1,3-DIPOLAR CYCLOADDITIONS OF AZIDOALKYLPHOSPHONATES TO ENAMINES. SYNTHESIS OF Δ^2-1,2,3-TRIAZOLINES AND TRIAZOLES#

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Abstract- 5-Amino-Δ^2-1,2,3-triazolines (3) and 1,2,3-triazoles (4) and (8) derived from aminoalkylphosphonates have been obtained in a regioselective fashion, by treating diethyl azidoalkylphosphonates (1) with enamines (2) and (6). Reaction of azidomethylphosphonate (1) with an excess of norbornadiene yields triazoline (10). This monoadduct undergoes nitrogen evolution and retro Diels-Alder reaction to give aziridine (11) and triazole (12), respectively.

Certain 1-aminoalkylphosphonic acids and their derivatives, the phosphonic analogues of important amino acids, are a new class of compounds with interesting biological properties; they are a unique class of simple mimetics of amino acids and are used as herbicides, insecticides, plant growth regulators, antibacterial agents, neuromodulators, antibiotics, anticancer and antihypertensive drugs, as well as enzyme inhibitors.[1,2]

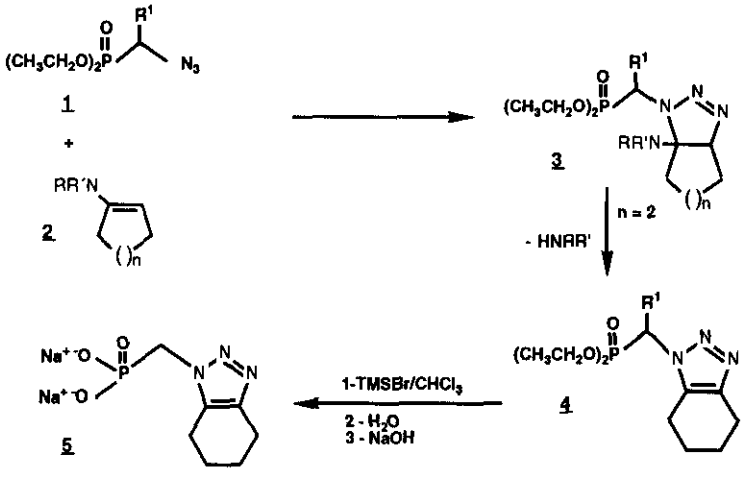
Furthermore, 1,2,3-triazole derivatives show significant interest not only in the area of medicinal chemistry[3] as cytostatic,[4] virostatic,[5] anti-inflammatory[6] and antimicrobial agents,[7] but also in the area of agrochemicals[8] due to their behaviour as antihelmintic agents[9] and their activity as fungicides[10] as well as regulating local plant growth.[11] Besides their biological activity, some other important industrial applications of triazoles are described, including the use as fluorescent compounds, optical brighteners,[12] corrosion inhibitors,[13] photostabilizers for fibers, plastics or dyestuffs as well as for the protection of human skin from harmful uv irradiations.[14]

In connection with our interest in the synthesis and reactivity of organic compounds containing both phosphorus and nitrogen atoms, we are involved in the chemistry of phosphazenes[15] and enamino functionalized phosphorus derivatives,[16] as well as in their use in the synthesis of heterocyclic[17] and acyclic[18] compounds. In this context, it is worth noting that 1,3-dipolar cycloaddition reactions have developed into a generally useful and versatile method for five-membered heterocyclic ring synthesis.[19,20] For this reason, this strategy could be very appropriate for the preparation of substituted triazoles from azides.[21]

Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.

Recently, we have reported a synthesis of diethyl 1,2,3-triazolealkylphosphonates through cycloaddition of azides with acetylenes,[22] the regioselectivity of this reaction is however low, and mixtures of triazoles are formed. On the other hand, exceptional reactivity has been reported for electron rich olefins such as enamines, and the azide addition is unidirectional and stereospecific.[21,23] Moreover, in this type of reaction, enamines can be considered as synthetic equivalents of alkynes, given that the initially formed triazolines undergo thermolysis and aromatize spontaneously to triazoles. Therefore, we have explored the intermolecular cycloaddition reactions of azidoalkylphosphonates with enamines and we report here a synthesis of the correspondent cycloadducts, the triazolines and triazoles.

The cycloaddition of simple azides with electron rich dipolarophiles, through the application of frontier molecular orbital (FMO) theory is azide LUMO controlled. Therefore, the reaction was initially explored by using cyclic enamines, easily available, that possess low ionization potentials, and hence could be very suitable to react with azides.[23] Thus, the reaction of azides derived from phosphonates (**1**) with cyclopentene enamines (**2**) (n=1) in tetrahydrofuran at room temperature (10 h) led to 5-amino-Δ^2-1,2,3-triazoline (**3**) derivatives with good yields[24] in a regioselective fashion (see Table and Scheme 1). When $R^1 \neq H$ a mixture of two diastereoisomers is obtained. Compounds (**3**) were characterized on the base of their spectroscopic data, with the presence of only one absorption in the ^{31}P-nmr spectra (δ = 21.0 ppm for **3a**) and of their mass spectrometry that shows the loss of nitrogen from **3** (*m/z*, 318 for **3a**). Thermolysis of triazolines (**3**) derived from cyclopentanone enamines fail to give triazole derivatives[25] and decomposition products are obtained. However, when enamines derived from cyclohexanone (**2**) (n=2) react with phosphorylated azides (**1**), cycloadducts (**3**) can not be isolated and triazolines (**3**) aromatize spontaneously to bicyclic 1,2,3-triazoles (**4**)[24] (Scheme 1). Spectral data are in agreement with structure (**4**). Thus, for compound (**4a**) mass spectrometry shows the molecular ion peak (*m/z*, 273), and the ^{31}P-nmr spectrum presents an absorption at δ = 17.1 ppm, while the phosphorus linked methylene group appears at δ 4.56 and 44.5 ppm in the ^1H and ^{13}C-nmr spectra as well resolved doublets, respectively.



Scheme 1

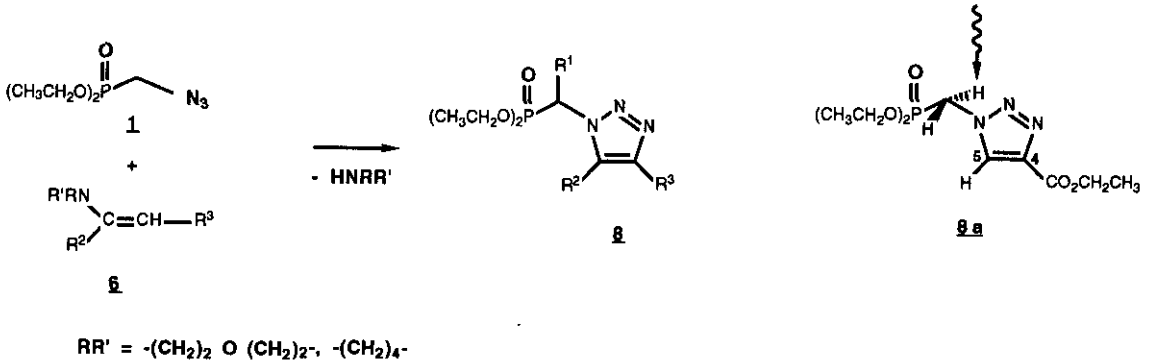
Table 1: 5-Amino-Δ^2-1,2,3-triazoline (**3**) and 1,2,3-triazole derivatives (**4, 8**)

Compound[a,b]	R^1	R R'	R^2	R^3	Conditions[c]	Yield (%)
3a	H	-$(CH_2)_2O(CH_2)_2$-			A	82
3b[d]	CH_3	-$(CH_2)_2O(CH_2)_2$-			A	76
3c	H	-$(CH_2)_4$-			A	80
3d[d]	C_6H_5	-$(CH_2)_4$-			A	88
4a	H				B	77
4b	CH_3				B	76
4c	C_6H_5				B	66
8a[e]	H		H	CO_2CH_3	C	63
8b	H		H	$CO_2CH_2CH_3$	C	65
8c	H		CH_3	CO_2CH_3	C	58
8d	H		CH_3	$PO(C_6H_5)_2$	C	56
8e	H		CH_3	$PO(OCH_2CH_3)_2$	C	60

[a]Compounds reported here gave satisfactory elemental analysis; solids· C± 0.25%; H± 0 20 %, N± 0.22 %; oils C± 0.40%; H± 0.28 %; N± 0.31 %. [b]Purified by flash column chromatography on silica gel. [c]A· THF, room temperature, 10 h. B: THF, 50°C, 24 h. C: Toluene, reflux, 48 h. [d]Obtained as a mixture of two diastereoisomers. [e]mp 85-86°C, recrystallized from CH_2Cl_2 / hexane.

Taking into account the interest of aminophosphonic acid derivatives,[1,2] the ester cleavage of phosphonates is explored. Phosphorylated triazole (**4a**) underwent ester cleavage with trimethylsilyl bromide in chloroform, followed by hydrolysis with water. Because of the hygroscopic nature of the aminophosphonic acid (**5**), it was isolated as its disodium salt (mp > 240°C (decomp.), yield 75%).

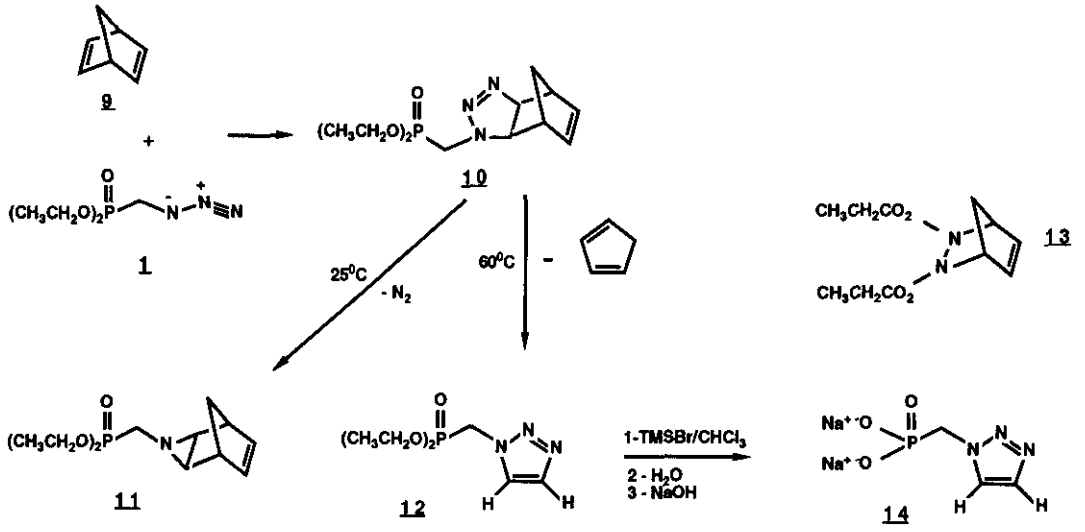
The introduction of electron withdrawing substituents in the enamine reduces the dipolarophilic activity of enamines towards azides and decreases the reaction rate;[23] however, the unidirectional pathway of this process could allow us the preparation of triazoles in a regioselective fashion. Thus, when azide (**1**) was allowed to react with enamines (**6**) derived from carboxylic esters (**6**) ($R^3 = CO_2Et$), phosphine oxide (**6**) ($R^3 = POPh_2$), and phosphonate (**6**) ($R^3 = PO(OEt)_2$) in refluxing toluene 1-phosphonomethyl-1,2,3-triazoles (**8**) were obtained[24] (see Table 1 and Scheme 2).



RR' = -$(CH_2)_2$ O $(CH_2)_2$-, -$(CH_2)_4$-

Scheme 2

Spectroscopic data are consistent with the proposal structure, in which the methylene group of compound **(8a)** gives a ^{1}H-resonance at $\delta = 4.79$ ppm ($^2J_{PH} = 13.2$ Hz) and a ^{13}C-resonance at $\delta = 45.9$ ppm ($^1J_{PC} = 155.1$Hz) as well resolved doublets, while the absorption of 5-H is shifted to a lower field ($\delta_H = 8.28$ ppm) in the ^{1}H-nmr spectrum. The structure of compounds **(8)** is confirmed by long range heteronuclear coupling with the aim of a selective experiment 1D SDEPT. Selective irradiation of the methylene signal of **8a** at $\delta = 4.79$ ppm resulted in the long range coupling between these protons and the methine carbon (5-C) of the triazole ring ($\delta = 128.5$ ppm) distant three bonds of the irradiated proton (see Scheme 2).



Scheme 3

Table 2. Selected spectral data for the compounds prepared.

Compound	ir (KBr)[a] ν (cm^{-1})	ms[b] (m/z)	^{1}H-nmr ($CDCl_3$)[c] δ (ppm)	^{13}C-nmr ($CDCl_3$)[e] δ (ppm)	^{31}P-nmr ($CDCl_3$)[d] δ (ppm)
3 a	1281 (P=O) 1025 (POC)	318(M^+-N_2, 25%)	1.19 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 1.79 (m, 6H), 2.31 (m, 4H), 3.47 (m, 4H), 3.60 (dd, $^2J_{HH}$ = 16.1 Hz, $^2J_{PH}$= 12.7 Hz, 1H), 3.93 (dd, $^2J_{HH}$= 16.1 Hz, $^2J_{PH}$= 9.7 Hz, 1H), 4.02 (m, 4H), 4.31 (d, $^3J_{HH}$ = 7.7 Hz, 1H)	16 0, 23.4, 32.1, 33.0, 41.3 (d, $^1J_{PC}$ = 163.0 Hz), 46.72, 61.8, 66.5, 79.1, 91.1	21 0
3b[e]	1267 (P=O) 1038 (POC)	332(M^+-N_2, 23%))	1.18 and 1.20 (m, 6H), 1.38 and 1.58 (dd, $^3J_{HH}$= 7.2 Hz, $^3J_{PH}$= 16.0 Hz, 3H), 1.84 (m, 6H), 2.38 (m, 4H), 3.52 and 3.57 (m, 4H), 3,72 and 4.34 (m, 1H), 4,04 (m, 4H)	16.2, 17.7, 23.3, 32 6,34.3, 46.7, 48.5 (d, $^1J_{PC}$ = 158.6 Hz, 2H), 61.7, 67,0, 78.0, 91.4	23.7 and 23 9
3 c	1236 (P=O) 1031 (POC)	233(M^+-N_2-C_4H_8N, 25%)	1.05 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 1 49 (m, 4H), 1.66 (m, 6H), 2.29 (m, 4H), 3.44 (dd, $^2J_{HH}$ = 16.2 Hz, $^2J_{PH}$= 12.3 Hz, 1H) 3.77 (dd, $^2J_{HH}$ = 16.2 Hz, $^2J_{PH}$= 9.0 Hz, 1H), 3.90 (m, 4H), 4 14 (d, $^3J_{HH}$ = 7.5 Hz, 1H)	16.1, 23 1, 32 3, 34.9, 40 9 (d, $^1J_{PC}$ = 165.0 Hz), 44.6, 46.9, 62.0, 78.4, 90 4	20.5
3d[e]	1250 (P=O) 1056 (POC)	308(M^+-N_2-C_4H_8N, 20%)	1 18 and 1.80 (m, 6H), 1.69 and 2.38 (m, 4H), 4 01 and 4.11 (m, 4H), 4.14 (m, 1H), 4.68 and 4.97(d, $^2J_{PH}$ = 26.0 Hz, d, 1H), 7.29-7.56 (m, 5H Ar)	16 2, 23.7, 24.2, 33.1 and 33.35, 35.6 and 36.31, 46.7 and 47.24, 57 2 and 58.6 (d, $^1J_{PC}$ = 153.4 Hz), 62.6 and 63.3, 77.7 and 79.3, 90.8, 128.6-129.3	21 6 and 22 3
4 a	1248 (P=O) 1028 (POC)	273(M^+, 38%)	1.24 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 1.77 (m, 4H), 2.67 (m, 4H), 4.06 (m, 4H), 4.56 (d, $^2J_{PH}$ = 12.4 Hz, 2H)	16.2, 19.9, 21.8, 22.3, 22 5, 44.5 (d, $^1J_{PC}$ = 156 7 Hz), 63.2, 133.2, 143.5	17.1
4 b	1239 (P=O) 1031 (POC)	287(M^+, 30%)	1.28 (t, $^3J_{HH}$ = 7.2 Hz, 6H), 1.78 (m, 4H), 1.81 (d, $^3J_{HH}$ = 7.5 Hz, 3H), 2.72 (m, 4H), 4.04 (m, 4H), 4.75 (dq, $^3J_{HH}$= 7 5 Hz, $^2J_{PH}$= 15.0 Hz, 1H)	14.5, 16.0, 20.1, 21.6, 22.2, 22.3, 51.5 (d, $^1J_{PC}$ = 157.8 Hz), 62 8, 132.5, 142.9	20.5
4 c	1239 (P=O) 1031 (POC)	349(M^+, 20%)	1.15 (t, $^3J_{HH}$ = 7.2 Hz, 6H), 1.69 (m, 4H), 2.54 (m, 4H), 4.02 (m, 4H), 5 69 (d, $^2J_{PH}$ = 22 9 Hz, 1H), 7.43 (m, 5H)	16.1, 19.9, 21.7, 22.2, 22 3, 60.3 (d, $^1J_{PC}$ = 156.3 Hz), 63.8, 128 6, 128.5, 128.7, 132.4, 143 3	15.8
5[f]	1137 (P=O)	261(M^+, 10%)	1.52 (m, 4H), 2.42 (m, 4H), 4.03 (d, $^2J_{PH}$ = 11.6 Hz, 2H)	20.6, 21.9, 22.7, 22.8, 48.5 (d, $^1J_{PC}$ = 132.5 Hz), 135.1, 144.1	10 5
8 a	1255(P=O) 1040 (POC)	249(M^+-N_2, 17%)	1 26 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 3.90 (s, 3H), 4.10 (m, 4H), 4.79 (d, $^2J_{PH}$ = 13 2 Hz, 2H), 8 28 (s, 1H)	16.1, 45.9 (d, $^1J_{PC}$=155.1 Hz), 52.1, 63.6, 128.5, 140.1, 160.7	15.8

Table 2.(continuation)

Compound	ir (KBr)[a] ν (cm^{-1})	ms[b] (m/z)	^{1}H-nmr ($CDCl_3$)[c] δ (ppm)	^{13}C-nmr ($CDCl_3$)[e] δ (ppm)	^{31}P-nmr ($CDCl_3$)[d] δ (ppm)
8 b	1243(P=O) 1043 (POC)	263(M^+-N_2, 20%)	1.30 (m, 12H), 4.09 (m, 4H), 4.36 (m, 2H), 4.79 (d, $^2J_{PH}$ = 13.2 Hz, 2H), 8 27 (s, 1H)	14.1, 16.1, 45.6 (d, $^1J_{PC}$=154.5 Hz), 60.5, 63.3, 128.6, 139.9, 160,0.	15.9
8 c	1246(P=O) 1047 (POC)	291(M^+, 62%)	1.28 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 2.63 (s, 3H), 3.92 (s, 3H), 4.10 (m, 4H), 4 68 (d, $^2J_{PH}$=12 6 Hz, 2H)	9.1, 16 2, 44 0 (d, $^1J_{PC}$ = 156.6 Hz), 51.9, 63.6, 131.7, 139 8, 159.5	16.5
8 d	1249(P=O) 1020 (POC)	404(M^+, 2%)	1.05 (t, $^3J_{HH}$ = 7.1 Hz, 6H), 2.40 (s, 3H), 3.87 (m, 4H), 4 52 (d, $^2J_{PH}$ = 12.7 Hz, 2H), 7.38 (m, 10H)	8.6, 16.2, 43.5 (d, $^1J_{PC}$ = 155.5 Hz), 63.2, 130.0, 133.6 (d,$^1J_{PC}$ = 268 Hz), 142 2 (d, $^2J_{PC}$ = 25.1 Hz)	17.6 20.8
8 e	1245(P=O) 1019 (POC)	369(M^+, 9%)	1.32 (m, 12H), 2.59 (s, 3H), 4.17 (m, 8H), 4.68 (d, $^2J_{PH}$ = 12.7 Hz, 2H)	8.7, 16.1, 44.1 (d, $^1J_{PC}$ = 155.5 Hz), 63.3, 132 1 (d,$^1J_{PC}$ = 238 Hz), 142.0 (d, $^2J_{PC}$ = 26.1 Hz)	16.1 7 9
1 0	1247(P=O) 1031 (POC)	191(M^+-N_2-C_5H_6, 15%)	1.21 (d, $^2J_{HH}$ = 10.0 Hz, 1H), 1 33 (m, 6H), 1 49 (d, $^2J_{HH}$ = 10.0 Hz, 1H), 3.21 (s, 1H), 3 32 (s, 1H), 3.75 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 3.85 (dd, $^2J_{HH}$ = 16.1 Hz, $^2J_{PH}$ = 7.7 Hz, 1H), 4 15 (m, 5H), 4.79 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 6.05 (d, $^3J_{HH}$ = 5.6 Hz, 1H), 6 16 (d, $^3J_{HH}$ = 5.6 Hz, 1H)	16.4, 42.3, 44.2 (d, $^1J_{PC}$ = 161.5 Hz), 46.5, 62.5, 63.3, 88.7, 137 4, 137.7.	20.7
1 1	1247(P=O) 1031 (POC)	257(M^+, 55 %)	0.94 (d, $^2J_{HH}$ = 7.7Hz, 1H), 1.31 (m, 6H), 1.72 (d, $^2J_{HH}$ = 7.7 Hz, 1H), 2.63 (s, 1H), 2.69 (s, 1H), 3 61 (d, $^3J_{HH}$ = 7.0 Hz, 1H), 3.70 (d, $^3J_{HH}$ = 7.0 Hz, 1H), 3.78 (d, $^2J_{PH}$ = 8.6 Hz, 2H), 4.15 (m, 4H), 6.28 (s, 1H), 6.30 (s, 1H)	16.4, 40.6, 42.4, 48.6, 52.5 (d, $^1J_{PC}$ = 160.3 Hz), 62 3, 140.0	21.0
1 2	1244(P=O) 1023 (POC)	219(M^+, 18 %)	1.19 (t, $^3J_{HH}$ = 7 1 Hz, 6H), 4.70 (d, $^2J_{PH}$ = 13.1 Hz, 2H), 7.71 (s, 1H), 7.78 (s, 1H)	16 2, 45.3 (d, $^1J_{PC}$ = 155.3 Hz), 63.1, 124 3, 133.8	15.6
14[f]	1240(P=O)		4.40 (d, $^2J_{PH}$ = 11.9Hz, 2H), 7 70 (s, 1H), 7.96 (s, 1H)	53.1 (d, $^1J_{PC}$ = 132.8 Hz), 129 4, 137.9	9.7

[a]Recorded in a Nicolet FTIR Magna 550. [b]Obtained on a Hewlett Packard 5890 Spectrometer. [c]Recorded in a Brucker AC-250 Spectrometer. [d]Obtained on a Varian VXR 300 Spectrometer. [e]Obtained as a mixture of two diasteroisomers, 50:50 ratio for 3b and 45:55 ratio for 3d by ^{31}P-nmr assign. [f]Nmr spectra of 5 and 14 are recorded using D_2O as solvent.

Angle strain can greatly enhance the rates of 1,3-dipolar cycloadditions relative to the cycloadditions of comparable but unstrained olefins. In this context it is worth noting that norbornadiene with azides showed reaction rates close to with enamines.[23] Thus, diethyl azidomethylphosphonate (**1**) reacts with an excess of norbornadiene (**9**) at room temperature in THF leading to the formation of cycloadduct (**10**) with an good yield (86%). Triazoline (**10**) loses nitrogen at room temperature and gives the phosphorylated aziridine (**11**) in good yield (92%), as viscous oil isolated by means of short column chromatography. However, thermolysis at 60°C of triazoline (**10**) gives the very simple 1,2,3-triazolemethylphosphonate (**12**) (yield 74%, m p 65-66°C, recrystallized from hexane / ether (Scheme 3). Formation of this product can be explained by retro Diels-Alder reaction[26] of compound (**10**) to give triazole (**12**) and cyclopentadiene. In order to test and confirm this behaviour, liberated cyclic diene is then trapped by means of [4+2] reaction with diethyl azodicarboxylate affording cycloadduct (**13**). Deprotection of triazole (**12**) with trimethylsilylbromide leads to 72% of compound (**14**) (mp > 240°C (decomp.)).

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24. Typical procedure: To the azide (**1**) (5 mmol) dissolved in 20 ml of THF or toluene (see Table 1), was added 5 mmol of enamines (**2**) and (**6**). The resulting mixture was stirred (see Table 1 for reaction temperatures and times). The solution was concentrated and the residue was then purified by flash chromatography (silica gel, hexane / ether, 1 : 1) to yield triazolines (**3**) or triazoles (**4**) and (**8**).
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