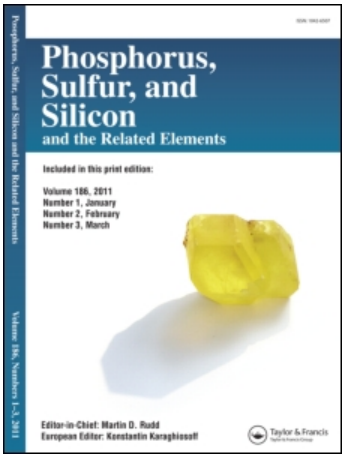

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 67. REACTIONS OF α-NITROALKENES WITH COMPOUNDS BEARING ACTIVE METHYLENE GROUPS. A NOVEL AND CONVENIENT SYNTHESIS OF 2-ISOXAZOLINE DERIVATIVES

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To cite this Article Yuan, Chengye and Li, Chaozhong(1993) 'STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 67. REACTIONS OF α-NITROALKENES WITH COMPOUNDS BEARING ACTIVE METHYLENE GROUPS. A NOVEL AND CONVENIENT SYNTHESIS OF 2-ISOXAZOLINE DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 78: 1, 47 — 53
To link to this Article: DOI: 10.1080/10426509308032421
URL: http://dx.doi.org/10.1080/10426509308032421

Phosphorus, Sulfur, and Silicon, 1993, Vol. 78, pp. 47–53
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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS 67. REACTIONS OF α-NITROALKENES WITH COMPOUNDS BEARING ACTIVE METHYLENE GROUPS. A NOVEL AND CONVENIENT SYNTHESIS OF 2-ISOXAZOLINE DERIVATIVES

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(Received December 2, 1992)

Reaction of α-nitroalkenes and compounds bearing an active methylene group followed by subsequent addition of trimethylchlorosilane leads to a series of 2-isoxazoline derivatives in good yield. The reaction proceeded through the formations of an alkene and a silyl nitronate as a 1,3-dipole. The reaction mechanisms and the chemical behaviour of the products are discussed.

Key words: Silyl nitronate; silyl migration; 1,3-dipole.

INTRODUCTION

Synthetic studies of heterocyclic compounds deserve considerable attention because of their potential biological activities. Among them, 2-isoxazolines are one of the most important classes. They are useful as flexible synthetic equivalents of β-hydroxyketones, γ-aminoalcohols and other related functions. These characteristic behaviours encourage continuing emphasis on their preparations. Unfortunately only a few methods are available for the synthesis of 2-isoxazolines, including regioselective 1,3-dipolar cycloaddition of nitrile oxides or silyl nitronates to substituted alkenes.[1] Recently we have reported the syntheses of 3,4-disubstituted-2-isoxazoline-5,5-diylbisphosphonates by the reactions of tetraethyl methylenebisphosphonate with α-nitroalkenes followed by the addition of trimethylchlorosilane.[2] Herein we wish to report our successful trials on the extention of this synthetic route leading to 2-isoxazoline derivatives based on the reaction of α-nitroalkene and compounds with an active methylene group. This is a novel and general method for the synthesis of various 2-isoxazoline derivatives having two electron-withdrawing substituents on position 5 of the heterocycles.

RESULTS AND DISCUSSION

As one of the most important versatile reagents in organic synthesis, α-nitroalkenes can be conveniently prepared by the condensation of aromatic aldehydes with nitroalkanes in an one-pot procedure[3] or by dehydration of the appropriate β-nitroalcohols using phthalic anhydride[4] or methane sulfonyl chloride[5] as the dehydrating agent. Additions of α-nitroalkenes to various nucleophiles gave func-

tionalized nitroalkanes, which can be converted to the corresponding compounds bearing a hydroxyamino or an amino group by subsequent reduction[6] or give various useful polyfunctionalized compounds by additional Michael condensation to electron-deficient alkenes or by the Henry reaction with aldehydes.[7] Recently Tamura reported the synthesis of 1-cyanocyclopropylcarboxylate derivatives by the reaction of α-cyanoacetate with α-nitroalkenes.[8] This result attracted our interest since similar compounds such as cyclopropane-1,1-dicarboxylic acid or cyclopropane-1,1-diphosphonic acid exhibited exciting potentials in medicinal applications.[9-11] Therefore we carried out the reaction of compounds **1a–1k** with 2-nitro-1-phenylpropene (**2**) (meaning of **a–k** see Table I).

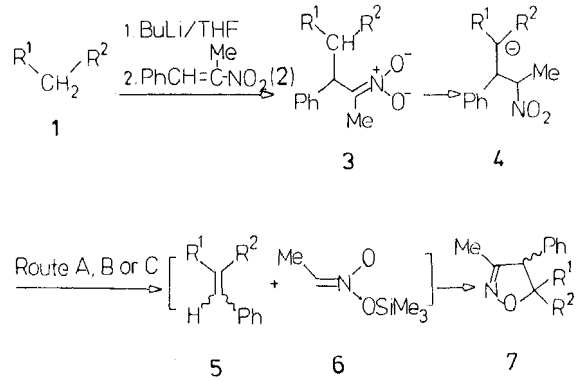
As shown in Scheme I, compounds **1a–1k** reacted with **2** in the presence of an equivalent of BuLi as the base to give anion **3**, which rearranged to the more stable anion **4**. Quite contrary to Tamura's result, no cyclopropane derivatives were detected even under prolonged reaction at room temperature for 2–3 days. This

TABLE I

2-Isoxazolines **7** synthesized

Entry	R^1	R^2	Rea. Time (h)	Yield (%)*
a	$P(O)(OEt)_2$	$P(O)(OEt)_2$	40	92
b	$P(O)(OEt)_2$	COOMe	60	82
c	COOEt	COOEt	60	76
d	CN	COOEt	48	68
e	COMe	COOEt	48	60
f	COMe	COMe	50	73
g	SO_2Ph	COOEt	60	64
h	SO_2Me	$P(O)(OEt)_2$	72	83
i	CN	SO_2Me	60	65
j	CN	CN	40	66
k	CN	$P(O)(OEt)_2$	40	86

* Isolated yield based on **1**.

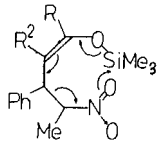


Route A: $R^1=R^2=P(O)(OEt)_2$, $ClSiMe_3$.
Route B: $R^1=COR$ or SO_2R, $ClSiMe_3/i\text{-}Pr_2NH$.
Route C: $R^1=CN$, $ClSiMe_3/i\text{-}Pr_2NH$

SCHEME I

result might be due to the poor leaving ability of the nitro group. On the other hand, an equilibrium between **4a** and alkene **5a** was observed in the reaction of **1a**. Since the anion of **1a** showed inertness toward trimethylchlorosilane,[12] we observed that with the addition of this silylating agent to the reaction solution, **5a** and trimethylsilyl nitronate **6** were formed. By further regioselective 1,3-dipolar cycloaddition of **5a** to **6**, 2-isoxazoline **7a** was isolated in high yield (route A in Scheme I). This caused us to investigate the reaction of **4b–4k** with trimethylchlorosilane. As for **4b–4i** bearing a carbonyl or sulfonyl group, silylation should occur at the oxygen atom of the carbony or sulfonyl group and the corresponding intermediate **8** or **9** would be produced. By quenching with an acid, only the normal Michael addition product was isolated in the case of **1b** or **1e** as the typical examples. When we added to the intermediate **8** or **9**, however, a catalytic amount of base such as triethylamine or diisopropylamine, the corresponding compound **7** was then isolated in good yield after stirring at room temperature for about 2 days. This result indicated that the intermediates **8** or **9** underwent base catalyzed rearrangement in which the trimethylsilyl group was transferred to the oxygen atom of the nitro group via a transition state involving an eight-membered ring and an alkene **5** and silyl nitronate **6** were produced. Further regioselective 1,3-dipolar cycloaddition of **5** and **6** gave the corresponding 2-isoxazoline **7** (route B, Scheme I). Compounds **5** and **7** could be both isolated if we quenched the reaction with an acid before cycloaddition was complete. This was the additional evidence supporting the proposed reaction mechanism. The rearrangement also indicated that the O—Si bond in the silyl nitronate might be more stable than that in **8** or **9**, and this difference serves as the driving force in the rearrangement.

As for anion **4j** and **4k** bearing a cyano group, silylation should occur at the nitrogen atom of the cyano group to give the intermediate **10**. Since the bond energy of O—Si is much higher than that of N—Si bond, transfer of the trimethylsilyl group from the nitrogen atom to the oxygen atom of the nitro group is much easier and the corresponding alkene **5** and **6** were also formed via the rearrangement. Further reaction between **5** and **6** also gave the 2-isoxazoline **7j** and **7k**, respectively (route C, Scheme I).



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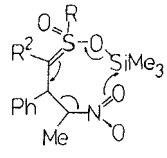

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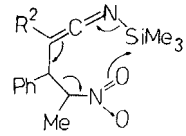

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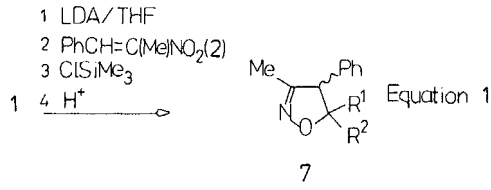
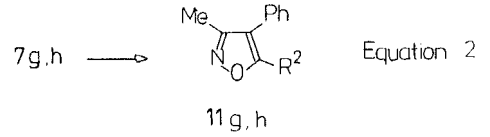
Based on the above discussion, Michael additions of compounds **1** to α-nitroalkene **2** in the presence of an equivalent of LDA as the base followed by the introduction of trimethylchlorosilane led to an one-pot synthesis of 2-isoxazoline derivatives **7**. This reaction provided a novel and convenient synthesis of 2-isoxazolines. A series of these novel derivatives of 2-isoxazolines thus synthesized are summarized in Table I. These compounds may possess important medicinal potential. For example, compound **7a** was reported to be useful as an antiarthritic agent and as a calcium metabolism regulator.[13]



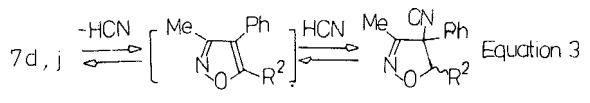
7

It should be noted that in this reaction, diisopropylamine played two important roles—to promote the rearrangement of intermediates **8**, **9** and **10**, and to stabilize the trimethylsilyl nitronate **6** formed in the rearrangement.[14]

It should be also noted that, when R^1 and R^2 are not identical, compounds **7** are obtained as the mixture of two stereoisomers which could not be separated by column chromatography on silica. In some cases, however, the ratio of the stereoisomers could be evaluated by the relative intensities of the proton chemical shifts of the 3-methyl group. For example, the ^1H NMR spectrum of **7b** showed two singlets at 2.18 ppm and 1.80 ppm with a 1:1 ratio, indicating that the two isomers were present in equal amounts. The ^{31}P NMR spectrum was in agreement with this conclusion. On the other hand, the chemical shift of the 3-methyl group was also strongly affected by the 4-phenyl ring. This influence made the situation more complicated and the problem needs further investigation.

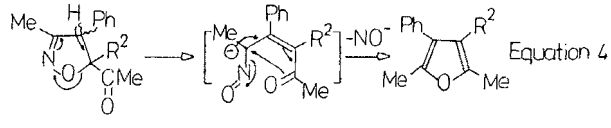


11 g, h



12 d, j

The chemical behaviours of compounds **7** are very interesting. Deliberate addition of base induced decomposition of **7g** and **7h** and gave the corresponding isoxazoles **11g** and **11h**, respectively, by the elimination of the sulfonyl group. (Equation 2) Base catalyzed reaction of **7d** and **7j** eliminated HCN, which was then added to the isoxazoles to give compounds **12d** and **12j**, respectively. The reaction was actually an equilibrium between **7** and **12**, and both of them were isolated (Equation 3). When to **7e** and **7f** a catalytic amount of base was added, the color of the solution turned purple and the furan derivatives **13e** and **13f** were isolated quantitatively. The rearrangement took place probably through the mechanism shown in Equation 4 with the elimination of HNO. Sometimes **13e** or **13f**



7 e, f

13 e, f

could also be isolated during the purification of **7e** or **f** by column chromatography on silica, indicating that acid catalysis of **7e** or **7f** might also lead to the corresponding **13**. All the above results showed the high acidity of the proton on position-4 of compounds **7**.

In conclusion, condensations of various compounds bearing an active methylene group with α-nitroalkenes followed by the addition of trimethylchlorosilane provided a facile synthesis of 2-isoxazolines.

EXPERIMENTAL

Infrared spectra were obtained on an IR-440 infrared spectrometer. ^{1}H NMR spectra were recorded on a XL-200 spectrometer. ^{31}P and ^{13}C NMR were taken with broad band decoupling on a FX-90Q spectrometer using TMS as the internal reference and 85% phosphoric acid as the external standard for ^{31}P NMR. Mass spectra were recorded on a Finnigan 4021 mass spectrometer. Butyllithium (2.5 M solution in hexanes) was purchased from Aldrich Chemical Co. Other reagents were obtained from local commercial source (Shanghai Chemical Co.). 2-Nitro-1-phenylpropene (**2**) was prepared according to the literature.[3] Diisopropylamine was treated with CaH_2 and distilled under nitrogen. Trimethylchlorosilane was distilled prior to use.

Diethyl 5-methoxycarbonyl-3-methyl-4-phenyl-2-isoxazoline-5-ylphosphonate (**7b**). *General Procedure.* Butyllithium (2.0 mL, 5 mmol, 2.5 M solution in hexane) was added to diisopropylamine (0.8 mL, 5.5 mmol) in dry, freshly distilled THF (25 mL) at −20°C and the solution was stirred for 5 min under nitrogen in a 100 mL 3-necked flask fitted with a drying tube and a rubber septum. The solution was cooled to −70°C and methyl diethoxyphosphonoacetate (**1b**, 1.05 g, 5 mmol) was added dropwise. After the complete addition, the solution was stirred for 30 min and 2-methyl-1-phenylpropene (**2**, 0.82 g, 5.25 mmol) was added. The reaction temperature was allowed to warm up to r.t. and the solution stirred for an additional 5 h. The solution was cooled to −40°C and trimethylchlorosilane (0.70 mL, 5.5 mmol) was added. The temperature was then allowed to warm up to r.t. again and the solution was stirred for 60 h (Table I). The resulting mixture was concentrated under vacuum and the residue was poured into water. Hydrochloric acid (1N) was added to the solution until the pH was slightly acidic. The mixture was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic layers dried with anhydrous sodium sulfate, concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica with ethyl acetate/acetone (5/1, v/v) as eluent to give the pure product **7b** as a colorless oil. Yield: 1.45 g (82%). IR (film) ν: 3050, 1740, 1450, 1240, 1025, 960, 730, 700. ^{1}H NMR ($CDCl_3$) δ: 1.29, 1.32 (2 × 3H, 2t, J = 8, $C\underline{H}_3CH_2O$), 1.80, 2.14 (3H, 2s (1/1), $CH_3C{=}N$), 3.40 (3H, s, CH_3O), 3.72 (1H, m, CH), 4.15 (4H, m, CH_2O), 7.24 (5H, m, C_6H_5). ^{31}P NMR ($CDCl_3$) 21.51, 21.76 (1/1). ^{13}C NMR ($CDCl_3$) δ: 13.28 ($\underline{C}{-}C{=}N$), 16.10, 16.20 ($\underline{C}H_3CH_2O$), 30.39 ($\underline{C}H{-}Ph$), 48.37 (d, J(C—P) = 97, C—P), 51.79, 52.04 (CH_3O), 62.86, 62.90 (CH_2O), 127.15, 128.4, 128.6, 128.8, 129.7, 138.1, 138.8 (Ph), 156.6 (C=N), 168.3 (C=O). Anal. Calcd. for $C_{16}H_{22}NO_6P$: C, 54.09; H, 6.24; N, 3.94. Found: C, 54.20; H, 6.07, N, 3.88.

Tetraethyl 3-methyl-4-phenyl-2-isoxazoline-5,5-diylbisphosphonate (**7a**). The spectra were identical with those reported in the literature.[2]

Diethyl 3-methyl-4-phenyl-2-isoxazoline-5,5-dicarboxylate (**7c**). Eluent: petroether/acetone (4/l, v/v). Colorless oil. IR(film) ν: 1750, 1735, 1575, 1450, 1290, 1030, 700. ^{1}H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 8, $C\underline{H}_3CH_2O$), 1.24, 1.28 (3H, 2t, J = 8, $C\underline{H}_3CH_2O$), 1.97, 2.12, 2.14 (3H, 3s, $CH_3C{=}N$), 3.85 (1H, q, J = 7.2, CHPh), 4.20 (4H, m, CH_2O), 7.26 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 13.62, 13.92 ($\underline{C}H_3CH_2O$), 19.03 ($CH_3C{=}N$), 28.84 (CH), 57.90 ($\underline{C}{-}COO$), 61.58, 61.81 (CH_2O), 128.2, 128.9, 129.2, 133.5, 133.9 (Ph), 167.0 (C=N), 167.7, 168.2 (COO). Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.95; H, 6.27; N, 4.59. Found: C, 63.22; H, 6.12; N, 4.39.

Ethyl 5-cyano-3-methyl-4-phenyl-2-isoxazoline-5-carboxylate (**7d**). Eluent: petroether/ethyl acetate (5/1, v/v). Colorless oil. IR(film) ν: 3040, 2200, 1750, 1555, 735, 700. ^{1}H NMR ($CDCl_3$) δ: 1.07 (3H, t, J = 8, $C\underline{H}_3CH_2O$), 1.59, 1.73 (3H, 2d(1/1), J = 5, $CH_3C{=}N$), 3.86 (1H, m, CH), 4.15 (2H, q, J = 8, CH_2O), 7.25 (3H, m, C_6H_5), 7.45 (2H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 13.56, 13.76 ($\underline{C}H_3C{=}N$), 17.30, 17.82 ($\underline{C}H_3CH_2O$), 40.05, 41.01 (CH), 63.22, 64.35 (CH_2O), 84.53 ($\underline{C}{-}CN$), 113.5, 114.0 (CN), 128.7, 128.8, 129.2, 129.6, 133.1 (Ph), 157.4 (C=N), 164.3 (C=O). Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.03; H, 5.34; N, 10.64.

Ethyl 5-acetyl-3-methyl-4-phenyl-2-isoxazoline-5-carboxylate (**7e**). Eluent: petroether/ethyl acetate (5/1, v/v). Yellowish oil. IR(film) ν: 3030, 1735, 1715, 1560, 735, 700. ^{1}H NMR ($CDCl_3$) δ: 1.00 (3H, t,

J = 7, CH_3CH_2O), 1.70 (3H, m, $CH_3C{=}N$), 2.10 (3H, m, $CH_3C{=}O$), 3.66 (1H, m, CH), 4.18 (2H, q, J = 7), 7.25 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 11.18 ($CH_3C{=}N$), 13.48, 14.06 (CH_3CH_2O), 29.11 ($CH_3C{=}O$), 51.50 (CH), 59.01 (CH_2O), 85.50 (C—C=O), 127.6, 128.4, 128.8, 128.9, 129.2, 129.3, 133.8, 133.9 (Ph), 156.7 (C=N), 165.8 (COO), 200.7 (C=O). Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.23; N, 5.09. Found: C, 65.16; H, 6.47; N, 5.07.

5,5-Diacetyl-3-methyl-4-phenyl-2-isoxazoline (**7f**). Eluent: petroether/acetone (3.5/1, v/v). Yellow solid, m.p. 60–62°C. IR (KBr) ν: 1730, 1710, 1600, 1550, 910, 730. ^1H NMR ($CDCl_3$) δ: 1.26 (3H, 3d, J = 8, $CH_3C{=}N$), 1.48, 1.70, 2.20, 2.40, 2.67 (6H, 5s, $2CH_3CO$), 3.53 (1H, q, J = 7, CH), 7.25 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 15.46 ($CH_3C{=}N$), 29.11, 31.60 ($CH_3C{=}O$), 53.65 (CH), 98.80 (C—C=O), 126.9, 127.5, 128.2, 128.7, 129.2 (Ph), 156.7 (C=N), 212.8, 212.9 (C=O). Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.17; N, 5.71. Found: C, 68.78; H, 6.23; N, 5.52.

Ethyl 5-benzenesulfonyl-3-methyl-4-phenyl-2-isoxazoline-5-carboxylate (**7g**). Eluent: petroether/acetone (2/1, v/v). Yellowish oil. IR(film) ν: 3050, 1740, 1555, 1450, 700. ^1H NMR ($CDCl_3$) δ: 0.89, 1.26, 1.33 (3 × 1H, 3t, J = 6, CH_3CH_2O), 1.77, 2.17 (3H, 2s(3/1), $CH_3C{=}N$), 3.82 (1H, q, J = 8, CH), 4.18 (2H, m, CH_2O), 7.20–7.70 (10H, br, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 10.62, 11.58 ($CH_3C{=}N$), 13.48, 13.87 (CH_3CH_2O), 29.24, 30.90 (CH), 61.67, 62.29 (CH_2O), 72.60, 73.79 (C—COO), 127.9, 128.0, 128.2, 128.3, 128.6, 128.8, 128.9, 129.1, 129.4, 129.6, 130.3, 130.1, 133.3, 134.0, 136.2 (Ph), 155.3, 157.5 (C=N), 164.5, 165.5 (C=O). Anal. Calcd. for $C_{19}H_{19}NO_5S$: C, 61.12; H, 5.13; N, 3.75. Found: C, 60.86; H, 5.43; N, 3.56.

Diethyl 5-methanesulfonyl-3-methyl-4-phenyl-2-isoxazoline-5-ylphosphonate (**7h**). Eluent: petroether/acetone (1.5/1, v/v). Yellowish oil. IR(film) ν: 1720, 1560, 1450, 1260, 1020, 980. ^1H NMR ($CDCl_3$) δ: 1.35 (9H, m, CH_3SO_2 + CH_3CH_2O), 1.60–2.40 (3H, m, $CH_3C{=}N$), 3.80 (1H, m, CH), 4.20 (4H, m, CH_2O), 7.37 (5H, m, C_6H_5). ^{31}P NMR ($CDCl_3$) δ: 21.64. ^{13}C NMR ($CDCl_3$) δ: 11.21, 11.56 ($CH_3C{=}N$), 16.06, 16.85 (CH_3CH_2O), 22.11, 22.35 (CH_3SO_2), 30.10, 30.89 (CH), 49.20 (d, J(C—P) = 95, C—P), 62.50, 62.80 (CH_2O), 127.8, 127.9, 128.2, 128.4, 128.7, 129.0, 129.9 (Ph), 156.4, 156.7 (C=N). Anal. Calcd. for $C_{15}H_{22}NO_6PS$: C, 48.00; H, 5.91; N, 3.73. Found: C, 48.16; H, 6.20; N, 3.78.

5-Cyano-5-methanesulfonyl-3-methyl-4-phenyl-2-isoxazoline (**7i**). Eluent: petroether/acetone (3/1, v/v). Yellowish oil. IR(film) ν: 2200, 1560, 1450, 730. ^1H NMR ($CDCl_3$) δ: 1.18 (3H, t, J = 7, CH_3SO_2), 1.22 (3H, d, J = 7.2, $CH_3C{=}N$), 3.44 (1H, q, J = 7.2, CH), 7.28 (5H, m, C_5H_5). ^{13}C NMR ($CDCl_3$) δ: 15.25 ($CH_3C{=}N$), 22.21 (CH_3S), 29.70 (CH), 65.86 (C—CN), 118.8 (CN), 127.8, 128.1, 128.4, 128.8, 129.0, 129.9 (Ph), 156.0 (C=N). Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60. Found: C, 54.67; H, 4.86; N, 10.33.

5,5-Dicyano-3-methyl-4-phenyl-2-isoxazoline (**7j**). Eluent: petroether/acetone (3/1, v/v). Yellowish oil. IR(film) ν: 3020, 2200, 1550, 740, 700. ^1H NMR ($CDCl_3$) δ: 1.18, 1.30, 1.43 (3 × 1H, 3d, J = 8, CH_3), 3.53 (1H, q, J = 8, CH), 7.40 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 15.23 ($CH_3C{=}N$), 29.69 (CH), 65.85 (C—CN), 127.1, 128.2 (CN), 128.5, 128.8, 129.1, 119.4, 130.0, 133.1 (Ph), 157.2 (C=N). Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.35; H, 4.41; N, 19.76.

Diethyl 5-cyano-3-methyl-4-phenyl-2-isoxazoline-5-ylphosphonate (**7k**). Eluent: petroether/acetone (2/1, v/v). Yellowish oil. IR(film) ν: 2200, 1555, 1450, 1260, 1025, 970, 700. ^1H NMR ($CDCl_3$) δ: 1.27, 1.34 (2 × 3H, 2t, J = 7, CH_3CH_2O), 2.18 (3H, s, $CH_3C{=}N$), 3.50 (1H, m, CH), 4.16 (4H, m, CH_2O), 7.20 (5H, m, C_6H_5). ^{31}P NMR ($CDCl_3$) δ: 21.70. ^{13}C NMR ($CDCl_3$) δ: 10.68, 11.64 ($CH_3C{=}N$), 16.19, 16.73 (CH_3CH_2O), 29.27, 30.92 (CH), 61.63 (CH_2O), 65.01 (d, J(C—P) = 100, C—P), 115.0 (CN), 128.4, 129.0, 129.2, 129.8, 130.7, (Ph), 158.5 (C=N). Anal. Calcd. for $C_{15}H_{19}N_2O_4P$: C, 55.90; H, 5.94, N. 8.69. Found: C, 55.72; H, 5.97; N, 8.98.

Ethyl 3-methyl-4-phenylisoxazole-5-carboxylate (**11g**). Typical Procedure: Triethylamine (0.16 mL, 1.1 mmol) was added to **7g** (0.373g, 1 mmol) in THF (10 mL) and the solution stirred for 2 h at r.t. The resulting mixture was concentrated in vacuo and the residue was purified by column chromatography on silica using petroether/acetone (2/1, v/v) as eluent to give pure **11g** as a yellowish oil. Yield: 0.20 g (90%). IR(film) ν: 3050, 1680, 1550, 960. ^1H NMR ($CDCl_3$) δ: 1.15 (3H, t, J = 8, CH_3CH_2O), 1.90 (3H, s, $CH_3C{=}N$), 4.20 (2H, q, J = 8, CH_2O), 7.25 (5H, m, C_6H_5). Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.67; N, 6.06. Found: C, 67.34; H, 5.85; N, 5.89.

Diethyl 3-methyl-4-phenylisoxazole-5-ylphosphonate (**11h**). Eluent: petroether/acetone (1.5/1, v/v). Yellowish oil. IR(film) ν: 1540, 1250, 1020, 970, 700. ^1H NMR ($CDCl_3$) δ: 1.30 (6H, t, J = 7, CH_3CH_2O), 1.85 (3H, s, $CH_3C{=}N$), 4.18 (4H, m, CH_2O), 7.28 (5H, m, C_6H_5). ^{13}P NMR ($CDCl_3$) δ: 10.69. Anal. Calcd. for $C_{14}H_{18}NO_4P$: C, 56.95; H, 6.15; N, 4.75. Found: C, 57.00; H, 6.23; N, 4.57.

Ethyl 4-cyano-3-methyl-4-phenyl-2-isoxazoline-5-carboxylate (**12d**). *Typical procedure*: To **7d** (0.26 g, 1 mmol) in THF (10 mL) was added 5 drops of triethylamine and the solution was stirred for 1 h at

r.t. The resulting mixture was concentrated in vacuo to leave the crude product as a mixture of **7d** and **12d**. Separation by column chromatography on silica using petroether/ethyl acetate (5/1, v/v) as eluent gave **12d** as a colorless oil. Yield: 0.13 g (50%). IR(film) ν: 2200, 1730, 1560, 730. ^{1}H NMR ($CDCl_3$) δ: 1.38 (3H, t, J = 6, CH_3CH_2O), 1.92, 2.04 (3H, 2s (1/4), $CH_3C{=}N$), 4.38 (2H, q, J = 6, CH_2O), 5.26 (1H, m, CH), 7.25 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 11.36 (CH_3—C=N), 17.50 (CH_3CH_2O), 48.50, 49.31 (C—CN), 63.22, 65.51 (CH_2O), 83.42, 83.72 (CH—COO), 114.8, 115.0 (CN), 128.0, 128.2, 128.8, 129.2, 129.6, 131.4 (Ph), 157.5, (C=N), 163.8 (C=O). Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.84; H, 5.76; N, 10.77.

4,5-Dicyano-3-methyl-4-phenyl-2-isoxazoline (**12j**). Eluent: petroether/acetone (3/1, v/v). Yield: 30%. Yellowish oil. IR(film) ν: 2200, 1550, 740, 700. ^{1}H NMR ($CDCl_3$) δ: 1.25–1.70 (3H, m, CH_3), 5.0 (1H, s, CH), 7.25 (5H, m, C_6H_5). Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.05; H, 4.44; H, 20.11.

Ethyl 2,5-dimethyl-4-phenylfuran-3-carboxylate (**13e**). *Typical procedure*: Triethylamine (0.14 mL, 1 mmol) was added to **7e** (0.275 g, 1 mmol) in THF (10 mL) and the solution was stirred for 30 min at r.t. The resulting mixture was concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica using petroether/ethyl acetate (5/1, v/v) as eluent to give pure **13e** as a yellowish oil. Yield: 0.24 g (100%). IR(film) ν: 3030, 1680, 1260, 740. ^{1}H NMR ($CDCl_3$) δ: 1.02 (3H, t, J = 7.2, CH_3CH_2O), 2.09 (3H, s, CH_3), 2.49 (3H, s, CH_3), 4.04 (2H, q, J = 7.2, CH_2O), 7.21 (5H, m, C_6H_5). ^{13}C NMR ($CDCl_3$) δ: 11.59, 13.85, 14.87, 59.50, 111.3, 123.3, 124.6, 126.6, 128.3, 131.8, 135.0, 138.3, 166.5. EIMS: m/e 244 (M^+), 243, 214, 198, 168, 154, 128. Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.76; H, 6.60. Found: C, 73.89; H, 6.68.

3-Acetyl-2,5-dimethyl-4-phenylfuran (**13f**). Eluent: petroether/acetone (3.5/1, v/v). Yellowish oil. IR(film) ν: 1695, 1640, 1550, 900, 730, 700. ^{1}H NMR ($CDCl_3$) δ: 1.20 (3H, s, $CH_3C{=}N$), 1.85, 2.05, 2.14, 2.33, 2.46, 2.60 (6H, 6s, 2,5-CH_3), 7.30 (5H, m, C_6H_5). EIMS: m/e 214 (M^+), 199, 91, 77. ^{13}C NMR ($CDCl_3$) δ: 10.92, 13.98, 29.11, 123.3, 126.4, 128.0, 128.4, 128.6, 129.3, 130.3, 133.4, 210.8. Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found, C, 78.28; H, 6.77.

ACKNOWLEDGEMENT

This project was supported by the National Natural Science Foundation of China.

REFERENCES

1. K. B. G. Torssell, Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis, VCH Publishers, Inc., New York, 1988.
2. C. Yuan and C. Li, *Phosphorus, Sulfur and Silicon*, **69**, 75 (1992).
3. C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, **18**, 1 (1953).
4. G. D. Buckley and C. W. Scaife, *J. Chem. Soc.*, 1471 (1947).
5. J. Melton and J. E. McMurry, *J. Org. Chem.*, **40**, 2138 (1975).
6. For example, see: M. Miyashita, B. Z. E. Awen and A. Yoshikoshi, *Tetrahedron*, **46**, 7569 (1990).
7. G. H. Posner and R. D. Crouch, *Tetrahedron*, **46**, 7509 (1990).
8. R. Tamura, A. Kamimura and N. Ono, *Synthesis*, 423 (1991), and references cited therein.
9. Y. Dong, J. Feng, Z. Huang, W. Tang, A. Dai, Z. Zhou and K. Yu, *Science in China, Series B*, **53**, 1297 (1990).
10. D. W. Hutchinson and D. M. Thornton, *Synthesis*, 135 (1990).
11. C. Yuan, C. Li and Y. Ding, *Synthesis*, 854 (1991).
12. C. Yuan and C. Li, unpublished results.
13. C. J. Dunn and R. A. Nugent, PCT Int. Appl. WO 9012, 017, 18 Oct. 1990. US Appl. 332, 618, 03 Apr. 1989. Chem. Abstracts 104:122364q.
14. K. Torssell and O. Zeuthen, *Acta. Chem. Scand. Ser. B.*, **B32(2)**, 118 (1978).