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Triphenylphosphine Mediated Efficient Synthesis of 4-Substituted-1-methyl-2,5-dioxo-3-imidazolines

Issa Yavari* and **Nader Zabarjad-Shiraz**

Department of Chemistry, University of Tarbiat Modarres, Tehran, Iran

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Summary. Stable crystalline phosphorus ylides are obtained in excellent yields from the 1:1:1 addition reaction between 1-methylparabanic acid (1-methylimidazoline-2,4,5-trione) and dialkyl acetylenedicarboxylates in the presence of triphenylphosphine. These ylides exist in solution as a mixture of two geometric isomers. This is due to the restricted rotation around the carbon–carbon partial double bond resulting from conjugation of the ylide moiety with the adjacent carbonyl group. These ylides undergo smooth intramolecular *Wittig* reaction followed by an electrocyclic ring opening to produce dialkyl (*E*)-2-(1-methyl-2,5-dioxo-3-imidazolin-4-yl)-but-2-enedioates in good yields.

Keywords. Triphenylphosphine; Acetylenic ester; 1-Methylparabanic acid; Dialkyl (*E*)-2-(1-methyl-2,5-dioxo-3-imidazolin-4-yl)-but-2-enedioate.

Introduction

Recently, many marine imidazole alkaloids have been isolated from sponges, and their antitumor and antibacterial activities have also been reported [1–5]. A structural characteristic of several imidazole alkaloids such as clathridine A, clathridine B, naamidine A, isonaamidine A, or pyrronaamidine A is the presence of a (1-methyl-2,5-dioxo-3-imidazolin-4-yl)-amino moiety. The first total synthesis of clathridine A has been achieved [6] by using a regioselective condensation as the key step, in which preclathridine A was treated with 1-methylparabanic acid (1-methylimidazoline-2,4,5-trione, **1**).

As part of our current studies on the development of new routes to heterocyclic and carboxylic systems [7–10], we now report on the reaction between 1-methylparabanic acid and dialkyl acetylenedicarboxylates in the presence of triphenylphosphine.

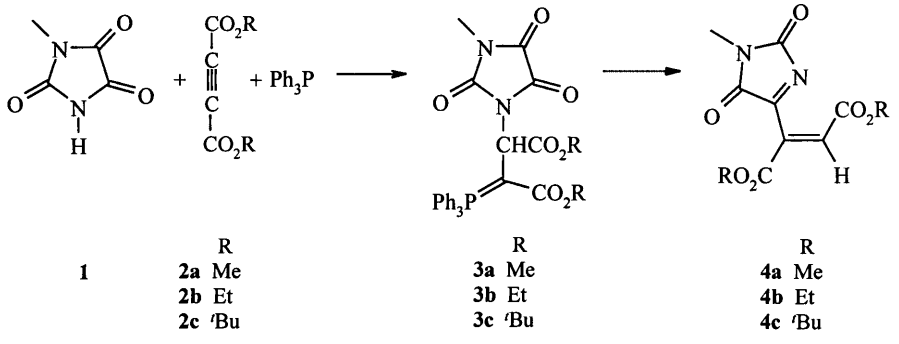
* Corresponding author. E-mail: isayavar@yahoo.com

Results and Discussion

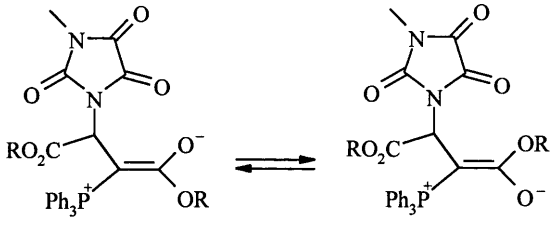
The reaction of 1-methylparabanic acid (**1**) with dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine proceeded at room temperature in ethyl acetate, and was complete within a few hours. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of stable phosphorus ylides **3** (Scheme 1). No other products than **3** could be detected. The structures of compounds **3a**–**3c** were deduced from their elemental analyses and IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra. The mass spectra of these stable ylides displayed molecular ion peaks at appropriate m/z values. Any initial fragmentation involves loss from, or complete loss of the side chains and scission of the heterocyclic ring system.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles [11–15], it is reasonable to assume that phosphorus ylides **3** result from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct followed by attack of the nitrogen atom of the anion of the NH-acid to the vinylphosphonium cations **5** to generate ylides **3** (Scheme 3).

^{1}H, ^{13}C, and ^{31}P NMR spectra of the ylides **3a**–**3b** are consisted with the presence of two diastereoisomers. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group and rotation about the partial double bond in the (*E*)-**3** and (*Z*)-**3** geometrical isomers (Scheme 2) is slow on the NMR time scale at ambient temperature. Selected ^{1}H, ^{13}C, and ^{31}P NMR chemical shifts and coupling constants in the major (M) and minor (m) geometrical isomers of compounds **3a**–**3c** are shown in Table 1. Only one geometrical isomer was

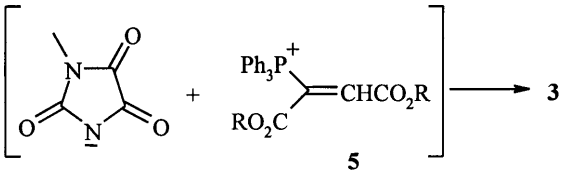


Scheme 1



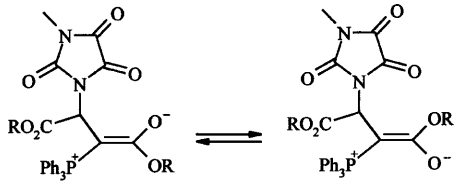
(*Z*)-**3**; Major (*E*)-**3**; Minor

Scheme 2



Scheme 3

Table 1. Selected ^{1}H, ^{13}C and ^{31}P NMR chemical shifts (δ/ppm) and coupling constants (J/Hz) for H-2, OR, CO_2R, C-2 and C-3 in the major (M) and minor (m) diastereomers of compounds **3a**–**3c**



Compound	Isomer (%)	^{1}H NMR			^{13}C NMR		^{31}P NMR
		H-2 ($^{3}J_{PH}$)	CO_2R	OR	C-2 ($^{2}J_{PC}$)	C-3 ($^{1}J_{PC}$)	
3a	M (57)	4.71 (15.5)	3.75	3.16	57.0 (17)	37.1 (131)	22.87
	m (43)	4.70 (17.5)	3.73	3.59	56.5 (17)	38.5 (140)	23.08
3b	M (59)	4.71 (16.4)	4.07–4.20[a]	3.64–3.82[a]	57.3 (17)	36.7 (129)	22.86
	m (41)	4.64 (17.8)	4.21–4.28[a]	4.11–4.17[a]	56.7 (18)	38.0 (130)	23.29
3c	M (>98)	4.50 (17.0)	1.54	0.97	58.2 (17)	36.3 (131)	21.72

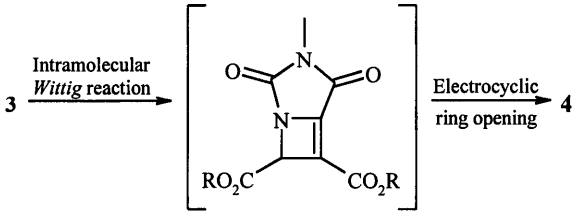
[a] The methylene group of the OR moiety

observed for the di-*tert*-butyl derivative **3c**, presumably, because of the bulky *tert*-butyl groups.

The methoxy region of the ^{1}H NMR spectrum of **3a** in $CDCl_3$ at ambient temperature (25°C) exhibits two sharp singlets for the CO_2CH_3 groups of (*E*) and (*Z*) isomers and two fairly broad singlets for the OCH_3 groups. Near 10°C the broad lines become sharper. The ^{1}H NMR of **3a** in 1,2-dichlorobenzene at 10°C is similar to that measured in $CDCl_3$ (Table 2). Increasing the temperature results in coalescence of the OCH_3 resonances. At 90°C, a relatively broad singlet was observed for the OCH_3 group, while the CO_2CH_3 protons appear as a sharp single resonance.

Table 2. Selected proton chemical shifts (at 500.1 MHz, TMS) and activation parameters for **3a** in 1,2-dichlorobenzene

Compound	Temp/°C	Resonance (P–C–CO_2CH_3)		$\Delta\nu$/Hz	k/s^{-1}	T_c/K	$\Delta G^{\neq}$/kJmol^{-1}
		ppm					
3a	10	3.16	3.59	215	477	345	67.1 ± 2
	90	3.38					



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Scheme 4

Although an extensive line-shape analysis of the dynamic ^{1}H NMR effect observed for **3a** was not undertaken, the variable temperature spectra allowed to calculate [16] the free energy barrier (if not the enthalpy and entropy of activation) for the dynamic NMR process in this ylide (see Table 2). The experimental data available are not suitable for obtaining meaningful values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the errors in $\Delta G^{\neq}$ are not large [17]. From coalescence of the methoxy proton resonances, the first-order rate constant for dynamic NMR in **3a** is $477\ s^{-1}$ at 345 K. The calculated free-energy of activation for the dynamic process in **3a** is $67.1 \pm 2\ kJ\ mol^{-1}$ (Table 2).

Phosphorus ylides **3** undergo a smooth reaction in boiling toluene to produce triphenylphosphine oxide and dialkyl (*E*)-2-(1-methyl-2,5-dioxo-3-imidazoline-4-yl)-but-2-enedioate **4** (Scheme 1). Structure **4** was assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H, and ^{13}C NMR and mass spectral data. Thus, the ^{1}H NMR spectrum of each of the isolated products exhibited a C=CH proton signal at about 6.9–7.2 ppm, which is in agreement with the (*E*) configuration [18] for the vinyl moiety in **4**. Further evidence was obtained from the ^{13}C NMR spectra, which displayed C=CH carbon resonances at about 129–131 ppm and C=N carbon signal at about 151 ppm.

Although we have not yet established the mechanism of formation of **4** in an experimental manner, a possible explanation is proposed in Scheme 4. Ylides **3** undergo intramolecular *Witting* reaction to produce the fused bicyclic intermediates **6**, which apparently isomerise under the reaction conditions employed to produce the final products **4** in excellent yields.

In conclusion, the present method features the advantages that can be the reaction performed under neutral conditions and the starting materials and reagents can be mixed without any activation or modification. Phosphorus ylides **3a–3c** can be considered as potentially useful synthetic intermediates. The procedure described here provides an acceptable method for the preparation of phosphoranes bearing a 1-methylparabanic acid residue, which can be employed for the synthesis of 4-substituted-3-imidazolin-2,5-diones.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. IR spectra were measured on a Shimadzu IR 460 spectrometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured on a BRUKER DRX-500 AVANCE instrument with $CDCl_3$ as the

solvent at 500.1, 125.8, and 202.4 MHz. The mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Dialkyl acetylenedicarboxylates **2a**–**2c**, were obtained from Fluka (Buchs, Switzerland) and used without further purification. 1-Methylparabanic acid (**1**) was prepared according to [19].

General procedure for the preparation of phosphorus ylides **3**

To a magnetically stirred solution of 0.256 g **1** (2 mmol) and 0.284 g dimethyl acetylenedicarboxylate (2 mmol) in 5 cm^3 ethyl acetate was added dropwise a solution of 0.524 g triphenylphosphine (2 mmol) in 2 cm^3 ethyl acetate at $-5°C$ over 10 min. After 24 h stirring at room temperature, the product was filtered and washed with cold ethyl acetate.

Dimethyl 2-(3-methyl-2,4,5-trioxo-imidazolin-1-yl)-3-(triphenylphosphanylidene)-succinate (**3a**, $C_{28}H_{25}N_2O_7P$)

Yellow powder; mp: 173–175°C; yield: 0.89 g (84%); IR (KBr): $\nu = 1720$, 1637, 1614 (C=O), 1429 (C=C) cm^{-1}; major isomer (*Z*)-**3a** (57%); ^{1}H NMR (500.1 MHz, δ, $CDCl_3$): 3.10 (3H, s, NCH_3), 3.16 and 3.75 (6H, 2s, $2OCH_3$), 4.71 (1H, d, $^3J_{PH} = 15.5$ Hz, CH), 7.3–7.7 (15H, m, $3C_6H_5$) ppm; ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 24.7 (NCH_3), 37.1 (d, $^1J_{PC} = 131$ Hz, P–C), 49.3 and 50.4 ($2OCH_3$), 57.0 (d, $^2J_{PC} = 17$ Hz, CH), 126.4 (d, $^1J_{PC} = 92$ Hz, P–C_{ipso}), 129.0 (d, $^3J_{PC} = 12$ Hz, C_{meta}), 132.1 (d, $^4J_{PC} = 2$ Hz, C_{para}), 137.1 (d, $^2J_{PC} = 11$ Hz, C_{ortho}), 153.3 [NC(O)N], 156.1 and 156.8 (2NC=O), 165.3 (OC=O), 170.2 (d, $^2J_{PC} = 13$ Hz, PC=*C*) ppm; ^{31}P NMR (202.4 MHz, δ, $CDCl_3$): 22.87 (Ph_3P^+–C) ppm; minor isomer (*E*)-**3a** (43%); ^{1}H NMR (500.1 MHz, δ, $CDCl_3$): 3.12 (3H, s, NCH_3), 3.59 and 3.73 (6H, 2s, $2OCH_3$), 4.71 (1H, d, $^3J_{PH} = 17.5$ Hz, CH), 7.3–7.7 (15H, m, $3C_6H_5$) ppm; ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 24.7 (NCH_3), 38.5 (d, $^1J_{PC} = 140$ Hz, P–C), 49.3 and 52.3 ($2OCH_3$), 56.5 (d, $^2J_{PC} = 17$ Hz, CH), 125.7 (d, $^1J_{PC} = 93$ Hz, P–C_{ipso}), 129.0 (d, $^3J_{PC} = 12$ Hz, C_{meta}), 132.1 (d, $^4J_{PC} = 2$ Hz, C_{para}), 137.1 (d, $^2J_{PC} = 11$ Hz, C_{ortho}), 153.5 [NC(O)N], 156.9 and 157.9 (2NC=O), 165.2 (OC=O), 169.2 (d, $^2J_{PC} = 14$ Hz, PC=*C*) ppm; ^{31}P NMR (202.4 MHz, δ, $CDCl_3$): 23.08 (Ph_3P^+–C) ppm.

Diethyl 2-(3-methyl-2,4,5-trioxo-imidazolin-1-yl)-3-(triphenylphosphanylidene)-succinate (**3b**, $C_{30}H_{29}N_2O_7P$)

Yellow powder; mp: 158–160°C; yield: 0.92 g (82%); IR (KBr): $\nu = 1763$, 1730 and 1637 (C=O), 1451 (C=C) cm^{-1}; major isomer (*Z*)-**3b** (59%); ^{1}H NMR (500.1 MHz, δ, $CDCl_3$): 0.48 and 1.28 (6H, 2t, $^3J_{HH} = 7.0$ Hz, $2CH_3$), 3.09 (3H, s, NCH_3), 3.64–3.82 (2H, complex (AB)X_3 system, OCH_2), 4.07–4.20 (2H, complex (AB)X_3 system, OCH_2), 4.71 (1H, d, $^3J_{PH} = 16.4$ Hz, CH), 7.3–7.7 (15H, m, $3C_6H_5$) ppm; ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 14.0 and 14.1 ($2CH_2CH_3$), 24.7 (NCH_3), 36.7 (d, $^1J_{PC} = 129$ Hz, P–C), 57.3 (d, $^2J_{PC} = 17$ Hz, CH), 57.9 and 61.9 ($2OCH_2$), 126.7 (d, $^1J_{PC} = 92$ Hz, P–C_{ipso}), 128.8 (d, $^3J_{PC} = 12$ Hz, C_{meta}), 132.2 (d, $^4J_{PC} = 2$ Hz, C_{para}), 133.6 (d, $^2J_{PC} = 11$ Hz, C_{ortho}), 153.4 [NC(O)N], 156.1 and 157.0 (2NC=O), 168.7 (OC=O), 169.8 (d, $^2J_{PC} = 14$ Hz, PC=*C*) ppm; ^{31}P NMR (202.4 MHz, δ, $CDCl_3$): 22.86 (Ph_3P^+–C); minor isomer (*E*)-**3b** (41%); ^{1}H NMR (500.1 MHz, δ, $CDCl_3$): 1.28 and 1.32 (6H, 2t, $^3J_{HH} = 7.0$ Hz, $2CH_3$), 3.10 (3H, s, NCH_3), 4.11–4.17 (2H, (AB)X_3 system, OCH_2), 4.21–4.28 (2H, (AB)X_3 system, OCH_2), 4.64 (1H, d, $^3J_{PH} = 17.8$ Hz, CH), 7.3–7.7 (15H, m, $3C_6H_5$) ppm; ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 14.1 and 14.7 ($2CH_2CH_3$), 24.7 (NCH_3), 38.0 (d, $^1J_{PC} = 130$ Hz, P–C), 56.7 (d, $^2J_{PC} = 18$ Hz, CH), 58.8 and 61.8 ($2OCH_2$), 125.1 (d, $^1J_{PC} = 93$ Hz, P–C_{ispo}), 128.9 (d, $^3J_{PC} = 12$ Hz, C_{meta}), 132.1 (d, $^4J_{PC} = 2$ Hz, C_{para}), 133.5 (d, $^2J_{PC} = 11$ Hz, C_{ortho}), 153.6 [NC(O)N], 155.9 and 157.1 (2NC=O), 168.6 (OC=O), 170.5 (d, $^2J_{PC} = 17$ Hz, PC=*C*) ppm; ^{31}P NMR (202.4 MHz, δ, $CDCl_3$): 23.29 (Ph_3P^+–C) ppm.

Di-tert-butyl 2-(3-methyl-2,4,5-trioxo-imidazolin-1-yl)-3-(triphenyl phosphanylidene)-succinate (**3c**, $C_{34}H_{37}N_2O_7P$)

Yellow powder; mp: 122–124°C; yield: 0.96 g (78%); IR (KBr): $\nu = 1769$, 1728 and (C=O), 1432 (C=C) cm^{-1}; major isomer (*Z*)-**3c**; ^1H NMR (500.1 MHz, δ, $CDC1_3$): 0.97 and 1.54 (18H, 2s, $2CMe_3$), 3.05 (3H, s, NCH_3), 4.50 (1H, d, $^3J_{PH} = 17.0$ Hz, CH), 7.5–7.7 (15 H, m, 3 C_6H_5) ppm; ^{13}C NMR (125.8 MHz, δ, $CDC1_3$): 24.8 (NCH_3), 28.1 and 28.3 (2 OC*Me*$_3$), 36.3 (d, $^1J_{PC} = 131$ Hz, P–C), 58.2 (d, $^2J_{PC} = 17$ Hz, CH), 77.5 and 81.7 (2 OC*Me*$_3$), 127.2 (d, $^1J_{PC} = 92$ Hz, P–C_{ipso}), 128.7 (d, $^3J_{PC} = 12$ Hz, C_{meta}), 132.2 (d, $^4J_{PC} = 2$ Hz, C_{para}), 136.6 (d, $^2J_{PC} = 11$ Hz, C_{ortho}), 153.6 [NC(O)N], 156.0 and 157.2 (2NC=O), 167.9 (d, $^3J_{PC} = 12$ Hz, OC=O), 168.8 (d, $^2J_{PC} = 13$ Hz, PC=*C*) ppm; ^{31}P NMR (202.4 MHz, δ, $CDC1_3$): 21.72 (Ph_3P^+–C) ppm.

General procedure for conversion of **3** *to* **4**

A mixture of 0.70 g **3a** (1.3 mmol) in 30 cm^3 toluene was refluxed for 48 h. The solvent was removed under reduced pressure and the yellowish oil was separated from triphenylphosphine oxide using cold diethyl ether. The solvent was removed and the product was crystallized from diethyl ether:*n*-hexane (1:1).

Dimethyl (E)-2-(1-methyl-2,5-dioxo-3-imidazolin-4-yl)-but-2-enedioate (**4a**, $C_{10}H_{10}N_2O_6$)

Colorless crystals; mp: 144–146°C; yield: 0.29 g (86%); IR (KBr): $\nu = 1763$, 1748 and 1722 (C=O), 1440 (C=C) cm^{-1}; ^1H NMR (500.1 MHz, δ, $CDCl_3$): 3.27 (3H, s, NCH_3), 3.80 and 3.90 (6H, 2s, $2OCH_3$), 7.20 (1H, s, CH) ppm; ^{13}C NMR (125.8 MHz, δ, $CDC1_3$): 25.4 (NCH_3), 52.8 and 53.9 ($2OCH_3$), 129.9 (*C*=CH), 130.0 (C=*CH*), 151.2 (C=N), 154.3 [NC(O)N], 155.9 (NC=O), 161.2 and 162.2 (2OC=O) ppm.

Diethyl (E)-2-(1-methyl-2,5-dioxo-3-imidazolin-4-yl)-but-2-enedioate (**4b**, $C_{12}H_{14}N_2O_6$)

Colorless crystals; mp: 131–133°C; yield: 0.28 g (68%); IR (KBr): $\nu = 1757$, 1743 and 1718 (C=O), 1423 (C=C) cm^{-1}; ^1H NMR (500.1 MHz, δ, $CDCl_3$): 1.28 and 1.33 (6H, 2t, $^3J_{HH} = 7.0$ Hz, $2CH_3$), 3.26 (3H, s, NCH_3), 4.22 and 4.35 (2H, 2q, $^3J_{HH} = 7.0$ Hz, $2OCH_2$), 7.18 (1H, s, CH) ppm; ^{13}C NMR (125.8 MHz, δ, $CDC1_3$): 13.9 and 14.0 ($2CH_3$), 25.4 (NCH_3), 62.1 and 63.4 ($2OCH_2$), 129.9 (*C*=CH), 130.2 (C=*CH*), 151.2 (C=N), 154.3 [NC(O)N], 155.9 (NC=O), 160.7 and 162.2 (2OC=O) ppm.

Di-tert-butyl (E)-2-(1-methyl-2,5-dioxo-3-imidazolin-4-yl)-but-2-enedioate (**4c**, $C_{16}H_{22}N_2O_6$)

White crystals; mp: 116–118°C; yield: 0.32 g (68%); IR (KBr): $\nu = 1751$, 1738 and 1715 (C=O), 1432 (C=C) cm^{-1}; ^1H NMR (500.1 MHz, δ, $CDC1_3$): 1.45 and 1.51 (18H, 2s, $2CMe_3$), 3.23 (3H, s, NCH_3), 6.91 (1H, s, CH) ppm; ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 25.4 (NCH_3), 27.7 and 27.8 (2C*Me*$_3$), 83.3 and 84.7 (2 OC*Me*$_3$), 129.6 (*C*=CH), 131.1 (C=*CH*), 151.4 (C=N), 154.4 (NC(O)N), 156.1 (NC=O), 161.6 and 164.4 (2OC=O) ppm.

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