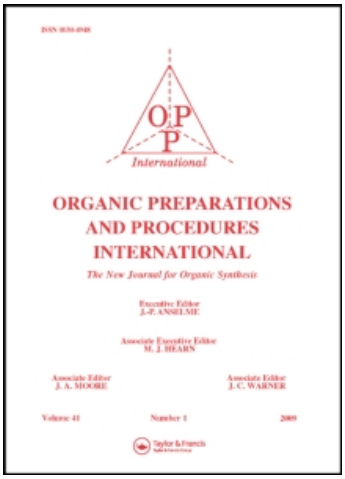

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"ONE POT" SYNTHESIS OF β-FUNCTIONALIZED VINYL AZIDES THROUGH ADDITION OF TETRAMETYLGUANIDINIUM AZIDE TO ACETYLENIC AND ALLENIC COMPOUNDS

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"ONE POT" SYNTHESIS OF β-FUNCTIONALIZED VINYL AZIDES THROUGH ADDITION OF TETRAMETYLGUANIDINIUM AZIDE TO ACETYLENIC AND ALLENIC COMPOUNDS

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The chemistry of azides has attracted a great deal of attention since the discovery of phenyl azide[1] and the first preparation of hydrazoic acid.[2] However, interest in this family of organic compounds waned until the second half of this century when azides became useful compounds for organic synthesis.[3-5] Furthermore, azide derivatives have recently gained importance in the area of medicinal chemistry due to, for example, the antiviral activity of azido deoxyuridines against herpes simplex virus type 1 and 2 (HSV-1, HSV-2),[6] azidonucleosides[7] such as azido deoxythymidine (AZT) that can act as potent inhibitors of human inmunodeficiency virus (HIV) in cell culture, and finally of the recently modified AZT nucleotides such as the acyl phosphate derivatives of the anti-HIV nucleoside analogue AZT.[8]

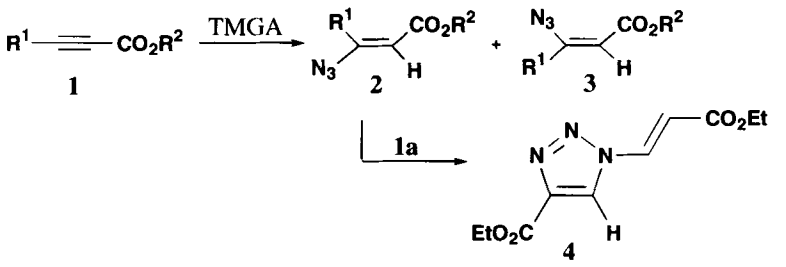
Vinyl azides represent a special and interesting group of azides not only because they undergo a variety of well established reactions such as pyrolysis, photolysis, cycloadditions and attack by electrophiles and nucleophiles,[9] but also because they can be used in the synthesis of biologically active natural products.[10] In recent years, we have been involved in the chemistry of azides[11] and phophazenes[12] obtained from azides and phosphines, as well as in the study and their usefulness in the preparation of acyclic[13] and heterocyclic[14] compounds. In this context, *N*-vinylic phosphazenes derived from α- and β-aminoacid esters, easily obtained by Staudinger reaction[12] of phosphine and azido esters, are very suitable for the synthesis of electron-poor 2-azadienes[15,16], and for the construction of nitrogen six-membered ring through [4+2] cycloaddition processes[16].

For the synthesis and use of *N*-vinylic phosphazenes derived from β-aminoacid esters[16] as synthetic intermediates, we required β-azido vinyl esters with different substitution patterns. A literature search showed that standard routes to vinyl azides involve: *a*) the introduction of the azido function to an existing double bond by nucleophilic displacement of halides by azide in vinyl halides,[9,17] *b*) the formation of the carbon-carbon double bond by condensation of aldehydes with α-azido esters or related compounds,[18,19] and *c*) the addition of halogen azides to olefins followed by treatment with

base.[9,20,21] However, this last procedure, which might be the most suitable for our goal, presents some disadvantages: *a*) a mixture of azides with a higher proportion of α-azido vinyl ester than the β-isomer (4:1) is obtained when methyl acrylate is used, *b*) the isolation of the vinyl azides is made difficult by the reaction conditions in some cases because azides rapidly lose nitrogen at room temperature giving the 1-aziridine, and *c*) lastly the process takes place in two steps, addition of IN_3 with isolation of β-iodo-azido derivative and secondly elimination of hydrogen iodide to give the vinyl azide.[20]

In this context, it is worth noting that simple alkynes do not add azides, and the addition of azides to acetylenic esters is restricted to the addition of hydrazoic acid to acetylene dicarboxylate to give a mixture of *Z* and *E* vinyl azides in a ratio of 6:4[22] at room temperature. The addition of metal azides (sodium or lithium azides) to functionalized acetylenic compounds such as ketones,[23] alcohols[24] and phosphonium salts,[25] causes intramolecular ring closure leading to triazole derivatives instead of vinyl azides. On the other hand, tetramethylguanidinium azide (TMGA), a reagent which has rarely been used as a source of azide ion,[26] possesses the advantages of both being thermally stable and a highly reactive source of azide ion. TMGA can be readily prepared[27] and recently has been successfully used for the preparation of glycosyl azides.[26] We now report here a new, easy and efficient method for synthesis of β-azido vinyl esters from easily available starting materials such as TMGA and commercially available esters. To our knowledge, TMGA has not been previously employed in the synthesis of azido vinyl esters.

TMGA adds regioselectively and in very high yield to ethyl propiolate in dichoromethane at 0° leading to a homogeneous solution which is stirred at 0-5° for 12 hrs (TLC control). After aqueous work-up, the crude reaction mixture shows the presence of *E*- and *Z*-stereoisomers **2a/3a** in an approximate ratio of 70:30 as evidenced by the relative peak areas from ^1H NMR (Scheme 1 and Table 1, entry 1). β-Azidoacrylates **2a** and **3a** are isolated as viscous oils by means of short column chromatography (Ether/Hexane). However, when the reaction is performed at room temperature (Table 1, entry 2) besides *Z*-vinyl azide **3a** (30%) a new product **4** (70%) appears. Formation of triazole **4** can be explained by 1,3-dipolar cycloaddition of vinyl azide **2a** initially formed with a second molecule of ethyl propiolate. Treatment of TMGA with an excess of ethyl propiolate leads directly to the formation of 1,2,3-triazole **4** (Scheme 1).



Scheme 1

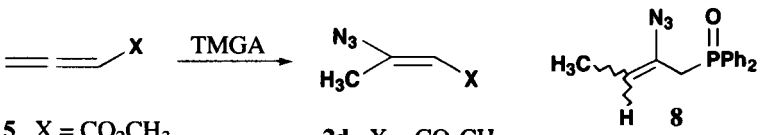
TABLE 1. TMGA Additions to Acetyenic Esters

entry	Compound	R^1	R^2	Temp. (°C)	Reaction Time (hrs)	2/3 ratio	Yield (%)
1	a	H	Et	0-5	72	70/30	85
2	a	H	Et	r.t.	36	[a]/30	83
3	b	$MeCO_2$	Me	r.t.	2	35/65	87
4	b	$MeCO_2$	Me	r.t.	72	0/100	85
5	c	Ph	CO_2Et	r.t.	72	100/0	80
6	d	Me	Me	r.t.	24	70/30	90

a) Compound **4** is obtained instead of **2a**.

The regiospecific addition of TMGA to terminal acetylenic esters has been extended to acetylene dicarboxylic acid esters, **1b** ($R^1 = MeO_2C$, R^2 = Me) as well as to substituted mono acetylenic esters such as ethyl phenylpropiolate **1c** ($R^1 = C_6H_5$, R^2 = Et) or methyl 2-butynoate **1d** (R^1 = Me, R^2 = Me). Thus, TMGA addition to methyl acetylene dicarboxylate at room temperature (2 hrs) leads to a mixture of vinyl azides **2b** and **3b** in an approximate ratio of 35:65 (Table 1, entry 3). However, when the reaction time (Table 1, entry 4) is lengthened (72 hrs) only one isomer, the *Z*-azidovinyl ester **3b**, is isolated.

Reaction of ester **1d** with TMGA at room temperature (24 hrs) gives *E*-stereoisomer **2d** as the major component (70%) and a white solid **3d** (30%), after the crude product is purified by flash chromatography (Table 1, entry 6). The ^1H NMR spectrum of **2d** gives a singlet at 5.49 ppm for the vinylic proton, while the methyl group resonates at 2.30 ppm, and is similar to that previously obtained[28] by addition of sodium azide to ethyl 2,3-butadienoate in THF-H_2O as solvent. With these results in mind, substitution of TMGA in CH_2Cl_2 for NaN_3 increased drastically the yield of the reaction[28] with allenic ester **5**, affording, after simple work-up, only the *E*-vinyl azide **2d** (Scheme 2).



5 X = CO_2CH_3
6 X = $POPh_2$

2d X = CO_2CH_3
7 X = $POPh_2$

8

Scheme 2

Given our interest in the chemistry of β-functionalized phosphorus derivatives[29], these results prompted us to explore the TMGA addition to phosphorylated allenes. Thus, reaction of TMGA with diphenylphosphoryl-1,2-propadiene **6** in dichloromethane at 40° (2 hrs) leads to the formation of *E*-azidovinyl phosphine oxide **7** in excellent yield as a single stereoisomer. Compound **7** was characterized on the basis of its spectroscopic data and mass spectrometry. The vicinal ^{13}C-^{31}P coupling constant ($^3J_{PC}$ = 4.1 Hz) is consistent with the *E* configuration of the carbon-carbon double

TABLE 2. Spectral Data of Compounds **2, 3, 4, 7, 8**

Cmpd	IR	^{1}H NMR (250 MHz, $CDCl_3$) (δ, Hz)	^{13}C NMR (75 MHz, $CDCl_3$) (δ, Hz)
2a	2120 (N3) 1716 (COO)	7.26 (d, 1H, $^3J_{HH}$ = 13Hz, HC=), 5.61 (d, 1H, $^3J_{HH}$ =13Hz, HC=), 4.16 (q, 2H, $^3J_{HH}$ = 7Hz, OCH_2), 1.25 (t, 3H, $^3J_{HH}$ = 7Hz, CH_3)	165.4 (COO), 143.9 (HC=), 109.09 (HC=), 60.1 (OCH_2), 13.9 (CH_3)
3a	2122 (N3) 1716 (COO)	6.67 (d, 1H, $^3J_{HH}$= 8.5 Hz, HC=), 5.23 (d, 1H, $^3J_{HH}$= 8.5 Hz, HC=), 4.16 (q, 2H, $^3J_{HH}$= 7Hz, OCH_2), 1.25 (t, 3H, $^3J_{HH}$ = 7Hz, CH_3)	163.7 (COO), 139.9 (HC=),107.2 (HC=), 59.85 (OCH_2), 20.2 (CH_3)
(2b,3b)	2135 (N3) 1737, 1734 (COO)	6.14 (s, 1H, HC=), 5.67 (s, 1H, HC=), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3)	164.5 (COO),163.7 (COO), 162.2 (COO), 162.0 (COO), 138.1 (C=), 133.2 (C=), 111.6 (HC=), 107.7 (HC=), 53.5 (OCH_3), 53.0 (OCH_3), 51.8 (OCH_3), 51.7 (OCH_3)
3b	2134 (N3) 1737, 1734 (COO)	6.14 (s, 1H, HC=), 3.85 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3)	164.5 (COO), 162.2 (COO), 138.1 (C=), 111.6 (HC=), 53.5 (OCH_3),51.7 (OCH_3)
2c	2142 (N3) 1707 (COO)	7.85-7.28 (m, 5 H, arom.), 5.75 (s, 1H, HC=), 4.23 (q, 2H, $^3J_{HH}$ =7Hz, OCH_2), 1.27 (t, 3H, $^3J_{HH}$ =7Hz, CH_3)	163.9 (COO), 153.4 (C=), 133.93-126.7 (m, C arom.)105.6 (HC=), 61.5 (OCH_2), 13.5 (CH_3)
2d	2132 (N3) 1721 (COO)	5.49 (s, 1H, HC=), 3.66 (s,3H, OCH_3) 2.30 (s, 3H, CH_3)	166.1 (COO), 154.6 (C=), 104.4 (HC=), 50.6 (OCH_3), 15.6 (CH_3)
3d	2130 (N3) 1722 (COO)	5.19 (s, 1H, HC=), 3.67 (s,3H, OCH_3), 2.12 (s, 3H, CH_3)	164.4 (COO), 148.5 (C=), 105.0 (HC=), 50.9 (OCH_3), 20.3 (CH_3)
4[a]	1742, 1702 (COO)	8.21 (s, 1H, HC=), 8.20 (d, 1H, $^3J_{HH}$ = 14 Hz, HC=), 6.80 (d, 1H, $^3J_{HH}$ = 14 Hz, HC=), 4.45 (q, 2H, $^3J_{HH}$ = 7Hz, OCH_2), 4.27 (q, 2H, $^3J_{HH}$ = 7Hz, OCH_2), 1.42 (t, 3H, $^3J_{HH}$ = 7Hz, CH_3) 1.33 (t, 3H, $^3J_{HH}$ = 7Hz, CH_3)	165.1 (COO), 164.3 (COO), 142.6 (HC=), 139.1 (HC=), 138.8 (C=), 112.5 (HC=), 62.0 (OCH_2), 61.2 (OCH_2), 14.2 (CH_3), (CH_3)
7[b]	2121 (N3) 1181 (P=O)	7.26-7.75 (m, 10H, arom.), 5.59 (d, 1 H, $^2J_{PH}$ = 17.1 Hz, CH), 2.23 (d, 3H, $^4J_{PH}$ = 1.9 Hz, CH_3)	155.1 (d, $^2J_{PC}$ = 10.3 Hz, C=), 127.8-134.9 (C-arom.), 103.9 (d, $^1J_{PC}$ = 110.8 Hz, CH), 17.3 (d, $^3J_{PC}$ = 4.1 Hz, CH_3)
8[c]	2107 (N3) 1173 (P=O)	7.26-7.82 (m, 10H, arom.), 5.27-5.37 and 4.80-4.85 (m, 1H, CH), 3.20 (d, 2H, $^2J_{PH}$ = 12.8 Hz, CH_2)and 3.12 (d, 2H, $^2J_{PH}$ = 13.8 Hz, CH_2), 1.52-1.58 (m, 3H, CH_3)	132.9 and 132.5 (C=), 125.7-132.2 (C arom.), 116.8 (d, $^3J_{PC}$ = 8.2 Hz, CH) and 113.6 (d, $^3J_{PC}$ = 8.9 Hz, CH), 34.2 (d, $^1J_{PC}$ = 66.8 Hz, CH_2) and 31.9 (d, $^1J_{PC}$ = 67.1 Hz, CH_2), 12.9 and 12.1 (CH_3)

a) MS: m/z 239 (M^+, 17 %). b) MS: m/z 283 (M^+, 1.4 %), ^{31}P NMR (120 MHz, $CDCl_3$, PO_4H_3) 21.9 ppm.
c) ^{31}P NMR (120 MHz, $CDCl_3$, PO_4H_3) 16.0 and 8.0 ppm.

bond and shows that the methyl group and the phosphoryl group are relatively *cis*.[30] Alkyl substituted allenes such as diphenylphosphoryl-1,2-butanediene react also with TMGA regioselectively to give azides **8**. In conclusion, the synthesis described in this communication provides an easy entry to β-functionalized vinyl azides, making use of readily available starting materials under mild reaction conditions.

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; CH_2Cl_2 (P_2O_5); $CHCl_3$ (P_2O_5). 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. Infrared spectra were taken on a Nicolet Magna-IR 550 spectrometer. ^1H NMR spectra were recorded on a Bruker 250 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in $CDCl_3$ solutions. ^{13}C NMR spectra were recorded at 75 MHz with chloroform (77.0 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. Infrared spectra (IR) were obtained as neat liquids, or solids in KBr. Peaks are reported in cm^{-1}. 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). All reactions were performed in oven (125°) or flame-dried glassware under an inert atmosphere of dry N_2.

General Procedure for the Addition of TMGA to Acetylenic Esters.- A solution of TMGA (25 mmol, 3.98 g) in dried $CHCl_3$ (15 mL) was added very slowly to a -10° solution of acetylenic ester (25 mmol) in $CHCl_3$ (40 mL), and the mixture was stirred to adequate temperature (see table 1) until TLC indicated the disappearance of the acetylenic ester. The mixture is poured into water at 0-5° and extracted with CH_2Cl_2. After drying ($MgSO_4$) and concentrating the extracts, the residue was purified by flash chromatography (ether/hexane; 1/5).

Ethyl 3-Azidoacrylate (2a, 3a).- Reaction with ethyl propiolate (25 mmol, 2.45 g) gives: 2.02 g (70%) of the *E*-isomer **2a** as a yellow oil, R_f (ethyl acetate: *n*-hexane =1:1) = 0.64.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.53; H, 5.00; N, 29.78. Found: C, 42.34; H, 5.04; N, 29.90

and 0.87 g (30%) of the *Z*-isomer **3a** as a colorless oil R_f (ethyl acetate: *n*-hexane =1:1) = 0.51.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.53; H, 5.00; N, 29.78. Found: C, 42.43; H, 5.02; N, 29.81

1-(2-Ethoxycarbony)ethenyl-5-ethoxycarbonyl-1,2,3-triazole (4).- Reaction with ethyl propiolate (25 mmol, 2.45 g) gives: 0.50 g (30%) of the Z-isomer **3a** (physical constants and spectral data are identical with those previously obtained) and 1.97 g (70%) of compound **4** as a white solid, mp. 79-80°. R_f (ethyl acetate: *n*-hexane =1:1) = 0.38.

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.19; H, 5.48; N, 17.57. Found: C, 50.10; H, 5.50; N, 17.61

When a solution of TMGA (25 mmol, 3.980 g) in dried $CHCl_3$ (15 mL) was added very slowly to a -10° solution of ethyl propiolate (50 mmol, 4.91 g) in $CHCl_3$ (80 mL), and worked-up as above, the triazole **4** only was obtained.

Dimethyl Azidoethylendicarboxylate (2b, 3b).- Reaction with dimethyl acetylendicarboxylate (25 mmol, 3.55 g) gives a mixture of 4.03 g (87%) of the *Z*- and *E*-isomers **3b** and **2b** (35/65) as a yellow oil. When the reaction was stirred at 25° during 72 hrs, and worked-up as above, only the *Z*-isomer **3b** (3.93 g, 85%) was isolated as a yellow oil.

Anal. Calcd. for $C_6H_7N_3O_4$: C, 38.91; H, 3.81; N, 22.70. Found: C, 39.06; H, 3.89; N, 22.76

Ethyl 3-Phenyl-3-azidoacrylate (2c).- Reaction with ethyl 3-phenylpropiolate (25 mmol, 4.35 g) gives 4.34 g (80%) of a yellow oil.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.81; H, 5.11; N, 19.35. Found: C, 60.63; H, 5.08; N, 19.37

Methyl 3-Azidocrotonate (2d, 3d).- Reaction with methyl 2-butynoate (25 mmol, 2.45 g) gives: 2.21 g (70%) of *E*-isomer **2d** as a yellow oil, R_f (ethyl acetate: *n*-hexane =1:1) = 0.64.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.53; H, 5.00; N, 29.78. Found: C, 42.63; H, 5.08; N, 29.65

and 0.95 g (30%) of Z-isomer **3d** as a white solid, mp. 54-55°. R_f (ethyl acetate: *n*-hexane =1:1) = 0.52.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.53; H, 5.00; N, 29.78. Found: C, 42.58; H, 5.04; N, 29.75

General Procedure for the addition of TMGA to Allenic Esters and Allenic Phosphine Oxides.- A solution of TMGA (5 mmol, 0.80 g) in dried CH_2Cl_2 (15 mL) was added very slowly to a -10° solution of allenic compound (5 mmol) in CH_2Cl_2 (20 mL), and the mixture was stirred until TLC indicated the disappearance of the allenic compound. The mixture is poured into water at 0-5° and extracted with CH_2Cl_2. After drying ($MgSO_4$) and concentrating the extracts, the residue was purified by flash chromatography.

Methyl 3-Azidocrotonate (2d).- Reaction with methyl 2,3-butadienoate[31] **5** (5 mmol, 0.5 g) at r.t. for 16 hrs gives after flash chromatography (ether/hexane; 1/5) 0.48 g (68%) of compound **2d** (Physical constants and spectral data were identical with those previously obtained.)

***E*-2-Azido-1-propenyldiphenylphosphine Oxide (7)**.- Reaction with allenediphenyl-phosphine oxide **6** (5 mmol, 1.20 g) under reflux for 1 hrs gives after flash chromatography (hexane/ethyl acetate; 2/1) 1.27 g (90%) of **7** as a yellow solid, mp 95-96°. R_f (ethyl acetate) = 0.43.

Anal. Calcd. for $C_{15}H_{14}N_3OP$: C, 63.59; H, 4.98; N, 14.84. Found: C, 63.61; H, 4.96; N, 14.80

1-Azido-2-butenyldiphenylphosphine Oxide (8).- Reaction with 1,2-butadienyldiphenyl-phosphine oxide (5 mmol, 1.27 g) under reflux for 1 hrs gives after flash chromatography (hexane/ethyl acetate; 2/1) 1.19 g (80%) of **8** as a yellow solid, mp 104-106 °. R_f (ethyl acetate) = 0.52.

Anal. Calcd. for $C_{16}H_{16}N_3OP$: C, 64.62; H, 5.43; N, 14.14. Found: C, 64.67; H, 5.48; N, 14.12

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