

Synthesis of 2-Substituted-1,3-Oxazole-4-Carboxaldehyde via 1,3-Dipolar Cycloaddition

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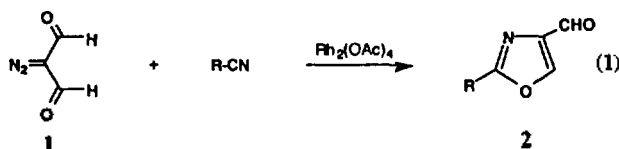
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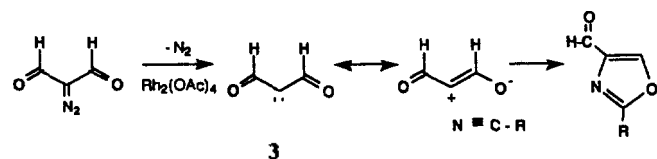
2,4-Disubstituted oxazole moiety has been found as subunit of the several natural products such as calyculins,¹ rhizoxin,² hennoxazoles,³ orbiculamide,⁴ keramamide,⁵ and discokiolides.⁶ Although a large number of synthetic methods have been developed for the construction of 2,4-disubstituted-1,3-oxazoles, often they required multistep sequence.^{7,8} Recently, Helquist,⁹ and Yoo¹⁰ have reported the method for the synthesis of 2-substituted-4-carboalkoxy-1,3-oxazoles by rhodium-catalyzed reaction of ethyl α -formyldiazoacetate, and methyl diazomalonate with nitriles. In continuation of our work on the use of diazomalonaldehyde for the synthesis of heterocycles such as β -furoic acid and γ -pyrone,¹¹ we investigate the decomposition of diazomalonaldehyde with nitriles to give 2.

Results and Discussion

The reaction of diazomalonaldehyde (1) with nitriles, catalyzed by rhodium(II) acetate gave 2-substituted-1,3-oxazole-4-carboxaldehyde (2) in moderate yields (Eq. 1).



As shown in Table 1, the reaction proceeds with aliphatic, vinylic and aromatic nitriles with different functional groups. Aromatic nitriles gave higher yields than aliphatic counterpart(s) (entry 8). In the case of para-substituted benzonitriles, electron withdrawing group such as chloro, cyano, and carbomethoxy have some inhibiting effect, but electron donating group of methyl and methoxy have almost no effects. The reaction with *p*-nitrobenzonitrile and 2,3,4-cyanopyridine did not give the product all. The reaction of the vinylic nitriles such as cinnamitrile, acrylonitrile, and methacrylonitrile with diazomalonaldehyde under similar conditions gave only the oxazoles in low yields¹²; presumably polymerization of the vinylic nitrile retards the reaction. Similarly, treatment of diazomalonaldehyde with nitrile using palladium acetate, copper sulfate, and copper acetoacetate as catalyst did not proceed at all. The reaction seems to proceed via [3+2]



Scheme 1.

Table 1. Synthesis of 2,4-Disubstituted-1,3-Oxazoles 2^a

Exp. #	Molar ratio (Nitrile/Diazo)	Product (R)	Solvent	Yield (%) ^b	Mp. (°C)
1	100	2a, CH ₃	neat	36	71-73
2	100	2b, ClCH ₂	neat	30	liquid
3	50	2c, C ₆ H ₅ CH ₂	neat	21	71-72
4	8	2d, Br(CH ₂) ₆	CICH ₂ CH ₂ Cl	11	liquid
5	50	2e, C ₆ H ₅ CH=CH	neat	23	108-109
6	15	2f, H ₂ C=CH ^c	CICH ₂ CH ₂ Cl	19	72-73
7	15	2g, H ₂ C=C(CH ₃)	CICH ₂ CH ₂ Cl	21	36-38
8	50	2h, C ₆ H ₅	neat	46	94-96
9	8	2i, C ₆ H ₅	CICH ₂ CH ₂ Cl	31	94-96
10	8	2j, <i>o</i> -CH ₃ C ₆ H ₄	CICH ₂ CH ₂ Cl	20	59-60
11	8	2k, <i>m</i> -CH ₃ C ₆ H ₄	CICH ₂ CH ₂ Cl	27	89-90
12	8	2l, <i>p</i> -CH ₃ C ₆ H ₄	CICH ₂ CH ₂ Cl	27	93-94
13	8	2m, <i>p</i> -CH ₃ OC ₆ H ₄	CICH ₂ CH ₂ Cl	28	116-117
14	8	2n, <i>p</i> -ClC ₆ H ₄	CICH ₂ CH ₂ Cl	16	140-141
15	8	2o, <i>p</i> -CH ₃ O ₂ CC ₆ H ₄	CICH ₂ CH ₂ Cl	13	150-151
16	8	2o, <i>p</i> -CNC ₆ H ₄	CICH ₂ CH ₂ Cl	10	205-207

^aAll reactions were carried out under N₂ at 80°C. ^bIsolated yields. ^cReaction with acrylonitrile was carried out at 70°C.

cycloaddition of acylcarbene (3) which was formed from 1 with nitriles.⁹

Although the yields of this reaction are not high, one-step synthesis of 2,4-disubstituted-oxazoles may be attractive for natural product synthesis. Application of this method to the synthesis of natural products is undergoing in our laboratory.

Experimental

Melting points were determined using a Yamato apparatus, and not corrected. Infrared spectra were recorded on a Matton GL-6030E spectrophotometer with KBr pellets or neat. ¹H and ¹³C-NMR spectra were measured on Bruker AM-300 in CDCl₃ solution. ¹H-NMR spectra (300.13 MHz) were referenced to tetramethylsilane, and ¹³C-NMR (75.5 MHz) were referenced to CDCl₃ at 77.0 ppm. Low resolution mass spectra (MS) were recorded on a Shimadzu QP-1000 quadrupole spectrometer with electron energy of 20 eV or 70 eV and direct sample introduction. Analytical TLC was performed on Merck-EM type 60 F₂₅₄ silica gel coated plates.

Preparation of Diazomalonaldehyde

N₂C(CHO)₂ was prepared according to the known procedure.¹³

Reaction of Diazomalonaldehyde with Nitrile

Method A. To a stirred solution of Rh₂(OAc)₄ (10 mg, 0.02 mmol) in benzonitrile (2 mL) was added a solution of diazomalonaldehyde (98 mg, 1 mmol) in benzonitrile (3 mL) with syringe pump over 10-h period at 80°C under N₂. After the reaction was completed, the solution was cooled to the room temperature and concentrated under a reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : hexane = 1 : 4) to give oxazole (93 mg, 46%). The solid product was recrystallized from ether.

Method B. To a stirred solution of Rh₂(OAc)₄ (10 mg,

0.02 mmol) in benzonitrile (825 mg, 8 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1 mL) was added a solution of diazomalonaldehyde (98 mg, 1 mmol) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (3 mL) with syringe pump for 10-h at 80°C under N_2 . After the work-up, 56 mg of oxazole (31%) was obtained.

Analytical Data of Oxazoles as Follows

2-Methyl-1,3-oxazole-4-carboxaldehyde (2a). Mp. $71-73^\circ\text{C}$ (lit.¹⁴ $71-73^\circ\text{C}$); $^1\text{H-NMR}$ δ 9.90 (s, 1H, CHO), 8.15 (s, 1H, H-5), 2.53 (s, 3H, CH_3); IR (KBr) 3127, 3088, 2928, 1682 (C=O), 1593, 1400, 1278, 1105, 785 cm^{-1} ; MS (m/z) 111 (M^+ , 46), 83 (16), 70 (39), 54 (25), 42 (base).

2-Chloromethyl-1,3-oxazole-4-carboxaldehyde (2b). Liquid; $^1\text{H-NMR}$ δ 9.94 (s, 1H, CHO), 8.28 (s, 1H, H-5), 4.66 (s, 2H, CH_2); IR (neat) 3153, 3095, 2856, 1698 (C=O), 1585, 1393, 1270, 1115, 795, 760 cm^{-1} ; MS 145 (M^+ , 19), 110 (14), 82 (9), 70 (base).

2-Benzyl-1,3-oxazole-4-carboxaldehyde (2c). Mp. $71-72^\circ\text{C}$; $^1\text{H-NMR}$ δ 9.91 (s, 1H, CHO), 8.17 (s, 1H, H-5), 7.34-7.26 (m, 5H, Ar-H), 4.17 (s, 2H, CH_2); IR (KBr), 3126, 3087, 2921, 2856, 1671 (C=O), 1586, 1111, 995, 772, 718 cm^{-1} ; MS 187 (M^+ , 42), 158 (9), 130 (12), 118 (22), 117 (21), 91 (base), 77 (16).

2-(1-Bromohexyl)-1,3-oxazole-4-carboxaldehyde (2d). Yellow liquid; $^1\text{H-NMR}$ δ 9.91 (s, 1H, CHO), 8.16 (s, 1H, H-5), 3.40 (t, 2H), 2.83 (t, 2H), 1.89-1.81 (m, 4H), 1.52-1.39 (m, 4H); IR (neat) 2937, 2859, 1698 (C=O), 1590, 1459, 1435, 1393, 1258, 1111, 995, 791, 760 cm^{-1} ; MS 260 (M^+ , 0.2), 231 (0.3), 202 (0.2), 180 (33), 124 (22), 111 (base), 83 (20), 69 (30), 55 (36), 41 (63).

2-[(2-Phenyl)ethenyl]-1,3-oxazole-4-carboxaldehyde (2e). Mp. $108-109^\circ\text{C}$; $^1\text{H-NMR}$ δ 9.97 (s, 1H, CHO), 8.23 (s, 1H, H-5), 7.66 (d, 1H, $J=16.4$, vinyl-H), 7.56-7.37 (m, 5H, Ar-H), 6.95 (d, 1H, $J=16.4$, vinyl-H); IR (KBr) 3127, 3081, 2845, 1688 (C=O), 1555, 1121, 964, 804, 760 cm^{-1} ; MS 199 (M^+ , base), 170 (37), 154 (28), 142 (16), 130 (40), 129 (44), 115 (base).

2-Vinyl-1,3-oxazole-4-carboxaldehyde (2f). Mp. $72-73^\circ\text{C}$; $^1\text{H-NMR}$ δ 9.95 (s, 1H, CHO), 8.20 (s, 1H, H-5), 6.64 (dd, 1H, $J=11.2, 17.4$, CH=), 6.33 (d, 1H, $J=17.6$, $\text{CH}_2=$), 5.79 (d, 1H, $J=11.3$, $\text{CH}_2=$); IR (KBr) 3133, 3082, 2998, 1696 (C=O), 1539, 1400, 1115, 990, 951, 799, 777 cm^{-1} ; MS 123 (M^+ , 67), 95 (41), 70 (58), 66 (20), 54 (97), 39 (base).

2-[(1-Methyl)vinyl]-1,3-oxazole-4-carboxaldehyde (2g). Mp. $36-38^\circ\text{C}$; $^1\text{H-NMR}$ δ 9.95 (s, 1H, CHO), 8.21 (s, 1H, H-5), 6.05 (s, 1H, vinyl-H), 5.51 (s, 1H, vinyl-H), 2.20 (s, 3H, CH_3); IR (KBr) 3133, 2971, 2938, 2874, 1697 (C=O), 1555, 1398, 1115, 997, 922, 789 cm^{-1} ; MS 137 (M^+ , 56), 109 (35), 80 (19), 68 (base).

2-Phenyl-1,3-oxazole-4-carboxaldehyde (2h). Mp. $94-96^\circ\text{C}$; $^1\text{H-NMR}$ δ 10.01 (s, 1H, CHO), 8.31 (s, 1H, H-5), 8.11-8.08 (m, 2H, Ar-H), 7.51-7.47 (m, 3H, Ar-H); $^{13}\text{C-NMR}$ (CDCl_3) 183.99 (CHO), 162.92 (C-2), 144.13 (C-5), 141.86 (C-4), 131.35 (C-4'), 128.86 (C-2', C-6'), 126.87 (C-3', C-5'), 126.17 (C-1'); IR (KBr) 3126, 3079, 2848, 1690 (C=O), 1559, 1486, 1115, 787, 698 cm^{-1} ; MS 173 (M^+ , 55), 145 (19), 117 (15), 116 (11), 104 (base), 90 (42), 77 (23).

2-(o-Tolyl)-1,3-oxazole-4-carboxaldehyde (2i). Mp. $59-60^\circ\text{C}$; $^1\text{H-NMR}$ δ 10.02 (s, 1H, CHO), 8.32 (s, 1H, H-5), 7.98 (d, 1H, Ar-H), 7.41-7.27 (m, 3H, Ar-H), 2.71 (s, 3H, CH_3); IR (KBr) 3140, 3092, 2837, 1697 (C=O), 1562, 1483, 1447, 1117, 1024, 756, 729 cm^{-1} ; MS 187 (M^+ , 68), 158 (22), 130

(34), 118 (88), 117 (base), 103 (33), 91 (39), 77 (53).

2-(m-Tolyl)-1,3-oxazole-4-carboxaldehyde (2j). Mp. $89-90^\circ\text{C}$; $^1\text{H-NMR}$ δ 10.00 (s, 1H, CHO), 8.92 (s, 1H, H-5), 7.94-7.30 (m, 4H, Ar-H), 2.42 (s, 3H, CH_3); IR (KBr) 3126, 3087, 2921, 2856 1671 (C=O), 1582, 1111, 776, 718 cm^{-1} ; MS 187 (M^+ , 64), 159 (24), 130 (31), 118 (base), 103 (21), 91 (20), 77 (26).

2-(p-Tolyl)-1,3-oxazole-4-carboxaldehyde (2k). Mp. $93-94^\circ\text{C}$; $^1\text{H-NMR}$ δ 10.00 (s, 1H, CHO), 8.30 (s, 1H, H-5), 8.01 (d, 2H, $J=8.28$, Ar-H), 7.30 (d, 2H, $J=8.10$, Ar-H), 2.43 (s, 3H, CH_3); IR (KBr) 3130, 3079, 2917, 2848, 1694 (C=O), 1501, 1393, 1119, 1053, 795, 729 cm^{-1} ; MS 187 (M^+ , 75), 159 (22), 130 (25), 118 (base), 104 (26), 103 (22), 91 (13), 77 (24).

2-(p-Methoxyphenyl)-1,3-oxazole-4-carboxaldehyde (2l). Mp. $116-117^\circ\text{C}$; $^1\text{H-NMR}$ δ 9.99 (s, 1H, CHO), 8.26 (s, 1H, H-5), 8.04 (d, 2H, $J=9.09$, Ar-H), 6.99 (d, 2H, $J=9.03$, Ar-H), 3.87 (s, 3H, OCH_3); IR (KBr) 3133, 3087, 2848, 1694 (C=O), 1616, 1505, 1262, 1181, 1119, 1030, 834 787 cm^{-1} ; MS 203 (M^+ , 12), 175 (3), 146 (3), 133 (12), 57 (13), 55 (14), 44 (base).

2-(p-Chlorophenyl)-1,3-oxazole-4-carboxaldehyde (2m). Mp. $140-141^\circ\text{C}$; $^1\text{H-NMR}$ δ 10.00 (s, 1H, CHO), 8.30 (s, 1H, H-5), 8.04 (d, 2H, $J=8.55$, Ar-H), 7.47 (d, 2H, $J=8.58$, Ar-H), IR (KBr) 3133, 3091, 2925, 2844, 1698 (C=O), 1609, 1486, 1408, 1096, 1050, 799, 733 cm^{-1} ; MS 207 (M^+ , 72), 179 (32), 151 (17), 150 (12), 138 (base), 124 (30), 111 (16), 102 (13), 89 (54).

2-(p-Carbomethoxyphenyl)-1,3-oxazole-4-carboxaldehyde (2n). Mp. $150-151^\circ\text{C}$; $^1\text{H-NMR}$ δ 10.04 (s, 1H, CHO), 8.37 (s, 1H, H-5), 8.19 (m, 4H, Ar-H), 3.97 (s, 3H, CO_2CH_3); IR (KBr) 3154, 3121, 3079, 2961, 1725, 1680 (C=O), 1591, 1433, 1413, 1279, 1109, 793, 723 cm^{-1} ; MS 231 (M^+ , 72), 203 (23), 200 (32), 172 (54), 162 (base), 144 (16), 130 (13), 102 (14), 89 (22), 70 (26).

2-(p-Cyanophenyl)-1,3-oxazole-4-carboxaldehyde (2o). Mp. $205-207^\circ\text{C}$; $^1\text{H-NMR}$ δ 10.03 (s, 1H, CHO), 8.36 (s, 1H, H-5), 8.22 (d, 2H, $J=8.43$, Ar-H), 7.80 (d, 2H, $J=8.04$, Ar-H), IR (KBr) 3141, 3095, 3040, 2234, 1690 (C=O), 1497, 1393, 1122, 1053, 953, 853, 791 cm^{-1} ; MS 198 (M^+ , 11), 167 (16), 149 (47), 129 (21), 117 (43), 77 (12), 71 (53), 70 (51), 69 (66), 57 (base).

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A Convenient Synthesis of β -Keto Phosphonates from Nitroalkenes

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β -Keto phosphonates are commonly employed as synthetic reagents for the synthesis of α,β -unsaturated carbonyl compounds by the Wadsworth-Horner-Emmons condensation.¹ Although a number of syntheses have been developed with

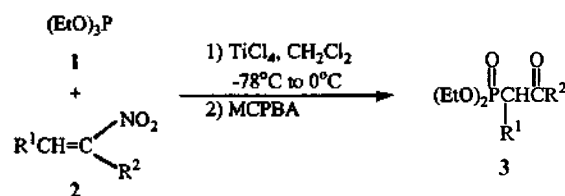
Table 1. Preparation of β -Keto Phosphonates 3

No.	R ¹	R ²	Isolated Yield (%) ^a
3a	C ₆ H ₅	Me	92
3b	C ₆ H ₅	Et	78
3c	<i>p</i> -OMe, C ₆ H ₄	Me	93
3d	<i>p</i> -OMe, C ₆ H ₄	Et	81
3e	<i>p</i> -Cl, C ₆ H ₄	Me	84
3f	<i>p</i> -Cl, C ₆ H ₄	Et	72
3g	H	C ₆ H ₅	85

^aBased on nitroalkenes.

the goal of providing a route to β -keto phosphonates, they have limitations in terms of the reaction conditions employed, competition from other reactions, and the preparation of starting materials. The commonly used methods for preparing β -keto phosphonates are the Arbuzov reaction² and the acylation of alkylphosphonate anions.³ Both methods suffer from individual restrictions and have a common limitation in their reliance upon nucleophilic phosphorus reagents. Syntheses involving acylation of 1-(trimethylsilyl)vinylphosphonate anions⁴ and hydrolysis of vinylogous phosphoramidates⁵ suffer from the limited availability of starting materials. Recently, Wiemer⁶ reported the preparation of β -keto phosphonates through C-P bond formation by the reaction of ketone enolates with dialkylphosphorochloridite, followed by aerial oxidation.

In the course of our studies on the addition to nitroalkenes, we recently reported a synthesis of 1-aryl-1-cyanomethylphosphonates,⁷ α -aryl ketones,⁸ and 1-aryl-2-oxoalkylphosphonates.⁹ We now report a facile synthesis of β -keto phosphonates 3 from readily available nitroalkenes. In the presence of titanium(IV) chloride, addition of triethyl phosphite 1 to nitroalkenes 2 affords α -phosphoryl nitronates^{7,9} which, on treatment with MCPBA, are smoothly converted into phosphonates 3.



Present procedure can guarantee excellent yields of β -keto phosphonates 3 which are summarized in Table 1. The identity of the phosphonates 3 was confirmed by IR, ¹H-NMR, and mass spectroscopy. In a previous paper,⁹ we have reported the preparation of 1-aryl-2-oxoalkylphosphonates from nitroalkenes and diethyl phosphite under basic condition. Compared with our previous approach,⁹ this procedure has some advantages in yields and reaction time.

The general experimental procedure is as follows: To a stirred solution of nitroalkene 2 (1 mmol) in methylene chloride (8 ml) was added dropwise TiCl₄ (0.11 ml, 1 mmol) at -78°C. After being stirred at -78°C for 10 min, triethyl phosphite 1 (0.19 ml, 1.1 mmol) was added dropwise and the reaction mixture was stirred at -78°C for 30 min. After being warmed to 0°C, MCPBA (0.414 g, 1.2 mmol, 50%