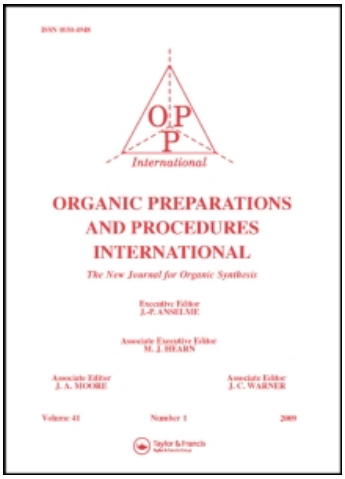

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1,3-DIPOLAR CYCLOADDITION OF AZIDOALKYLPHOSPHONATES AND CARBOXYLATES TO MALEIMIDE AND NAPHTHOQUINONE

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1,3-DIPOLAR CYCLOADDITION OF AZIDOALKYLPHOSPHONATES AND CARBOXYLATES TO MALEIMIDE AND NAPHTHOQUINONE

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1-Aminoalkylphosphonate derivatives, isostere phosphonic analogues of α-aminoacids, are a new class of compounds with interesting biological properties[1] and thus are of significant interest in medicinal chemistry.[1-5] They are a unique class of simple mimetics of aminoacids and are used as antibacterial agents, neuromodulators, antibiotics, anticancer and antihypertensive drugs,[1] as well as neutral endopeptidase inhibitors[2], endotheling-converting enzyme inhibitors,[3] irreversible inhibitors for blood coagulation,[4] and as other enzyme inhibitors.[5] Furthermore, heterocycles derived from maleimides are utilized in the synthesis of polymers,[6] while quinone derivatives exhibit high anti-cancer activity.[7] Maleimide and naphthoquinone are widely used as dipolarophiles in 1,3-dipolar cycloaddition reactions.[8] In spite of the potential interest of the cycloadducts, there is little information about the reaction of both these dipolarophiles with azides.[9] To the best of our knowledge, the reaction with maleimide is restricted to the use of aryl,[10] silylazides[11] and azidoalkylindoles,[12] while in the case of quinones the reaction with aryl[13] and glicosylazides[14] has been reported.

In recent years, we have been involved in the chemistry of phosphazenes[15] derived from azides[16] and enamino functionalized phosphorus derivatives,[17] in their use in the synthesis of the heterocyclic[18] and acyclic[19] compounds as well as in the 1,3-cycloaddition reaction of azides derived from aminophosphonates with alkynes and electron-rich olefines such as enamines.[20] We now describe the intermolecular cycloaddition of azidoalkyl-phosphonates and carboxylates with electron-poor double bonds such as maleimide and naphtoquinone.

Maleimide **1** adds azidoalkylphosphonates **2** in tetrahydrofuran at room temperature (48 hrs) to give isolable triazolinealkylphosphonates **3** (E = $PO(OEt)_2$), members of the 2,3,4,7-tetraazabicyclo[3.3.0]octane family. When R ≠ H a mixture of two diastereoisomers is obtained. The spectral data (Table 1) are in agreement with bicyclic compounds **3**. The vicinal coupling constants are in the range of 10.9-11.2 Hz for H-1 and H-5 protons, evidence for the *syn* configuration of the ring junction protons[11] and they are consistent with a stereospecific *cis* addition[21] of maleimide to the azide. Thermolysis of triazolines **3** triggers nitrogen evolution and leads to the enamines **4**. Spectroscopic data are consistent with the proposed structure, showing in the ^1H NMR spectrum of **4a** a singlet at δ 5.10 ppm

for the heterocyclic proton at the 4-position. Azides derived from aminoesters such as azidoalkylcarboxylate **5** react similarly with maleimide yielding triazolinealkylcarboxylate **6** (E = CO_2Et). Thermal nitrogen elimination from triazoline gives the corresponding aminosubstituted maleimide **7** (Scheme 1).

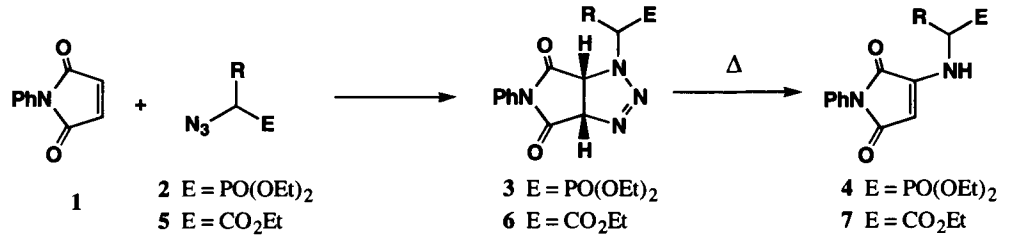
Table 1. Spectral Data of Triazolines (**3**, **6**) and Enamines (**4**, **7**).

Cmpd	^{31}P NMR (δ, ppm)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
3a	19.6	1.35 (t, 6H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.19 (m, 5H, OCH_2, CHN), 4.57 (dd, 1H, $^{2}J_{PH}$ = 16.3 Hz, $^{2}J_{HH}$ = 13.1 Hz, CHN), 4.89 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 5.67 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 7.22-7.48 (m, 5H, arom.)	16.4 (CH_3), 43.8 (d, $^{1}J_{PC}$ = 155.1 Hz, CH_2N), 57.5 (CH), 62.9 (OCH_2), 81.9 (CH), 126.2-130.8 (C arom.), 169.4 (C=O), 170.9 (C=O)
3b	23.5	1.32 (t, 6H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 1.72 (dd, 3H, $^{3}J_{PH}$ = 16.3 Hz, $^{3}J_{HH}$ = 7.5 Hz, CH_3), 4.15 (m, 4H, OCH_2), 4.69 (m, 1H, CHN), 4.91 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 5.74 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 7.25-7.46 (m, 5H, arom.)	15.1 (CH_3), 16.4 (CH_3), 52.1 (d, $^{1}J_{PC}$ = 149.1 Hz, CHN), 57.2 (CH), 62.8 (OCH_2), 82.6 (CH), 126.2-130.8 (C arom.), 168.8 (C=O), 171.3 (C=O)
3b'	21.8	1.35 (m, 6H, CH_3), 1.79 (dd, 3H, $^{3}J_{PH}$ = 16.1 Hz, $^{3}J_{HH}$ = 7.3 Hz, CH_3), 4.16 (m, 4H, OCH_2), 4.30 (m, 1H, CHN), 4.96 (d, 1H, $^{3}J_{HH}$ = 11.2 Hz, CH), 5.70 (d, 1H, $^{3}J_{HH}$ = 11.2 Hz, CH), 7.24-7.47 (m, 5H, arom.)	15.0 (CH_3), 16.4 (CH_3), 52.3 (d, $^{1}J_{PC}$ = 152.9 Hz, CHN), 59.0 (CH), 62.8 (OCH_2), 81.3 (CH), 126.2-130.9 (C arom.), 169.5 (C=O), 171.6 (C=O)
3c	17.5	1.18 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 1.25 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.12 (m, 4H, OCH_2), 4.28 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 5.35 (d, 1H, $^{2}J_{PH}$ =24.2 Hz, CHN), 5.61 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 7.30-7.48 (m, 10H, arom.)	16.2 (CH_3), 56.9 (CH), 60.5 (d, $^{1}J_{PC}$ = 152.6 Hz, CHN), 63.5 (OCH_2), 80.7 (CH), 126.2-132.3 (C arom.), 168.9 (C=O), 170.6 (C=O)
3c'	17.6	1.25 (m, 6H, CH_3), 4.10 (m, 4H, OCH_2), 4.76 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 5.29 (d, 1H, $^{2}J_{PH}$ =21.9 Hz, CHN), 5.73 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 7.35-7.55 (m, 10H, arom.)	16.2 (CH_3), 59.3 (CH), 61.7 (d, $^{1}J_{PC}$ = 152.1 Hz, CHN), 63.5 (OCH_2), 81.0 (CH), 126.0-132.9 (C arom.), 169.8 (C=O), 170.7 (C=O)
4a	20.5	1.37 (m, 6H, CH_3), 3.56 (dd, 2H, $^{2}J_{PH}$ = 12.8 Hz, $^{3}J_{HH}$ =6.2 Hz, CH_2N), 4.21 (m, 4H, OCH_2), 5.10 (s, 1H, CH=), 5.74 (broad t, 1H,$^{3}J_{HH}$ =6.2 Hz, NH)[a], 7.26-7.47 (m, 5H, arom.)	16.5 (CH_3), 40.5 (d, $^{1}J_{PC}$ = 158.7 Hz, CH_2N), 63.0 (OCH_2), 86.4 (CH=), 125.8-131.8 (C arom.), 148.9 (C=), 165.9 (C=O), 170.8 (C=O)

Table 1. Continued

Cmpd	^{31}P NMR (δ, ppm)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
4b	23.5	1.30 (m, 6H, CH_3), 1.47 (dd, 3H, $^3J_{PH}$ = 16.6 Hz, $^3J_{HH}$ = 7.3 Hz, CH_3), 3.60 (m, 1H, CHN), 4.13 (m, 4H, OCH_2), 5.02 (s, 1H, CH=), 5.54 (d, 1H, $^3J_{HH}$ =8.3 Hz, NH)[a], 7.24-7.41 (m, 5H, arom.)	15.1 (CH_3), 16.5 (CH_3), 47.5 (d, $^1J_{PC}$ = 160.1 Hz, CHN), 62.9 (OCH_2), 86.2 (CH=), 125.7-131.6 (C arom.), 147.7 (C=), 165.9 (C=O), 170.7 (C=O)
4c	19.6	1.15 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.31 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.75-4.14 (m, 4H, OCH_2), 4.62 (dd, 1H, $^2J_{PH}$ =21.4 Hz, $^3J_{HH}$ = 7.3 Hz, CHN), 4.86 (s, 1H, CH=), 6.28 (t, 1H, $^3J_{HH}$ = 7.3 Hz, NH)[a], 7.27-7.45 (m, 10H, arom.)	16.4 (CH_3), 56.7 (d, $^1J_{PC}$ = 153.3 Hz, CHN), 63.9 (OCH_2), 88.4 (CH=), 125.8-132.8 (C arom.), 147.6 (C=), 166.0 (C=O), 170.5 (C=O)
6a		1.29 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 4.23 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 4.60 (d, 1H, $^3J_{HH}$ = 10.9 Hz, CH), 4.62 (d, 1H, $^2J_{HH}$ = 18.3 Hz, CHN), 4.83 (d, 1H, $^2J_{HH}$ = 18.3 Hz, CHN), 5.79 (d, 1H, $^3J_{HH}$ = 10.9 Hz, CH), 7.25-7.48 (m, 5H, arom.)	14.1 (CH_3), 49.0 (CH_2N), 57.4 (CH), 61.9 (OCH_2), 82.6 (CH), 126.3-129.3 (C arom.), 168.5 (COO), 169.3 (C=O), 170.9 (C=O)
7a		1.33 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.97 (d, 2H, $^3J_{HH}$ =5.4 Hz, CH_2N), 4.30 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2), 5.01 (s, 1H, CH=), 5.97 (broad t, 1H, $^3J_{HH}$ =5.4 Hz, NH)[a], 7.29-7.48 (m, 5H, arom.)	14.1 (CH_3), 45.3 (CH_2N), 62.2 (OCH_2), 86.5 (CH=), 125.8-131.6 (C arom.), 148.0 (C=), 165.7 (C=O), 167.9 (COO), 170.7 (C=O)

[a] Exchangeable proton with D_2O



1 + **2** E = PO(OEt)$_2$, **5** E = CO_2Et → **3** E = PO(OEt)$_2$, **6** E = CO_2Et → (Δ) **4** E = PO(OEt)$_2$, **7** E = CO_2Et

a) R = H, b) R = CH_3, c) R = C_6H_5

Scheme 1

Table 2. Spectral Data of Triazoles (**11**, **12**) and Enaminones (**13**, **14**).

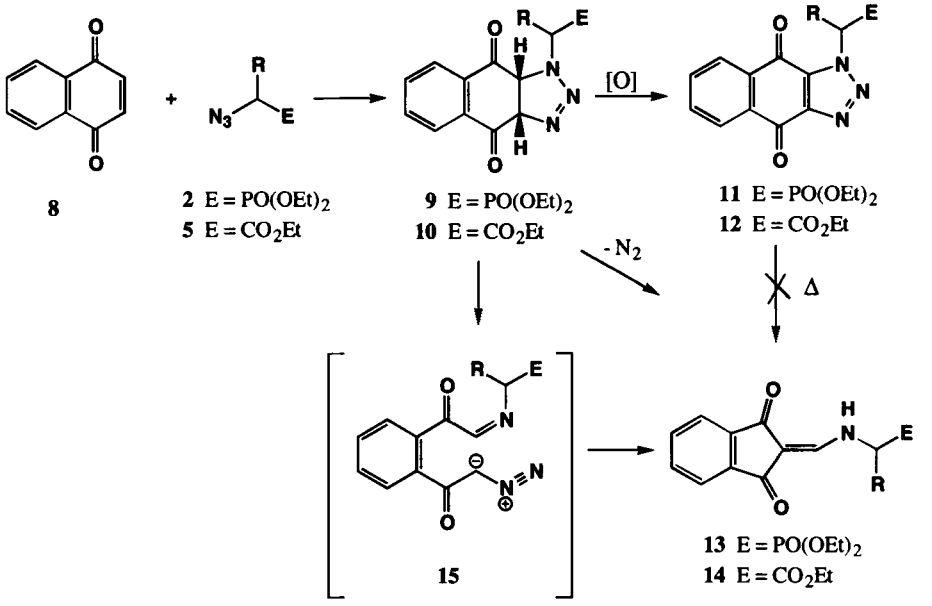
Cmpnd	^{31}P NMR (δ, ppm)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
10a		1.30 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.26 (q, 2H, $^{3}J_{HH}$ = 7.1 Hz, OCH_2), 4.56 (s, 2H, CH_2N), 5.94 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 6.75 (d, 1H, $^{3}J_{HH}$ = 10.9 Hz, CH), 7.72-8.46 (m, 4H, arom.)	14.1 (CH_3), 54.3 (CH_2N), 61.9 (OCH_2), 112.3 (CH), 122.3-137.5 (C arom., CH), 167.3 (C=O), 167.8 (COO), 187.2 (C=O)
11a	14.5	1.28 (t, 6H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.16 (m, 4H, OCH_2), 5.30 (d, 2H, $^{2}J_{PH}$ = 13.5 Hz, CH_2N), 7.78-8.30 (m, 4H, arom.)	16.2 (CH_3), 45.4 (d, $^{1}J_{PC}$ = 152.1 Hz, CH_2N), 63.7 (OCH_2), 127.3-145.1 (C arom., =C, C=), 175.1 (C=O), 176.4 (C=O)
11b	18.3	1.27 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 1.34 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 2.04 (dd, 3H, $^{2}J_{PH}$ = 15.8 Hz, $^{3}J_{HH}$ = 7.4 Hz, CH_3), 4.17 (m, 4H, OCH_2), 5.96 (m, 1H, CHN), 7.80-8.36 (m, 4H, arom.)	15.2 (CH_3), 16.4 (CH_3), 53.3 (d, $^{1}J_{PC}$ = 154.1 Hz, CHN), 63.7 (OCH_2), 127.4-145.0 (C arom., =C, C=), 175.5 (C=O), 176.7 (C=O)
11c	14.7	1.21 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 1.26 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.08 (q, 2H, $^{3}J_{HH}$ = 7.1 Hz, OCH_2), 4.23 (t, 2H, $^{3}J_{HH}$ = 7.1 Hz, OCH_2), 6.94 (d, 1H, $^{2}J_{PH}$ =21.7 Hz, CHN), 7.35-8.28 (m, 9H, arom.)	16.3 (CH_3), 61.33 (d, $^{1}J_{PC}$ = 155.1 Hz, CHN), 64.2 (OCH_2), 127.3-145.0 (C arom., =C, C=), 175.4 (C=O), 176.5 (C=O)
12a		1.31 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.29 (q, 2H, $^{3}J_{HH}$ = 7.1 Hz, OCH_2), 5.59 (s, 2H, CH_2N), 7.77-8.36 (m, 4H, arom.)	14.1 (CH_3), 51.0 (CH_2N), 62.8 (OCH_2), 127.3-145.2 (C arom., =C, C=), 165.2 (COO), 175.3 (C=O), 176.5 (C=O)
13a	18.9	1.32 (t, 6H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 3.73 (dd, 2H, $^{2}J_{PH}$ = 12.4 Hz, $^{3}J_{HH}$ = 6.4 Hz, CH_2N), 4.16 (m, 4H, OCH_2), 7.56-7.74 (m, 5H, arom., CH=), 9.15 (m, 1H, NH)[a]	16.4 (CH_3), 45.4 (d, $^{1}J_{PC}$ = 155.4 Hz, CH_2N), 63.3 (OCH_2), 121.5-133.6 (C arom.), 139.8 (C=), 152.2 (CH=), 189.6 (C=O), 193.5 (C=O)
13b	21.9	1.35 (t, 6H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 1.61 (dd, 3H, $^{2}J_{PH}$ = 16.7 Hz, $^{3}J_{HH}$ = 7.3 Hz, CH_3), 3.73 (m, 1H, CHN), 4.19 (m, 4H, OCH_2), 7.60-7.78 (m, 5H, arom., CH=), 9.20 (m, 1H, NH)[a]	15.2 (CH_3), 16.5 (CH_3), 52.2 (d, $^{1}J_{PC}$ = 157.1 Hz, CHN), 63.4 (OCH_2), 121.4-133.5 (C arom.), 139.7 (C=), 150.5 (CH=), 189.8 (C=O), 193.6 (C=O)
13c	18.1	1.14 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 1.21 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 3.84-4.10 (m, 4H, OCH_2), 4.74 (dd, 1H, $^{2}J_{PH}$ = 19.4 Hz, $^{3}J_{HH}$ =8.2 Hz, CHN), 7.32-7.72 (m, 10H, arom., CH=), 9.80 (m, 1H, NH)[a]	16.2 (CH_3), 60.9 (d, $^{1}J_{PC}$ = 153.6 Hz, CHN), 63.8 (OCH_2), 121.3-133.5 (C arom.), 139.7 (C=), 151.1 (CH=), 189.6 (C=O), 193.6 (C=O)

Table 2. Continued

Cmpnd	^{31}P NMR (δ, ppm)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
14a		1.36 (t, 3H, $^{3}J_{HH}$ = 7.1 Hz, CH_3), 4.20 (d, 2H, $^{3}J_{HH}$ =6.1 Hz, CH_2N), 4.32 (q, 2H, $^{3}J_{HH}$ = 7.1 Hz, OCH_2), 7.62-7.76 (m, 5H, arom., CH=), 9.29 (m, 1H, NH)[a]	4.0 (CH_3), 50.1 (CH_2N), 162.1 (OCH_2), 121.3-133.3 (C arom.), 139.7 (C=), 152.0 (CH=), 167.8 (COO), 189.8 (C=O), 193.2 (C=O)

a) Exchangeable proton with D_2O.

The cycloaddition of azides derived from α-aminophosphonates **2** and aminoacids **5** to 1,4-naphthoquinone gives, depending on the reaction conditions, triazoles **11**, **12** and indan-1,3-diones **13**, **14** (Scheme 2). Thus, when azides **2** or **5** and naphthoquinone are allowed to react at room temperature in tetrahydrofuran for two weeks the 1-phosphanoalkyl- **11** or 1-ethoxycarboxyalkyl-naphto(2.3-d)triazol-4,9-dione **12** are isolated in low yields. However, the reaction of phosphorus containing azide **2** with 1,4-naphtoquinone in refluxing THF allows the isolation of triazole derivative **11** (75%); while when the reaction is run in refluxing toluene a (80/20) mixture of triazole **11** and the enamine **13**, and traces of triazoline **9** is obtained (Scheme 2). It is noteworthy that triazole compounds **11** were thermally stable and do not undergo nitrogen elimination even after prolonged boiling in refluxing toluene (72 hrs). The treatment of azidoalkylcarboxylate **5** with quinone **8** (room temperature, refluxing THF, or toluene) gives similar results to that observed in the case of azide **2**.



a) R = H, b) R = CH_3, c) R = C_6H_5

Scheme 2

These results suggest that the process is initiated by the 1,3-cycloaddition reaction giving rise to the bicyclic triazolines **9** or **10**, which subsequently undergo either dehydrogenation to yield substituted triazoles **11** or **12**. Elimination of a nitrogen molecule affords the contracted ring compounds **13** or **14**. Formation of these enamine derivatives is favored by the use of a higher reaction temperature. Thermolysis of triazolines to give indan-1,3-diones has been previously reported[14,22] and could be explained through 1,3-dipolar cycloreversion[23] of bicyclic triazolines **9** or **10** to give a new dipole **15**. The elimination of N_2 of the diazoimine **15**, followed by ring closure could undergo the ring contraction from the six-membered quinoinic ring of triazoline **9** to the indan-1,3-diones **13** in a fashion similar to that suggested for the thermolysis of bicyclic triazolines.[24,25]

In conclusion, new 1,3-dipolar cycloaddition reactions of azides derived from α-aminophosphonates and α-aminoacids with maleimides and quinones are described and new families of ethoxycarboxyl- and phosphoryl-alkyltriazolines **3** and **6**, triazoles **11** and **12** and enamines **4**, **7**, **13**, **14** are reported.

EXPERIMENTAL SECTION

Melting points were determined with a Buchi SPM-20 apparatus and are uncorrected. *Anal*ytical 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 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. ^{31}P NMR spectra were recorded at 120 MHz with 85% phosphoric acid as an external reference. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), dd (double-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 *N*-Phenylmaleimide with Azidoalkyl-phosphonates and carboxylates.- To a solution of diethyl 1-azidoalkylphosphonate[20] **2** (R = H, CH_3, Ph) or ethyl 1-azidocarboxylate **5** (R=H) (3 mmol) in THF (15 mL) was added dropwise with stirring a solution of *N*-phenylmaleimide 1 (3 mmol, 0.52 g), and the reaction mixture was stirred at room temperature for 48 hrs. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel) with ether:hexane as eluent and recrystallized to give triazolines **3** or **6**.

2,N-[1-(Diethoxyphosphonylmethyl)]-7,N-Phenyl-2,3,4,7-tetraazabicyclo[3.3.0]octane (3a).- Reaction with diethyl 1-azidomethylphosphonate **2a** (3 mmol, 0.58 g) gave: 0.93 g (85%) of the compound **3a** as a yellow solid, mp.79-80°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 338 (M^+-N_2, 25%).

Anal. Calcd. for $C_{15}H_{19}N_4O_5P$: C, 49.17; H, 5.23; N, 15.30. Found: C, 49.10; H, 5.29; N, 15.33.

2,*N*-[1-(1-Diethoxyphosphonylethyl)]-7,*N*-Phenyl-2,3,4,7-tetraazabicyclo[3.3.0]octane (3b).- Reaction with diethyl 1-azido-1-ethylphosphonate **2b** (3 mmol, 0.62 g) gave: 1.03 g (90%) of the

mixture of two diastereoisomers **3b** and **3b'** isolated by flash column chromatography (silica gel) with ether:hexane as eluent. Data for **3b**: Obtained as a white solid, mp. 98-99°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 352 (M^+-N_2, 8%).

Anal. Calcd. for $C_{16}H_{21}N_4O_5P$: C, 50.51; H, 5.57; N, 14.74. Found: C, 50.93; H, 5.49; N, 14.79

Data for **3b'**: Obtained as a white solid, mp. 99-100°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 352 (M^+-N_2, 12%).

Anal. Calcd. for $C_{16}H_{21}N_4O_5P$: C, 50.51; H, 5.57; N, 14.74. Found: C, 50.60; H, 5.63; N, 14.68

2,*N*-[1-(Diethoxyphosphonyl-1-phenylmethyl)]-7,*N*-Phenyl-2,3,4,7-tetraazabicyclo-[3.3.0]octane (3c).- Reaction with diethyl 1-azido-1-phenylmethylphosphonate **2c** (3 mmol, 0.81 g) gave: 1.06 g (80%) of the mixture of two diastereoisomers **3c** and **3c'** isolated by flash column chromatography (silica gel) with ether:hexane as eluent. Data for **3c**: Obtained as a yellow solid, mp. 128-129°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 414 (M^+-N_2, 9%).

Anal. Calcd. for $C_{21}H_{23}N_4O_5P$: C, 56.99; H, 5.24; N, 12.67. Found: C, 57.06; H, 5.18; N,12.72

Data for **3c'**: Obtained as a yellow solid, mp. 129-130°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 414 (M^+-N_2, 2%).

Anal. Calcd. for $C_{21}H_{23}N_4O_5P$: C, 56.99; H, 5.24; N, 12.67. Found: C, 57.15; H, 5.33; N, 12.58

2,*N*-[1-(Ethoxycarbonylmethyl)]-7,*N*-Phenyl-2,3,4,7-tetraazabicyclo[3.3.0]octane(6a).- Reaction with ethyl 1-azidomethylcarboxylate **5a** (3 mmol, 0.39 g) gave: 0.81 g (90%) of the compound **6a** as a yellow solid, mp. 141-142°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 274 (M^+-N_2, 80%).

Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.61; H, 4.67; N, 18.54. Found: C, 55.50; H, 4.73; N, 18.59

General Procedure for the Thermolysis of Triazolinealkyl-phosphonates and carboxylates.- A solution of triazolinealkyl-phosphonate **3** or -carboxylate **6** (3 mmol) in toluene (15 mL) was stirred in refluxing for 15 hrs. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel) with ether:hexane as eluent to give enamines **4** or **7**.

3-(Diethoxyphosphonylmethylamine)-*N*-Phenylmaleimide (4a).- Thermolysis of 2,*N*-[1-(diethoxyphosphonylmethyl)]-7,*N*-phenyl-2,3,4,7-tetrabicyclo[3.3.0]octane **3a** (3 mmol, 1.10 g) gave: 0.91 g (90%) of the compound **4a** as a yellow solid, mp. 124-125°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 338 (M^+, 62%).

Anal. Calcd. for $C_{15}H_{19}N_2O_5P$: C, 53.25; H, 5.66; N, 8.28. Found: C, 53.21; H, 5.71; N, 8.36

3-(1-Diethoxyphosphonylethylamine)-*N*-Phenylmaleimide (4b).- Thermolysis of 2,*N*-[1-(1-diethoxyphosphonylethyl)]-7,*N*-phenyl-2,3,4,7-tetrabicyclo[3.3.0]octane **3b** (3 mmol,1.14 g) gave: 0.92 g (87%) of the compound **4b** as a yellow solid, mp. 116-117°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 352 (M^+, 37%).

Anal. Calcd. for $C_{16}H_{21}N_2O_5P$: C, 54.53; H, 6.01; N, 7.95. Found: C,54.60; H, 6.10; N, 7.89

3-(Diethoxyphosphonyl-1-phenylmethylamine)-*N*-Phenylmaleimide (4c).- Thermolysis of 2,*N*-[1-(diethoxyphosphonyl-1-phenylmethyl)]-7,*N*-phenyl-2,3,4,7-tetrabicyclo[3.3.0]octane **3c** (3 mmol, 1.33 g) gave:1.03 g (83%) of the compound **4c** as a yellow solid, mp.133-134°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 414 (M^+, 13%).

Anal. Calcd. for $C_{21}H_{23}N_2O_5P$: C, 60.85; H, 5.60; N, 6.76. Found: C,60.80; H, 5.67; N, 6.82

3-(Ethoxycarbonylmethylamine)-*N*-Phenylmaleimide (7a).- Thermolysis of 2,*N*-[1-(ethoxycarbonylmethyl)]-7,*N*-phenyl-2,3,4,7-tetrabicyclo[3.3.0]octane **6a** (3 mmol, 0.91 g) gave:0.70 g (85%) of the compound **7a** as a yellow solid, mp.119-120°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 274 (M^+, 87%).

Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C, 61.29; H, 5.15; N, 10.22. Found: C, 61.38; H, 5.08; N, 10.29

General Procedure for the Preparation of Triazolealkyl-phosphonates and carboxylates.- To a solution of diethyl 1-azidoalkylphosphonate **2** (R=H, CH_3, Ph) or ethyl 1-azidoalkylcarboxylate **5** (R=H) (3 mmol) in THF (15 mL) was added dropwise with stirring a solution of 1,4-naphthoquinone **8** (3 mmol, 0.47 g), and the reaction mixture was stirred in refluxing THF for 20 hrs. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel) with ether:hexane as eluent to give triazoles **11** or **12**.

1-(Diethoxyphosphonylmethyl)naphtho[2.3-*d*]triazol-4,9-dione (11a).- Reaction with diethyl 1-azidomethylphosphonate **2a** (3 mmol, 0.58 g) gave:0.79 g (75%) of the compound **11a** as a brown solid, mp.145-146°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 349 (M^+, 27%).

Anal. Calcd. for $C_{15}H_{16}N_3O_5P$: C, 51.56; H, 4.62; N, 12.03. Found: C, 51.47; H, 4.54; N, 12.12

1-(1-Diethoxyphosphonylethyl)naphtho[2.3-*d*]triazol-4,9-dione (11b).- Reaction with diethyl 1-azido-1-ethylphosphonate **2b** (3 mmol, 0.62 g) gave: 0.76 g (70%) of the compound **11b** as a brown solid, mp.114-115°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 363 (M^+, 10%).

Anal. Calcd. for $C_{16}H_{18}N_3O_5P$: C, 52.88; H, 5.00; N, 11.57. Found: C, 52.90; H,4.95; N, 11.50

1-(Diethoxyphosphonyl-1-phenylmethyl)naphtho[2.3-*d*]triazol-4,9-dione (11c).- Reaction with diethyl 1-azido-1-phenylmethylphosphonate **2c** (3 mmol, 0.81 g) gave: 0.97g (76%) of the compound **11c** as a brown solid, mp.168-169°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 425 (M+, 5%).

Anal. Calcd. for $C_{21}H_{20}N_3O_5P$: C, 59.28; H, 4.74; N, 9.88. Found: C, 59.38; H, 4.70; N, 9.81

1-(Ethoxycarbonylmethyl)naphtho[2.3-*d*]triazol-4,9-dione (12a).- Reaction with ethyl 1-azidomethylcarboxylate **5a** (3 mmol, 0.39 g) gave: 0.68 g (80%) of the compound **12a** as a brown solid, mp.154-155°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 285 (M^+, 2%).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.93; H, 3.89; N, 14.74. Found: C, 58.99; H, 3.81; N, 14.65

General Procedure for the Cycloaddition of Naphthoquinone with azidoalkyl-phosphonates and -carboxylates in refluxing toluene.- To a solution of diethyl 1-azidoalkylphosphonate **2** (R=H, CH_3, Ph) (3 mmol) in toluene (15 mL) was added dropwise with stirring a solution of 1,4-naphthoquinone **8** (3 mmol, O.47 g), and the reaction mixture was stirred in refluxing for 36 hrs. Concentration in vacuum gave the mixture of triazolealkyl-phosphonates **11**, indan-1,3-diones **13** (80/20), isolated by flash column chromatography (silica gel) with ether:hexane as eluent, and traces of triazoline compounds **9**. When ethyl 1-azidoalkylcarboxylate **5** (R=H) is used a (75/20/5) mixture of triazole **12**, indan-1,3-dione **14** and triazoline **10** are obtained.

Products **11,** and **12**, their physical constant and spectral data are identical with those previously obtained.

2-(Diethoxyphosphonylmethylaminomethylen)-indan-1,3-dione (13a).- Reaction with diethyl 1-azidomethylphosphonate **2a** (3 mmol, 0.58 g) gave a (80/20) mixture of **11a** and **13a** (70%). Data of **13a**: 0.14 g, obtained as a brown solid, mp.120-121°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 323 (M^+, 35%).

Anal. Calcd. for $C_{15}H_{18}NO_5P$: C, 55.71; H, 5.62; N, 4.33. Found: C, 55,67; H, 5.69; N, 4.27

2-(1-Diethoxyphosphonylethylaminomethylen)-indan-1,3-dione (13b).- Reaction with diethyl 1-azido-1-ethylphosphonate **2b** (3 mmol, 0.62 g) gave a (78/22) mixture of **11b** and **13b** (75%). Data of **13b**: 0.15 g, obtained as a syrup. Rf (ethyl acetate)= 0.19; MS, *m/z*: 337 (M^+, 50%).

Anal. Calcd. for $C_{16}H_{20}NO_5P$: C, 56.96; H, 5.98; N, 4.15. Found: C, 56.85; H, 5.92; N, 4.21

2-(Diethoxyphosphonyl-1-phenylmethylaminomethylen)-indan-1,3-dione (13c).- Reaction with diethyl 1-azido-1-phenylmethylphosphonate **2c** (3 mmol, 0.81 g) gave a (81/19) mixture of **11c** and **13c** (70%). Data of **13c**: 0.17 g, obtained as a syrup. Rf (ethyl acetate:hexane=1:1)= 0.19; MS, *m/z*: 399(M^+, 6%).

Anal. Calcd. for $C_{21}H_{22}NO_5P$: C, 63.14; H, 5.56; N, 3.51. Found: C, 63.22; H, 5.47; N, 3.59

1-(Ethoxycarbonylmethyl)naphtho[2.3-*d*]triazoline-4,9-dione (10a) and 2-(Ethoxycarbonyl-methylaminomethylen)-indan-1,3-dione (14a).- Reaction with ethyl 1-azidomethylcarboxylate **5a** (3 mmol, 0.39 g) gave a (75/20/5) mixture of **12a, 14a** , and **10a** (82%). Data of **10a**: 0.04 g, obtained as a brown solid, mp. 84-85°. Recrystallized from hexane:CH_2Cl_2; MS, *m/z*: 259 (M^+-N_2, 11%).

Anal. Calcd. for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.61; H, 4.49; N, 14.70.

Data of **14a**: 0.12 g, obtained as a syrup. Rf (ethyl acetate:hexane=1:1)= 0.33; MS, *m/z*: 259 (M^+, 10%).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.84; H, 5.06; N, 5.41. Found: C, 64.91; H, 5.00; N, 5.60

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