CYCLOADDITION REACTIONS OF AZIDOMETHYL PHOSPHONATE WITH ACETYLENES AND ENAMINES. SYNTHESIS OF TRIAZOLES

Frédéric Louërat[&], Khalid Bougrin[&+], André Loupy[&*], Ana Mª Ochoa de Retana[$], Jaione Pagalday[$], and Francisco Palacios[$*]

[&]Laboratoire des Réactions Sélectives sur Supports, CNRS UA 478, Université Paris-Sud, Bât. 410, 91405 Orsay, France. [$]Departamento de Química Orgánica, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain

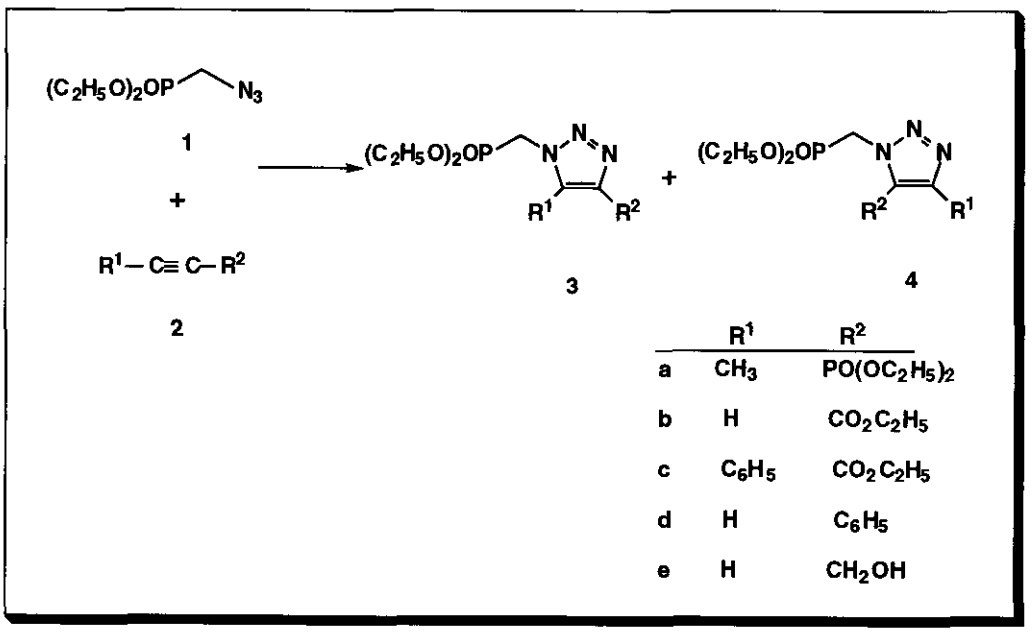
Abstract - β-Functionalized alkyltriazoles can be efficiently prepared under solvent-free conditions, eventually by coupling with microwave activation. Cycloadditions of azides and poorly activated acetylenes or enamines are thus possible with interesting selectivity in the latter case.

The chemistry of 1,2,3-triazoles has attracted an attention since the first example of an azide cycloaddition with an acetylenic ester was reported in the last century.[1] 1,2,3-Triazole derivatives are of significant interest not only for their presence in human metabolites[2] and synthetic value as key intermediates in organic synthesis for the preparation of antibiotics,[3] nucleosides,[4a,b] rotaxanes,[4c] and polyheterocyclic compounds with neuroleptic activity[5a] as well as antirheumatic,[5b] antihistaminic agents[5c] and for the treatment of Alzheimer diseases,[5d] but also for their industrial applications as optical brighteners,[6a,b] corrosion inhibitors,[6c-f] photostabilizers for fibers, plastic or dyestuffs as well as for the protection of human skin from harmful U.V. irradiation.[6g] Furthermore, a wide range of 1,2,3-triazole derivatives are bioactive heterocyclic compounds and are of interest not only in the area of agrochemicals,[7a] due to their activity as insecticides[7b] and fungicides[7c,d] as well as regulatory local plant growth,[7e] but also are of interest in the area of medicinal chemistry[8] as cytostatic,[9a] virostatic,[9b] anti-inflammatory,[5b] antiproliferative agents,[9c] as well as GABA-antagonists[9d,e] and enzymatic inhibitors.[9f] Recently, moreover, 1,2,3-triazole derivatives were prepared by solid-phase synthesis[10a] with potential interest in combinatorial chemistry and they have also been used for the preparation of new nucleosides for evaluation of their inhibitory effect against HIV 1 induced cytopathicity[10a,b] and for testing as inhibitors of human leukocyte elastase[10c] (HLE) for the treatment of emphysema and inflammatory pulmonary diseases.[10d] On

+ On leave from Université Mohammed V, Faculté des Sciences, Rabat (Maroc).

the other hand, 1-aminoalkylphosphonate derivatives, isostere phosphonic analogues of α-aminoacids, are a new class of compounds with interesting biological properties[11] and thus are of significant interest in medicinal chemistry.[11-15] They constitute a unique class of simple mimetics of amino acids and are used as antibacterial agents, neuromodulators, antibiotics, anticancer and antihypertensive drugs,[11] as well as neutral endopeptidase inhibitors,[12] endotheling-converting enzyme inhibitors,[13] irreversible inhibitors for blood coagulation,[14] and as other enzyme inhibitors.[15]

The 1,3-dipolar cycloadditions have been extensively reviewed and provide considerable scope for the synthesis of five membered heterocyclic rings,[16] and one of the most versatile preparations of triazoles involves the ring formation through thermal 1,3-dipolar cycloaddition of azides and alkynes.[17] In this context, it is noteworthy that certain variations in the starting azides might permit easier refunctionalization of the resultant cycloadducts. In connection with our interest in the synthesis of five-[18,19] and six-membered[20] phosphorylated nitrogen heterocycles and in the study of the synthesis and reactivity of phosphazenes[21] derived from azides, we have prepared β-functionalized azides[22] and we have reported the use of azides as synthetic intermediates in the preparation of acyclic[23] and heterocyclic[19] compounds. In a previous paper, we reported that electron-deficient acetylenes[19b] such as diethyl 2-propyn-phosphonate (Table 1, Entry 1) and acetylenecarboxylates (ethyl propiolate and ethyl phenylpropiolate) (Table 1, Entries 6, 11) add to azidomethylphosphonate to form regioisomeric substituted 1,2,3-triazoles (**3**) and (**4**). However, this process requires drastic reaction conditions such as high temperature (toluene at reflux) and very long reaction times (30-40 h).



	R^1	R^2
a	CH_3	$PO(OC_2H_5)_2$
b	H	$CO_2C_2H_5$
c	C_6H_5	$CO_2C_2H_5$
d	H	C_6H_5
e	H	CH_2OH

Scheme 1

Continuing our interest in the synthetic use of β-functionalized alkyl azides, we here extend the process to new acetylenes such as phenylacetylene and propargyl alcohol and explore the effect of exposure to microwaves,[24] the salt effects[25] and especially $LiClO_4$ / Et_2O[26] and the solvent-free reaction[27] in order to optimize and activate the cycloaddition reaction of dipoles derived from α-azidomethylphosphonate (**1**) with alkynes and enamines for the synthesis of substituted triazoles.

Table 1. Cycloaddition reactions of (**1**) with acetylenic dipolarophiles

Entry	Dipolarophile	T(° C)	t (min)	Solvent	Technique	Yield(%)	**3:4**[a]
1	**2a**	110	1800	toluene	Δ^b	88	50:50
2		100	3600	-	Δ^c	93	75:25
3		25	10080	ether	$LiClO_4$	12	93:7
4		90	20	-	Δ^c	5	66:34
5		90	20	-	M.W[d]	78	66:34
6	**2b**	110	1800	toluene	Δ^b	86	75:25
7		100	2880	-	Δ^c	98	88:12
8		25	10080	ether	$LiClO_4$	90	83:17
9		100	5	-	Δ^c	70	75:25
10		100	5	-	M.W[d]	92	66:34
11	**2c**	110	1800	toluene	Δ^b	83	50:50
12		100	2880	-	Δ^c	90	61:39
13		25	10080	ether	$LiClO_4$	7	79:21
14		160	10	-	Δ^c	99	58:42
15		160	10	-	M.W[d]	99	63:37
16	**2d**	60	3300	-	Δ^c	95	55:45
17		120	30	-	Δ^c	40	70:30
18		120	30	-	M.W[d]	99	55:45
19		120	10	-	M.W[d]	40	70:30
20	**2e**	60	2100	-	Δ^c	92	60:40
21		100	30	-	Δ^c	40	70:30
22		100	30	-	M.W[d]	99	70:30

[a] Determined by GC from crude reaction mixtures. Δ^b: Conventional heating with solvent. Δ^c: Conventional heating without solvent. [d] Microwaves exposure (120 W).

The reaction conditions, the yields and the regioisomeric ratios are given in Table1. Regioisomeric triazoles (**3**) and (**4**) was characterized on the basis of their spectroscopic data. In ^{1}H-NMR spectrum of compound (**3a**), methylene protons resonate at δ_H 4.68 ppm and the methyl group gives a singlet at δ_H 2.59 ppm, while the ^{13}C-NMR spectrum reveals absorptions at δ_C 132.1 ppm and 142.0 ppm assignable to C-4 and C-5. Conversely, regioisomeric triazole (**4a**) showed clearly different absorptions, namely a singlet at δ_H 5.00 ppm for the methylene protons and a highfield signal for the methyl group at δ_H 2.26 ppm, while in the ^{13}C-NMR spectrum the absorptions of C-4 and C-5 appear at δ_C 150.0 and 122.5 ppm. Structures of regioisomeric compounds (**3a**) and (**4a**) were confirmed by long range heteronuclear coupling with the aim of a selective experiment 1D SDEPT.[28] Selective irradiation of the methylene signal of **3a** at δ= 4.68 ppm resulted in the long range coupling between these protons and the methine carbon (C-5) of the triazole ring (δ=142 ppm, $^2J_{PC}$=26.1 Hz) (see Figure 1). However, selective irradiation of lower field methylene protons (δ=5.00 ppm) in **4a** underwent coupling with the methine carbon (C-5) substituted with the phosphonyl group at δ=122.5 ppm. ($^1J_{PC}$=219.6Hz) (see Figure 1). This result supports the proposed structures for regioisomers (**3a**) and (**4a**) and are consistent with those reported assignments for 1,2,3-triazoles.[10d,17c-e,19] The structures of **3b-e** and **4b-e** were assigned on the basis of comparison of the ^{1}H- and ^{13}C-NMR data with compounds (**3a**) and (**4a**) and with previously reported data.[10d,19] It is noteworthy that simple acetylenes such as 1-, 2-, and 3-butyns are also used but no reactions have been observed recovering the starting reagents.

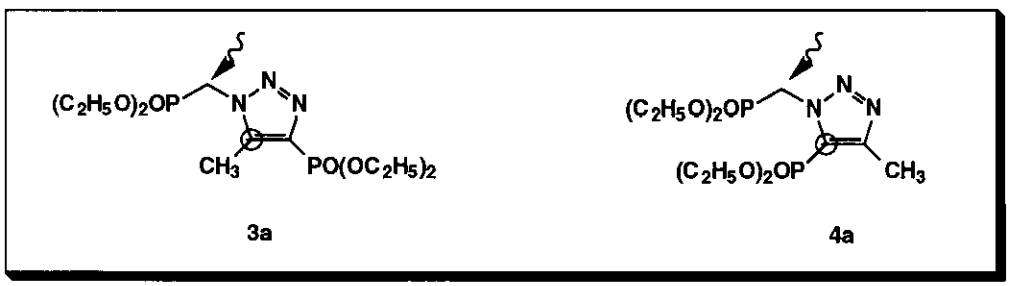


Figure 1

From the Table, one can conclude a lot of facts:

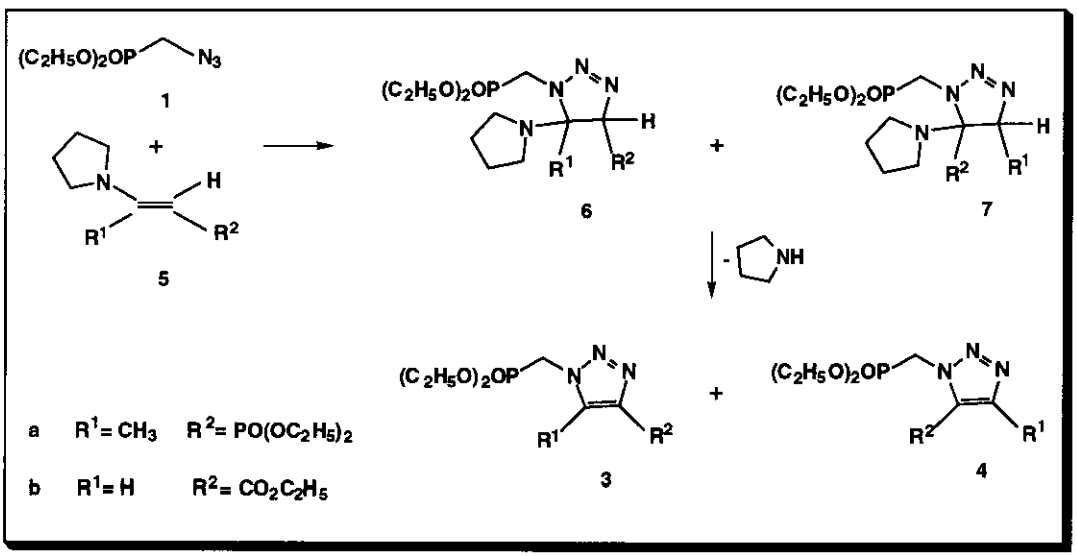
i) the solvent-free method is especially interesting in terms of yields and reaction conditions as results are at least equivalent to those obtained in toluene solutions. There is no need to operate in the presence of a solvent for this type of dipolar cycloaddition. This conclusion was yet advocated for other 1-3 dipolar cycloadditions involving diphenyl nitrilimine[29] or nitrones[30-32] as dipoles. It constitutes thus an efficient, clean and more economic method.

ii) yields obtained under microwave activation are always by far the best ones within very short times (10-30 min, Entries 5,10,15,19,22). The specific effect of the radiation is clearly dependent on the dipolarophile nature: it is absent for the most activated acetylenic **2c** (Entries 14,15) and becomes very important for the less activated ones (**2a**, **2d**) and (**2e**) (Entries 4-5, 17-18, 21-22). This specific (non purely thermal) microwave effect on reactivity is probably due to the polarity and reactivity of these

dipolarophiles. This phenomenon was yet described and involved in a lot of reactions along a same series with poorly reactive substrates.[33-36]

iii) selectivities (**3/4**) are rather the same whatever the mode of activation. We have shown that this is connected to the reversibility of the cycloaddition. When pure isomer (**4**) was introduced in the same recation conditions in the presence of **2c** (10 min at 160°C), a mixture (**3/4**)=62/38 is removed under microwaves, showing thus the thermodynamical equilibration of the regioisomers.

iiii) the effect of $LiClO_4$ / Et_2O, known as an efficient Lewis acid able to activate C=O or P=O groups of dipolarophiles by complexation, is here limited as reactions were performed at room temperature. Yields are very poor except for **2b** and selectivity only noticeably enhanced in the case of **2a** .



Scheme 2

The low observed regiochemistry was supported by the frontier molecular orbital (FMO) theory[37] and isomer mixtures are formed, since acetylenes undergo simultaneously both azide-LUMO and azide-HOMO controlled cycloadditions and seems to be scarcely dependent of the technique used in the process. However, unlike acetylenes, the reaction of azides with unsymmetrical olefins gives only one cycloadduct. Therefore, enamines could be used as synthetic equivalents for acetylenes in 1,3-dipolar cycloaddition reactions. Given that enamines are excellent dipolarophiles, that they react under mild conditions and that the amino group controls the regiochemistry of the reactions,[38] we have also explored the reaction of azidomethylphosphonates (**1**) with enamines. In this case, the cycloaddition of azide (**1**) with functionalized enamines (**5a,b**) needed more time and higher temperature (Table 2, Entries 1, 5) than simple enamines.[19a] The expected triazoles (**3**) were obtained when the reaction was performed in refluxing toluene given that the dipolarophilic activity of enamines is reduced by the introduction of electron-withdrawing groups and therefore the enamino-phosphonate (**5a**) or - ester (**5b**) do not behave as acrylic derivatives but as enamines (LUMO azide controlled processes). It is noteworthy that when the

process was performed by the exposure of microwaves a mixture of both regioisomers (**3**) and (**4**) was obtained (see Table 2, Entries 4 and 8).

Table 2. Synthesis of substituted triazoles (**3/4**)

Entry	Dipolarophile	T(° C)	t (min)	Solvent	Technique	Yield(%)	**3:4**[a]
1	**5a**	110	2880	toluene	Δ^a	60	100:0
2		100	3600	-	Δ^b	70	100:0
3		90	20	-	Δ^b	0	-
4		90	5	-	M.W.[c]	30	85:15
5	**5b**	110	2880	toluene	Δ^a	63	100:0
6		100	3600	-	Δ^b	86	100:0
7		90	20	-	Δ^b	0	-
8		90	20	-	M.W.[c]	55	85:15

Δ^a Conventional heating with solvent. Δ^b : Conventional heating without solvent. [c] : Microwaves exposure (120 W)

The better yields are obtained in solvent-free conditions for very long reaction times at 100°C (60 hours). For shorter times (5-20 min), there is no reaction under classical heating whereas some reactions occurred under microwaves in the same conditions (Entries 4 and 8). Unfortunately, in this last case, we put into evidence a loss in regioselectivity due to microwaves probably due to dipolar polarization, favouring the interactions between two mutually oriented dipoles.

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SPM-20 apparatus and are uncorrected. Analytical TLC was performed on 0.25 mm silica gel plates (Merck). Visualization was accomplished by UV light and iodine. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents. All solvents used in reactions were freshly distilled from appropriate drying agents before use; toluene (Na); ether (Na). All other reagents were recrystallized or distilled when necessary. Column (flash) chromatography was carried out on silica gel (Merck, 70-230 mesh). Elemental analyses were performed in a LEO CHNS-93S apparatus. MS spectra were obtained on a Hewlett Packard 5971 spectrometer (70eV). ^{1}H and ^{13}C NMR and NOE. experiment were recorded on a Varian VXR 300 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ solutions. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet) q (quadruplet) or m (multiplet). Coupling constants, J, are reported in Hertz. Data are given in the form m/z (intensity relative to base = 100). The products (**3b,c** and **4b,c**) and their physical constant and spectral data are identical with those previously obtained.[19]

Microwave equipment. Microwave irradiations were carried out with a Synthewave ™ S402 monomode reactor from Prolabo (2450 MHz, 300 W) fitted with a stirring system of variable speed rotation, a visual control and with irradiation monitoring by PC computer, IR [33] measurement and continual feedback temperature control (adjusted and controlled by an optical fiber). The power is continuously emitted all along the reaction as the incident one, modulated in order to maintain the temperature at a limited value. For sake of comparison, reactions were conducted under classical heating in a thermostated (oil or sand bath) and measuring the evolution of temperature inside the reaction medium with a digital thermometer.

General Procedure for the Cycloaddition of Azidomethylphosphonate (1) with Acetylenes. Heating with Solvent: To a solution of ethyl 1-azidomethylphosphonate **(1)** (3 mmol, 0.58 g) in toluene (10mL) was added dropwise with stirring a solution of acetylenic compound **(2)** (3 mmol). The reaction mixture was stirred under reflux at 110°C for 30 h. Concentration under vacuum gave the mixture of the two regioisomeric cycloadducts **(3)** and **(4)** were isolated by flash column chromatography (silica gel, eluent: n-hexane-ether) (see Table 1). The ratio **(3/4)** is evaluated either by ^{1}H NMR or GC using an internal standard.

Heating without Solvent: Ethyl 1-azidomethylphosphonate **(1)** (3 mmol, 0.58 g) was added with stirring to acetylenic dipolarophile **(2)** (3 mmol), and the reaction mixture was stirred to adequate temperature (see Table 1). The mixture of two regioisomeric cycloadducts **(3)** and **(4)** was isolated by flash column chromatography (silica gel, eluent: n-hexane-ether) and analyzed as above.

Reaction in the Presence of Lithium Perchlorate in Ether (LP-Et_2O): To a solution of ethyl 1-azidomethylphosphonate **(1)** (5 mmol, 0.97 g) in Et_2O (10 mL) were added (5 mmol) of alkyne and 5.320 g (0.050 mol) of $LiClO_4$. The mixture was stirred at rt under N_2 and was pourred on CH_2Cl_2 (20 mL), washed with a saturated solution of $NaHCO_3$, extracted with three 20 mL portions of CH_2Cl_2, and dried ($MgSO_4$). Evaporation of solvent under reduced pressure afforded the mixture of the two regioisomeric cycloadducts **(3)** and **(4)** which was isolated by flash column chromatography (silica gel, eluent: n-hexane-ether).

Activation by Microwaves: A mixture of ethyl 1-azidomethylphosphonate **(1)** (3 mmol, 0.58 g) and acetylenic dipolarophile **(2)** (4.8 mmol) in a Pyrex tube of 1 cm diameter was introduced in the microwave reactor for the times and temperatures as indicated in Table 1. CH_2Cl_2 (20 mL) was then added. The reaction mixture was analyzed by GC (capillary column) and by ^{1}H NMR

5-Diethoxyphosphoryl-1-diethoxyphosphorylmethyl-4-methyl-1,2,3-triazole (3a) and 4-Diethoxyphosphoryl-1-diethoxyphosphorylmethyl-5-methyl-1,2,3-triazole (4a). Reaction with diethyl 2-propyn-phosphonate (3 mmol, 0.53 g) gave the mixture of **3a** and **4a** (see Table 1). Data for **3a** : MS, m/z: 369 (M^+, 9%). Anal. Calcd for $C_{12}H_{25}N_3O_4P_2$: C, 39.01; H, 6.83; N, 11.38. Found: C, 39.09; H, 6.89; N, 11.42. ^{1}H-NMR, δ_H : 1.32 (m, 12H), 2.59 (s, 3H), 4.17 (m, 8H), 4.68 (d, $^2J_{PH}$ = 12.7 Hz, 2H); ^{13}C-NMR, δ_C : 8.7, 16.1, 44.1 (d, $^1J_{PC}$ = 155.5 Hz), 63.3, 132.1 (d, $^1J_{PC}$ = 238 Hz), 142.0 (d, $^2J_{PC}$ = 26 Hz) ; ^{31}P-NMR, δ_P: 16.12, 7.93 ppm.
Data for **4a** : MS, m/z: 369 (M^+, 9%). Anal. Calcd for $C_{12}H_{25}N_3O_4P_2$: C, 39.01; H, 6.83; N, 11.38. Found: C, 39.11; H, 6.86; N, 11.29. ^{1}H-NMR, δ_H : 1.15 (m, 12H), 2.26 (s, 3H), 4.00 (m, 8H), 5.00 (d, $^2J_{PH}$ = 13.6 Hz, 2H); ^{13}C-NMR, δ_C : 11.4, 16.2, 45.4 (d, $^1J_{PC}$ = 154.0 Hz), 63.2, 122.5 (d, $^1J_{PC}$ = 219.6 Hz), 150.0 (d, $^2J_{PC}$ = 20.6 Hz) ; ^{31}P-NMR, δ_P: 17.35, 5.12 ppm.

1-Diethoxyphosphorylmethyl-4-phenyl-1,2,3-triazole (3d) and 1-Diethoxyphosphoryl methyl-5-phenyl-1,2,3-triazole (4d). Reaction with phenylacetylene (3 mmol, 0.307 g) gave the mixture of **3d** and **4d** (see Table 1). Data for **3d** : MS, m/z: 295 (M^+, 15%). Anal. Calcd for $C_{13}H_{18}N_3O_3P$: C, 52.88 ; H, 6.10; N, 14.23. Found: C, 52.60; H, 6.12; N, 14.26 . ^{1}H-NMR, δ_H : 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 4.12 (m, 4H), 4.75 (d, $^2J_{PH}$ = 13.1 Hz, 2H), 7.50 (m, 5H), 7.82 (s,1H); ^{13}C-NMR, δ_C : 15.9, 43.5 (d, $^1J_{PC}$ = 155.6 Hz), 63.3, 127.9, 128.4-129.9, 147.72; ^{31}P-NMR, δ_P: 16.49ppm.

Data for **(4d)**: MS, m/z: 295 (M^+, 23%). Anal. Calcd for $C_{13}H_{18}N_3O_3P$: C, 52.88 ; H, 6.10; N, 14.23. Found: C, 52.75; H, 6.9; N, 14.21. ^{1}H-NMR, δ_H : 1.30 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 4.14 (m, 4H), 4.86 (d, $^2J_{PH}$ = 13.1 Hz, 2H), 7.42 (m, 5H), 8.09 (s,1H); ^{13}C-NMR, δ_C : 15.9, 43.5 (d, $^1J_{PC}$ = 155.6 Hz), 63.3, 127.9, 128.4-129.9, 147.72; ^{31}P-NMR, δ_P: 16.51ppm.

1-Diethoxyphosphorylmethyl-4-hydroxymethyl-1,2,3-triazole (3e) and 1-Diethoxyphos phorylmethyl-5-hydroxymethyl-1,2,3-triazole (4e). Reaction with propargyl alcohol (3 mmol, 0.168 g) gave the mixture of **3e** and **4e** (see Table 1). Data for **3e** : MS, m/z: 249 (M^+, 7%). Anal. Calcd for $C_8H_{16}N_3O_4P$: C, 38.55; H, 6.42; N, 16.86. Found: C, 38.40; H,6.39; N, 16.88. ^{1}H-NMR, δ_H : 1.29 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 4.12 (m, 4H), 4.79(s, 2H), 4.84 (d, $^2J_{PH}$ = 12.9 Hz, 2H), 5.08 (s,1H), 7.62 (s, 1H); ^{13}C-NMR, δ_C : 15.8, 45.4 (d, $^1J_{PC}$ = 155.0 Hz), 63.2, 123.0, 148.3; ^{31}P-NMR, δ_P: 16.68ppm.
Data for **4d** : MS, m/z: 249 (M^+, 2%). Anal. Calcd for $C_8H_{16}N_3O_4P$: C, 38.55; H, 6.42; N, 16.86. Found: C,38.60; H, 6.39; N, 16.77. ^{1}H-NMR, δ_H : 1.30 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 4.14 (m, 4H), 4.77(s, 2H), 4.92 (d, $^2J_{PH}$ = 12.7 Hz, 2H), 5.07 (s,1H), 7.86 (s, 1H); ^{13}C-NMR, δ_C : 16.0, 43.7 (d, $^1J_{PC}$ = 155.6 Hz), 62.2, 123.8, 137.5; ^{31}P-NMR, δ_P: 17.38ppm.

General Procedure for the Cycloaddition of Azidomethylphosphonate with Enamines. Heating with Solvent: To a solution of ethyl 1-azidomethylphosphonate **(1)** (3 mmol, 0.58 g) in toluene (10 mL) was added dropwise under stirring a solution of enamine **(5)** (3 mmol). The reaction mixture was stirred under reflux at 110°C for 30 h. Evaporation of solvent under reduced pressure afforded the product **(3)** which was purified by flash column chromatography (silica gel, eluent: n-hexane-ether) (see Table 2).

Heating without Solvent: To pure ethyl 1-azidomethylphosphonate **(1)** (3 mmol, 0.58 g) was added enamine **(5)** (3 mmol) under stirring. The reaction mixture was stirred to adequate condition temperature (see Table 2). Crude residue was purified by flash column chromatography (silica gel, eluent: n-hexane-ether) to give product **(3)**.

Activation by Microwaves: A mixture of ethyl 1-azidomethylphosphonate **(1)** (3 mmol, 0.58 g) and enamine **(5)** (4.8 mmol) in a Pyrex tube of 1 cm diameter was introduced in the microwave reactor for the times and temperatures indicated in Table 2. CH_2Cl_2 (20 mL) was then added. The reaction mixture was analyzed by GC (capillary column) and by ^{1}H-NMR

Gas Chromatography Data: Analyses were performed using an OV1 25 m **(a, b, c)** or OV1 12 m **(d, e)** capillary column on an apparatus Carlo Erba CG 800 (flame ionization) ; gaz carrier = helium (p = 70 kPa **(a, b, c)** or 50 kPa **(d, e)** ; injector and detector temperature = 290 °C ; oven temperature programmation : 100 °C (5 min) to 280 °C/10 °C per min (5 min) **(b, c)** ; 100 °C to 180 °C/10 °C per min (6 min) then to 280 °C/10 °C per min **(a)** ; 100 °C (5 min) to 200 °C/10 °C per min (5 min) **(e)** ; 70 °C (5 min) to 280 °C/10 °C per min (5 min) **(d)**.

Retention times (min) : **(3a)** = 17.47 ; **(3b)** = 16.33 ; **(3c)** = 19.90 ; **(3d)** = 19.49 ; **(3e)** = 15.80 ; **(4a)** = 12.22 ; **(4b)** = 14.25 ; **(4c)** = 19.10 ; **(4d)** = 20.75 ; **(4e)** = 17.68.

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