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ARTICLE

A greener procedure for the synthesis of α-ureidophosphonates under ultrasound irradiation. X-ray crystallographic study

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Abdeslem Bouzina[a], Malika Berredjem[a]*, Sofiane Bouacida[b,c], Hocine Merazig[c] and Nour-eddine Aouf[a]

An efficient, eco-sustainable and greener procedure for the synthesis of α-ureidophosphonates via a one-pot three-component reaction of aldehyde, urea/thiourea and triethylphosphite or diethylphosphite using ultrasonic irradiation under solvent- and catalyst-free conditions at 75°, is developped. The desired products were obtained in excellent yie within short reaction times (15-30 min). Crystals of Diethyl [α-ureido-(4-methylphenyl)]methyl phosphonate suitable for X-ray study have been obtained after recrystallization in mixture of diethyl ether and n-hexane. The detailed analysis molecular and crystal structure is presented.

Introduction

The synthesis of α-aminophosphonates has attracted much attention in organic synthesis due to their structural analogy to α-amino acids[1] and α-aminophosphonic acids[2]. These compounds possess diverse biological and pharmacological properties. Among them, α-ureidophosphonates continue to attract the attention of chemists because they have been used as precursor for the synthesis of chiral α-aminophosphonates[3].α-ureidophosphonates have gained diverse biological activities in pharmaceutical as fungal pathogens[4],enzyme inhibitors[5], antibiotics[6],pharmacological agents[7],peptidomimetics[8]andantitumor[9]. They also display powerful antiviral activities against TMV[10]. Metal chelating ability[11], and these compounds used as active ingredients in pesticides especially insecticides and acaricides[12]. Because of their chemical and biological importance, many procedures for the synthesis of α-ureidophosphonates and α-amidophosphonates derivatives have been developed. Generally, these methods could be fulfilled in the catalysis such as; BF_3 $(OEt)_2$[13, 3], (H_2N–SO_3H, $PhSO_3H$, CH_3SO_3H)[14], $LiClO_4$[15] and$InCl_3$[16], in the solvent THF[17]at 50 °C or toluene[18] at 50 °C. However there are some problems associated with these methods including harsh reaction conditions, long reaction times and side reactions.On the other hand, one of the powerful tools used to connect economic features with the green concerns is performing organic reactions under ultrasound irradiation[19-23] and solvent-free conditions[24-27]. This powerful technique became extremely efficient and attractive in synthetic organic chemistry, and is able to activate many reactions due to cavitational collapse. Ultrasound irradiation provides higher yields and selectivities, shorter reaction times and milder reaction conditions, nontoxic, environmentally friendly solvent, in a one-step reaction, without isolation of any intermediate thus reducing time, saving money, energy and raw materials.

In addition, Multi-component reactions (MCRs) constitute one of the best tools for modern organic synthesis because they can use most of the constituent atoms of several reactant molecules to form a product molecule. Such reactions present remarkable advantages for library synthesis aimed at carrying out structure-activity relationship (SAR) studies of drug-like compounds, in a single procedural step such as; high degree of atom economy, reduction in reaction steps and the number of workup, reduction in energy consumption[28-30]. In the present research, we wish to describe a new and *eco-friendly* method for the preparation of α-ureidophosphonates through a one-pot reaction of three component condensation of aldehyde with urea/thiourea and triethylphosphite or diethylphosphite under catalyst- and solvent-free conditions using ultrasonic irradiation at 75 °c.

Results and discussion

In continuation of our investigations on the use of ultrasound irradiation for fine chemical preparation of α-amidophosphonates derivatives[31-33].

The α-ureidophosphonates (b) were obtained by the one-pot three component condensation of aldehyde with urea/thiourea and triethylphosphite or diethylphosphite under ultrasonic irradiation at

[a] *Laboratory of Applied Organic Chemistry, Synthesis of biomolecules and molecular modelling Group, Sciences Faculty, Chemistry Department, Badji-Mokhtar - Annaba University, Box 12, 23000 Annaba, Algeria. *Corresponding author. Email: malika.berredjem@univ-annaba.org, mberredjem@yahoo.fr*

[b] *Département sciences de la matière, université Oum El Bouaghi, 04000 Oum El Bouaghi, Algérie.*

[c] *Unité de Recherche de Chimie de l'Environnement et Moléculaire Structurale, Université Constantine 1. Constantine 25000, Algérie.*

† Spectral data and crystallographic data for the synthesis of α-ureidophosphonatesprepared in this work are available in the supporting information joined to this manuscript DOI: 10.1039/x0xx00000x

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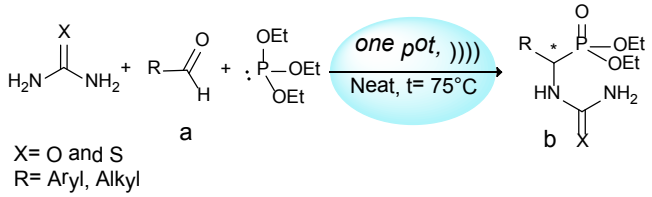
75 °C and solvent-, catalyst-free conditions in excellent yields (Scheme 1).



Scheme 1 One-pot synthesis of α-ureidophosphonates under ultrasound irradiation.

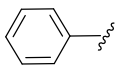
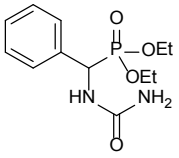
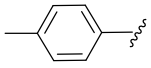
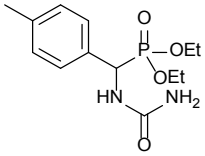
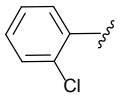
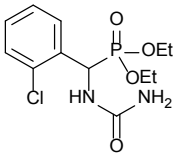
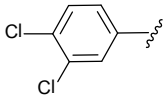
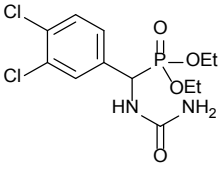
To evaluate the feasibility of α-ureidophosphonates (b), a modal reaction involving urea, benzaldehyde and triethylphosphite were carried out at different temperatures (r.t, 30, 50 and 75 °C) in the presence of different solvents or without solvent under ultrasonic irradiation (table1).

Table 1 Optimization of reaction time and solvent for the synthesis of α–ureidophosphonate.

Entry	Solvent	Time (min)	Temperature °C	Yields %
1	No solvent	18	75	85
2	EtOH	60	75	58
3	MeOH	60	75	55
4	CH_3CN	120	75	23
5	CH_2Cl_2	120	75	25
6	THF	100	75	50
7	DMF	100	75	56

At room temperature in ethanol, product formation was not observed after 3h working time, at 30 °C we obtained a low yield (10-15%) after 2h, but when the temperature increases until 50 °C the yield is improved. Under ultrasonic irradiation at 75°C, We have obtained a good yield in short reaction time (15-30 min). At these optimistic conditions (ultrasonic irradiation, catalyst-, solvent-free, and 75 °C), a series of α-ureidophosphonates (b) were obtained by various aromatic aldehyde and urea/thiourea. The results of these studies are presented in Table 2.

Table 2 Multicomponent synthesis of α-ureidophosphonates under ultrasound irradiation.

Entry	*R*	*Product*	*Time /min*	*Yield%*	*M.p. ^0C*
1b			18	85	197-199
2b			20	78	184-186
3b			22	83	202-204
4b			21	77	196-198

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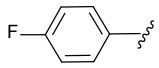
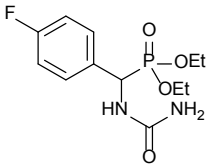
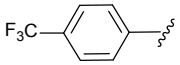
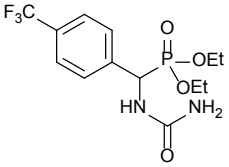
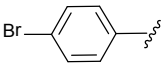
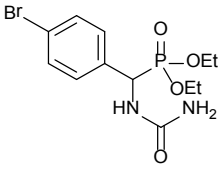
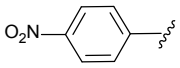
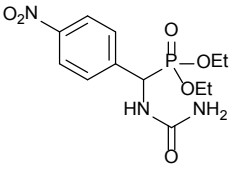
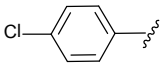
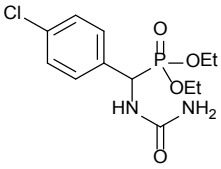
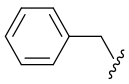
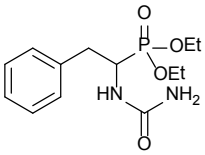
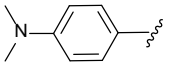
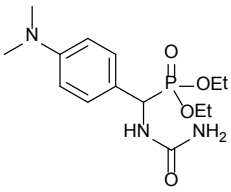
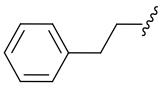
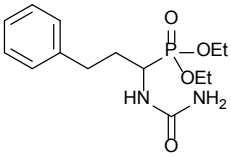
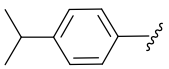
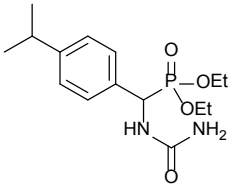
5b			25	81	198-200
6b			26	75	186-188
7b			28	79	188-190
8b			23	85	203-205
9b			25	80	201-203
10b			30	76	199-201
11b			20	85	192-194
12b			15	81	190-192
13b			25	85	197-199

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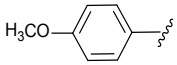
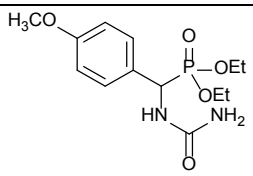
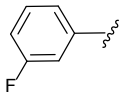
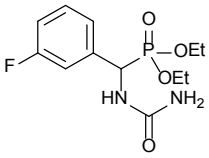
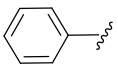
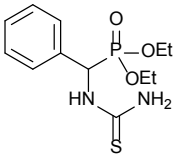
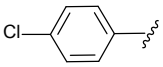
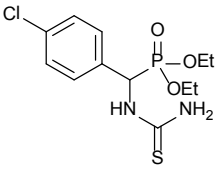
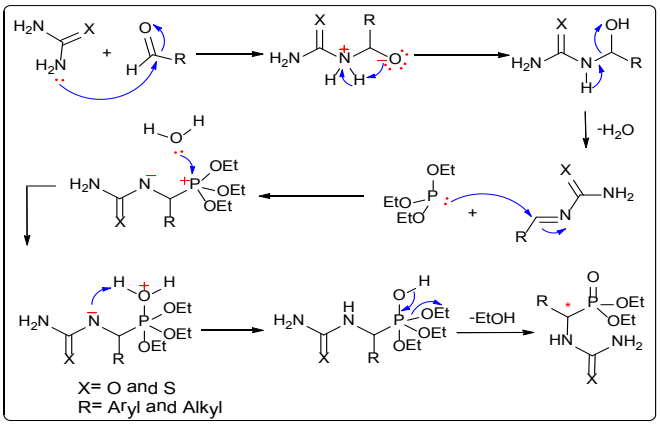
14b			20	78	204-206
15b			20	80	199-201
16b			17	83	198-200
17b			23	81	201-203

The structures of the synthesized compounds are confirmed by elemental analysis as well as by IR and ^{1}H, ^{13}C, ^{31}P NMR spectral data and MS.

Mechanistic proposal

The ultrasonic energy applying to the reaction generates the acoustic cavitation mechanical effect when sonic waves propagate through the medium. Vibrations of molecules generate compressions and rarefactions which give rise to the phenomenon of bubble formation and collapse in the reaction mixture urea/thiourea, aldehyde and triethylphosphite or diethylphosphite to facilitate the nucleophilic attack of the amino functional (urea/thiourea) on the carbonyl group (aldehyde). During cavitation, the chemical bonds break, and water eliminated for imine formation, the last one undergo to nucleophilic attack of triethylphosphite or diethylphosphite and formation to water in the reaction and EtOH eliminated for the α-ureidophosphonates formation according to the mechanism below.



Scheme 2 Mechanistic proposal for the synthesis of α-ureidophosphonates**.**

X-ray analysis of the Diethyl [α-ureido-(4-isopropylphenyl)] methylphosphonate: The formation of compound 13b was furtherconfirmed by single crystal X-ray diffraction analyses; the ORTEP-3[34] diagram of complex is shown in Fig. 1.

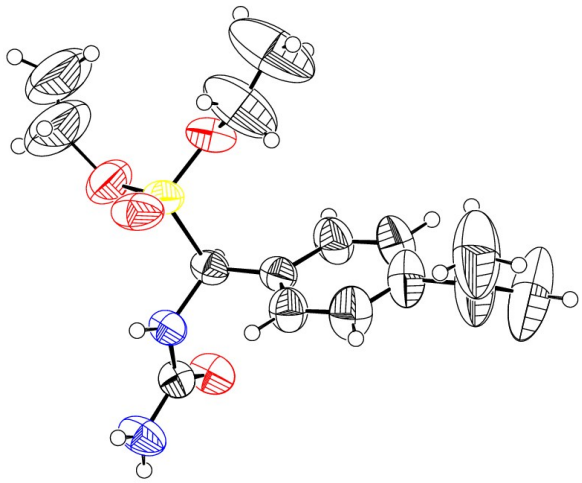


Figure 1 ORTEP for diethyl [α-ureido-(4-isopropylphenyl)]methylphosphonate.

The reported structure was solved by direct methods with SIR2002 [35] to locate all the non-H atoms which were refined anisotropically with SHELXL97[36] using full-matrix least-squares on F2 procedure from within the WinGX[34] suite of software used to prepare material for publication. All the H atoms were placed in the calculated positions and constrained to ride on their parent atomsCCDC 1424911 contains the supplementary crystallographic data for

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compound 13b. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Experimental

General data

All chemicals and solvents were purchased from common commercial sources and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F_{254} percolated aluminum plates and were developed by spraying with ninhydrin solution. Column chromatography was performed with Merck silica gel (230-400 mesh). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Brücker or Jeol spectrometer at 250, or 400 MHz. Chemical shifts is reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (*J*) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Brücker or Jeol at 60, 75 or 100 MHz. Chemical shifts are reported in δ units (ppm) relative to $CDCl_3$ (δ 77.0). Phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded on a Brücker or Jeol at 75, 100 or 161 MHz. Infrared spectra were recorded on a Perkin Elmer 600 spectrometer. Elemental analysis was recorded on a EURO E.A 3700. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Ultrasound assisted reactions were carried out using a FUNGILAB ultrasonic bath with a frequency of 40 kHz and a nominal power of 250 W. The reactions were carried out in an open glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 mL) at 75°C.

Crystallography

A single crystal of the studied compound, 13b, $C_{15}H_{24}N_2O_4P$, with dimensions of 0.06×0.11× 0.13 mm^3, was selected for single crystal X-ray diffraction analysis. Data collection was performed, at 295(2)K, on a Brücker APEX II diffractometer, CCD area detector equipped with a graphite monochromatized MoKα radiation (λ= 0.71073Å).***Crystallographic data*** for 13b: $C_{15}H_{24}N_2O_4P$, M = 327.33, T = 295(2) K, monoclinic, space group P21/n (no. 14), a = 9.6789(5), b = 9.1089(4), c = 20.6717(9)Å , β=93.303(2)°, V = 1819.48(15) Å3, Z = 4, Dc = 1.195 Mg m−3, μ= 0.169 mm−1, independent reflections = 3602 [Rint = 0.0379], R1 [for 2291 reflections with I > 2r(I)] = 0.0675, wR2 (all data = 0.1907).

Typical experimental procedure for the synthesis of α-ureidophosphonates

In a glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 mL)taken a mixture of aldehyde (1 mmol) and urea/thiourea (1 mmol) at 75^0 C, then the triethylphosphite or diethylphosphite (1 mmol) was added. The reaction mixture was subjected to the ultrasonication with a frequency of 40 kHzfor appropriate time. After completion of the reaction, as indicated by TLC, silica gel; dichloromethane:methanol (9:1), a (6:4) mixture of diethyl ether and n-hexane was added to the reaction mixture and pure product was crystallized to 6° C overnight. The product was finally filtered and dried.

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Conclusions

In conclusion we have developed a simple and new multicomponent method for the synthesis of α-ureidophosphonates under ultrasound irradiation and solvent-catalyst-free conditions at 75°C, the derivatives of α-ureidophosphonates were obtained by condensation of aldehyde with urea/thiourea and triethylphosphite or diethylphosphite in excellent yields. This new protocol has advantages such as; the use of cheap, short reaction times (15–30 min), high yields (75–85%), easy of product isolation/purification, Solvent- and catalyst-free.

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Notes and references

‡Spectral data and crystallographic for the synthesis of α-ureidophosphonates, prepared in this work are available in the supporting information joined to this manuscript.

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