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Selected Reactions of Diethyl (*E*)-1-(bromomethyl)-2-cyanovinylphosphonate with Secondary and Tertiary Amines

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ABSTRACT: *An easy regio- and stereoselective synthesis of new nitrogenous molecules* **2a–e** *was successfully realized via an effective coupling reaction of diethyl (E)-1-(bromomethyl)-2-cyanovinylphosphonate* **1** *with various secondary amines in methanol. Hence, the use of less and more bulky secondary amines gives rise, respectively, to the successive (S_N2') substitution–isomerization and (S_N2) substitution derivatives* **2a–c** *and* **2d–e**. *Moreover, the addition of tertiary amines to* **1** *in the same reaction conditions, leads exclusively to the rearranged vinyl ether* **3** *in good yields.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem. 24:460–465, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21112

INTRODUCTION

The addition of amines to C—C multiple bonds is one of the most convenient procedures for the generation of carbon–nitrogen ones [1]. This approach provides an attractive route to a variety of biologically important natural products [2], antibiotics [3], β-amino alcohols [4], chiral auxiliaries [5] and other nitrogen-containing molecules [6–9]. That is why different protocols [10] have been developed in this context, but much of them have many constraints such as harsh reaction conditions and long reaction times. On the other hand, displacement reaction of allyl halides using amines as nucleophilic reagents seems to be the most effective one due to its atom economy and operational simplicity. It was considered as the most successful pathway for carbon–heteroatom bond formation [11–14]. Considering the importance of C—N bonding creation in organic synthesis and in connection with our research projects aimed to develop new routes to α-functional allylamines [15–20], we report herein the behavior of diethyl (*E*)-1-(bromomethyl)-2-cyanovinylphosphonate **1** as a powerful Michael acceptor [21], toward secondary and tertiary amines as a source of *N*-nucleophilic reagents.

RESULTS AND DISCUSSION

We have recently reported a highly stereoselective synthesis of diethyl (*E*)-1-(bromomethyl)-2-cyanovinylphosphonate **1** [21], using an unusual successive S_N2'-S_N2' reaction of 1,4-diazabicyclo[2.2.2]octane (DABCO) then KCN on available diethyl 1-(acethoxymethyl) vinylphosphonate, followed by a radical brominating reaction of the resulting β-cyanophosphonate *E* as shown in Scheme 1.

We have also demonstrated that allylic halide *E*-**1** could be used efficiently in the one-step synthesis of a new family of functionalized allylamines in good yields, through its exclusive (S_N2') substitution reaction with primary amines in methanol at low temperature (Scheme 2).

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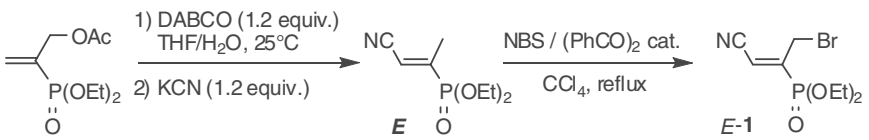
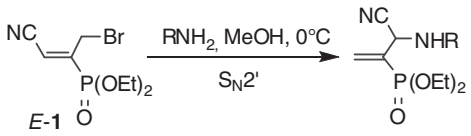


SCHEME 1 Synthesis of diethyl (*E*)-1-(bromomethyl)-2-cyanovinylphosphonate **1**.



SCHEME 2 Preparation of a new family of plurifunctionalized allylamines.

To extend our research program aimed to elucidate the factors that influence the reactivity of allyl systems with different amines to access newly functionalized nitrogenous molecules [22], we first studied the reactivity of excess of some secondary amines on allyl bromide *E*-**1** in methanol at room temperature. In fact, under the conditions described above, the starting material *E*-**1** was consumed within 15 to 30 min providing enamines **2a–c** in good yields. Thus, the reaction of the electrophile *E*-**1** with dimethylamine exclusively gives compound *E*-**2a** with the retention of configuration, while diethylamine and dipropylamine lead to a mixture of stereoisomeric enamines *Z*/*E*-**2a–c**. As shown below, the formation of enamines can be explained by proposing a two-step mechanism, which involves first conjugate addition of amine (two equivalents) to *E*-**1**, followed by a spontaneous isomerization (Scheme 3, Table 1).

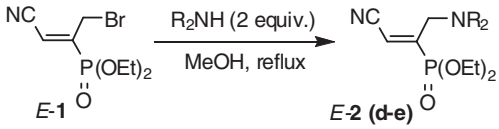
Notice that the coupling reaction of dimethylamine, diethylamine, and dipropylamine with allyl bromide *E*-**1** provides a class of enamines **2a–c**, not well known, that belongs to an important class of reactive intermediates in organic synthesis [23–33] and may also be classified as synthons for the construction of heterocyclic skeletons of various biologically active analogues, including anticonvulsant [34], anti-inflammatory [35], and antitumor agents [36]. At this stage, an original task was satisfactorily accomplished; however the observed results may raise a question: Could the conjugated addition of secondary amines to the allylic halide *E*-**1** be governed by the steric factor of secondary amines? To answer this question, reactions described above were carried out with more bulky amines like dicyclohexylamine and diphenylamine. Indeed, it was found that the coupling reaction of allyl bromide *E*-**1** with these bulky secondary amines in methanol at reflux provide unexpected allylamines **2d–e**, resulting from a predictable nucleophilic substitution (S_N2) (Scheme 4, Table 2).

For both compounds *E*-**2d** and *E*-**2e**, the preferred configuration is *E,* as confirmed by Nuclear Overhauser Effect SpectroscopY (NOESY).

TABLE 1 Synthesis of Enamines **2a–c**

Product	*R*	*Time (min)*	*Yield (%)*	*(E/Z)*[a]
2a	Me	15	78	100/0
2b	Et	30	72	65/35
2c	^{n}Pr	30	74	60/40

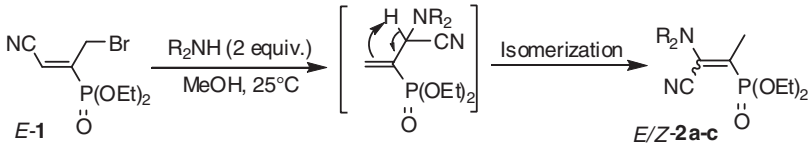
[a]Stereochemical assignements and isomeric purities were based on the difference in chemical shifts and integration ratios of protons of vinyl methyl group in ^{1}H NMR analysis and in correlation between protons in NOESY and HMBC spectra.
^{n}Pr, unbranched or linear propyl.



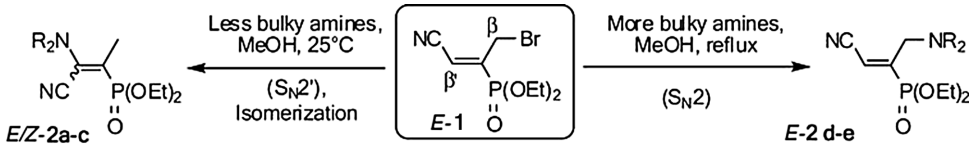
SCHEME 4 Preparation of new allylamines *E*-**2d–e**.

TABLE 2 Synthesis of New Allylamines *E*-**2d–e**

Product	*R*	*Time (day)*	*Yield (%)*
2d	Ph	10	64
2e	C_6H_{11}	12	58



SCHEME 3 Stereoselective synthesis of enamines **2a–c**.



SCHEME 5 Regioselective substitution of allylbromide *E*-**1** with bulky secondary amines.

There is no correlation between the vinylic proton (6.31 ppm) and those of CH_2NPh_2 (4.79 ppm) for **2d**, then the ethylenic proton (6.31 ppm) and those of $CH_2N(C_6H_{11})_2$ (4.56 ppm) in the case of **2e**. This result may justify the geometry of each synthetic intermediates *E*-**2d-e**. While the electrophilic behavior of diethyl (*E*)-1-(bromomethyl)-2-cyanovinylphosphonate **1** toward different secondary amines is summarized in Scheme 5. First, the regioselective and the abnormal (S_N2') substitution of bromide, observed with less bulky amines (cases **a–c**), may be due to the increased electrophilicity of β'-carbon of compound **1**. With more bulky amines, reaction on sp^2-hybridized β'-carbon is not possible. Thus the S_N2 mechanism takes place occasionally at an elevated temperature leading to a geometrically pure allylamines **2d–e** in 100% *E* configuration.

To optimize our research in this area, we treated allyl bromide *E*-**1** with an excess of tertiary amines (2 equivalents) like triethylamine, triethanolamine and ethyldiisopropylamine at 25°C in methanol as the solvent. Initially, the result did not seem to be satisfactory, because the reaction of tertiary amines with Michael acceptor *E*-**1** will not occur due to the steric hindrance, thus providing the possibility of addition of methanol, which yields to an allyl ether, which rearranges to its vinylic isomer in *Z* configuration and with good yields (Scheme 6, Table 3).

It should be noted that the reaction described in Scheme 6 cannot take place in the absence of an excess of tertiary amines which ensured permanent activation of the methanol to obtain the new vinyl ether's family **3**.

CONCLUSIONS

A synthesis of new functionalized nitrogen molecules **2a–e** was successfully completed by the coupling reaction of secondary amines with Michael acceptor **1** in methanol. We also isolated a new vinyl ether **3** which could be used as key synthetic intermediate for the generation of new polymeric materials [37].

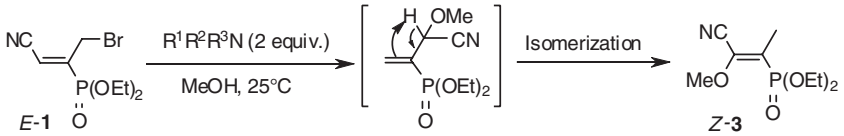
TABLE 3 Preparation of Vinyl Ether *Z*-**3**

Ether[a]	R^1	R^2	R^3	*Time (h)*	*Yield (%)*
3	Et	Et	Et	1	83
3	Et	^{i}Pr	^{i}Pr	4	69
3	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH	3	76

[a]Configurational assignment of product **3** was established by ^{1}H NMR and HMBC spectroscopy.
^{i}Pr, isopropyl.

EXPERIMENTAL

Starting materials and solvents were used without further purification. ^{1}H-NMR, ^{31}P-NMR, and ^{13}CNMR spectra were recorded on a Bruker AMX 300 spectrometer (El Manar University, Tunis, Tunisia) working at 300 MHz, 121 MHz, and 75 MHz, respectively, for ^{1}H, ^{31}P, and ^{13}C with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. The chemical shifts (δ) and coupling constants (J) are, respectively, expressed in parts per million (ppm) and Hertz (Hz). All NMR spectra were acquired at room temperature. Assignments of proton (^{1}H-NMR) and carbon (^{13}C-NMR) signals were secured by distortionless enhancement by polarization transfer (DEPT-135) and heteronuclear multiple bond correlation (HMBC) experiments. Multiplicity of peaks is indicated by the following: s, singlet; d, doublet; t, triplet; q, quartet; dq, doublet of quartets; and m, multiplet. Infrared spectra were recorded on a Bruker Vertex 70 FT-IR spectrophotometer (INRAP, Tunis, Tunisie). The elementary analyses (C, H, and N) were performed on a Perkin–Elmer Series II CHNS/O Analyzer 2400 (INRAP, Tunis,



SCHEME 6 Synthesis of diethyl (*Z*)-[2-(cyano)(methoxy)-1-methyl]vinylphosphonate **3**.

Tunisia). All reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Fluka Kieselgel 60 F254, Merck) eluting with the solvents indicated, visualized by a 254 nm UV lamp and aqueous potassium permanganate solution. For column chromatography, Fluka Kieselgel 70–230 mesh was used.

*General Procedure for the Synthesis of Enamines (**2a–c**)*

In a one-neck 25-mL round bottomed flask, was introduced 0.7g of allyl bromide (*E*)-**1** (2.25 mmol) diluted in 5 mL of absolute methanol then, secondary amine (4.5 mmol) was added dropwise with vigorous stirring. The reaction mixture was stirred at room temperature until all starting allyl bromide was consumed (TLC monitoring). The mixture was concentrated and the methanol was evaporated in vacuum. The obtained liquid was purified by column chromatography (Hexane-AcOEt, 6:4). The *Z/E*- enamine isomers **2b–c** could not be separated by column chromatography.

*Diethyl (E) 2-[(cyano)(dimethylamino)]-1-methylvinylphosphonate (**2a**)*

Yield: 78 %; yellow liquid; IR (neat): 2220, 1713, 1242 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ: 4.15 (dq, 4H, $J = 7.5$ Hz, $J = 7.5$ Hz, $2OCH_2$), 2.73 (s, 6H, $2CH_3N$), 2.07 (d, 3H, $^3J_{HP} = 15$ Hz, CH_3),1.36 (t, 6H, $J = 7.5$ Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$/TMS) δ: 151.2 (d, =C, $^1J_{CP} = 174.7$ Hz), 133.6 (d, =C, $^2J_{CP} =$ 18.7 Hz), 111.0 (d, CN, $^3J_{CP} = 31.5$ Hz), 63.0 (d, $2OCH_2$, $^2J_{CP} = 7.5$ Hz), 38.6 (s, $2CH_3N$), 17.6 (d, CH_3, $^2J_{CP} = 7.5$ Hz), 16.3 (d, $2CH_3$, $^3J_{CP} = 6$ Hz); ^{31}P-NMR (121 MHz, $CDCl_3$/TMS) δ: 13.95; Anal. calcd for $C_{10}H_{19}N_2O_3P$: C, 48.78; H, 7.78; and N, 11.38. Found: C, 48.71; H, 7.82; and N, 11.41.

*Diethyl (E, Z) 2-[(cyano)(diethylamino)]-1-methylvinylphosphonate (**2b**)*

Yield: 72 %; yellow liquid; IR (neat): 2222, 1728, 1245 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ: 4.15 (dq, 4H, $J = 7.5$ Hz, $J = 7.5$ Hz, $2OCH_2$), 2.93 (q, 4H, $J = 7.5$ Hz, $2CH_2N$), 2.21 (d, $^3J_{HP} = 15$ Hz, CH_3-*Z*), 2.05 (d, $^3J_{HP} = 16$ Hz, CH_3-*E*), 1.38 (t, 6H, $J = 7.5$ Hz, $2CH_3$-*Z*), 1.35 (t, 6H, $J = 7.5$ Hz, $2CH_3$-*E*), 1.07 (t, 6H, $J = 7.5$ Hz, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$/TMS) δ: 151.3 (d, =C, $^1J_{CP} = 174.75$ Hz), 131.4 (d, =C, $^2J_{CP} = 17.4$ Hz), 114.5 (d, CN-*Z*, $^3J_{CP} = 23.7$ Hz), 112.7 (d, CN-*E*, $^3J_{CP} = 30.75$ Hz), 62.7 (d, $2OCH_2$, $^2J_{CP} = 7.5$ Hz), 47.5 (s, $2CH_2N$), 18.3 (d, CH_3-*Z*, $^2J_{CP} =$ 7.5 Hz), 17.6 (d, CH_3-*E*, $^2J_{CP} = 8$ Hz), 16.3 (d, $2CH_3$, $^3J_{CP} = 6$ Hz), 13.3 (s, $2CH_3$); ^{31}P-NMR (121 MHz, $CDCl_3$/TMS) δ: 15.90; Anal. calcd for $C_{12}H_{23}N_2O_3P$: C, 52.54; H, 8.45; and N, 10.21. Found: C, 52.59; H, 8.46; and N, 10.23.

*Diethyl (E, Z) 2-[(cyano)(dipropylamino)]-1-methylvinylphosphonate (**2c**)*

Yield: 74 %; yellow liquid; IR (neat): 2222, 1721, 1244 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ: 4.15 (dq, 4H, $J = 7.5$ Hz, $J = 7.5$ Hz, $2OCH_2$), 2.63 (t, 4H, $J = 7.3$ Hz, $2CH_2$), 2.18 (d, $^3J_{HP} = 14$ Hz, CH_3-*Z*), 2.03 (d, $^3J_{HP} = 15$ Hz, CH_3-*E*), 1.64 (m, 4H, $2CH_2$), 1.36 (t, 6H, $J = 7.3$ Hz, $2CH_3$-*Z*), 0.84 (t, 6H, $J =$ 7.5 Hz, $2CH_3$-*E*); ^{13}C-NMR (75 MHz, $CDCl_3$/TMS) δ: 151.2 (d, =C, $^1J_{CP} = 174.5$ Hz), 134.6 (d, = C, $^2J_{CP} =$ 18.25 Hz), 113.3 (d, CN-*Z*, $^3J_{CP} = 22.8$ Hz), 111.2 (d, CN-*E*, $^3J_{CP} = 30.2$ Hz), 63.0 (d, $2OCH_2$, $^2J_{CP} =$ 7.5 Hz), 51.8 (s, $2CH_2$), 22.6 (s, $2CH_2$), 16.9 (d, CH_3-*Z*, $^2J_{CP} = 7.5$ Hz), 16.3 (d, CH_3-*E*, $^2J_{CP} = 7.5$ Hz), 15.8 (d, $2CH_3$, $^3J_{CP} = 6$ Hz), 13.2 (s, $2CH_3$); ^{31}P-NMR (121 MHz, $CDCl_3$/TMS) δ: 14.5; Anal. calcd for $C_{14}H_{27}N_2O_3P$: C, 55.61; H, 9.00; and N, 9.27. Found: C, 55.66; H, 9.03; and N, 9.23.

*General Procedure for the synthesis of allylamines (**2d–e**)*

To a solution of allyl bromide **(*E*)-1** (0.7g, 2.25 mmol) in 5 mL of absolute methanol, secondary amine (4.5 mmol) was dropwise added. The reaction mixture was stirred at reflux for 10–12 days, then the mixture was cooled and the methanol was removed under reduced pressure. The obtained liquid was purified by column chromatography (Hexane-AcOEt, 3:7).

*Diethyl (E)-[2-cyano-1-(diphenylamino) methyl]vinylphosphonate (**2d**)*

Yield: 64 %; brown liquid; IR (neat): 2221, 1610, 1241, 1451 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ: 7.27 (t, 4H, $J = 6$ Hz, aromatic H), 7.09 (d, 4H, $J = 6$ Hz, aromatic H), 7.00 (t, 2H, $J = 6$ Hz, aromatic H), 6.31 (d, 1H, $^3J_{HP} = 21$ Hz, = CH), 4.79 (d, 2H, $^3J_{HP} = 12$ Hz, CH_2N), 4.05 (dq, 4H, $J =$ 7.5 Hz, $J = 7.5$ Hz, $2OCH_2$), 1.25 (t, 6H, $J = 7.5$ Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$/TMS) δ: 152.7 (d, =C, $^1J_{CP} = 171$ Hz), 147.7 (s, aromatic C), 129.2 (s, aromatic CH), 121.4 (s, aromatic CH), 120.4 (s, aromatic CH), 114.4 (d, CN, $^3J_{CP} = 30.75$ Hz), 111.8 (d, =CH, $^2J_{CP} = 18.75$ Hz), 63.1 (d, $2OCH_2$, $^2J_{CP} =$ 6 Hz), 53.8 (d, CH_2N, $^2J_{CP} = 9.75$ Hz), 16.2 (d, $2CH_3$,

$^3J_{CP}$ = 6 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$/TMS) δ: 13.29; Anal. calcd for $C_{20}H_{23}N_2O_3P$: C, 64.86; H, 6.26; and N, 7.56. Found: C, 64.78; H, 6.23; and N, 7.59.

*Diethyl (E)-[2-cyano-1-(dicyclohexylamino) methyl]vinylphosphonate (**2e**)*

Yield: 58 %; yellow liquid; IR (neat): 2220, 1689, 1245 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ: 6.31 (d, $^3J_{HP}$ = 21 Hz, =CH), 4.56 (d, $^3J_{HP}$ = 12 Hz, CH_2N), 4.15 (dq, 4H, J = 7.5 Hz, J = 7.5 Hz, $2OCH_2$), 2.74–2.69 (m, 2H, 2CH), 1.42–1.33 (m, 20H, $10CH_2$), 1.26 (t, 6H, J = 6 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$/TMS) δ: 151.3 (d, =C, $^1J_{CP}$ = 174.75 Hz), 114.5 (d, CN, $^3J_{CP}$ = 30.75 Hz), 112.3 (d, =CH, $^2J_{CP}$ = 14.25 Hz), 55.3 (s, 2CHN), 53.8 (d, CH_2N, $^2J_{CP}$ = 9.75 Hz), 52.6 (s, 2CH), 31.2 (s, $4CH_2$), 26.9 (s, $2CH_2$), 22.8 (s, $4CH_2$), 16.3 (d, $2CH_3$, $^3J_{CP}$ = 6 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$/TMS) δ: 13.53; Anal. calcd for $C_{20}H_{35}N_2O_3P$: C, 62.80; H, 9.22; and N, 7.32. Found: C, 62.73; H, 9.23; and N, 7.35.

*Diethyl (Z)-[2-(cyano)(methoxy)-1-methyl]vinylphosphonate (**3**)*

Compound **3** was similarly prepared as **2a–c** from **1**. The compound **3** was purified by column chromatography (CH_2Cl_2-AcOEt, 7:3). Yellow liquid; IR (neat): 2224, 1713, 1244, 1171, 1014 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/TMS) δ: 4.15 (dq, 4H, J = 7.5 Hz, J = 7.5 Hz, $2OCH_2$), 3.92 (s, 3H, CH_3), 1.90 (d, 3H, $^3J_{HP}$ = 15 Hz, CH_3), 1.37 (t, 6H, J = 6 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$/TMS) δ: 136.5 (d, =C, $^2J_{CP}$ = 21 Hz), 119.6 (d, =C, $^1J_{CP}$ = 189 Hz), 111.1 (d, CN, $^3J_{CP}$ = 5.25 Hz), 62.6 (d, $2OCH_2$, $^2J_{CP}$ = 5.25 Hz), 58.6 (s, OCH_3), 16.2 (d, $2CH_3$, $^3J_{CP}$ = 6 Hz), 12.8 (d, CH_3, $^2J_{CP}$ = 4.5 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$/TMS) δ: 14.85; Anal. calcd for $C_9H_{16}NO_4P$: C, 46.35; H, 6.92; and N, 6.01. Found: C, 46.22; H, 6.95; and N, 6.05.

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