

Synthesis of New Beta-Amidophosphonates and Theoretical Evaluation of Related Features

Yasaman Ashjaee¹, Nader Zabarjad-Shiraz^{1,✉}, Hasan Zandi²

¹Department of Chemistry, Central Tehran Branch, Islamic Azad University, Tehran, Iran

²Department of Chemistry, Faculty of Science, University of Qom, Qom, Iran

✉ Corresponding author: N. Zabarjad-Shiraz; E-mail address: zabarjad_sh@iauctb.ac.ir, ORCID: 0000-0001-5189-0005.

Copyright © 2021 to Advanced Journal of Science and Engineering as a Member of SciEng Publishing Group (SciEng)



This work is licensed under a [Creative Commons Attribution 4.0 International License \(CC-BY 4.0\)](https://creativecommons.org/licenses/by/4.0/).

Received: 03 June 2021 / Revised: 24 June 2021 / Accepted: 29 June 2021 / Published Online: 30 June 2021

ABSTRACT

This work was done employing theoretical and experimental methodologies to show synthesis process of new compounds in addition to evaluating their features. In this case, phosphorus ylide intermediates were initially resulted from the three-component reaction between dialkyl acetylenedicarboxylate and theophiline in the presence of phosphits ((R'O)₃P). Next, they were converted to stable diastereoisomeric beta-amidophosphonates. Density functional theory (DFT) calculations at the B3LYP/6-311+G* level of theory indicated that (2S, 3S) and/or (2R, 3R) diastereomers of phosphonates were about 18-28 kcal/mol more stable than (2R, 3S) and/or (2S, 3R) diastereomers. As a consequence, the targeted compounds were synthesized and they very confirmed by performing DFT calculations as an advantage of combinations of experimental and theoretical approaches for solving the problems in chemistry.

KEYWORDS Three-component reaction, Stable phosphorus ylides, Beta-amidophosphonates, DFT.

CITE Ashjaee Y, Zabarjad-Shiraz N, Zandi H. Synthesis of New Beta-Amidophosphonates and Theoretical Evaluation of Related Features. *Advanced Journal of Science and Engineering*. 2021;2(2):99-102.

DOI <https://doi.org/10.22034/advjscieng21022099>

URL <https://sciengpub.com/adv-j-sci-eng/article/view/advjscieng21022099>

INTRODUCTION

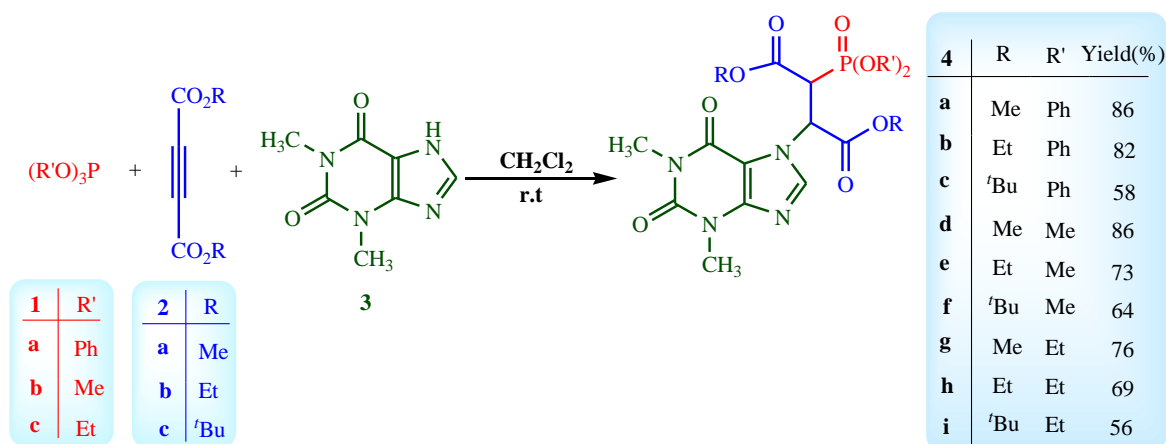
Organophosphorus compounds are important substrates in the study of biochemical processes.^{1, 2} Phosphorus analogues of amino acids, in which the carboxylic acid group is replaced with phosphonate group, P(O)(OR)₂, have attracted particular interest in preparing analogues of numerous natural products.³⁻⁵ In this area beta (β)-amidophosphonates as isosteres of β-amino acids occupy an important place and reveal diverse and interesting biological and biochemical properties.^{6, 7} There are several methods for synthesis of β-amidophosphonates. In most of them, nucleophilic trivalent phosphorus has been attached to electrophilic carbon.⁸ Multicomponent reactions have proven highly efficient in the assembly of diversified molecules.^{9, 10} Zwitterionic species often result from addition of nucleophiles to activated alkynes. Triphenylphosphine (Ph₃P) has been the most studied nucleophilic species.¹¹ Considering these strategies and importance of multicomponent reactions in organic synthesis, and as a part of our earlier studies on the development of new routes to organophosphorus compounds,^{12, 13} we now report on the reaction of (R'O)₃P and dialkyl acetylenedicarboxylates in the presence of theophiline to produce β-amidophosphonates. Synthesis of new compounds are always important regarding their roles for developing new materials in various aspects of science and engineering to reach new products. Additionally, recognition of mechanism of synthesis and evaluation of related features are important due to their role of developing for further applications, in which the computational works could also help to achieve the purpose.

MATERIALS & METHODS

Details and descriptions of synthesis and mechanism features would be discussed through next section. For characterizations, melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. These data were in good agreement with the calculated values. IR spectra were measured on a Shimadzu IR 460 spectrometer. ^1H and ^{13}C NMR spectra were measured with BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. Mass spectra were recorded with a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Triphenylphosphine, triphenylphosphite, theophiline, dimethyl acetylenedicarboxylate were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Additionally, Full optimizations were performed for geometries of the structures at the B3LYP/6-311+G* level of theory without any constrains using Gaussian 98 program.¹⁴ The obtained results of measurements and characterizations of this work in both of experimental and computational aspects were summarized in the supplementary file.

RESULTS & DISCUSSION

Reaction of dialkyl acetylenedicarboxylate **2** and theophiline **3** in the presence of trialkylphosphite **1** in dichloromethane as solvent and at ambient temperature proceeded to produce β -amidophosphonates **4** in good yields (Scheme 1).



Scheme 1: Reaction of dialkyl acetylenedicarboxylate and theophiline in the presence of trialkylphosphite in CH_2Cl_2 .

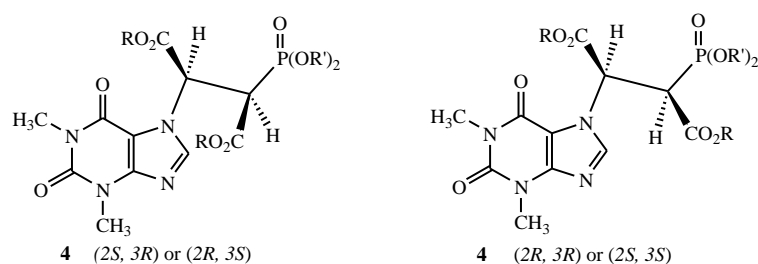
^1H , ^{13}C , and ^{31}P NMR spectra of these crude products clearly indicated the formation of phosphonates **4** in good yields (Scheme 1, Tables S1 and S2). Structures of ylides **4a-i** were deduced from their elemental analysis and IR, ^1H , ^{13}C , and ^{31}P NMR spectra. The mass spectra of these compounds displayed molecular ion peaks. In spite of theophiline **3**, IR didn't show N-H stretching absorption for **4**. ^1H NMR spectra indicate four peaks for N- CH_3 . The ^1H NMR spectra of phosphonates **4** display signals for *vicinal* methine protons at $\delta = 4.22 - 5.62$ ppm, which appear as doublet of doublets for each isomer with $^2J_{\text{PH}} = 23.8$, $^3J_{\text{PH}} = 18.0$ and $^3J_{\text{HH}} = 5.6$ Hz for (2*R*, 3*S*) or (2*S*, 3*R*)-**4** isomer, and $^2J_{\text{PH}} = 24.0$, $^3J_{\text{PH}} = 9.0$ and $^3J_{\text{HH}} = 3.5$ Hz for (2*R*, 3*R*) or (2*S*, 3*S*)-**4** isomer.

^{13}C NMR spectra of **4** showed four NCH₃ groups. Resonance of CH-P groups appeared at about 31 ppm as doublets ($^1J_{\text{PC}} = 92$ Hz). ^{31}P NMR indicated two peaks at about 9.5 and 11.5 ppm for two phosphonate structures (**4**, C-P(=O)(OR')₂) (See experimental section in *supporting information*).

The presence of ^{31}P nucleus in compounds **4** contributes in assignment of signals by coupling with ^1H and ^{13}C nuclei (See experimental section in *supporting information*). The vicinal proton-proton coupling constant ($^3J_{\text{HH}}$) as a function of torsion angle can be obtained from Karplus equation.^{15,16} Typically, $^3J_{\text{gauche}}$ varies between 1.5-6 Hz, and $^3J_{\text{anti}}$ between 10-16 Hz. The observation of $^3J_{\text{HH}} = 3.5$ and 5.6 Hz for *vicinal* protons in two isomers of **4** indicated a *gauche* arrangement for this protons.

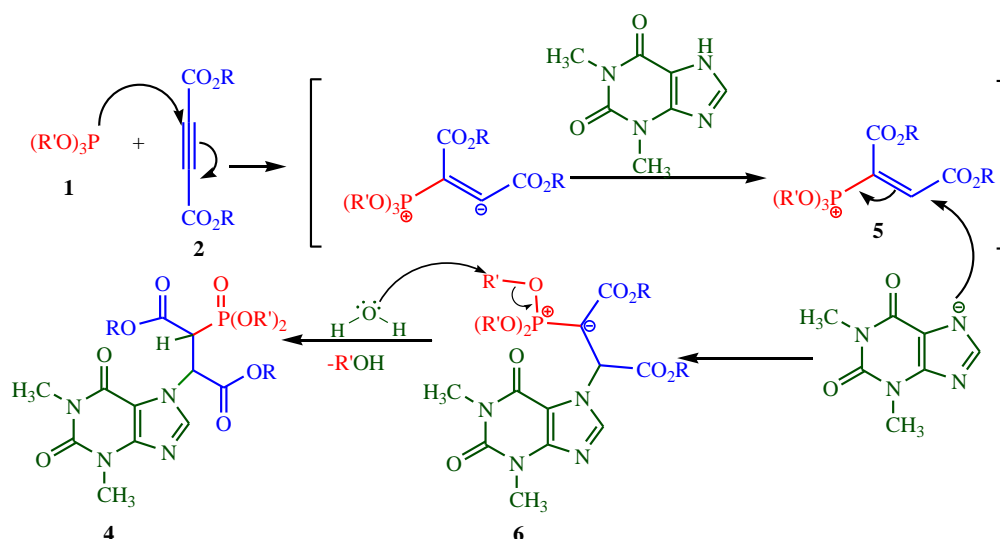
The three-bond carbon-phosphorus coupling, $^3J_{\text{PC}}$, depends on the configuration and as expected, *transoid* couplings are larger than the *cisoid* ones. The Karplus relation can be derived from the data for organophosphorus compounds with tetra and pentavalent phosphorus.¹⁶ The observation of $^3J_{\text{PC}} = 4$ Hz is in agreement with *cisoid* arrangement of P with C=O of ester. Accordingly, (2*R*, 3*S*) or (2*S*, 3*R*) configuration was represented for one isomer. $^3J_{\text{PC}} = 22$ Hz value

indicated *transoid* arrangement, which was in agreement with (2*R*, 3*R*) or (2*S*, 3*S*) configuration for other isomer (Scheme 2).



Scheme 2: Configuration for other isomer.

We have not yet established the mechanism of the formation of ylides **4** on the basis of chemistry of trivalent phosphorus nucleophiles.¹⁷⁻¹⁹ It is reasonable to assume that phosphorus ylides **4** resulted from the initial addition of trivalent phosphorus **1** to the acetylenic ester **2**. Subsequent protonation of the 1:1 adduct followed by attacking the nitrogen atom of the anion of NH-acid **3** on the vinylphosphonium cations **5** to generate ylides **6**. In the presence of moisture, H₂O attacked to phosphorus atom of **6**, which underwent R'OH elimination to form phosphonate **4** compound (Scheme 3).



Scheme 3: The proposed mechanism of the reaction.

To investigate on diastereoselectivity of the reaction of trivalent phosphites, studies on the diastereomeric phosphonates of **4** were carried out at B3LYP/6-31+G* level of theory using the Gaussian 98 software.^{14, 20} Each structure was optimized without any constrain. Relative energies (E_{rel}) along with structural parameters are summarized in Table S3 and S4. Results indicated that (2*S*, 3*S*) and/or (2*R*, 3*R*) isomers of **4** are more stable than (2*R*, 3*S*) or (2*S*, 3*R*) ones about 18-28 kcal/mol. According to the calculated and experimental NMR studies vicinal H-atoms of H-C-C-H moieties occupy *gauche* positions except for (2*R*, 3*S*) and/or (2*S*, 3*R*) **4a-c** (R' = Ph) which prefer *anti* conformations.

CONCLUSION

In conclusion, the present method features the advantages that the reaction can be performed under neutral conditions, and the starting materials and reagents can be mixed without any modifications. Phosphorus ylides can be considered as potentially useful synthetic intermediates. Although three component reactions between trivalent phosphorus, acetylenic esters, and N-H acids are well studied, prediction of final product is complicated, and should be considered while paying attention to solvent, temperature, presence or absence of moisture, type of solvent, as well as functionality of starting materials. The procedure described here provides an acceptable method for preparation of phosphorus ylides and diastereomeric phosphonates in good yields. Theoretical calculations indicated that distribution of diastereomeric isomers of phosphonates **4** is according to kinetic control.

SUPPORTING INFORMATION

Tables S1-S5, explanations of experimental and computational methods of optimized structures for all the molecules studied in this work, and the evaluated spectra were presented in a supplementary file available at the article page (<https://sciengpub.com/adv-j-sci-eng/article/view/advjscieng21022099>) in the journal website.

DISCLOSURE STATEMENT

The author(s) did not report any potential conflict of interest.

REFERENCES

1. Noyori R. Asymmetric catalysis in organic synthesis. John Wiley & Sons: NY. 1994.
2. Palacios F, Alonso C, de Los Santos JM. Synthesis of β -Aminophosphonates and Phosphinates. *Chemical Reviews*. 2005;105:899-932.
3. Engel R. Synthesis of carbon-phosphorus bond. CRC Press: Boca Raton, FL. 1988.
4. Kafarski P, LeJczak B. Biological activity of aminophosphonic acids. *Phosphorus, Sulfur, and Silicon and the Related Elements*. 1991;63:193-215.
5. Zare L, Nikpassand M. Multicomponent synthesis of dihydropyridines catalyzed by L-proline. *Chinese Chemical Letters*. 2011;22:531-534.
6. Allen JG, Atherton FR, Hall MJ, Hassall CH, Holmes SW, Lambert RW, Nisbet LJ, Ringrose PS. Phosphono-peptides, a new class of synthetic antibacterial agents. *Nature*. 1978;272:56-58.
7. Hakimelahi GH, Moosavi-Movahedi AA, Tsay SC, Tsai FY, Wright JD, Dudev T, Hakimelahi S, Lim C. Design, synthesis, and SAR of novel carbapenem antibiotics with high stability to xanthomonas maltophilia oxyiminocephalosporinase type II. *Journal of Medicinal Chemistry*. 2000;43:3632-3640.
8. Castellet-Deliencourt G, Roger E, Pannecoucke X, Quirion JC. Diastereoselective synthesis of chiral amidophosphonates by 1, 5-asymmetric induction. *European Journal of Organic Chemistry*. 2001;2001:3031-3038.
9. Dömling A, Ugi I. Multicomponent reactions with isocyanides. *Angewandte Chemie International Edition*. 2000;39:3168-3210.
10. Baharfar R, Baghbanian SM. Synthesis of novel uracil based 2, 5-diaminofurans using multi-component reactions. *Chinese Chemical Letters*. 2012;23:677-680.
11. Cherkasov RA, Pudovik MA. Heterophosphacyclanes in organic synthesis. *Russian Chemical Reviews*. 1994;63:1019-1045.
12. Yavari I, Bayat M. Synthesis of highly functionalized cyclobutene derivatives. *Monatshefte für Chemie*. 2003;134:1221-1227.
13. Yavari I, Kowsari E. Synthesis, spectral, and thermal properties of some phosphorus-containing 9, 10-anthraquinoid, thermally stable dyes. *Dyes and Pigments*. 2008;77:103-110.
14. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian 98 Program. Gaussian, Inc.: Pittsburgh, PA. 1998.
15. Karplus M. Vicinal proton coupling in nuclear magnetic resonance. *Journal of the American Chemical Society*. 1963;85:2870-2871.
16. Breitmaier E, Voelter W. Carbon-13 NMR spectroscopy. 3rd Ed. VCH: NY. 1990.
17. Norris WP, Henry RA. Cyanoguanyl Azide Chemistry. *The Journal of Organic Chemistry*. 1964;29:650-660.
18. Francl MM, Pietro WJ, Hehre WJ, Binkley JS, Gordon MS, DeFrees DJ, Pople JA. Self-consistent molecular orbital methods. XXIII. A polarization-type basis set for second-row elements. *The Journal of Chemical Physics*. 1982;77:3654-3665.
19. Yavari I, Zabarjad-Shiraz N. Three-component reaction between triphenylphosphine, dialkyl acetylenedicarboxylates and urea or N-methylurea. *Molecular Diversity*. 2006;10:23-27.
20. Becke AD. Density-functional exchange-energy approximation with correct asymptotic behavior. *Physical Review A*. 1988;38:3098-3100.

Please visit the journal homepage:

<https://adv-j-sci-eng.com>