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

Abdeslem Bouzina, Malika Berredjem*, Sofiane Bouacida, Hocine Merazig and Nour-eddine Aouf

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°C, is developed. The desired products were obtained in excellent yield 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 of 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 and α-aminophosphonic acids. 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. α-ureidophosphonates have gained diverse biological activities in pharmaceutical as fungal pathogens, enzyme inhibitors, antibiotics, pharmacological agents, peptidomimetics and antitumor. They also display powerful antiviral activities against TMV. Metal chelating ability, and these compounds used as active ingredients in pesticides especially insecticides and acaricides. 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; BF3 (OEt)2, (H2N–SO3H, PhSO3H, CH3SO3H), LiClO4 and InCl3 and InCl3, in the solvent THF at 50 °C or toluene 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 and solvent-free conditions. This powerful technique became extremely efficient and attractive in synthetic organic chemistry, and is able to activate many reactions due to cavitation 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. 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. 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
To evaluate the feasibility of $\alpha$-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 (table 1).

### Table 1
Optimization of reaction time and solvent for the synthesis of $\alpha$--ureidophosphate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Temperature °C</th>
<th>Yields %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No solvent</td>
<td>18</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>60</td>
<td>75</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>60</td>
<td>75</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$CN</td>
<td>120</td>
<td>75</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$Cl$_2$</td>
<td>120</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>100</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>100</td>
<td>75</td>
<td>56</td>
</tr>
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</table>

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 $\alpha$-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 $\alpha$-ureidophosphonates under ultrasound irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time /min</th>
<th>Yield%</th>
<th>M.p. °C</th>
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<tbody>
<tr>
<td>1b</td>
<td>Me</td>
<td><img src="image" alt="Product 1b" /></td>
<td>18</td>
<td>85</td>
<td>197-199</td>
</tr>
<tr>
<td>2b</td>
<td>Ph</td>
<td><img src="image" alt="Product 2b" /></td>
<td>20</td>
<td>78</td>
<td>184-186</td>
</tr>
<tr>
<td>3b</td>
<td>PhCl</td>
<td><img src="image" alt="Product 3b" /></td>
<td>22</td>
<td>83</td>
<td>202-204</td>
</tr>
<tr>
<td>4b</td>
<td>PhCl</td>
<td><img src="image" alt="Product 4b" /></td>
<td>21</td>
<td>77</td>
<td>196-198</td>
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<td>Journal Name</td>
<td>Chemical Structure</td>
<td>RSC Advances, 2013, 00, 1-3</td>
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<td>15</td>
<td>81</td>
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<td>13b</td>
<td><img src="image" alt="Structure" /></td>
<td>25</td>
<td>85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 $\alpha$-ureidophosphonates formation according to the mechanism below.

![Scheme 2 Mechanistic proposal for the synthesis of $\alpha$-ureidophosphonates.](image)

**X-ray analysis of the Diethyl [($\alpha$-ureido-(4-isopropylphenyl)]methylphosphonate**: The formation of compound 13b was further confirmed by single crystal X-ray diffraction analyses; the ORTEP-3$^{34}$ diagram of complex is shown in Fig. 1.

![Figure 1 ORTEP for diethyl [($\alpha$-ureido-(4-isopropylphenyl)]methylphosphonate.](image)

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 14b, 15b, 16b, and 17b.
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 commercial sources and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F254 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 (1H NMR) spectra were recorded on a Brukerr or Jeol spectrometer at 250, or 400 MHz. Chemical shifts are 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 (13C NMR) spectra were recorded on a Brukerr or Jeol at 75, 100 or 161 MHz. Infrared spectra were recorded on a Perkin Elmer 600 spectrometer. Phosphorus nuclear magnetic resonance (31P NMR) spectra were recorded on a Brukerr 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 EA 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, C15H24N2O4P, with dimensions of 0.06×0.11×0.13 mm³, was selected for single crystal X-ray diffraction analysis. Data collection was performed, at 295(2)K, on a Brukker APEX II diffractometer, CCD area detector equipped with a graphite monochromatized MoKα radiation (λ = 0.71073Å). Crystallographic data for 13b: C15H24N2O4P, M = 327.33, R1 = 0.0675, wR2 (all data = 0.1907). Proton nuclear magnetic resonance (1H NMR) spectra were recorded on a Brukker or Jeol spectrometer at 250, or 400 MHz. Chemical shifts are reported in δ units (ppm) relative to CDCl3 (δ 77.0). Phosphorus nuclear magnetic resonance (31P NMR) spectra were recorded on a Brukker 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 EA 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.

**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°C, then the triethylphosphate or diethylphosphate (1 mmol) was added. The reaction mixture was subjected to the ultrasonication with a frequency of 40 kHz for 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.

**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 triethylphosphate or diethylphosphate 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.

**Acknowledgments**

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**Notes and references**


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