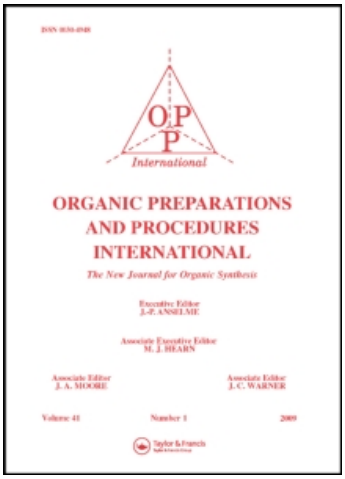

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CYCLOADDITIONS OF AZIDOALKYLCARBOXYLATES TO ACETYLENES AND ENAMINES. REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED TRIAZOLES

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CYCLOADDITIONS OF AZIDOALKYLCARBOXYLATES TO ACETYLENES AND ENAMINES. REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED TRIAZOLES

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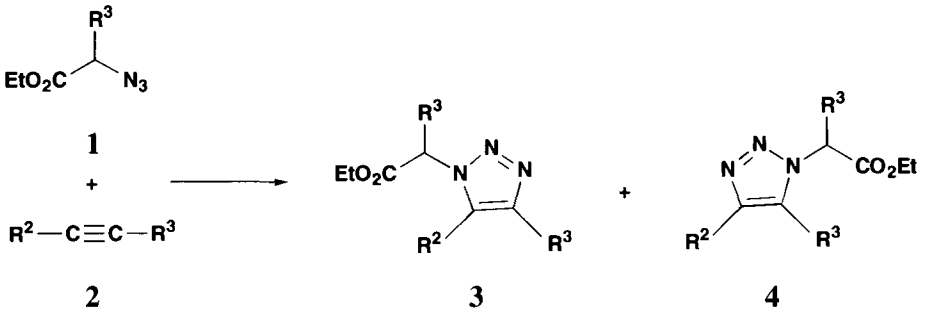
The chemistry of 1,2,3-triazoles has attracted a great deal of attention since the first example of an azide cycloaddition with an acetylenic ester was reported in the last century.[1] 1,2,3-Triazole derivatives are of significant interest not only for their theoretical interest and synthetic value as intermediates in organic synthesis,[2,3] but also for their industrial applications as optical brighteners,[4] corrosion inhibitors,[5] photostabilizers for fibers, plastic or dyestuffs as well as for the protection of human skin from harmful U.V. irradiation.[6] 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,[7] due to their behavior as anthelmintic agents[8] and their activity as fungicides[9] as well as regulatory local plant growth,[10] but also are of interest in the area of medicinal chemistry[11] as cytostatic,[12] virostatic,[13] anti-inflammatory,[14] antimicrobial agents,[15] and thymidate kinase inhibitors.[16] Moreover, 1,2,3-triazole derivatives were prepared for testing as inhibitors of human leukocyte elastase[17] (HLE) for the treatment of emphysema and as inflammatory pulmonary diseases.[18]

The 1,3-dipolar cycloadditions have been extensively reviewed and provide considerable scope for the synthesis of five-membered heterocyclic rings,[19] and one of the most versatile preparations of triazoles involves the ring formation through thermal 1,3-dipolar cycloaddition of azides and alkynes.[20,21] In this context, it is worth noting that certain variations in the starting azides, by using azidoalkyl compounds derived from trimethylsilyl compounds,[22] phosphonic acids,[23] sugars[2] and heterocycles,[17,24] might permit easier refunctionalization of the resultant cycloadducts. In connection with the study of the synthesis and reactivity of phosphazenes[25] derived from azides, we have prepared β-functionalized azides[26] and we have reported the use of azides as synthetic intermediates in the preparation of acyclic[27] and heterocyclic[28] compounds. As a continuation of our interest in the synthetic use of β-functionalized alkyl azides, we now report our investigation of the cycloaddition reaction of dipoles derived from α-aminoacids such as azidoalkylcarboxylates, isostere analogues of azidoalkylphosphonates,[28] with alkynes and enamines and describe an efficient synthesis of substituted triazoles.

Electron-deficient acetylenes add to azides to form 1,2,3-triazoles. Thus, when ethyl

azidoalkylcarboxylates **1** were treated with dimethyl acetylenedicarboxylate (Table 1) in refluxing tetrahydrofuran, 1-ethoxycarbonylalkyl-1,2,3-triazole **3a** was obtained in good yield. Similarly, the cycloaddition reaction of azides **1** with acetylenecarboxylates (ethyl propiolate, ethyl phenylpropiolate), acetylenephosphonate and propargyl bromide gave regioisomeric substituted triazoles **3** and **4**.



Scheme 1

The reaction conditions, the yields and the regioisomeric ratios are given in Table 1. The more electron-deficient dipolarophiles react at faster rates, compared with the less electron-deficient and sterically hindered dipolarophiles.

Table 1. Cycloaddition Reactions with Acetylenic Dipolarophile

Entry	Compound	R^1	R^2	R^3	T (°C)	Reaction Time (hrs)	**3/4** ratio[a]	Yield (%)
1	**a**	H	$MeCO_2$	$MeCO_2$	66	36	b	80
2	**b**	H	H	$EtCO_2$	66	50	75/25	85
3	**c**	Me	H	$EtCO_2$	66	52	80/20	90
4	**d**	H	Ph	$EtCO_2$	110	72	50/50	88
5	**e**	Me	Ph	$EtCO_2$	110	80	50/50	90
6	**f**	H	H	$BrCH_2$	110	90	70/30[c]	60
7	**g**	H	Me	$(EtO)_2PO$	110	96	30/70	75
8	**h**	Me	Me	$(EtO)_2PO$	110	96	50/50	70

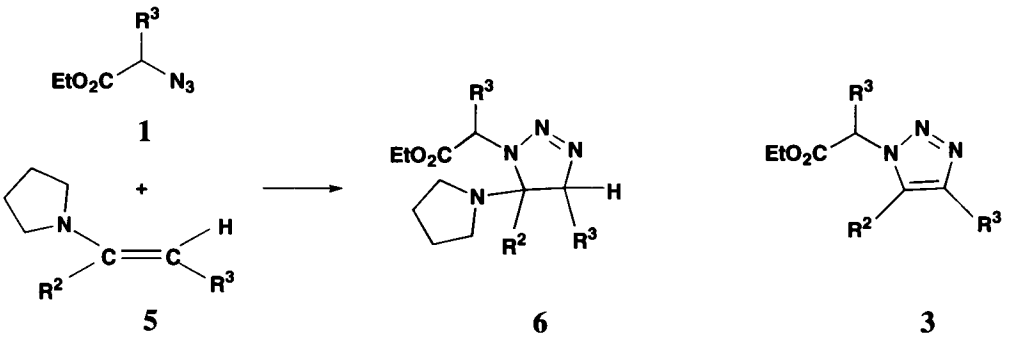
a) Determined by GC from crude reaction mixtures; b) Only one triazole is obtained; c) Obtained as a mixture of both isomers

Regioisomeric triazoles **3** and **4** were characterized on the basis of their spectroscopic data. In ^1H NMR spectrum of compound **3b**, the methylene protons resonate at δ 5.16 ppm and the heterocyclic proton gives a singlet at δ 8.20 ppm, while the ^{13}C NMR spectrum reveals absorptions at δ 140.3 and 129.1 ppm attributable to C-4 and C-5. Conversely, regioisomeric triazole **4b** showed clearly different absorptions, namely a singlet at δ 5.44 ppm for the methylene protons and a downfield signal for the heterocyclic proton at δ 8.11 ppm, while in the ^{13}C NMR spectrum the absorptions

of C-4 and C-5 appear at δ 137.5 and 128.5 ppm. NOE difference experiments were used to assign the structure of regioisomers **3** and **4**. Irradiation of the methylene protons of **3b** led to enhancement of the heterocyclic 5-position proton. However, no enhancement was detected in the related irradiation experiment with compound **4b**. This result supports the proposed structures for regioisomers **3b** and **4b** and is consistent with those reported assignments for 1,2,3-triazoles.[17,21c-e,28a] The structures of **3c-h** and **4c-h** were assigned on the basis of comparison of the ^1H NMR and ^{13}C NMR data with compounds **3b** and **4b** and with previously reported data.[17,28a] Comparison of the ^1H NMR chemical shifts of the methylene protons of compounds **3** with **4** showed that the **3** regioisomers methylene shift is in the range of 0.44-0.19 ppm further highfield relative to the **4** isomer CH_2 shift.

The low regiochemistry observed was supported by the frontier molecular orbital (FMO) theory,[29] since acetylenes undergo simultaneously both azide-LUMO and azide-HOMO controlled cycloadditions. Therefore, enamines could be used as synthetic equivalents of acetylenes in 1,3-dipolar cycloaddition reactions. Enamines are excellent dipolarophiles and react under mild conditions; the amino group controls the regiochemistry of the reaction. The process is unidirectional and stereospecific.[30] Thermal elimination of the amino group from the initially formed triazolines gives triazoles **3**. With this in mind, we explored the reaction of azidoalkylcarboxylates **1** with enamines **5** with the aim of obtaining functionalized triazoles **3** in a regioselective fashion.

The cycloaddition reaction of azides derived from α-aminoacids **1** with cyclopentenylpyrrolidine (**5**, $R^2R^3 = (CH_2)_3$) proceeded in good yield at room temperature for 24 hrs and afforded 5-amino substituted triazoline **6** ($R^2R^3 = (CH_2)_3$) in a regioselective fashion (Scheme 2). Thermolysis of **6** ($R^2R^3 = (CH_2)_3$) did not give the corresponding triazole.[31]



Scheme 2

However, when cyclohexenylpyrrolidine (**5i**, $R^2R^3 = (CH_2)_4$) was used, triazoline **6** was not isolated but underwent spontaneous aromatization to triazoles **3i, j** (Table 2, entries 6, 7) by elimination of pyrrolidine. In order to enhance the scope and the synthetic use of this reaction, the synthesis of triazole derivatives substituted with phosphoric and carboxylic ester groups was explored and the regiospecific addition of azides to enamines has been extended to functionalized enamines **5** (R^2 = H, $R^3 = CO_2Et$, $PO(OEt)_2$).

Table 2. Regioselective Synthesis of Substituted Triazole **3**

Entry	Compound	R^1	R^2	R^3	T (°C)	Reaction Time (hrs)	Yield (%)
1	b	H	H	$EtCO_2$	110	120	50
2	c	Me	H	$EtCO_2$	110	120	50
3	d	H	Ph	$EtCO_2$	110	120	40
4	e	Me	Ph	$EtCO_2$	110	120	50
5	g	H	Me	$(EtO)_2PO$	110	120	60
6	i	H	$(CH_2)_4$		66	48	60
7	j	Me	$(CH_2)_4$		66	48	70

Table 3. Spectral Data of Compounds **3**, **4** and **6**

Cmpd	^{1}H NMR (250 MHz, $CDCl_3$) (δ, Hz)	^{13}C NMR (75 MHz, $CDCl_3$) (δ, Hz)
3a	1.23 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.20 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 5.39 (s, 2H, NCH_2)	13.7 (CH_3), 51.3 (NCH_2), 52.5 (OCH_3), 53.1 (OCH_3), 62.3 (OCH_2), 129.7 (C =), 139.9 (= C), 158.3 (COO), 159.9 (COO), 165.3 (COO)
3b	1.24 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.35 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 4.21 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.37 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 5.16 (s, 2H, NCH_2), 8.20 (s, 1H, HC =)	13.8 (CH_3), 14.1 (CH_3), 50.9 (NCH_2), 61.0 (OCH_2), 62.4 (OCH_2), 129.1 (HC =), 140.3 (= C), 160.9 (COO), 165.7 (COO)
4b	1.20 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.34 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 4.17 (q, 3H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.33 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 5.44 (s, 2H, NCH_2), 8.11 (s, 1H, = CH)	13.9 (CH_3), 14.1 (CH_3), 51.2 (NCH_2), 62.2 (OCH_2), 62.3 (OCH_2), 128.5 (C =), 137.5 (= CH), 158.8 (COO), 165.3 (COO)
3c	1.18 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.31 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.80 (d, 3H, $^3J_{HH}$ = 7.3 Hz , CH_3), 4.15 (q, 2H,$^3J_{HH}$ = 7.1 Hz, OCH_2), 4.33 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 5.46 (q, 1H, $^3J_{HH}$ = 7.3 Hz, NCH), 8.28 (s, 1H, HC =)	13.7 (CH_3), 14.1 (CH_3), 17.8 (CH_3), 58.3 (NCH), 61.0 (OCH_2), 62.4 (OCH_2), 127.3 (HC =), 140.0 (= C), 160.5 (COO), 168.7 (COO)
4c	1.20 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.34 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.95 (d, 3H, $^3J_{HH}$ = 7.3 Hz , CH_3), 4.17 (q, 2H,$^3J_{HH}$ = 7.1 Hz, OCH_2), 4.33 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 5.83 (q, 1H, $^3J_{HH}$ = 7.3 Hz, NCH), 8.13 (s, 1H, = CH)	13.9 (CH_3), 14.1 (CH_3), 16.4 (CH_3), 58.6 (NCH), 61.9 (OCH_2), 52.1 (OCH_2), 62.1 (OCH_2), 128.4 (C =), 137.8 (= CH), 158.5 (COO), 168.9 (COO)
3d	1.23 (m, 6H, CH_3), 4.17 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.30 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.99 (s, 2H, NCH_2), 7.37-7.50 (m, 5H, arom.)	13.7 (CH_3), 13.8 (CH_3), 49.0 (NCH_2), 60.8 (OCH_2), 62.2 (OCH_2), 125.2 (C =), 128.5-130.1 (C arom.), 141.8 (= C), 160.5 (COO), 165.7 (COO)
4d	1.21 (m, 6H, CH_3), 4.22 (m, 4H, OCH_2), 5.43 (s, 2H, NCH_2), 7.35-7.69 (m, 5H, arom.)	13.7 (CH_3), 14.0 (CH_3), 52.2 (NCH_2), 62.0 (OCH_2), 62.2 (OCH_2), 124.9 (C =), 127.9-129.9 (C arom.), 150.2 (= C), 158.9 (COO), 166.4 (COO)

Table 3. Continued

Cmpd	^{1}H NMR (250 MHz, $CDCl_3$) (δ, Hz)	^{13}C NMR (75 MHz, $CDCl_3$) (δ, Hz)
3e	1.17 (m, 6H, CH_3), 1.83 (d, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3), 4.12 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.24 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.93 (q, 1H, $^3J_{HH}$ = 7.3 Hz, NCH), 7.25-7.50 (m, 5H, arom.)	13.9 (CH_3), 14.0 (CH_3), 17.0 (CH_3), 56.4 (NCH), 60.8 (OCH_2), 62.3 (OCH_2), 125.8 (C =), 128.7-136.2 (C arom.), 141.6 (= C), 160.8 (COO), 168.4 (COO)
4e	1.22 (m, 6H, CH_3), 2.02 (d, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3), 4.25 (m, 4H, OCH_2), 5.83 (q, 1H, $^3J_{HH}$ = 7.3 Hz, NCH), 7.38-7.74 (m, 5H, arom.)	13.6 (CH_3), 14.0 (CH_3), 16.6 (CH_3), 59.3 (NCH), 61.9 (OCH_2), 62.0 (OCH_2), 124.6 (C =), 127.8-130.2 (C arom.), 150.3 (= C), 159.3 (COO), 169.2 (COO)
3f	1.30 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 4.28 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.59 (s, 2H, $BrCH_2$), 5.14 (s, 2H, NCH_2), 7.74 (s, 1H, HC =)	14.0 (CH_3), 21.5 ($BrCH_2$), 50.9 (NCH_2), 62.5 (OCH_2), 124.3 (HC =), 144.9 (= C), 166.1 (COO)
4f	1.28 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 4.25 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.51(s, 2H, $BrCH_2$), 5.27 (s, 2H, NCH_2), 7.69 (s, 1H, = CH)	14.0 (CH_3), 17.1 ($BrCH_2$), 49.5 (NCH_2), 62.5 (OCH_2), 133.8 (C =), 134.1 (= CH), 166.2 (COO)
3g	1.26 (m, 9H, CH_3), 2.45 (s, 3H, CH_3), 4.18 (m, 6H, OCH_2), 5.09 (s, 2H, NCH_2)	8.5 (CH_3), 14.0 (CH_3), 16.1 (CH_3), 48.7 (NCH_2), 62.5 (OCH_2), 62.9 (OCH_2), 134.3 ($^1J_{PC}$ = 238.5 Hz, = C), 141.8 ($^2J_{PC}$ = 34.9 Hz, C =), 165.6 (COO)
4g	1.21 (m, 9H, CH_3), 2.36 (s, 3H, CH_3), 4.10 (m, 6H, OCH_2), 5.30 (s, 2H, NCH_2)	10.9 (CH_3), 13.7 (CH_3),15.6 (CH_3), 51.0 (NCH_2), 61.7 (OCH_2), 62.5 (OCH_2), 122.7 ($^1J_{PC}$ = 218.6 Hz, C =), 149.7 ($^2J_{PC}$ = 20.4 Hz, = C), 166.6 (COO)
3h	1.17 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.27 (m, 6H, CH_3), 1.89 (d, 3H, $^3J_{HH}$ = 7.3 Hz , CH_3), 2.46 (s, 3H, CH_3), 4.14 (m, 6H, OCH_2), 5.13 (q, 1H, $^3J_{HH}$ = 7.3 Hz , CH)	8.7 (CH_3), 13.9 (CH_3), 16.1 (CH_3), 16.5 (CH_3), 56.4 (CH), 62.4 (OCH_2), 62.8 (OCH_2), 134.3 ($^1J_{PC}$ = 237.2 Hz, = C), 141.0 ($^2J_{PC}$ = 34.7 Hz, C =), 168.3 (COO)
4h	1.19 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.27 (m, 6H, CH_3), 1.90 (d, 3H, $^3J_{HH}$ = 7.3 Hz , CH_3), 2.43 (s, 3H, CH_3), 4.11 (m, 6H, OCH_2), 5.78 (q, 1H, $^3J_{HH}$ = 7.3 Hz , CH)	11.3 (CH_3), 13.8 (CH_3), 15.9 (CH_3), 16.8 (CH_3), 58.1 (CH), 61.8 (OCH_2), 62.9 (OCH_2), 122.6 ($^1J_{PC}$ = 220.0 Hz, C =), 150.0 ($^2J_{PC}$ = 19.9 Hz, = C), 169.2 (COO)
3i	1.26 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.82 (m, 4H, CH_2), 2.54 (m, 2H, CH_2), 2.74 (m, 2H, CH_2), 4.22 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.98 (s, 2H, NCH_2)	14.2 (CH_3), 19.9 (CH_2), 21.9 (CH_2), 22.4 (CH_2), 22.6 (CH_2), 48.8 (NCH_2), 62.3 (OCH_2), 133.1 (C =), 143.7 (= C), 166.5 (COO)
3j	1.25 (t, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.82 (m, 4H, CH_2), 1.86 (d, 3H, $^3J_{HH}$ = 7.3 Hz , CH_3), 2.62 (m, 2H, CH_2), 2.72 (m, 2H, CH_2), 4.20 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 5.24 (q, 1H, $^3J_{HH}$ = 7.3 Hz , CH)	13.8 (CH_3), 16.2 (CH_3), 20.1 (CH_2), 21.6 (CH_2), 22.2 (CH_2), 22.4 (CH_2), 56.2 (NCH), 61.7 (OCH_2), 132.1 (C =), 143.1 (= C), 168.8 (COO)
6	1.23 (m, 3H, $^3J_{HH}$ = 7.1 Hz , CH_3), 1.70 (m, 4H, CH_2), 1.92 (m, 6H, CH_2), 2.46 (m, 4H, CH_2), 4.11 (d, 1H, $^2J_{HH}$ = 17.8 Hz, NCH), 4.12 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.32 (d, 1H, $^3J_{HH}$ = 7.5 Hz, CH), 4.42 (d, 1H, $^2J_{HH}$ = 17.8 Hz, NCH)	13.8 (CH_3), 23.5 (CH_2), 23.9 (CH_2), 32.6 (CH_2), 35.5 (CH_2), 46.5 (NCH_2), 46.9 (CH_2), 60.9 (OCH_2), 78.1 (CH), 89.4 (C-N), 169.5 (COO)

The dipolarophilic activity of enamines is reduced by the introduction of electron-withdrawing groups; the enamino-esters or -phosphonates do not behave as acrylic derivatives but as enamines (LUMO azide controlled processes). Thus, cycloaddition of azides **1** and functionalized enamines **5** required more time and higher temperature (Table 2, entries 6, 7) than simple enamines, and the expected triazoles **3** were obtained when the reaction was performed in refluxing toluene. Triazolines **6b-g** resulting from the reaction of azides and enamino ester and enaminophosphonates are unstable in the reaction conditions and are not isolated because they aromatize to triazoles **3** by expulsion of a molecule of amine. In conclusion, the synthesis described in this communication provides an easy access to regioselective triazoles **3** substituted with electron-withdrawing groups at position 4, making use of readily available starting materials.

EXPERIMENTAL SECTION

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); tetrahydrofuran (Na). All other reagents were recrystallized or distilled as necessary. Column (flash) chromatography was carried out on silica gel (Merck, 70-230 mesh). Mass spectra were obtained on a Hewlett Packard 5890 spectrometer. ^{1}H and ^{13}C NMR and NOE experiments were recorded on a Bruker 75 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. Mass spectra (EI) were obtained with a ionization voltage of 70 eV. Data are reported in the form *m/z* (intensity relative to base = 100).

General Procedure for the Cycloaddition of Azidoalkylcarboxylates with Acetylenes.- To a solution of ethyl 1-azidoalkylcarboxylate **1** (R = H, CH_3,[32,33] 3 mmol, 0.39g) in THF or toluene (15 mL) was added dropwise with stirring a solution of acetylene **2** (3 mmol), and the reaction mixture was stirred at the appropriate temperature (see Table 1). Concentration in vacuum gave the mixture of two regioisomeric cycloadducts **3** and **4** isolated by flash column chromatography (silica gel).

1-(Ethoxycarbonylmethyl)-4,5-*bis*(methoxycarbonyl)-1,2,3-triazole (3a).- Reaction with dimethyl acetylenedicarboxylate (3 mmol, 0.43g) in refluxing THF, gave 0.65g (80%) of the compound **3a** as a white solid, mp. 123-124°, R_f (ethyl acetate/*n*-hexane 1:1): 0.48. MS, *m/z*: 243 ($M^+ - N_2$, 4%).

Anal. Calcd. for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.80; N, 15.50. Found: C, 44.34; H, 4.78; N, 15.53

1-(Ethoxycarbonylmethyl)-4-ethoxycarbonyl-1,2,3-triazole (3b) and 1-(Ethoxycarbonylmethyl)-5-ethoxycarbonyl-1,2,3-triazole (4b).- Reaction with ethyl propiolate (3 mmol, 0.29g) in refluxing THF gave 0.61g (85%) of the mixture of **3b** and **4b** (75/25). Data for **3b**: Obtained as a white solid, mp. 88-89°. R_f (ethyl acetate/*n*-hexane 1:1): 0.27. MS, *m/z*: 199 ($M^+ - N_2$, 2%).

Anal. Calcd. for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.72; N, 18.50. Found: C, 47.71; H, 5.71; N, 18.52

Data for **4b**: Obtained as a yellow oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.59. MS, *m/z*: 185 ($M^+ - N_2$, 32%).

Anal. Calcd. for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.72; N, 18.50. Found: C, 47.68; H, 5.70; N, 18.53

1-(1-Ethoxycarbonylethyl)-4-ethoxycarbonyl-1,2,3-triazole (3c) and 1-(1-Ethoxycarbonylethyl)-5-ethoxycarbonyl-1,2,3-triazole (4c).- Reaction with ethyl propiolate (3 mmol, 0.29g) in refluxing THF gave 0.65g (90%) of the mixture of **3c** and **4c** (80/20). Data for **3c**: Obtained as a yellow oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.54. MS, *m/z*: 213 ($M^+ - N_2$, 11%).

Anal. Calcd. for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.22; N, 17.43. Found: C, 49.81; H, 6.25; N, 17.47

Data for **4c**: Obtained as a yellow oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.70. MS, *m/z*: 213 ($M^+ - N_2$, 5%).

Anal. Calcd. for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.22; N, 17.43. Found: C, 49.84; H, 6.26; N, 17.44

1-(Ethoxycarbonylmethyl)-4-ethoxycarbonyl-5-phenyl-1,2,3-triazole (3d) and 1-(Diethoxycarbonylmethyl)-5-ethoxycarbonyl-4-phenyl-1,2,3-triazole (4d).- Reaction with ethyl phenylpropiolate (3 mmol, 0.52g) in refluxing toluene gave 0.80g (88%) of the mixture of **3d** and **4d** (50/50). Data for **3d**: Obtained as a white solid, mp. 71-72°. R_f (ethyl acetate/*n*-hexane 1:1): 0.60. MS, *m/z*: 303 (M^+, 6%).

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.41; H, 5.61; N, 13.86. Found: C, 59.48; H, 5.65; N, 13.89

Data for **4d**: Obtained as a yellow oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.71. MS, *m/z*: 303 (M^+, 47%).

Anal. Calcd. for $C_{15}H_{17}N_3O_4$: C, 59.41; H, 5.61; N, 13.86. Found: C, 59.44; H, 5.66; N, 13.84.

1-(1-Ethoxycarbonylethyl)-4-ethoxycarbonyl-5-phenyl-1,2,3-triazole (3e) and 1-(1-Ethoxycarbonylethyl)-5-ethoxycarbonyl-4-phenyl-1,2,3-triazole (4e).- Reaction with ethyl phenylpropiolate (3 mmol, 0.52g) in refluxing toluene gave 0.85g (90%) of the mixture of **3e** and **4e** (50/50). Data for **3e**: Obtained as a yellow oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.65. MS, *m/z*: 317 (M^+, 30%).

Anal. Calcd. for $C_{16}H_{19}N_3O_4$: C, 60.57; H, 5.99; N, 13.25. Found: C, 60.63; H, 6.05; N, 13.29

Data for **4e**: Obtained as a yellow oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.80. MS, *m/z*: 317 (M^+, 20 %).

Anal. Calcd. for $C_{16}H_{19}N_3O_4$: C, 60.57; H, 5.99; N, 13.25. Found: C, 60.59; H, 6.02; N, 13.30

5-Bromomethyl-1-(Ethoxycarbonylmethyl)-1,2,3-triazole (3f) and 4-Bromomethyl-1-(Ethoxycarbonylmethyl)-1,2,3-triazole (4f).- Reaction with propargyl bromide (3 mmol, 0.36g) in refluxing toluene gave 0.45g (60%) of the mixture of **3f** and **4f** (70/30). Data of the mixture of **3f** and **4f**: Obtained as white solid, mp. 80-82°. R_f (ethyl acetate/*n*-hexane 1:1): 0.71. MS, *m/z*: 249 (M^++1, 2%).

Anal. Calcd. for $C_7H_{10}BrN_3O_2$: C, 33.87; H, 4.03; N, 16.94. Found: C, 33.93; H, 4.05; N, 16.99

1-(Ethoxycarbonylmethyl)-4-diethoxyphosphoryl-5-methyl-1,2,3-triazole (3g) and 1-(Ethoxycarbonylmethyl)-5-diethoxyphosphoryl-4-methyl-1,2,3-triazole (4g).- Reaction with diethyl 2-propinylphosphonate (3 mmol, 0.53g) in toluene refluxing toluene gave 0.69g (75%) of the mixture of **3g** and **4g** (30/70). Data for **3g**: Obtained as a yellow oil. R_f (ethyl acetate): 0.45. MS, *m/z*: 305 (M^+, 2%).

Anal. Calcd. for $C_{11}H_{20}N_3O_5P$: C, 43.28; H, 6.56; N, 13.77. Found: C, 43.30; H, 6.59; N, 13.80

Data for **4g**: Obtained as a yellow oil. R_f (ethyl acetate): 0.55. MS, *m/z*: 305 (M^+, 7%).

Anal. Calcd. for $C_{11}H_{20}N_3O_5P$: C, 43.28; H, 6.56; N, 13.77. Found: C, 43.34; H, 6.60; N, 13.79

1-(1-Ethoxycarbonylethyl)-4-diethoxyphosphoryl-5-methyl-1,2,3-triazole (3h) and 1-(1-Ethoxycarbonylethyl)-5-diethoxyphosphoryl-4-methyl-1,2,3-triazole (4h).- Reaction with diethyl 2-

propinylphosphonate (3 mmol, 0.53g) in toluene refluxing toluene gave 0.67g (70%) of the mixture of **3h** and **4h** (50/50). Data for **3h**: Obtained as a yellow oil. R_f (ethyl acetate): 0.34. MS, *m/z*: 319 (M^+, 4%).

Anal. Calcd. for $C_{12}H_{22}N_3O_5P$: C, 45.14; H, 6.89; N, 13.16. Found: C, 45.16; H, 6.90; N, 13.19

Data for **4h**: Obtained as a yellow oil. R_f (ethyl acetate): 0.60. MS, *m/z*: 319 (M^+, 1%).

Anal. Calcd. for $C_{12}H_{22}N_3O_5P$: C, 45.14; H, 6.89; N, 13.16. Found: C, 45.18; H, 6.91; N, 13.18

General Procedure for the Cycloaddition of Azidoalkylcarboxylates with Enamines.- To a solution of ethyl 1-azidoalkylcarboxylate **1** (3 mmol, 0.39g) in THF or toluene (15 mL) was added dropwise with stirring a solution of enamine **5** (3 mmol), and the reaction mixture was stirred to adequate temperature (see Table 2), and the solvent was evaporated. Crude residue was purified by flash column chromatography (silica gel) to give product **3**.

The products **3b-e** and **3g** and their physical constant and spectral data are identical with those previously obtained.

4,5-Tetramethylene-1-(ethoxycarbonylmethyl)-1,2,3-triazole (3I).- Reaction with cyclohexanepyrrolidine (3 mmol, 0.45g) in refluxing THF gave 0.38g (60%) of **3i**. Data for **3i**: Obtained as a white solid, mp. 97-98°. R_f (ethyl acetate/*n*-hexane 1:1): 0.19. MS, *m/z*: 209 (M^+, 13%).

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.42; H, 7.18; N, 20.09. Found: C, 57.44; H, 7.21; N, 20.13

4,5-Tetramethylene-1-(1-ethoxycarbonylethyl)-1,2,3-triazole (3j).- Reaction with cyclohexanepyrrolidine (3 mmol, 0.45g) in refluxing THF gave 0.46g (70%) of **3j**. Data for **3j**: Obtained as a yellow oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.39. MS, *m/z*: 223 (M^+, 15%).

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.19; H, 7.62; N, 18.83. Found: C, 59.23; H, 7.65; N, 18.86

1-(Ethoxycarbonylmethyl)-5-N-pyrrolidinyl-4,5-trimethylene-1,2,3-triazole (6, $R^2R^3 = (CH_2)_3$).- Reaction with cyclohexanepyrrolidine (3 mmol, 0.45g) in THF at room temperature for 24 hrs gave 0.55g (70%) of **6** ($R^2R^3 = (CH_2)_3$). Data for **6**: Obtained as a brown oil. R_f (ethyl acetate/*n*-hexane 1:1): 0.41.

Anal. Calcd. for $C_{13}H_{22}N_4O_2$: C, 58.65; H, 8.27; N, 21.05. Found: C, 58.69; H, 8.29; N, 21.09

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