method A, B and C, see the footnotes to Scheme 1. [b] Yields are based on **1** in Method A, **2** in Method B and **3** in Method C, respectively.

Method B, isolated *O*-stannylated aldoxime **2** was employed as the starting aldoxime species and was treated with Bu^{t}OCl analogously to Method A in the presence of the dipolarophile. In Method C, the reaction was conducted by treating halogenated aldoxime species **3** with $(Bu_3Sn)_2O$ and the dipolarophile in dichloromethane at room temperature.

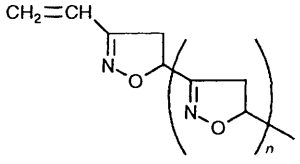
The reaction in the presence of a variety of dipolarophiles proceeded effectively to give the cyclic products **4** and **5** (Tables 1 and 2). These results showed that all three methods utilizing the organotin compound were suitable for the preparation of isoxazoles having various functional groups. A characteristic of these procedures was that isoxazolines having an acetoxy and a butoxy substituent were obtained readily in reactions using vinyl acetate and butyl vinyl ether without the elimination of the acetoxy and the alkoxy group, respectively (Runs 7, 8 and 9). The use of these olefins for the 1,3-dipolar cycloaddition of nitrile oxides in the presence of a base or heat is reported to afford isoxazoles through the elimination of those groups.[8] The reaction system employing the organotin species was also applicable for the preparation of products having a halogenated substituent (Runs 13 and 24). Such compounds have been reported to be used for the preparation of acylated and α-amino-alkylated allylic derivatives.[9] Furthermore, these results indicated that the dehydrochlorination of hydroximoyl chlorides **3** to give nitrile oxides proceeded preferentially to the dehalogenation from allylic and prop-2-ynylic halogen compounds.

The preparation of isoxazole derivatives having a hydroxy group was also possible by Method A, as shown in the examples using allyl and prop-2-ynyl alcohol (Runs 10 and 23). In these reactions, oxidation of the alcohols by the active halogen compound and the organotin species was not observed. Accordingly, the aldoxime **1** and/or the aldoxime derivative **2** were thought to react with Bu^{t}OCl more readily than the unsaturated alcohols, although they existed in excess in the reaction solution.

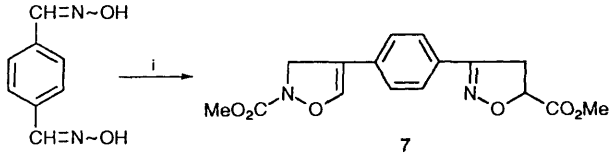
The preparation of isoxazole derivatives having an organometallic substituent, which seemed to be useful intermediates for the regioselective introduction of various substituents to the isoxazole ring, were examined.[10] When allyltrimethylsilane was used as the dipolarophile, the corresponding isoxazole was obtained in 83% yield by Method C (Run 11). However, the preparation of tributyltin-substituted isoxazolines using vinyltributyltin or allenyltributyltin as the dipolarophile were unsuccessful, and only the elimination of tributyltin group was observed. On the other hand, triphenyltin dipolarophiles such as vinyl and allyltriphenyltin gave the corresponding isoxazolines in 30–60% yields, respectively (Runs 14 and 15). Although the reasons for the differences in the results obtained with the tributyltin reagents are not clear these may be attributable not

to their reactivity as dipolarophiles, but to their sensitivity to the halogenated reagent. Phenyl groups bonded to tin are reported to be substituted by halogens more readily than the alkyl groups.[4]

When *O*-stannylated acrylaldehyde oxime **2c** was used as the precursor to the nitrile oxide, the corresponding isoxazolines were obtained. However, in the reaction using methyl acrylate as the dipolarophile, the yield of the corresponding isoxazoline was rather low compared with those of reactions employing other aldoximes (Run 18). From ^{1}H NMR spectroscopic analysis of the reaction mixture, the existence of the other cyclic product, which seemed to be formed from acrylonitrile oxide itself, was suggested. It was thought that the vinyl group of **2c** had an analogous reactivity to that of methyl acrylate, and acted as a co-dipolarophile. This assumption seems to be supported by the fact that polymeric compounds are obtained from **2c** in the reaction conducted without a dipolarophile.[11]



The procedure was also effective for the preparation of the bis-adduct **7** (Scheme 3). The use of an equimolar amount of



Scheme 3 *Reagents:* i, $(Bu_3Sn)_2O$, MeO_2C–CH=CH_2, Bu^{t}OCl (Method A)

$(Bu_3Sn)_2O$ and terephthalaldehyde oxime **6** resulted in the preparation of the corresponding bis-isoxazoline compound **7** in moderate yield. This result indicated that 0.5 equiv. of $(Bu_3Sn)_2O$ was adequate for *O*-stannylation of one oxime group. Comparison of the results obtained from Methods A–C provided some information on certain features of these reactions. In the reactions using benzaldehyde oxime **1a** and methyl acrylate, the isoxazoline could be obtained by Method A and B in yields such as 62 and 67%, respectively (Runs 4 and 5). An almost quantitative yield was obtained by Method C, in which the corresponding hydroximoyl chloride **3a** was employed as the starting material (Run 6). The latter result illustrated that the halogen affinity of the organotin species is adequate for efficient access to nitrile oxides. Therefore, the lower yields observed in Methods A and B seemed to be caused by an inefficiency in the chlorination of the aldoxime species by Bu^{t}OCl. In addition, the similarity of the yields in Methods A and B suggested that the transformation of the aldoxime **1a** to the *O*-stannylated species **2a** occurs first in Method A. This presumption is supported by the ^{1}H NMR measurement mentioned above, in which the rapid proton exchange of the hydroxy group of the aldoxime to the tributyltin group is exhibited. In addition, the rapid formation of nitrile oxides at a lower temperature demonstrates that the halogenated aldoximes are much more active than the alkyl halides; intramolecular dehalogenation of 1, ω-halogenostannyloxy compounds to give cyclic ether requires a higher reaction temperature of over 100 °C.[5]

Thus, the reaction with both Methods A and B seems to proceed through the *O*-stannylated hydroximoyl chloride, although attempts to identify and isolate such key intermediates have been unsuccessful. Reaction systems consisting of the aldoxime, organotin species and an unsaturated compound, such as *N*-bromo- and *N*-chloro-succinimide instead of Bu^{t}OCl were also effective for formation of the desired isoxazole. However, an additional step to remove the precipitated by-product succinimide was required. On the other hand, the use of bis(chlorodibutyltin) oxide instead of $(Bu_3Sn)_2O$ and *O*-trimethylsilyl aldoximes afforded no isoxazole compound. In these cases, dichlorodibutyltin and chlorotrimethylsilane are expected to be formed with the generation of the nitrile oxide. The unsuccessful results seem to be caused by the complexation of the nitrile oxide with dichlorodibutyltin and chlorotrimethylsilane,[12] which are stronger Lewis acids than chlorotributyltin. In fact, the use of *O*-trimethylsilylaldoxime for the generation of nitrile oxides requires the presence of potassium fluoride to trap the resulting trimethylchlorosilane.[13]

As to the effects caused by the geometrical isomers of the aldoximes on the reactions, we could not find any clear evidence. Acetaldehyde oxime **1b** and acrylaldehyde oxime **1c**, which consisted of almost equal amounts of the *E*- and *Z*-isomers, afforded the isoxazolines **4** and isoxazoles **5** in reasonable yields. These results seem to indicate that the halogenation and/or dehalogenation of both geometrical isomers occurred similarly, and that both were appropriate for the construction of the isoxazole ring.

The combination of the aldoxime, $(Bu_3Sn)_2O$ and an active halogen compound was found to be a facile procedure for the generation of nitrile oxides under neutral and mild conditions. Furthermore, the procedure demonstrated its essential utility in this field, *i.e.*, it was applicable for the synthesis of isoxazoline and isoxazole derivatives having various functional groups such as halogens, hydroxy and organometallic groups as substituents.

Experimental

IR spectra were recorded on a Jasco A-3 IR spectrometer and ^{1}H NMR on a JEOL FX90Q instrument using tetramethylsilane as an internal standard in $CDCl_3$. The silica gel used for column chromatography was Wakogel C-200 (100–200 mesh). M.p.s. were determined on a Meihou apparatus in open capillaries and are uncorrected. The following materials were prepared by literature methods: vinyltriphenyltin,[14] allyltriphenyltin,[15] acrylaldehyde oxime **1c**[16,17] and terephthalaldehyde oxime **6**.[16] Benzohydroximoyl chloride **3a**[18] was prepared by the use of Bu^{t}OCl from benzaldehyde oxime **1a** and obtained in 80% yield. Other organic reagents and solvents were purchased and used without purification.

General Procedure for the Preparation of O-*Stannylated Oximes* **2**.—*Benzaldehyde oxime* O-*tributylstannyl ether* **2a**. A mixture of *syn*-benzaldehyde oxime **1a** (1.00 g, 8.25 mmol) and $(Bu_3Sn)_2O$ (2.46 g, 4.13 mmol) in benzene (5 cm^3) was stirred for 30 min. After the evaporation of the solvent, the resulting solution was distilled under reduced pressure to give the title product **2a** as a colourless oil (3.02 g, 89%); b.p. 180 °C/0.3 mmHg (Kugelrohr) (Found: C, 55.7; H, 8.15; N, 3.35; Sn, 29.98. $C_{19}H_{33}NOSn$ requires C, 55.64; H, 8.11; N, 3.41; Sn, 28.94%); ν_{max}(neat)/cm^{-1}; 675, 690, 950, 2850 and 2950; δ_H 8.10 (1 H, s), 7.50 (2 H, m), 7.30 (3 H, m) and 0.60–1.95 (27 H, br m).

Acetaldehyde oxime O-*tributylstannyl ether* **2b**. This compound was obtained from acetaldehyde oxime **1b** and $(Bu_3Sn)_2O$ in 78% yield; b.p. 125 °C/1 mmHg (Kugelrohr) (Found: C, 48.2; H, 8.9, N, 3.9; Sn, 34.55. $C_{14}H_{31}NOSn$ requires C, 48.31; H, 8.98; N, 4.02; Sn, 34.10%); ν_{max}(neat)/cm^{-1} 680, 770, 880, 1380, 1465, 2850 and 2950; δ_H 7.40 (0.5 H, m), 6.80 (0.5 H, m) and 0.60–2.00 (30 H, br m).

Acryaldehyde oxime O-*tributylstannyl ether* **2c**. This compound was obtained from acrylaldehyde oxime **1c** and $(Bu_3Sn)_2O$ in 65% yield; b.p. 120 °C/5 mmHg (Kugelrohr) (Found: C, 50.1; H, 8.7; N, 3.81; Sn, 34.0. $C_{15}H_{31}NOSn$ requires C, 50.03; H, 8.68; N, 3.89; Sn, 32.96%); ν_{max}(neat)/cm^{-1}; 665, 940, 975, 2850 and 2950; δ_H 7.80 (1 H, d, *J* 10.0), 6.20–6.65 (1 H, m), 5.20–5.45 (2 H, m) and 0.70–1.80 (27 H, br m).

General Procedure for the Preparation of Isoxazole Derivatives **4** *and* **5**.—*Method A*. 3,5-*Diphenyl*-4,5-*dihydroisoxazole*.[19] To a solution of *syn*-benzaldehyde oxime **1a** (0.20 g, 1.65 mmol), $(Bu_3Sn)_2O$ (0.50 g, 0.84 mmol) and styrene (0.34 g, 3.26 mmol) in dichloromethane (1 cm^3), Bu^{t}OCl (0.18 g, 1.66 mmol) in dichloromethane (2 cm^3) was added dropwise keeping the reaction temperature below −20 °C. After the mixture had been stirred for 5 h at room temperature, diethyl ether (10 cm^3) was added and treated with aqueous potassium fluoride solution. The precipitate so formed was filtered off and the ethereal solution was dried over magnesium sulfate. The solvent was evaporated off, and the residue was then purified by column chromatography on silica, with chloroform as eluent, to give the title product (0.27 g, 73%); m.p. 73–74 °C; δ_H 7.60 (2 H, m), 7.30 (8 H, m), 5.65 (1 H, dd, *J* 9 and 10) and 3.20–3.80 (2 H, m).

Method B. To a solution of benzaldehyde oxime *O*-tributylstannyl ether **2a** (0.60 g, 1.46 mmol) and styrene (0.30 g, 2.88 mmol) in dichloromethane (1 cm^3), Bu^{t}OCl (0.16 g, 1.47 mmol) was added dropwise keeping the reaction temperature below −20 °C. After the mixture had been stirred for additional 5 h at room temperature, the product (0.25 g, 77%) was isolated by the work-up mentioned in Method A.

Method C. A solution of benzohydroximoyl chloride **3a** (0.20 g, 1.29 mmol), styrene (0.27 g, 2.59 mmol) and $(Bu_3Sn)_2O$ (0.39 g, 0.65 mmol) in dichloromethane (2 cm^3) was stirred at room temperature for 7 h. After work-up as described in Method A, the product (0.25 g, 87%) was obtained.

Methyl 3-*Phenyl*-4,5-*dihydroisoxazole*-5-*carboxylate*.[20]—From **1a** (0.20 g, 1.65 mmol) and methyl acrylate (0.29 g, 3.37 mmol), the product (0.21 g, 62%) was obtained by Method A; from **2a** (0.60 g, 1.46 mmol) and methyl acrylate (0.26 g, 3.02 mmol), the product (0.20 g, 67%) was obtained by Method B; from **3a** (0.20 g, 1.29 mmol) and methyl acrylate (0.23 g, 2.67 mmol), the product (0.24 g, 91%) was obtained by Method C. In these products, a small amount of the regioisomer, methyl 3-phenyl-4,5-dihydroisoxazole-4-carboxylate was contained; m.p. 71–72.5 °C; δ_H 7.60 (2 H, m), 7.40 (3 H, m), 5.15 (1 H, dd, *J* 9 and 10) and 3.45–3.80 (5 H, s).

5-*Acetoxy*-3-*phenyl*-4,5-*dihydroisoxazole*.[21]—From **1a** (0.20 g, 1.65 mmol) and vinyl acetate (0.29 g, 3.36 mmol), the product (0.19 g, 56%) was obtained by Method A; from **2a** (0.60 g, 1.46 mmol) and vinyl acetate (0.25 g, 2.90 mmol), the product (0.19 g, 63%) was obtained by Method B; m.p. 101–102 °C; δ_H 7.65 (2 H, m), 7.40 (3 H, m), 6.80 (1 H, dd, *J* 8, 8), 3.30 (2 H, dd, *J* 14 and 9) and 2.20 (3 H, s).

5-*Butoxy*-3-*phenyl*-4,5-*dihydroisoxazole*.[22]—From **2a** (0.60 g, 1.46 mmol) and butyl vinyl ether (0.74 g, 7.39 mmol), the product (0.22 g, 69%) was obtained by Method B; b.p. 143–145 °C/1 mmHg (Kugelrohr); δ_H 7.60 (2 H, m), 7.35 (3 H, m), 5.60 (1 H, dd, *J* 7 and 6), 3.60–3.90 (4 H, m), 1.00–1.70 (4 H, br m) and 0.88 (3 H, tr, *J* 7).

5-*Hydroxymethyl*-3-*phenyl*-4,5-*dihydroisoxazole*.[23]—From **1a** (0.50 g, 4.13 mmol) and allyl alcohol (1.20 g, 20.66 mmol), the product (0.53 g, 72%) was obtained by Method A; ν_{max}(KBr)/cm^{-1} 3300, 1440, 1375, 1040, 750 and 680; δ_H 7.65 (2 H, m), 7.40 (3 H, m), 4.85 (1 H, m), 3.80 (2 H, m), 3.30 (2 H, d, *J* 11) and 2.35 (1 H, br).

3-*Phenyl*-5-*trimethylsilylmethyl*-4,5-*dihydroisoxazole*.—From **3a** (0.20 g, 1.29 mmol) and allyltrimethylsilane (0.45 g, 3.94 mmol), the product (0.25 g, 83%) was obtained by Method C as a colourless oil (Found: C, 67.1; H, 8.55; N, 5.85. $C_{13}H_{19}NOSi$ requires C, 66.90; H, 8.21; N, 6.00%); ν_{max}(neat)/cm^{-1} 2950, 1355, 1250, 910, 850, 760 and 690; δ_H 7.80 (2 H, m), 7.70 (3 H, m), 4.95 (1 H, m), 2.85–3.70 (2 H, m), 1.40 (2 H, m) and 0.20 (9 H, s).

3-*Methyl*-5-*phenyl*-4,5-*dihydroisoxazole*.[24]—From **2b** (0.50 g, 1.44 mmol) and styrene (0.30 g, 2.80 mmol), the product (0.14 g, 60%) was obtained by Method B; b.p. 130–133 °C/5 mmHg (Kugelrohr); δ_H 7.30 (5 H, s), 5.50 (1 H, dd, *J* 8 and 10), 2.60–3.40 (2 H, m) and 2.00 (3 H, s).

5-(1-*Chloroethyl*)-3-*methyl*-4,5-*dihydroisoxazole*.—From **2b** (0.70 g, 2.01 mmol) and 3-chlorobut-1-ene (0.91 g, 10.05 mmol), the product (0.15 g, 54%) was obtained by Method B as a colourless oil (Found: C, 49.0; H, 6.75; Cl, 24.2; N, 9.4. $C_6H_{10}ClNO$ requires C, 48.83; H, 6.83; Cl, 24.02; N, 9.49%); ν_{max}(neat)/cm^{-1} 2950, 1440, 1390 and 870; δ_H 4.35–4.65 (1 H, m), 3.80–4.10 (1 H, m), 3.00 (2 H, m), 2.00 (3 H, s) and 1.55 (3 H, d, *J* 7).

3-*Methyl*-5-*triphenylstannylmethyl*-4,5-*dihydroisoxazole*.—From **2b** (0.60 g, 1.72 mmol) and allyltriphenyltin (1.00 g, 2.56 mmol), the product (0.36 g, 63%) was obtained by Method B; m.p. 107–108 °C (Found: C, 83.1; H, 7.1; N, 4.55. $C_{23}H_{23}NOSn$ requires C, 83.86; H, 7.04; N, 4.25%); ν_{max}(KBr)/cm^{-1}; 1425, 1075, 740 and 700; δ_H 7.50 (6 H, m), 7.35 (9 H, m), 4.80–5.00 (1 H, m), 2.10–2.80 (2 H, m), 1.90 (2 H, d, *J* 7) and 1.70 (3 H, s).

3-*Methyl*-5-*triphenylstannyl*-4,5-*dihydroisoxazole*.—From **1b** (0.06 g, 1.02 mmol) and vinyltriphenyltin (0.80 g, 2.12 mmol), the product (0.15 g, 37%) was obtained by Method A (Found: C, 57.55; H, 5.35; N, 3.75. $C_{19}H_{21}NOSn$ requires C, 57.33; H, 5.32; N, 3.52%); ν_{max}(KBr)/cm^{-1} 2950 and 700; δ_H 7.10–8.00 (15 H, br m), 4.70 (1 H, dd, *J* 16 and 16), 2.80–3.60 (2 H, m) and 1.95 (3 H, s).

5-*Phenyl*-3-*vinyl*-4,5-*dihydroisoxazole*.[25]—From **1c** (0.50 g, 7.03 mmol) and styrene (2.20 g, 21.12 mmol), the product (0.64 g, 53%) was obtained by Method A; from **2c** (0.50 g, 1.39 mmol) and styrene (0.43 g, 4.16 mmol), the product (0.17 g, 71%) was obtained by Method B; b.p. 50–53 °C/0.5 mmHg (Kugelrohr); δ_H 7.35 (5 H, s), 6.70 (1 H, dd, *J* 12 and 12), 5.30–5.70 (3 H, m) and 3.00–3.50 (2 H, m).

Methyl 3-*vinyl*-4,5-*dihydroisoxazole*-5-*carboxylate*.[26]—From **2c** (0.50 g, 1.39 mmol) and methyl acrylate (0.36 g, 4.16 mmol), the product (0.10 g, 46%) (which contained a small amount of other cyclic products) was obtained by Method B; ν_{max}(neat)/cm^{-1}; 1740, 1455, 1345, 1220 and 890; δ_H 6.70 (1 H, dd, *J* 16 and 16), 5.40–5.70 (2 H, m), 5.10 (1 H, t, *J* 10), 3.80 (3 H, s) and 3.40 (2 H, d, *J* 10).

1,3-*Bis*(5-*methoxycarbonyl*-4,5-*dihydroisoxazol*-3-*yl*)*benzene* **7**.—The reaction was carried out using a similar procedure to Method A in the presence of an equimolar amount of $(Bu_3Sn)_2O$. From benzene-1,3-dicarbaldehyde dioxime **6** (0.20 g, 1.22 mmol) and methyl acrylate (0.63 g, 7.31 mmol), the title compound **7** (0.31 g, 77%) was obtained (Found: C, 57.5; H, 4.9; N, 8.8. $C_{16}H_{16}N_2O_6$ requires C, 57.83; H, 4.85; N, 8.43%); ν_{max}(KBr)/cm^{-1}; 2950, 1750, 1440, 1320 and 1220; δ_H 7.40–7.90 (4 H, m), 5.20 (1 H, dd, *J* 10 and 12) and 3.50–3.80 (10 H, s m).

3,5-*Diphenylisoxazole*.[27]—From **1a** (0.50 g, 4.13 mmol) and ethynylbenzene (0.84 g, 8.22 mmol), the product (0.50 g, 55%) was obtained by Method A; from **2a** (0.60 g, 1.46 mmol) and ethynylbenzene (0.30 g, 2.94 mmol), the product (0.19 g, 60%) was obtained by Method B; from **3a** (0.20 g, 1.29 mmol) and ethynylbenzene (0.27 g, 2.64 mmol), the product (0.20 g, 70%) was obtained by Method C; ν_{max}(KBr)/cm^{-1} 1455, 1410, 765 and 695; δ_H 7.80 (4 H, m), 7.40 (6 H, m) and 6.75 (1 H, s).

5-*Hydroxymethyl*-3-*phenylisoxazole*.—From **1a** (1.00 g, 8.25 mmol) and prop-2-yn-1-ol (2.31 g, 41.3 mmol), the title product (1.06 g, 73%) was obtained by Method A; m.p. 48–50 °C (Found: C, 68.5; H, 5.15; N, 8.05. $C_{10}H_9NO_2$ requires C, 68.56; H, 5.18; N, 7.99%); ν_{max}(KBr)/cm^{-1} 3250, 1610, 1465, 1400, 1040, 980, 760 and 690; δ_H 7.70 (2 H, m), 7.40 (3 H, m), 6.50 (1 H, s), 4.80 (2 H, s) and 2.95–3.20 (1 H, br).

5-*Bromomethyl*-3-*phenylisoxazole*.—From **2a** (0.50 g, 1.22 mmol) and 3-bromopropyne (0.77 g, 6.14 mmol., the title product (0.16 g, 55%) was obtained by Method B (Found: C, 50.5; H, 3.4; N, 5.85. $C_{10}H_8BrNO$ requires C, 50.43; H, 3.39; N, 5.88%); ν_{max}(KBr)/cm^{-1} 2950, 1605, 1460, 1440, 1400, 760 and 680; δ_H 7.70 (2 H, m), 7.40 (3 H, m), 6.55 (1 H, s) and 4.42 (2 H, s).

3-*Methyl*-5-*phenylisoxazole*.[28]—From **2b** (0.50 g, 1.44 mmol) and ethynylbenzene (0.59 g, 5.78 mmol), the product (0.22 g, 69%) was obtained by Method B; ν_{max}(KBr)/cm^{-1}; 2950, 1430, 765 and 700; δ_H 7.70 (2 H, m), 7.40 (3 H, m), 6.30 (1 H, s) and 2.30 (3 H, s).

Methyl 3-*methylisoxazole*-5-*carboxylate*.[27]—From **2b** (0.50 g, 1.44 mmol) and propiolic acid methyl ester (0.48 g, 5.71 mmol), the product (0.13 g, 64%) was obtained by Method B; ν_{max}(KBr)/cm^{-1} 2950, 1740, 1440, 1210 and 890; δ_H 6.78 (1 H, s), 3.92 (3 H, s) and 2.35 (3 H, s).

References

1 Part of this work has been published in preliminary communications: O. Moriya, Y. Urata and T. Endo, *J. Chem. Soc., Chem. Commun.*, 1991, 17; O. Moriya, H. Takenaka, Y. Urata and T. Endo, *J. Chem. Soc., Chem. Commun.*, 1991, 1671.

2 For reviews see: R. Huisgen, *Angew. Chem.*, 1963, **75**, 604; C. Grundmann, *Synthesis*, 1970, 344; P. Caramella and P. Grünanger in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, Chichester, 1984, vol. 1, p. 291.

3 A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410; K. R. Rao, N. Bhanumathi and P. B. Sattur, *Tetrahedron Lett.*, 1990, **31**, 3201; W. Oppolzer, A. J. Kingma and S. K. Pillai, *Tetrahedron Lett.*, 1991, **32**, 4893; S. Kanemasa, Y. Asai and J. Tanaka, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 375; J. Zhang and D. P. Curran, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2627 and references cited therein.

4 P. K. Ingham, S. D. Rosenberg and H. Gilman, *Chem. Rev.*, 1960, 459.

5 B. Delmond, J. C. Pommier and J. Valade, *J. Organometal. Chem.*, 1972, **35**, 91.

6 A. G. Davies, D. C. Kleinshmidt, P. R. Palan and S. C. Vasishta, *J. Chem. Soc. C*, 1971, 3972.

7 R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, 1960, **25**, 546.

8 P. Vita Finzi and M. Arbasino, *Ann. Cheim. (Roma)* 1964, **54**, 1165; R. Paul and S. Tchelitchefe, *Bull. Soc. Chim. Fr.*, 1962, 2215.

9 V. Jäger, H. Grund and W. Schwaw, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 78.

10 T. Sakamoto, Y. Kondo, D. Uchiyama and H. Yamanaka, *Tetrahedron*, 1991, **47**, 5111.

11 A. Baranski, *Pol. J. Chem.*, 1984, **58**, 425 (*Chem. Abstr.*, 1984, **103**, 123393h).

12 N. A. LeBel and N. Balasubramanian. *Tetrahedron Lett.*, 1985, **26**, 4331.

13 R. F. Cunico and L. Bedell, *J. Org. Chem.*, 1983, **48**, 2780.

14 D. Seyferth and F. G. A. Stone, *J. Am. Chem. Soc.*, 1957, **79**, 515.

15 H. Gilman and J. Eisch, *J. Org. Chem.*, 1955, **20**, 763.

16 E. H. Ungnade and A. D. McLaren, *J. Org. Chem.*, 1945, **10**, 29.

17 Z. W. Walkowski, J. Naguyen and J. Wiemann, *Tetrahedron Lett.*, 1970, 93.

18 G. W. Perold, A. P. Steyn and F. V. K. von Reiche, *J. Am. Chem. Soc.*, 1957, **79**, 462.

19 K. Bast, M. Christl, R. Huisgen, W. Mack and R. Sustmann, *Chem. Ber.*, 1973, **106**, 3258.

20 M. Christl, R. Huisgen and R. Sustmann, *Chem. Ber.*, 1973, **106**, 3275.

21 R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 1962, 2215.

22 T. Shimizu, Y. Hayashi, H. Shibafuchi and K. Terashima, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2827.

23 D. P. Curan, K-S, Jeang, T. A. Heffner and J. Rebek Jr., *J. Am. Chem. Soc.*, 1989, **111**, 9238.

24 A. Rahman and L. B. Clapp, *J. Org. Chem.*, 1976, **41**, 122.

25 P. A. Wade, N. V. Amin, H-K, Yen, D. T. Price and G. F. Huhn, *J. Org. Chem.*, 1984, **49**, 4595.

26 A. Baranski, *Pol. J. Chem.*, 1984, **58**, 40 (*Chem. Abstr.*, 1984, **110**, 56835h).

27 G. Bianchi and P. Grünger, *Tetrahedron*, 1965, **21**, 817.

28 H. C. van der Plas, M. C. Wollering, H. Jongejan and B. Zuurdeeg, *Recl. Trav. Chim. Pays-bas*, 1974, **93**, 225.

Paper 3/05100E
Received 8*th October* 1993
Accepted 17*th October* 1993