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ARTICLE TYPE

A novel, rapid and green method of phosphorylation under ultrasound irradiation and catalyst free conditions

Abdeslem Bouzina, Billel Belhani, Nour-Eddine Aouf, Malika Berredjem*

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DOI: 10.1039/b000000x

The phosphorylation reaction of various *N*-acylamines, *N*-acylaminoesters *N*-acylaminoalcohols and *N*-acylsulfonamides with trimethylphosphite or triethylphosphite was effectively promoted under ultrasound irradiation, solvent and catalyst free conditions to produce the corresponding amidophosponate. This rapid method produced the products in short reaction times (5–15 min) and excellent yields (75–90%). This technique at a frequency of 40 kHz, strongly accelerate the process of formation P-C bond compared to the classic Arbuzov reaction.

Introduction

Amidophosponate have received considerable attention for organic chemists,[1-3] they are considered as an important class of compounds, with several interesting biological activities. Their applications are significant in agriculture as plant regulators, herbicides,[4] pesticides and in medicine as anticancer agents,[5] enzyme inhibitors,[6] peptide mimics,[7] antibiotics and pharmacological agents.[8] To the best of our knowledge, some papers deal with amidophosponate structures.[9–16] Several methods have been described to introduce the phosphonate group, using trialkylphosphite via Arbuzov reaction or under a variety of conditions.[17] Most of the methods reported above use expensive catalysts, strong acidic conditions, and higher temperatures and require longer reaction times. These include palladium complex $Pd(dba)_2$ or $PdCl_2$ and $PtBr_2$,[18] room temperature imidazolium ionic liquids, [Rmim][X].[19] Besides, copper and nickel-catalyzed C–P coupling reactions have also been developed.[20-21]

To synthesize organic substances efficiently in an artificial way, it is required to develop convenient methods for forming carbon-phoshore bond. Under this situation, we tried to discover an efficient novel C-P bond forming reactions by using ultrasound irradiation.

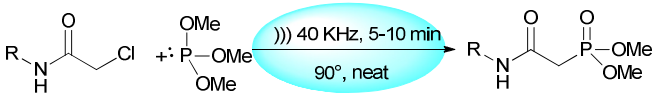
Therefore the development of new methods at moderate temperature, milder reaction conditions, short reaction times and better yields can possibly would extend the scope of the Arbuzov reaction.

In continuation with our research on the synthesis of novel phosphonate derivatives[22-24] and in order to enlarge the application of ultrasound irradiation[25-26] in the synthesis of novel compounds, we report herein a simple and efficient method for the preparation of fully amidophosphonate under ultrasound irradiation (scheme 1, 2, 3 and 4).

Results and discussion

We report here the application of the ultrasound induced phosphorylation of *N*-acylamines, *N*-acylaminoesters, *N*-acylaminoalcohols and *N*-acylsulfonamides, under catalyst-free and solvent-free conditions. Thus, cavitation serves as a means of concentrating the diffuse energy of sound to accelerate the Arbuzov reaction. The process was promoted by directly immersing of reaction vessels into the ultrasonic cleaning bath which provides a fairly even distribution of energy into the reaction medium.

The reaction was completed within 5-10 minutes (Scheme 1).



R= Aryl

Scheme 1 Ultrasoundassisted phosphorylation of various structurally *N*-acylamines.

The results are summarized in (Table 1, entry 1a-4a). This is an efficient and environmentally benign methodology for the synthesis of α-amidophosphonate at 90°C temperatures. This reaction was established with many advantages, including simple work-up procedures, short reaction times and excellent yields.

Table1 Phosphorylation of *N*-acylamines under ultrasound irradiation

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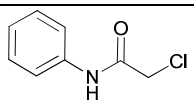
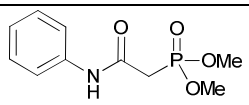
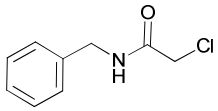
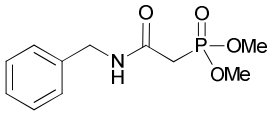
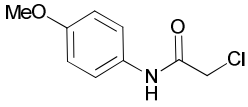
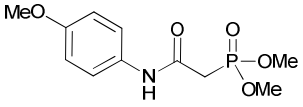
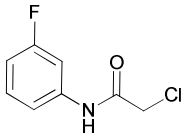
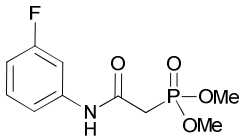
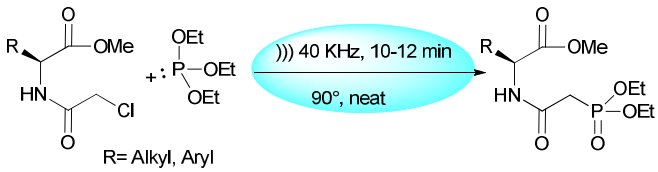
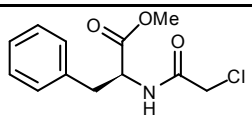
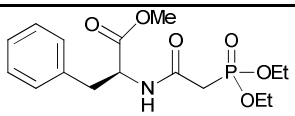
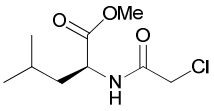
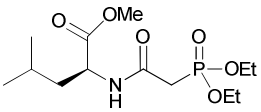
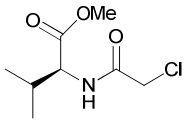
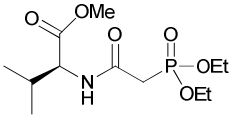
Entry	Substrat	Product	Time (min)	Yield (%)
1a			8	90
2a			6	89
3a			10	84
4a			12	86

To increase the scope of this reaction, we attempted the phosphorylation to *N*-acylaminoesters synthesized from primary amino acid esters (Scheme 2). The isolated yields of products (Table 2, entry 1b–3b) were in the range of 80–88 % after 10-15 minutes of reaction..



Scheme 2 Ultrasound assisted phosphorylation of various structurally *N*-acylaminosters.

Table 2 Phosphorylation of *N*-acylaminoesters under ultrasound irradiation

Entry	Substrat	Product	Time (min)	Yield (%)
1b			10	80
2b			12	82
3b			15	88

The mildness of this procedure was next illustrated by arrange of *N*-acylaminoalcohols (Scheme 3) (Table 3, entries 1c–3c), the reaction worked very well.

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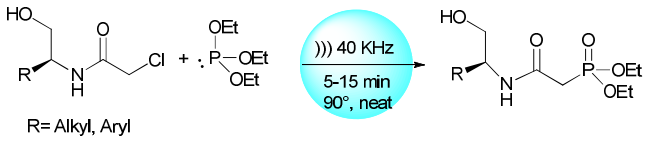
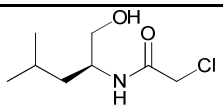
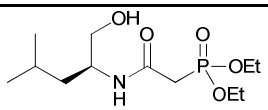
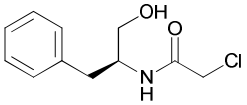
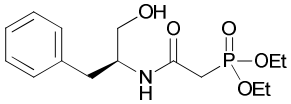
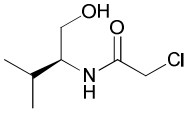
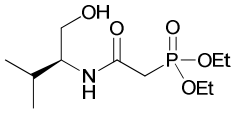
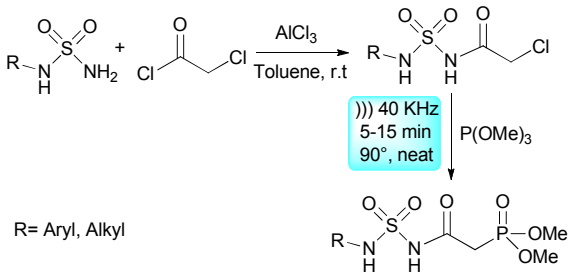


Scheme 3 Ultrasound assisted phosphorylation of various structurally *N*-acylaminoalcohols.

Table 3 Phosphorylation of *N*-acylaminoalcohols sunder ultrasound irradiation

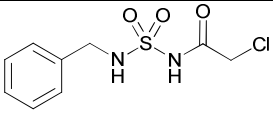
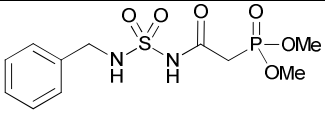
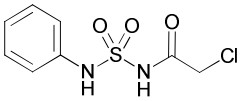
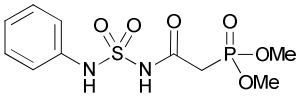
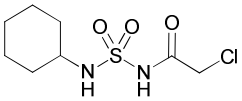
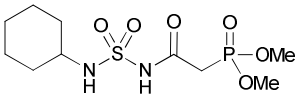
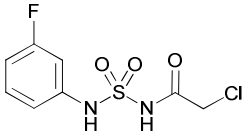
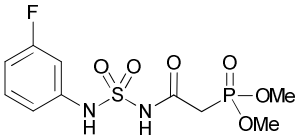
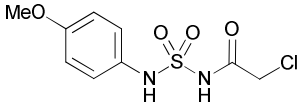
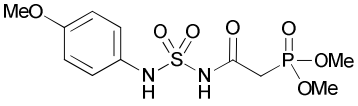
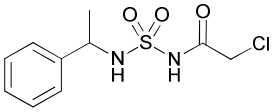
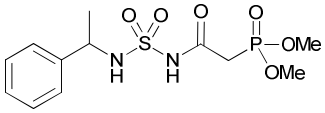
Entry	Substrat	Product	Time (min)	Yield (%)
1c			10	79
2c			15	75
3c			12	83

Encouraged by the preliminary result and to increase the scope of this reaction, we extended this study to *N*-acylsulfonamides (Scheme 3). The N-acylsulfonamides were prepared starting from chlorosulfonylisocyanate (CSI), primary amine in three steps (carbamoylation-sulfamoylation, deprotection and acylation).[27] The results are summarized in (Table 4, entry 1d-6d).



Scheme 4 Ultrasound assisted phosphorylation of various structurally *N*-acylsulfonamides.

Table 4 Phosphorylation of *N*-acylsulfonamide s under ultrasound irradiation

Entry	Substrat	Product	Time (min)	Yield (%)
1d			10	85
2d			5	90
3d			10	80
4d			10	83
5d			15	88
6d			5	75

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Experimental

1. General:

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 spectrometer at 250, 300 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 (^{13}CNMR) spectra were recorded on a Brücker at 60, 75 or 100 MHz. Chemical shifts are reported in δ units (ppm) relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a SHIMADZU FT-IR 8000 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 90°.

2. Typical experimental procedure for the phosphorylation

In a 10 ml round bottom flask taken a mixture of *N*-acylsulfonamide (1 mmol) with triethylphosphite or trimethylphosphite (1 mmol) was added. Then reaction mixture was subjected to the ultrasonication for appropriate time. After completion of the reaction, as indicated by TLC, silica gel; dichloromethane:methanol (9,5:0.5),
Surplus reactants were removed by column chromatography eluted with dichloromethane.

Conclusions

In conclusion, a simple, efficient, and environmentally benign methodology towards the synthesis of α-amidophosponate has been reported. The use of ultrasound irradiation as an effective basic promoter supports the practical utility of this procedure for a wide variety of substrates. Further studies to develop new clean methodology towards the synthesis of biologically active compounds are in progress.
The effect of ultrasound has mostly been shown by increasing the yields of reactions and in some cases the ratio of formed products.

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This work was supported financially by The General Directorate for Scientific Research and Technological Development (DG-RSDT), Algerian Ministry of Scientific Research, Applied Organic ChemistryLaboratory (FNR 2000). We also thank Mr. Jacques Lebreton Professor at University of Nantes for his help in the identification for all products in NMR and MS.

Notes and references

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**Corresponding author. Email: malika.berredjem@univ-annaba.org*

† Spectral data for the synthesis of *N*-acylamines, *N*-acylaminoesters, *N*-acylaminoalcoholsand*N*-acylsulfonamides,prepared in this work are available in the supporting information joined to this manuscript.

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A novel, rapid and green method of phosphorylation under ultrasound irradiation and catalyst free conditions

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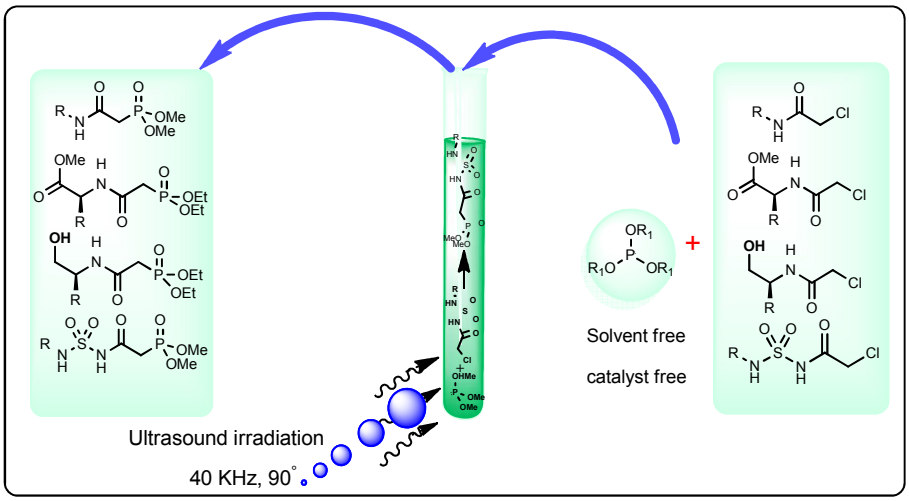
Abstract

The phosphorylation reaction of various *N*-acylamines, *N*-acylaminoesters *N*-acylaminoalcohols and *N*-acylsulfonamides with trimethylphosphite or triethylphosphite was effectively promoted under ultrasound irradiation, solvent and catalyst free conditions to produce the corresponding amidophosponate. This rapid method produced the products in short reaction times (5–15 min) and excellent yields (75–90%). This technique at a frequency of 40 kHz, strongly accelerate the process of formation P-C bond compared to the classic Arbuzov reaction.



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