J. prakt. Chem. 334 (1992) 278 – 280

Journal für praktische Chemie
Chemiker-Zeitung

Arbeitsvorschriften und Meßwerte · Procedures and Data

Convenient Synthesis of Diethyl 3-methylisoxazoline and Isoxazolephosphonates, Potent Synthons to Biological Active Compounds

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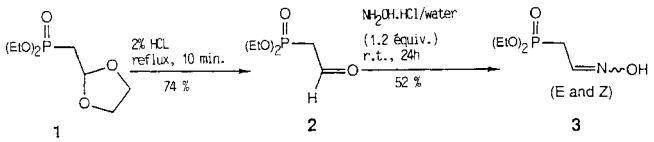
Received October 28th, 1991.

Since isoxazolines and isoxazoles have been shown to synthetically good versatile heterocycles [1, 2] and since they can be readily used as intermediates in a large variety of biologically active compounds [3, 4] and in organic syntheses [5, 9] many authors have tried in many instances their syntheses. But little has been done for the preparation of suitable 3-substituted isoxazolines and isoxazoles and it was noted that many of these preparations are complicated by the presence of 5-substituted products [10]. Otherwise even the introduced 3-substitutions were generally unreactive or could only be labouriously functionalised.

We tried a convenient introduction of a versatile group in position 3. Usually isoxazolines and isoxazoles are obtained by 1,3 dipolar addition of nitrile oxides to olefines and acetylenes [11]. We prepared the diethyl-2-acetaldoximephosphonate **3** in moderate yield by condensation of hydroxylamine with diethyl 2-acetaldehydephosphonate **2**, which was prepared as described [12].



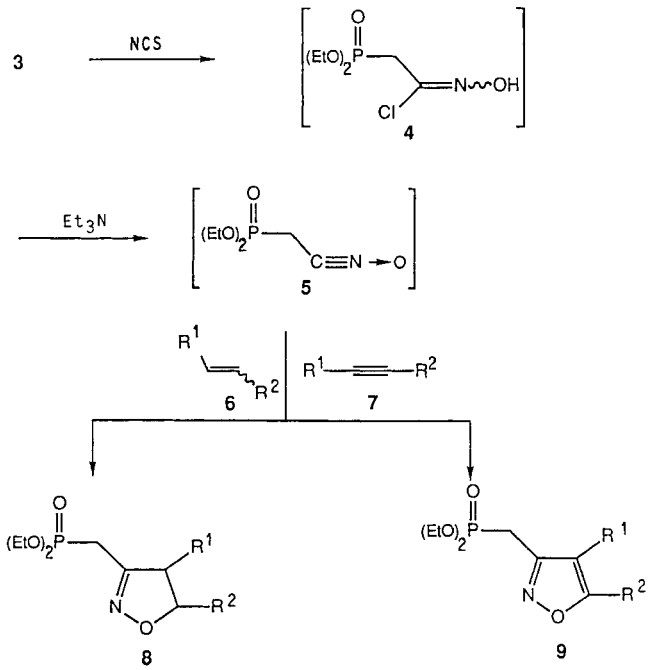
Scheme A

N-Chlorsuccinimide (NCS) provides a convenient method for chlorination of **3** in chloroform with a trace of pyridine. This procedure offers many advantages such as reaction control, conditions, selectivity and yields [13]. The generation of the nitrile oxide **5** is performed by dehydrohalogenation of the hydroxamic acid chloride **4** in presence of triethylamine. Subsequent addition of the olefine **6** or the acetylene **7** at room temperature affords methyl-3-yl-isoxazolinephosphonates **8** and -isoxazolephosphonates **9** in high yields.

The most important side reaction of nitrile oxides to dipolarophiles is their dimerisation to furoxans under basic conditions [11, 14, 15]. In order to prevent furoxan formation, it is important to add triethylamine, which liberates the nitrile oxide in the final step.

Since we don't need to isolate the hydroxamic acid chloride derivate **4** nor the nitrile oxide **5**, we performed this reaction as a one step reaction. We didn't observe any traces of furoxan, even the phosphonate group showed to be inert toward N-chlorsuccinimide, which shows once more the regioselectivity of this procedure [13].

Therefore, this method provides a successfull procedure to synthesize 3-substituted isoxazolines and isoxazoles which can be easily functionalised (forthcoming paper), and



Scheme B

6 – 9	R^1	R^2
a	H	C_6H_5
b	H	CO_2CH_3
c	H	CN
d	H	$COCH_3$
e	H	CH_2OH

Table 1 Compounds **8** and **9** Prepared.

Product	Yield[a] (%)	Molecular[b] Formula	i.r. (Film)[c] ν (cm^{-1})	^{1}H-n.m.r. ($CDCl_3$)[d] δ (ppm), J (Hz)	^{13}C-n.m.r. ($CDCl_3$)[d] δ (ppm), J (Hz)	m.s. EI (70eV)[c] m/z (%)
8a	78	$C_{14}H_{20}NO_4P$ (297.3)	1336, 1260, 1055, 1030, 970, 770	1.33 (t, 6H, J = 8.0, CH_3), 3.00 (d, 2H, J = 21.6, CH_2-P), 3.51 (m, 2H, H_2-4), 4.12 (m, 4H, J = 8.0, CH2-O-P), 5.6 (q, 1H, H-5), 7.33 (m, 5H_{arom})	16.20 (d, J = 6.0, CH_3), 26.37 (d, J = 141.8, **C**H_2-P), 45.09 (+, C-4), 62.41 (d, J = 6.0, **C**H_2-O-P), 82.19 (−, C-5), 125.72 − 128.56 ($C_{arom.}$), 140.66 (+, C-1$_{arom.}$), 150.81 (d, J = 6.1, C-3)	297 (M^+, 44.1), 296 (100), 268 (14.9), 220 (18.9), 164 (32.4), 77 (18.1)
8b	79	$C_{10}H_{18}NO_6P$ (279.2)	1750, 1445, 1345, 1225, 1055, 1030, 970	1.33 (t, 6H, J = 8.0, CH_3), 3.00 (d, 2H, J = 21.4, CH_2-P), 3.41 (m, 2H, H_2-4), 3.80 (s, 3H, O-CH_3), 4.13 (m, 4H, J = 8.0, CH_2-O-P), 5.06 (q, 1H, H-5)	16.25 (d, J = 6.0, CH_3), 25.83 (d, J = 140.0, **C**H_2-P), 41.10 (+, C-4), 52.60 (−, -CH_3), 62.60 (d, J = 6.0, **C**H_2-O-P), 77.66 (−, C-5), 151.10 (d, J = 6.0, C-3), 170.14 (+, C = O)	279 (M^+, 3.0), 278 (5.3), 220 (94.6), 164 (100)
8c	74	$C_9H_{15}N_2O_4P$ (246.2)	2260, 1260, 1055, 1030, 970	1.34 (t, 6H, J = 8.1, CH_3), 3.02 (d, 2H, J = 21.6, CH_2-P), 3,51 (m, 2H, H_2-4), 4.12 (m, J = 8, CH_2-O-P), 5.28 (q, 1H, H-5)	16.20 (d, J = 6.0, CH_3), 26,10 (d, J = 141.6, **C**H_2-P), 43.09 (+, C-4), 62.68 (d, J = 6.0, **C**H_2-O-P), 66.40 (−, C-5), 117.30 (+, CN), 151.20 (d, J = 6.3, C-3)	246 (M^+, 13.5), 220 (48.9), 209 (25.5), 192 (26.6), 164 (37.2), 109 (100)
8d	73	$C_{10}H_{18}NO_5P$ (263.2)	1725, 1270, 1060, 1030, 980	1.33 (t, 6H, J = 8.0, CH_3), 2.69 (s, 3H, **C**H_3CO), 2.99 (d, 2H, J = 21.2, CH_2-P), 3.42 (m, 2H, H_2-4), 4.16 (m, 4H, J = 8.1, CH_2-O-P), 5.26 (q, 1H, H-5)	16.23 (d, J = 6.0, CH_3), 26.10 (d, J = 141.0, **C**H_2-P), 32.51 (−, **C**H_3-CO), 42.34(+, C-4), 62.57 (d, J = 6.0, **C**H_2-O-P), 77.50 (−, C-5), 151.00 (d, J = 6.0, C-3), 205.88 (+, C = O)	263 (M^+, 2.71), 220 (5.73), 209 (54.5), 164 (18.9), 109 (100)
9a	78	$C_{14}H_{18}NO_4P$ (295.3)	1720, 1455, 1265, 1060, 1040, 970, 770	1.33 (t, 6H, J = 8.2, CH_3), 3.30 (d, 2H, J = 21.4, CH_2-P), 4.14 (m, 4H, J = 8.0, CH_2-O-P), 6.66 (s, 1H, H-4), 7.40 − 7.80 (br, 5$H_{arom.}$)	16.27 (d, J = 6.0, CH_3), 24.70 (d, J = 142.0, **C**H_2-P), 62.54 (d, J = 6.0, **C**H_2-O-P), 100.19 (−, C-4), 125.77 − 130.18 (q, $C_{arom.}$), 156.32 (d, J = 6.0, C-3), 170.23 (+, C-5)	295 M^+, 57.2), 239 (33.5), 218 (10.7), 159 (100), 109 (42.3), 77 (47.2)
9b	72	$C_{10}H_{16}NO_6P$ (277.2)	1750, 1720, 1300, 1260, 1050, 1030	1.32 (t, 6H, J = 8.2, CH_3), 3.31 (d, 2H, J = 21.2, CH_2-P), 3.98 (s, 3H, O-CH_3), 4.14 (m, 4H, J = 8, CH_2-O-P), 7.04 (s, 1H, H-4)	16.22 (d, J = 6.0, CH_3), 24.61 (d, J = 142.0, **C**H_2-P), 52.76 (−, O-**C**H_3), 62.65 (d, J = 6.0, **C**H_2-O-P), 110.06 (−, C-4), 156.73 (d, J = 6.4, C-3), 156.97 (+, C-5), 192.40 (+, C = O)	277 (M^+, 7.4), 218 (20.7), 190 (41.9), 141 (82.9), 109 (100)
9e	76	$C_9H_{16}NO_5P$ (249.2)	2760, 1720, 1260, 1125, 1060	1.33 (t, 6H, J = 8.2, CH_3), 3.18 (br, OH), 3.30 (d, 2H, J = 21.2, CH_2-P), 3.95 (d, 2H, **C**H_2-OH), 4.17 (m, 4H, J = 8.0, CH_2-O-P), 6.57 (m, 1H, H-4)	16.23 (d, J = 6.0, CH_3), 24.66 (d, J = 142.0, **C**H_2-P), 57.1 (+, **C**H_2-OH), 62.50 (d, J = 6.0, **C**H_2-O-P), 101.50 (−, C-4), 157.20 (d, J = 6.0, C-3), 173.55 (+, C-5)	249 (M^+, 20.1), 218 (15.2), 190 (27.1), 176 (30.1), 109 (68.9), 86 (100)

[a] Yield refer to pure and isolated compounds; [b] Microanalyses were carried out on automatic Heraeus CHN R-G-S. Satisfactory microanalysis obtained: C ± 0.27, H ± 0.24, N ± 0.21; [c] Recorded on a Perkin-Elmer 325 spectrometer; [d] ^{1}H-NMR and ^{13}C-NMR measured on a Brucker WM-250 spectrophotometer in $CDCl_3$/TMS(^{13}C-NMR: Spin-echo); [e] Recorded on a Varian MAT 311 A mass spectrophotometer

have potential uses as synthons to synthesis of active compounds.

Generous support of this work by BASF AG, Verband der Chemischen Industrie – Fonds der Chemie –, and Deutsche Forschungsgemeinschaft is gratefully acknowledged. We are indebted to Dr. W. Kramer, Mrs. A. Schormann and Mrs. U. Hertle for NMR-spectra to Mr. H. Rudy and Mr. P. Weyrich for Mass spectra, elementary analyses and IR spectra. G. Nkusi thanks the "Deutscher Akademischer Austauschdienst" for a postdoctoral scholarship: We also thank Bayer AG and Hoechst AG for general gifts of chemicals as well as ICN Biomedicals GmbH (Eschwege) for providing us generously with silica gel.

Experimental

Diethyl-2-acetaldoximephosphonate (**3**)

To a cooled (0° C) and stirred mixture of hydroxylamine hydrochlorid (1.39 g, 20 mmol) and Sodium carbonate (1.6 g, 10 mmol) in water (20 ml) a solution of diethyl-2-acetaldehydphosphonate **2** (3 g, 17 mmol) in water (10 ml) is added dropwise. After 24 hours stirring at room temperature, the solution is saturated with NaCl (9 g), extracted with CH_2Cl_2 (3 x 20 ml) and the organic phase dried (Na_2SO_4). The solvent removed under reduced pressure. The resulting solution is purified by preparative TLC with CH_2Cl_2/EtOAc (1:1) as eluent to give the pure compound; yield: 1.72 g (52 %)

$C_6H_{14}NO_4P$
(195.2)

calcd.	C 36.89	H 7.23	N 7.18	P 15.87
found	C 36.98	H 7.16	N 7.12	P 15.83

IR (film): $\nu = 3250, 3000, 2920, 1650, 1560, 1450, 1250, 1170, 1025, 980\,cm^{-1}$

^{1}H-NMR (250 MHz, $CDCl_3$, TMS): $\delta = 1.33$ (t, 6H, CH_3), 2.71 – 3.13 [br, 2 x qd, 2H, CH_2-P (isomerisation E/Z)], 4.16 (m, 4H, CH_2-O-P), 6.78 – 7.48 [br, 2 x qd, 1H, CH = N (isomerisation)], 9.65 (s, 1H, OH)

^{13}C-NMR (Spin-Echo, 62.89 MHz, $CDCl_3$): $\delta = 16.20$ (d, CH_3), 22.43 – 29.27 (br, qd, CH_2-P), 62.40 (d, CH_2-O-P), 140.90 – 142.40 (br, qd, C = N)

MS (70 eV, 68 °C): m/z(%) = 195 (M^+, 75,1), 178 (1.5), 167 (65.24), 150 (19.1), 139 (100), 137 (5.7), 127 (8.1), 125 (10.9), 122 (61.8), 109 (85.7), 104 (22.3), 99 (80.3), 96 (45.0), 91 (22.8), 81 (79.7)

Diethyl-(isoxazolin-3-yl-methyl) phosphonates (**8 a – d**) and *diethyl-(isoxazol-3-yl-methyl) phosphonates* (**9 a – e**)

A suspension of N-chlorosuccinimide (NCS)(0.7 g, 5 mmol) in dry $CHCl_3$ (10 ml) is stirred in presence of pyridine (3 drops). A solution of oxime **3** (1 g, 5.1 mmol) in $CHCl_3$ (10 ml) is added in one portion. The suspension turns to blue at once and is usually clear after 10 min., when the suspended NCS completely disappeares. At room temperature the alkene **6** or the alkyne **7** (6 mmol) is added dropwise and the temperature raise to 40 – 50° C. After 10 min. triethylamine (0.6 g, 6 mmol) is added drop by drop over 30 min. and stirring continued for another 30 min. The reaction is controlled by TLC. The solution is washed with water (3 × 10 ml), dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The resulting product is purified by preparative TLC with EtOAc/CH_2Cl_2 (2 : 1) as eluent to afford the product **8** or **9**, yield 74 – 78 %.

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