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A CONVENIENT SYNTHESIS OF 5-SUBSTITUTED 1-[1-(DIETHOXYPHOSPHORYL)ALKYL]-1*H*-1,2,3-TRIAZOLES

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Abstract: 5-Substituted 1-[1(diethoxyphosphoryl)alkyl]-1*H*-1,2,3-triazoles were prepared in good yields (61-83%) *via* thermal 1,3-dipolar cycloaddition of diethyl 1-azidoalkylphosphonates and 2-oxoalkylidene triphenylphosphoranes.

1,2,3-Triazoles have found wide application in organic synthesis[1] as well as in agriculture, medicine, and industry.[2]

Among numerous synthetic methods for the preparation of 1,2,3-triazoles thermal 1,3-dipolar cycloadditions of organic azides and alkynes are the most versatile tool in the construction of the triazole ring.[2,3] Despite good yields, however, 1,3-dipolar cycloadditions of azides and unsymmetrically substituted alkynes usually provides the mixture of regioisomeric 4- and 5-substituted 1,2,3-triazoles,[4-13] which has to be separated by means of chromatography. This inconvenience can be overcome by regiospecific

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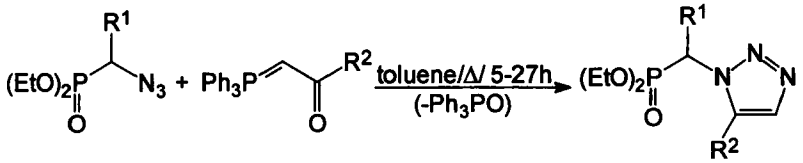
synthesis of differently substituted 1,2,3-triazoles. 4-Substituted 1,2,3-triazoles can be obtained by 1,3-dipolar cycloadditon of azides and enamines.[9,10] The regiospecific cycloaddition of azides to 2-oxoalkylidene triphenylphosphorane yields in turn 5-substituted 1,2,3-triazoles and has been previously applied for the synthesis of 1-alkyl-,[14-16] 1-aryl-[17] and 1-alkenyl-1,2,3-triazoles[18,19] as well as their nucleotide analogues.[20-22]

Recently we have been involved in the chemistry of 1-azidoalkylphosphonates[23] and 1-azidoalkylphosphinates[24] and their application in the synthesis of appropriate aminophosphonates[25,26] and aminophosphinates.[24] Over the past few years only limited examples of cycloaddition of organophosphorus alkyl azides to acetylenes have been published.[6-10,19,27,28] To the best of our knowledge, however, 1,3- dipolar cycloaddition of 1-azidoalkylphosphonates to α-ketophosphorus ylides has not been developed.

We wish to report herein the results of the regiospecific 1,3-dipolar cycloaddition of diethyl 1-azidoalkylphosphonates **1** and 2-oxoalkylidene triphenylphosphoranes **2**.

The above mentioned reaction performed in refluxing toluene affords, after flash chromatography, the expected 5-substituted 1,2,3-triazole derivatives **3** in good yields (61-83%) (Table 1) (Scheme).

The structures of the triazoles **3** have been unequivocally confirmed by means of ^{1}H-, ^{31}P-, and ^{13}C-NMR spectroscopy (Table 2).



1a-b **2a-c** **3aa-bc**

1	R^1	2	R^2	3	R^1	R^2	3	R^1	R^2
a	H	a	Me	aa	H	Me	ba	Ph	Me
b	Ph	b	Ph	ab	H	Ph	bb	Ph	Ph
		c	CO_2Et	ac	H	CO_2Et	bc	Ph	CO_2Et

Scheme

Table 1. 5-Substituted 1-[1-(diethoxyphosphoryl)alkyl]-1*H*-1,2,3-triazoles **3** prepared[a]

Product	Reaction time (h)	Yield[b] (%)	n_D^{20}	R_f[c]	Molecular Formula	FAB/MS (MH^+) (%)
3aa	11	61	1.4852	0.25	$C_8H_{16}N_3O_3P$ (233.21)	234 (100)
3ab	11	82	1.5346	0.50	$C_{13}H_{18}N_3O_3P$ (295.28)	296 (100)
3ac	27[d]	83	1.4694	0.67	$C_{10}H_{18}N_3O_5P$ (291.24)	292 (100)
3ba	5	81	-	0.19	$C_{14}H_{20}N_3O_3P$ (309.30)	310 (100)
3bb	10	70	-	0.66	$C_{19}H_{22}N_3O_3P$ (371.37)	372 (45)
3bc	27[d]	77	1.5154	0.37	$C_{16}H_{22}N_3O_5P$ (367.34)	368 (100)

[a]Satisfactory microanalyses obtained C±0.20, H±0.25, N±0.28; [b]Yields of pure triazoles **3**, based on **1**, isolated after flash chromatography; [c]Eluents: EtOAc/hexane (30:1) (**3aa**, **3bc**); Hexane/EtOAc/MeOH (8:2:1) (**3ab**, **3ba**); Acetone/hexane (10:1) (**3ac**); Acetone/hexane (2:1) (**3bb**); [d]1.15 mol. equivalent of ylide **2** was used.

Table 2. NMR Data of triazoles **3**.

Product	^{31}P-NMR ($CDCl_3$) δ (ppm)	^{1}H-NMR ($CDCl_3$, TMS) δ (ppm), J (Hz)	^{13}C-NMR[a] ($CDCl_3$) δ (ppm), J (Hz)
3aa	16.83	1.3 (t, 6H, J=7.0, $2CH_3$), 2.4 (s, 3H, CH_3), 4.12 (dq, 4H, J=7.0, $^{3}J_{HP}$=8.0, $2CH_2$), 4.68 (d, 2H, $^{2}J_{HP}$=12.51, CH_2P), 7.19 (s, 1H, =CH)	8.24 (s, CH_3), 16.11 (d, $^{3}J_{CP}$= 5.8, CH_3), 43.59 (d, $^{1}J_{CP}$ = 156.68, CH_2P), 63.19 (d, $^{2}J_{CP}$=6.6, CH_2), 132.84 (s, =CH), 133,79 (s, C=)
3ab	16.62	1.28 (t, 6H, J=7.0, $2CH_3$) 4.12(qt, 4H, J=7.0, $2CH_2$), 4.74 (d, 2H, $^{2}J_{HP}$=13.0, CH_2P) 7.40-7.60 (m,5H_{ar}), 7.73(s, 1H, =CH)	16.13 (d, $^{3}J_{CP}$=6.0, CH_3), 43.69 (d, $^{1}J_{CP}$=155.96, CH_2P), 63.28 (d, $^{2}J_{CP}$=6.53, CH_2), 126.35, 128.94, 129.05, 129.62 (C_{ar}), 132.81 (s, =CH), 138.82 (d, $^{3}J_{CP}$= 2.33, C=)
3ac	16.27	1.30 (t, 6H, J=7.0, $2CH_3$), 1.41 (t, 3H, J=7.15, $\underline{CH_3}CH_2OC$), 4.14 (qt, 4H, J=7.0, $2CH_2$), 4.41 (q, 2H, J=7.15, $CH_3\underline{CH_2}OC$), 5.26 (d, 2H, $^{2}J_{HP}$=14.0, CH_2P), 8.13 (s, 1H, =CH)	14.04 (s, $\underline{C}H_3CH_2OC$), 16.18 (d, $^{3}J_{CP}$=6.11, CH_3), 45.15 (d, $^{1}J_{CP}$=153.3, CH_2P), 61.94 (s, $CH_3\underline{C}H_2OC$), 63.26 (d, $^{2}J_{CP}$=6.35, $\underline{C}H_2$), 128.57 (d, $^{3}J_{CP}$=1.32, C=), 137.41 (s, =CH), 158.34 (s, C=O)
3ba	15.94	1.15, 1.26(2t, 6H, J=7.0, $2CH_3$), 2.19(s, 3H, CH_3), 3.95-4.30 (m, 4H, $2CH_2$), 5.73 (d, 2H, $^{2}J_{HP}$=25.0, CH_2P), 7.30-7.50 (m, 5H, $CH_{ar.}$), 7.47 (s, 1H, =CH)	8.36 (s, CH_3), 16.05 (d, $^{3}J_{CP}$ =5.77, CH_3), 16.11 (d, $^{3}J_{CP}$=5.88, CH_3), 60.06 (d, $^{1}J_{CP}$=155.73, CH_2P), 63.70 (d, $^{2}J_{CP}$=7.13, CH_2), 63.91 (d, $^{2}J_{CP}$=6.76, CH_2), 128.57, 128.60, 128.71, 132.50 (C_{ar}), 132.86 (s, =CH), 133,39 (d, $^{3}J_{CP}$= 5.28, C=)
3bb	15.99	1.15, 1.22 (2t, 6H, J=6.75, $2CH_3$), 3.90-4.30 (m, 4H, $2CH_2$), 5.75 (d, 2H, ^{2}J=23.26, CH_2P), 7.20-7.55 (m,5H_{ar}), 7.74 (s, 1H, =CH)	16.11 (d, $^{3}J_{CP}$=5.81, CH_3), 16.18 (d, $^{3}J_{CP}$ =5.92, CH_3), 59.82 (d, $^{1}J_{CP}$ =154.94, CH_2P), 63.83 (d, $^{2}J_{CP}$=7.19, CH_2), 64.12 (d, $^{2}J_{CP}$=6.75, CH_2), 126.41, 128.49, 128.66, 128.76, 129.02, 129.12, 129.72, 132.90 (C_{ar}), 132.53 (s, =CH), 138.92 (d, $^{3}J_{CP}$=5.47, C=)
3bc	15.81	1.20, 1.26 (2t, 6H, J=7.0, $2CH_3$), 1.36 (t, 3H, J=7.12, $\underline{CH_3}CH_2OC$), 4.00-4.40 (m, 6H, $2CH_2$, $\underline{CH_3}CH_2OC$), 6.95 (d, 1H, $^{2}J_{HP}$=22.01, CH_2P), 7.30-7.40 (m, 5$H_{ar.}$), 8.16 (s, 1H, =CH)	13.95 (s, $\underline{C}H_3CH_2OC$), 16.11 (d, $^{3}J_{CP}$=5.82, CH_3), 16.17 (d, $^{3}J_{CP}$=5.96, CH_3), 60.38 (d, $^{1}J_{CP}$= 155.3, CH_2P), 61.88 (s, $CH_3\underline{C}H_2OC$), 63.58 (d, $^{2}J_{CP}$=7.0, CH_2), 64.08 (d, $^{2}J_{CP}$=6.53, CH_2), 127.95, 128.49, 128.89, 129.03 (C_{ar}), 132.29 (d, $^{3}J_{CP}$=3.08, C=), 137.44 (s, =CH), 158.28 (s, C=O)

[a] ^{1}H-^{13}C assignments were checked by shift correlation on the basis of COSY experiment.

Experimental section

NMR spectra were recorded on a Bruker AC 250 instrument at 250.13 MHz for ^{1}H- and 62.9 MHz for ^{13}C-NMR, respectively using $CDCl_3$ as solvent unless otherwise specified. ^{31}P-NMR spectra were recorded on a Bruker AC 250 spectrometer at 101.3 MHz. Positive chemical shifts are downfield from ext. 85% H_3PO_4. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. FAB/MS were recorded on a APO Electron (Ukraine) Modell MI 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). Flash chromatography was performed with glass column packed with Baker silica gel (230-400 mesh). All reagents were purchased from Fluka and used without further purification. The diethyl 1-azidoalkylphosphonates **1a-b**[23] and 2-oxoalkylidene triphenylphosphoranes **2a-b**,[29] **2c**,[30] were prepared according to the literature procedures.

5-Substituted 1-[1-(diethoxyphosphoryl)alkyl]-1*H*-1,2,3-triazoles 3; General Procedure:

A solution of diethyl 1-azidoalkylphosphonate **1** (2.0 mmol) and 2-oxoalkylidene triphenylphosphorane **2** (2.0-2.3 mmol) in dry toluene (15 mL) was refluxed for 5-27 h. The solvent was then evaporated in vacuo. The product was separated from the triphenylphosphine oxide by flash chromatography to give analytically pure triazole **3** in good yield (see Table 1 and 2 for details).

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