

Microwave assisted BiCl₃ catalyzed synthesis of α -hydroxyphosphonates [†]

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Abstract: In this study, we present a straightforward, resource-efficient, and environmentally sustainable approach for the synthesis of α -hydroxyphosphonate derivatives. This synthetic methodology involves the reaction of aromatic aldehydes with triethylphosphite and utilizes microwave irradiation as a source of activation energy, and was catalyzed by bismuth chloride III in an amount of 20 mol%. The protocol affords rapid and highly efficient results, yielding α -hydroxyphosphonates in high yields while minimizing reaction times.

Keywords: α -hydroxyphosphonates; Microwave irradiation; Catalyst-free; Green synthesis; Solvent-free.

1. Introduction

Recently, the synthesis of α -hydroxyphosphonate derivatives has attracted significant attention owing to their role as promising precursors in organophosphorus compound synthesis and the formation of organometallic complexes [1]. α -Hydroxyphosphonates have also piqued considerable interest due to their demonstrated potent biological activities [2]. These compounds exhibit a broad spectrum of captivating and valuable properties, making them appealing for applications in pharmaceutical chemistry as antibiotics [3], antiviral [4], and anticancer agents [5]. Additionally; α -Hydroxyphosphonates were used as active ingredients in pesticides [6] and herbicides [7].

One of the current primary challenges is the development of synthetic methods that are environmentally friendly, aiming to design green chemical transformations and clean technologies. In this context, the utilization of microwave irradiation to expedite reactions has proven to be a particularly crucial tool in achieving the goals of green chemistry, which include waste minimization and reduced energy requirements [8].

Catalysis using Lewis acids also constitutes a noticeable green method that accelerates the production of selectively precise new molecules and helps providing them in excellent yields with avoiding the fabrication of unwanted by-products [9]. Choosing insoluble Lewis acids as a catalyst to proceed a microwave-assisted reaction has a positive impact since it provides a renewable method that facilitates the recovery and separation of final products from the catalyst and accordingly the reuse of this latter.

As part of our research program aimed at developing highly efficient methods for synthesizing diverse phosphonate derivatives, our focus has centered on combining microwave irradiation with the utilization of the Lewis catalyst BiCl₃ to achieve a green synthesis of a series of α -hydroxyphosphonates.

2. Materials and methods

2.1. General data

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All chemicals and solvents were procured from Sigma Aldrich and used as received without any purification. Reaction progress was assessed via thin-layer chromatography (TLC) on silica Merck 60 F₂₅₄-coated aluminum plates, visualized through ninhydrin solution spraying. Proton nuclear magnetic resonance (¹H NMR) spectra were acquired on a Brücker spectrometer at either 250 or 400 MHz. Chemical shifts are reported in δ units (ppm), with TMS serving as the reference (δ 0.00). Coupling constants (J) are expressed in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Brücker instrument at either 60 or 100 MHz. Phosphorus nuclear magnetic resonance (³¹P NMR) spectra were also recorded on a Brücker instrument at 161 MHz. Chemical shifts are reported in δ units (ppm) relative to CDCl₃ (δ 77.0). Infrared spectra were collected using a Perkin Elmer 600 spectrometer. Mass spectra were obtained via a Shimadzu QP 1100 Ex mass spectrometer operating with an ionization potential of 70 eV.

Microanalysis spectra were performed using an Elemental Analyzer (Euro E.A. 3000-V3.0-single-2007), and the determined values fell within acceptable limits of the calculated values. Melting points were measured using a Büchi B-545 apparatus in open capillary tubes.

Microwave-assisted reactions were conducted in a 10 mL microwave reactor under pressure, utilizing a Biotage Initiator Microwave Synthesizer 2.0 operating at a nominal power of 400 W.

2.2. Synthesis of α-hydroxyphosphonates

In a 10 mL microwave reactor, a 1:1 mixture of trialkylphosphite and an aromatic aldehyde was introduced. To this mixture, 0.2 mmol of BiCl₃ was added, and the reaction mixture was subjected to microwave irradiation for a varying time between 2 and 4 min. The progress of the reaction was monitored by TLC. Upon completion of the reaction, 3 mL of ethanol was added, and the catalyst was recovered through filtration. After evaporating the reaction mixture using a rotary evaporator, a mixture of diethyl ether and n-hexane (6:4) was introduced to the reaction mixture. The pure product crystallized when the solution was cooled to 6°C overnight

- Diethyl (hydroxy(phenyl)methyl)phosphonate (**1a**, C₁₁H₁₇O₄P)

Crystals; 90 % yield; ³¹P NMR (100 MHz, CDCl₃): δ = 21.44 ppm; ¹H NMR (400 MHz, CDCl₃): δ = 1.20 (t, J = 7.20 Hz, 3H, CH₃-CH₂O), 1.25 (t, J = 6.93 Hz, 3H, CH₃-CH₂O), 3.90-3.96 (m, 2H, CH₂-O), 3.97-4.07 (m, 2H, CH₂-O), 5.02 (d, J = 11.2 Hz, 1H, CH*), 7.25-7.37 (m, 3H, H-Ar), 7.46-7.49 (m, 2H, H-Ar) .pm; ¹³C NMR (100 MHz, CDCl₃): δ = 16.53, 16.58, 63.26, 63.55, 70.22, 71.80, 127.27, 128.26, 128.44, 130.30, 136.80, 136.82 ppm; IR (KBr): ν = 3382.45, 1514.49, 1251.33, 1033.44 cm⁻¹; MS: (m/z) = 245.1 (M+1); Anal. Calc. for C₁₁H₁₇O₄P: C, 54.10; H, 7.02; Found: C, 54.16; H, 7.03.

- Diethyl (hydroxy(4-chlorophenyl)methyl)phosphonate (**2a**, C₁₁H₁₆ClO₄P)

Crystals; 85 % yield; ³¹P NMR (100 MHz, CDCl₃): δ = 21.21 ppm; ¹H NMR (250 MHz, CDCl₃): δ = 1.16 (t, J = 7.16 Hz, 3H, CH₃-CH₂O), 1.23 (t, J = 7.04 Hz, 3H, CH₃-CH₂O), 3.88 (m, 2H, CH₂-O), 3.96 (m, 2H, CH₂-O), 5.00 (d, J = 10.13 Hz, 1H, CH*), 7.31-7.45 (m, 4H, H-Ar), ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 16.15, 16.51, 61.21, 62.35, 69.04, 70.75, 120.15, 125.17, 126.45, 132.45, 136.50 ppm; IR (KBr): ν = 3249.69, 1491.85, 1234.20, 1029.13 cm⁻¹; MS: (m/z) = 279 (M+1); Anal. Calc. for C₁₁H₁₆ClO₄P: C, 47.41; H, 5.79; Found: C, 47.37; H, 5.78.

- Dimethyl (hydroxy(4-methoxyphenyl)methyl)phosphonate (**3a**, C₁₀H₁₅O₅P)

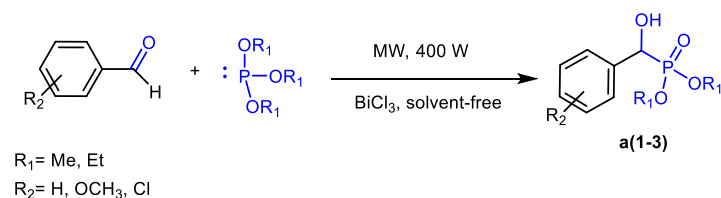
White powder; 82 % yield; ³¹P NMR (100 MHz, CDCl₃): δ = 21.61 ppm; ¹H NMR (250 MHz, CDCl₃): δ = 3.61 (d, J = 9.11 Hz, 3H, CH₃-O), 3.79 (d, J = 10.81 Hz, 3H, CH₃-O), 3.82 (s, 3H, CH₃-O), 5.02 (d, J = 14.81 Hz, 1H, CH*), 7.01-7.35 (m, 2H, H-Ar), 7.37-7.48 (m, 2H, H-Ar) ppm; ¹³C NMR (75 MHz, CDCl₃): δ = 53.82, 53.94, 55.40, 69.98, 71.54, 114.02, 120.40,

128.55, 128.64, ppm; IR (KBr): $\nu = 3319.75, 1479.54, 1235.79, 1066.29 \text{ cm}^{-1}$; MS: (m/z) = 247 (M+1); Anal. Calc. for $\text{C}_{10}\text{H}_{15}\text{O}_5\text{P}$: C, 48.78; H, 6.14; Found: C, 48.81; H, 6.09.

3. Results and discussion

Organic synthesis aided by microwave irradiation has appeared as a highly efficient energy source, enabling the production of diverse organic compounds with interesting structural frameworks [10]. This current approach offers several advantages, notably time and energy savings, improved yields, and a reduction in the use of less sustainable conventional chemical methods. These favorable attributes of microwave heating contribute to a more environmentally responsible and eco-friendly approach in the field of organic chemistry.

In this context, we present our application of microwave irradiation for the synthesis of α -hydroxyphosphonate derivatives. This reaction, conducted under solvent-free conditions, involves the condensation of aromatic aldehydes and trialkyl phosphite, utilizing a solid, environmentally conscious Lewis acid catalyst, BiCl_3 as illustrated in Scheme 1.



Scheme 1. This is a figure. Schemes follow the same formatting.

The structure and yields of obtained α -hydroxyphosphonate derivatives are summarized in **Table 1**. The desired compounds were achieved in excellent yields ranging between 82 and 90%, which indicates the efficiency of the used protocol involving the combination of two aspects of green chemistry; heterogeneous catalysis and microwave-assisted synthesis. Further, it proves the role of BiCl_3 in enhancing the electrophilicity of the aldehyde and consequently improving the quality and yields of the synthetic process.

Table 1. This is a table. Tables should be placed in the main text near to the first time they are cited.

Entry	Product	Yield (%)	Time (min)
1a		90	2
2a		85	3
3a		82	3

4. Conclusion

In summary, our study has presented a green, efficient, and environmentally friendly methodology for the synthesis of α -hydroxyphosphonates. This novel synthesis protocol, which utilizes microwave irradiation and employs BiCl_3 as a solid catalyst, has yielded significant advantages over traditional methods.

The influence of microwave irradiation and the catalytic role of BiCl_3 have been prominently showcased through substantial enhancements in reaction yields and a nota-

ble reduction in reaction times, as well as the mitigation of undesired side product formation. These findings underscore the feasibility and efficacy of our approach for the streamlined and sustainable production of α -hydroxyphosphonates.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

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Conflicts of Interest: The authors declare no conflict of interest.

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