Preparation, Alkylation, and Olefination Reaction of 5-Phosphonomethyl-3-methylisoxazole

Shi Yong Lee, Bum Sung Lee, Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1, Kusong-dong, Yusong-gu, Taejon, 305-701, Korea
Fax +82(42)8692810; E-mail: dyoh@sorak.kaist.ac.kr

Received 19 July 1999

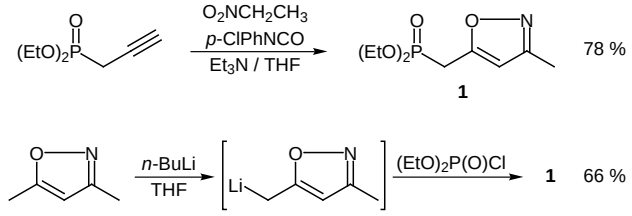
Abstract: 5-Diethylphosphonomethyl-3-methylisoxazole (**1**) was synthesized by two methods, 1) cycloaddition of nitrile oxide and 2) nucleophilic reaction of the 3,5-dimethylisoxazole anion. This phosphonoisoxazole **1** was alkylated and olefinated by reaction of its anion with alkyl halides and aldehydes, respectively.

Key words: phosphonates, isoxazoles, alkenations of phosphonates, alkylations, cycloadditions of nitrile oxides

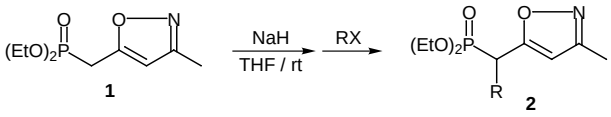
Isoxazoles have served as versatile building blocks through their ability to function as masked forms of various functionalities such as 1,3-diketones, α,β-unsaturated ketones, β-amino ketones, and β-keto nitriles.[1] The phosphonate functional group is usually thought to be stable under the various transformations of isoxazoles including their reductive N-O bond cleavage. Therefore, isoxazoles accompanying the phosphonate group are very useful heterocycles, as they can be manipulated to provide access to variously functionalized phosphonates. In addition, it is possible for phosphonomethylisoxazoles to undergo olefination under Wadsworth-Emmons conditions. This olefination reaction of phosphonates is generally restricted to phosphonates bearing an α-substituent that can stabilize a carbanion.[2] A variety of functional groups are known as α-stabilizing substituents but isoxazole has hardly been tried yet in this manner.[3] There have been a limited number of reports about phosphonate-involving isoxazoles, wherein, 5-phosphonomethylisoxazole was prepared by Arbuzov reaction,[3] and 3-phosphonomethylisoxazoles by cycloaddition of α-phosphonoacetonitrile oxide[4] or dehydrogenation of 2-isoxazolines.[5] We herein report the synthesis of 5-phosphonomethyl-3-methylisoxazole, its alkylation and olefination.

We have synthesized 5-diethylphosphonomethyl-3-methylisoxazole (**1**) by two different pathways. Firstly, 1,3-dipolar cycloaddition of acetonitrile oxide, generated in situ by Mukaiyama's procedure,[6] to diethylpropargylphosphonate was carried out to give the isoxazole ring **1** in 78% yield (Scheme 1). On the other hand, **1** could be also synthesized from 3,5-dimethylisoxazole. The 5-methyl anion of 3,5-dimethylisoxazole,[7] generated by *n*-BuLi, underwent nucleophilic reaction toward diethyl chlorophosphate affording **1** in a lower yield of 66%.

Alkylation increases the variety of phosphonoisoxazoles. On treatment of **1** with most bases, deprotonation occurs at the 5-methyl carbon on account of the anion-stabilizing ability of the phosphonate substituent. Treating **1** with sodium hydride in THF at room temperature, followed by addition of alkyl halides, provided the alkylated products **2** (Scheme 2, Table). The employment of allyl and phenylselenenyl bromide yielded a small amount of dialkylated products as side products,[8] leading to somewhat low yields (entry 2 and 4).



Scheme 1



Scheme 2

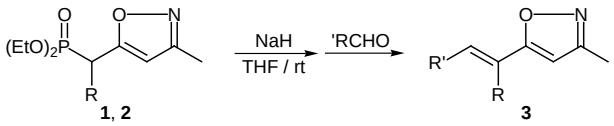
We then performed the olefination reaction of aldehydes with the phosphonoisoxazoles. The sodium anions of **1** and **2** were allowed to react with aldehydes in THF at room temperature to afford the olefinated isoxazoles **3**

Table Alkylation of **1** with Alkyl Halides and Olefination of Aldehydes with **1** or **2**

Entry	Substrate	Electrophile	Product	Yield[a] (%)
1	**1**	MeI	**2a**	93
2	**1**	CH_2=$CHCH_2Br$	**2b**	72
3	**1**	$PhCH_2Br$	**2c**	80
4	**1**	PhSeBr	**2d**	56
5	**1**	PhCHO	**3a**[b]	83
6	**1**	2-furaldehyde	**3b**[b]	90
7	**1**	*n*-PrCHO	**3c**[b]	63
8	**2a**	PhCHO	**3d**[b]	81
9	**2b**	PhCHO	**3e**[b]	77
10	**2c**	4-ClPhCHO	**3f-*E*** / **3f-*Z***	53 / 33

[a]Yield of isolated product after chromatography.
[b](*E*)-Olefin product only, identified by NOE experiment and ^{1}H NMR analysis.

(Scheme 3). For all cases inclusive of aliphatic and aromatic aldehydes as well as substituted and unsubstituted phosphonoisoxazoles, the Wadsworth-Emmons reaction proved successful (Table). Only when butyraldehyde was employed (entry 7), was the yield relatively low, which seems to be due to side reactions of the acidic α-proton of the aliphatic aldehyde. Most olefin products were typically in a pronounced *E* geometry. Exceptionally, for **3f** a significant amount of (*Z*)-olefin was obtained along with the *E*-isomer (*E*:*Z*, 53:33), which is attributed to a steric interaction of the bulky benzyl group. The geometries were identified by NOE experiments and ^{1}H NMR analysis.



Scheme 3

In summary, we have provided two synthetic approaches to 5-diethylphosphonomethyl-3-methylisoxazole, which can be a precursor to variously functionalized phosphonates. The phosphonoisoxazole was diversified by its alkylation and employed as an olefinating agent.

Mps were determined in open capillary tubes using a Buchi 535 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer in $CDCl_3$ using either TMS or residual $CHCl_3$ as an internal standard. HRMS was measured on a V.G. Autostec Ultima mass spectrometer.

5-Diethylphosphonomethyl-3-methylisoxazole (1)

a) To a stirred soln of diethyl propargylphosphonate (1.20 g, 6.0 mmol), nitroethane (0.56 g, 7.2 mmol) and 4-chlorophenylisocyanate (1.88 g, 12.0 mmol) in anhyd THF (20 mL) under N_2 at r.t., was added 20 drops of Et_3N. After stirring for 15 h, Et_2O (200 mL) was poured into the mixture and the resulting solution was washed with H_2O (3 x 5 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column (EtOAc only) to give pure **1** (1.09 g, 78%) as a colorless oil.

b) To a stirred soln of 1,3-dimethylisoxazole (0.40 g, 4.0 mmol) in anhyd THF (15 mL) under N_2 at –78°C, was added BuLi (2.63 mL of a 1.6 M soln in hexanes, 4.2 mmol) dropwise. After stirring for 1 h diethyl chlorophosphate (0.66 mL, 4.4 mmol) was added. The reaction mixture was allowed to warm slowly to r.t. and stirred for 2 h. An aq NH_4Cl soln (2 mL) was added and the resulting solution extracted with Et_2O (3 x 50 mL). The organic extracts were washed with H_2O (2 x 5 mL), dried ($MgSO_4$), and evaporated. The residue was purified by chromatography as described in a) to give **1** (0.62 g, 66%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 6H, *J* = 7.1 Hz, 2 x OCH_2CH_3), 2.22 (s, 3H, CH_3), 3.24 (d, 2H, *J* = 21.2 Hz, CH_2), 4.00-4.11 (m, 4H, 2 x OCH_2CH_3), 6.04 (d, 1H, *J* = 3.0 Hz, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 16.2 (d, *J* = 5.9 Hz), 25.4 (d, *J* = 141.8 Hz), 62.6 (d, *J* = 6.5 Hz), 104.0 (d, *J* = 5.5 Hz), 160.1 (d, *J* = 2.9 Hz), 163.3 (d, *J* = 7.1 Hz).

Alkylation of 1 to 2; General Procedure

To a suspension of NaH (0.040 g, 60%, 1.0 mmol) in anhyd THF (3 mL) under N_2 at r.t. was added **1** (0.233 g, 1.0 mmol) in anhyd THF (3 mL) slowly. After stirring until hydrogen evolution had ceased and the solution was homogeneous (ca. 1 h), alkyl halide (2.0 mmol) in anhyd THF (2 mL) was added. After stirring for 5 h, aq NH_4Cl (2 mL) was added and the resulting solution extracted with Et_2O (3 x 30 mL). The organic extracts were washed with H_2O (2 x 5 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column (EtOAc:hexane, 3:1) to give pure product **2** as a colorless oil.

5-(1-Diethylphosphonoethyl)-3-methylisoxazole (2a)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20-1.28 (m, 6H, 2 x OCH_2CH_3), 1.47-1.55 (m, 3H, $CHCH_3$), 2.21 (s, 3H, CH_3), 3.36 (dq, 1H, *J* = 23.1, 7.4 Hz, $CHCH_3$), 3.96-4.09 (m, 4H,2 x OCH_2CH_3), 5.99-6.01 (m, 1H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 13.4 (d, *J* = 5.4 Hz), 16.3 (d, *J* = 5.9 Hz), 31.6 (d, *J* = 141.5 Hz), 62.5-62.8 (m), 102.9 (d, *J* = 5.3 Hz), 159.8 (d, *J* = 9.9 Hz), 169.0 (d, *J* = 5.9 Hz).

5-(1-Diethylphosphonobut-3-enyl)-3-methylisoxazole (2b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19-1.29 (m, 6H, 2 x OCH_2CH_3), 2.22 (s, 3H,CH_3), 2.56-2.83 (m, 2H, $CHCH_2CH$), 3.35 (ddd, 1H, *J* = 22.7, 10.9, 4.2 Hz, $CHCH_2$), 3.95-4.09 (m, 4H, 2 x OCH_2CH_3), 4.93-5.03 (m, 2H, $CHCH_3$), 5.56-5.70 (m, 1H, $CHCH_2$), 6.01 (d, 1H, *J* = 3.0 Hz, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 16.2 (d, *J* = 5.8 Hz), 24.4, 32.6 (d, *J* = 3.3 Hz), 37.4 (d, *J* = 139.9 Hz), 62.7 (dd, *J* = 13.0, 6.8 Hz), 103.7 (d, *J* = 5.6 Hz), 117.6, 133.9 (d, *J* = 14.9 Hz), 159.9, 167.4 (d, *J* = 6.3 Hz).

5-(1-Diethylphosphono-2-phenylethyl)-3-methylisoxazole (2c)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21-1.29 (m, 6H, 2 x OCH_2CH_3), 2.19 (s, 3H, CH_3), 3.13-3.24 (m, 1H, 1/2 x $CHCH_2C_6H_5$), 3.34-3.44 (m, 1H, 1/2 x $CHCH_2C_6H_5$), 3.60 (ddd, 1H, *J* = 22.7, 11.3, 4.1 Hz, $CHCH_2$), 3.97-4.13 (m, 4H, 2 x OCH_2CH_3), 5.96 (d, 1H, *J* = 3.1 Hz, CH), 7.03-7.20 (m, 5H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 16.3 (d, *J* = 5.7 Hz), 34.3, 39.5 (d, *J* = 138.4 Hz), 62.8 (dd, *J* = 13.6, 6.9 Hz), 104.2 (d, *J* = 5.7 Hz), 126.7, 128.2, 128.4, 137.8 (d, *J* = 14.7 Hz), 159.7, 167.0 (d, *J* = 7.0 Hz).

5-Diethylphosphonophenylselanylmethyl-3-methylisoxazole (2d)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23-1.34 (m, 6H, 2 x OCH_2CH_3), 2.20 (s, 3H, CH_3), 4.03-4.30 (m, 4H, 2 x OCH_2CH_3), 4.43 (d, 1H, *J* = 18.5 Hz, CH), 6.04 (d, 1H, *J* = 2.1 Hz, CH), 7.20-7.36 (m, 3H, 3/5 x C_6H_5), 7.52-7.55 (m, 2H, 2/5 x C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 16.4 (d, *J* = 6.3 Hz), 31.8 (d, *J* = 151.1 Hz), 63.9 (dd, *J* = 24.1, 6.9 Hz), 104.5 (d, *J* = 3.9 Hz), 129.0, 129.2, 135.4, 138.2, 160.1, 166.7.

Olefination of Aldehydes with 1 or 2 to 3; General Procedure

To a suspension of NaH (0.020 g, 60%, 0.50 mmol) in anhyd THF (2 mL) under N_2 at r.t. was slowly added **1** or **2** (0.50 mmol) in anhyd THF (3 mL). After stirring until hydrogen evolution had ceased and the soln was homogeneous (ca. 1 h), the aldehyde (0.60 mmol) was added. Stirring for about 2 h was followed by addition of aq NH_4Cl (1 mL), extraction with CH_2Cl_2 (3 x 20 mL), and drying ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on a silica gel column (EtOAc:hexane, 10:90) to give pure product **3** as a white solid or colorless oil.

(*E*)-3-Methyl-5-(2-phenylethenyl)isoxazole (3a)[9]

Mp 89°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3), 6.08 (s, 1H, CH), 6.90 (d, 1H, *J* = 16.5 Hz, C*H*CH), 7.28 (d, 1H, *J* = 16.5 Hz, CHC*H*), 7.30-7.50 (m, 5H, C_6H_5).

NOE data: 6.90 (6.08, 3 %; 7.28, 0.5 %; 7.47-7.50, 11.0 %)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 102.4, 111.1, 111.9, 112.0, 121.4, 143.4, 151.7, 160.1, 167.8.

(*E*)-5-[2-(2-Furyl)ethenyl]-3-methylisoxazole (3b)
Mp 41°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H, CH_3), 6.03 (s, 1H, CH), 6.42 (dd, 1H, *J* = 3.3, 1.7 Hz, CHC*H*CH), 6.46 (d, 1H, *J* = 3.3 Hz, C*H*CH), 6.78 (d, 1H, *J* = 16.2 Hz, CHCH), 7.03 (d, 1H, *J* = 16.2 Hz, CHC*H*), 7.41 (d, 1H, *J* = 1.7 Hz, CHC*H*).

NOE data: 6.78 (6.03, 3.2 %; 7.03, 0 %; 7.41, 0.1 %).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 102.4, 111.1, 111.9, 112.0, 121.4, 143.4, 151.7, 160.1, 167.8.

(*E*)-3-Methyl-5-pent-1-enylisoxazole (3c)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3H, *J* = 7.4 HzCH_2CH_3), 1.47 (sextet, 2H, *J* = 7.4 Hz, $CH_2CH_2CH_3$), 2.13-2.21 (m, 2H, $CHCH_2CH_2$), 2.24 (s, 3H, CH_3), 5.88 (s, 1H, CH), 6.23 (dt, 1H, *J* = 16.1, 1.4 Hz, C*H*CH), 6.46 (dt, 1H, *J* = 16.1, 7.0 Hz, CHC*H*CH_2).

NOE data: 6.23 (5.88, 2.4 %; 6.46, 0 %).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 13.6, 21.8, 34.9, 100.5, 115.9, 138.2, 159.8, 168.4.

HRMS: *m/z* Calcd for $C_9H_{13}NO$ 151.0997, found 151.0992.

(*E*)-3-Methyl-5-(1-methyl-2-phenylethenyl)isoxazole (3d)
Mp 43°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.10 (s, 1H, CH), 7.24-7.38 (m, 6H, CHC_6H_5).

NOE data: 2.20 (6.10, 6.2 %; 7.36-7.38, 6.7 %).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 15.3, 101.0, 123.8, 127.6, 128.3, 129.4, 130.6, 136.3, 160.1, 171.6.

HRMS: *m/z* Calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0997.

(*E*)-3-Methyl-5-[2-phenyl-1-(prop-2-enyl)ethenyl]isoxazole (3e)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3), 3.32-3.35 (m, 2H, CH_2CH), 5.12-5.19 (m, 2H, CHCH_2), 5.93-6.04 (m, 1H, CH_2CHCH_2), 6.08 (s, 1H, CH), 7.29-7.38 (m, 5H, C_6H_5), 7.44 (s, 1H, CH).

NOE data: 3.32-3.35 (5.93-6.04, 7.1 %; 6.08, 5.6 %; 7.35-7.38, 7.5 %).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 33.1, 101.5, 116.7, 125.5, 128.0, 128.4, 129.0, 132.1, 135.0, 135.9, 160.1, 170.8.

HRMS: *m/z* Calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1154.

(*E*)-5-[1-Benzyl-2-(4-chlorophenyl)ethenyl]-3-methylisoxazole (3f-*E*)
Mp 68-69°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 5.89 (s, 1H, CH), 7.20-7.33 (m, 9H, C_6H_4 and C_6H_5), 7.55 (s, 1H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 34.6, 102.2, 126.2, 126.6, 127.8, 128.7, 128.8, 130.1, 131.4, 134.0, 134.1, 138.2, 160.2, 170.3.

NOE data: 3.97 (5.89, 8.5 %; 7.20-7.33, 22.5 %; 7.55, 1.7 %).

HRMS: *m/z* Calcd for $C_{19}H_{16}ClNO$ 309.0920, found 309.0898.

(*Z*)-5-[1-Benzyl-2-(4-chlorophenyl)ethenyl]-3-methylisoxazole (3f-*Z*)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.17 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 5.64 (s, 1H, CH), 6.60 (s, 1H, CH), 7.05-7.08 (m, 2/5 x C_6H_5), 7.18-7.29 (m, 7H, 3/5 x C_6H_5 and C_6H_4).

NOE data: 3.82 (5.64, 2.1 %; 6.60, 10.0 %; 7.20-7.29, 10.1 %).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 42.4, 104.2, 126.7, 128.5, 128.6, 128.8, 128.9, 129.9, 132.7, 133.5, 134.9, 138.1, 159.6, 168.5.

References

(1) a) Lang, S. A.; Lin, Y.-i In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: Oxford, 1984; p 12.
b) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857.
c) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988.
d) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Thieme: Stuttgart, 1995.

(2) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(3) Crimmin, M. J.; O'Hanlon, P. J.; Rogers, N. H.; Walker, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2047.

(4) Tsuge, O.; Kanemasa, S.; Suga, H. *Chem. Lett.* **1987**, 323.

(5) Tsuge, O.; Kanemasa, S.; Suga, H.; Nakagawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2463.

(6) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(7) Kashima, C.; Yamamoto, Y.; Tsuda, Y. *Heterocycles* **1977**, *6*, 805.

(8) The diallylated side product has both allyl groups at the 5-methyl group of **1**. The use of phenylselenenyl bromide gave two kinds of diphenylselenenylated side products. One of which involved both of the phenylselenenyl groups at the 5-methyl position, and the other having one phenylselenenyl group at the 5-methyl position and one at the 4-position of the isoxazole ring.

(9) Flynn, D. L.; Belliotti, T. R.; Boctor, A. M.; Connor, D. T.; Kostlan, C. R.; Nies, D. E.; Ortwine, D. F.; Schrier, D. J.; Sircar, J. C. *J. Med. Chem.* **1991**, *34*, 518.

Article Identifier:
1437-210X,E;1999,0,12,2027,2029,ftx,en;F04499SS.pdf