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Современные аспекты синтеза и химических трансформаций α-гидроксифосфонатов

© Заборский[1,2] Макар Андреевич, Миронов[1,2]*⁺ Владимир Федорович
[1] *Институт органической и физической химии им. А.Е. Арбузова. КазНЦ РАН. ул. Академика Арбузова, 8. г. Казань, 420088. Республика Татарстан. Россия.*
[2] *Химический институт им. А.М. Бутлерова. Казанский (Приволжский) федеральный университет. ул. Кремлевская, 18. г. Казань, 420008. Республика Татарстан. Россия. E-mail: mironov@iopc.ru*

*Ведущий направление; ⁺Поддерживающий переписку

Ключевые слова: триалкилфосфит, диалкилфосфит, карбонильные соединения, реакция Абрамова, фосфа-альдольная реакция, α-гидроксифосфонат, фосфонат-фосфатная перегруппировка, перегруппировка [1,2]-фосфа-Брука, фосфат-фосфонатная перегруппировка.

Аннотация

В последние десятилетия наблюдается значительный интерес к синтезу и использованию α-гидроксифосфонатов для получения более сложных фосфорорганических соединений. Это связано с выраженной биологической активностью многих представителей данного класса веществ, а также с достаточной простотой методик их синтеза, зачастую исключающих применение сложных и дорогих реагентов и растворителей. В данном обзоре были обобщены и систематизированы новейшие данные (2018-2025 гг.), касающиеся способов получения и возможностей химической модификации α-гидроксифосфонатов. Значительное внимание уделено их получению по реакции карбонильных соединений с диалкилфосфитами в присутствии основных катализаторов – реакции Абрамова (фосфа-альдольной реакции). Рассмотрен также метод получения α-гидроксифосфонатов в трехкомпонентной реакции триалкилфосфит – карбонильное соединение – протонодонор. Среди других методов представлены реакции α-кетофосфонатов с реактивами Гриньяра, восстановление кето-группы, а также реакции окисления алкилфосфонатов. Реакция Абрамова и близкая реакция в трехкомпонентной системе триалкилфосфит – карбонильное соединение – протонодонор охарактеризованы более детально, с указанием катализаторов и условий процесса, их преимуществ и недостатков. Также были продемонстрированы различные аспекты реакционной способности α-гидроксифосфонатов. Было обсуждено использование различных окислителей и восстановителей для α-гидроксифосфонатов. Описано множество реагентов и условий проведения *O*-алкилирования, *O*-аллилирования, *O*-ацилирования, *O*-сульфонилирования и *O*-фосфорилирования α-гидроксифосфонатов. Представлен эффективный метод защиты гидроксильной группы α-гидроксифосфонатов путем силилирования. Рассмотрена реакция гидролиза α-гидроксифосфонатов до α-гидроксифосфоновых кислот, предложен метод селективного гидролиза в мягких условиях. Обсуждены фосфонат-фосфатная ([1,2]-фосфа-Брука) и фосфат-фосфонатная перегруппировки при действии на α-гидроксифосфонаты различных оснований и представлены возможные синтетические применения. Продемонстрировано нуклеофильное замещение гидроксильной группы α-гидроксифосфонатов на галоген, остаток 1,3-дикетона, аминогруппу, сульфонамидную, азидную, тиоцианатную и изотиоцианатную группы. Рассмотрено взаимодействие α-гидроксифосфонатов с различными ароматическими субстратами по реакции Фриделя-Крафтса. В том числе показано подобное взаимодействие по трехкомпонентной реакции, в которой образование α-гидроксифосфонатов происходит *in situ*. Представлено перспективное направление синтеза винилфосфонатов из α-гидроксифосфонатов. Кроме того, в ряде случаев кроме описания особенностей методик, представлены литературные данные по биологическим свойствам полученных соединений. Библиография 244 ссылки.

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Modern aspects of synthesis and chemical transformations of α-hydroxyphosphonates

© **Makar A. Zaborsky**,[1,2] **Vladimir F. Mironov**[1,2]*[+]
[1] *A.E. Arbuzov Institute of Organic and Physical Chemistry. FRC Kazan Scientific Center of RAS. Arbuzov St. 8. Kazan, 420088. Republic of Tatarstan. Russia.*
[2] *A.M. Butlerov Chemical Institute. Kazan (Volga Region) Federal University. Kremlevskaya St. 18. Kazan, 420008. Republic of Tatarstan. Russia. E-mail: mironov@iopc.ru*

*Supervising author; [+]Corresponding author

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Abstract

In recent decades, there has been considerable interest in the synthesis and use of α-hydroxyphosphonates to produce more complex organophosphorus compounds. This is due to the pronounced biological activity of many representatives of this class of substances, as well as the sufficient simplicity of their synthesis techniques, which often exclude the use of complex and expensive reagents and solvents. This review summarizes and systematizes the latest data (2018-2025) concerning the methods of obtaining and possibilities of chemical modification of α-hydroxyphosphonates. Considerable attention has been paid to their preparation by the reaction of carbonyl compounds with dialkyl phosphites in the presence of the basic catalysts, the Abramov reaction (phospha-aldol reaction). The method for obtaining α-hydroxyphosphonates in the three-component reaction of trialkylphosphite with carbonyl compound and proton donor is also considered. Other methods include reactions of α-ketophosphonates with Grignard reagents, keto-group reduction, and alkyl phosphonate oxidation reactions. The Abramov reaction and a similar process in the three-component system of trialkylphosphite – carbonyl compound – proton donor are characterized in more detail, indicating the catalysts and process conditions, their advantages and disadvantages.

Various aspects of the reactivity of α-hydroxyphosphonates have also been demonstrated. The use of various oxidizing and reducing agents for α-hydroxyphosphonates was discussed. A variety of reagents and conditions for *O*-alkylation, *O*-allylation, *O*-acylation, *O*-sulfonylation, and *O*-phosphorylation of α-hydroxyphosphonates have been described. An effective method of protecting the hydroxyl group of α-hydroxyphosphonates by silylation is presented. The hydrolysis reaction of α-hydroxyphosphonates to α-hydroxyphosphonic acids is considered, and a method of selective hydrolysis under mild conditions is presented. The phosphonate-phosphate and phosphate-phosphonate rearrangements ([1,2]-phospha-Brook rearrangement) of α-hydroxyphosphonates under the action of various bases are discussed and possible synthetic applications are shown. The nucleophilic substitution of the hydroxyl group of α-hydroxyphosphonates for a halogen, a 1,3-diketone residue, an amino group, sulfonamide, azide, thiocyanate, and isothiocyanate and others groups has been demonstrated. The interaction of α-hydroxyphosphonates with aromatic substrates by the Friedel-Crafts reaction is considered. In particular, a similar interaction has been shown in a three-component reaction in which the formation of α-hydroxyphosphonates occurs *in situ*. A promising direction for the synthesis of vinyl phosphonates from α-hydroxyphosphonates is presented. In addition to describing the features of the techniques, literature data on the biological properties of the compounds obtained are presented. The bibliography contains 244 references.

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