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술팜산: 초음파 조사를 이용한 α-히드록시 인산염 합성의 효과적인 촉매

Sandip A. Sadaphal, Swapnil S. Sonar, Rajkumar U. Pokalwar, Nanasaheb V. Shitole, and Murlidhar S. Shingare*

Organic Research Laboratory, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, (M. S.) 431004, India
Corresponding author E-mail address: prof_msshingare@rediffmail.com
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Sulphamic Acid: an Efficient Catalyst for the Synthesis of α-Hydroxy Phosphonates Using Ultrasound Irradiation

Sandip A. Sadaphal, Swapnil S. Sonar, Rajkumar U. Pokalwar, Nanasaheb V. Shitole, and Murlidhar S. Shingare*

Organic Research Laboratory, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, (M. S.) 431004, India
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요 약. 무용제하에서 α-히드록시 인산염을 합성하기 위해 술팜산은 비용효율이 높고 일반적인 산들의 친환경적인 대안으로 활용되었다. 초음파 조사를 이용하여 더 나은 수율을 얻었고 반응시간이 짧았다.

주제어: α-히드록시 인산염, 술팜산, 초음파 조사, 무용제

ABSTRACT. Sulphamic acid has been exploited as a cost-effective catalyst and green alternative for conventional acidic materials to synthesize α-hydroxy phosphonates under solvent-free condition. The reaction carried out using ultrasound irradiation with better yields and shorter reaction time.

Keywords: α-Hydroxy phosphonates, Sulphamic acid, Ultrasound irradiation, Solvent-free

INTRODUCTION

Phosphonic acids and their phosphonate derivatives are of great interest in organic chemistry due to their biological activity.[1] Recently, some new vinyl phosphates have been reported as potent mechanism-based inhibitors of phosphates[2-4] or phosphodiesterase.[5-6] There are only few reports about synthesis and bioactivity of their analogues with C-P bond, which have been found to have insecticidal[7] and antifungal activities.[8] Phosphonates,[9] α-substituted phosphonate and α-hydroxyphosphonates[10] in particular are the quinvalent organophosphorus compounds of wide applicability in terms of biological activities. α-Hydroxy phosphonates, especially enantiomerically pure α-functionalized phosphonates,[11] have been used for generating α-substituted phosphonates such as α-halo phosphonates, synthesis of α-halo substituted alkenes and alkynes, which are important intermediate in organic synthesis.[12-13] A number of synthetic methods for the preparation of α-hydroxy phosphonates have been reported during the past two decades.[11, 14-16]

However, these reported methods have some disadvantages like use of hazardous, volatile and flammable solvents[16] and additional heat source.[17] To overcome all these difficulties, in recent year's solvent-free organic-synthesis have been favored to prepare α-hydroxy phosphonates.

Solvent-free reactions attracted more attention in

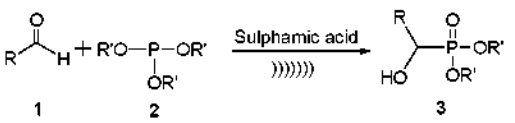
comparison with their homogeneous counterparts due to the growing concern for the influence of organic solvent on the environment as well as on human body, economical demands and simplicity in the processes.[18] Herein, we wish to report solvent-free synthesis of α-hydroxy phosphonates using cost-effective sulphamic acid catalyst in ultrasound irradiation. Sulphamic acid has been used as an efficient catalyst for various reactions such as acetolysis of cyclic ethers,[19] esterifecation,[20] synthesis of xanthenes,[21] chemo selective allylation of aldehydes,[22] deprotection of acetals[23] and Beckmann rearrangement.[24] Hence, we exploited such efficient catalyst for synthesis of α-hydroxy phosphonates.

EXPERIMENTAL

All the reagents and aromatic aldehydes were commercially obtained and the hetero-aryl aldehydes were prepared by conventional methods and were purified by recrystallization method. Reactions were carried out in a Bandelin Sonorex (35 KHz) ultrasonic bath. Melting points were determined in open capillaries and are reported uncorrected. The test for the purity of products and the progress of the reactions were accomplished by TLC on Merck silica gel plates. IR spectra (KBr) were recorded on a Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded on Varian NMR spectrometer. Model Mercury Plus (400 MHz), Mass spectra [ES-MS] were recorded on a Water-Micro mass Quattro-II spectrophotometer.

General Procedure:

Aldehyde (1 mmol) and phosphorous reagents (1.25 mmol) were taken in sealed tubes in which added a sulphamic acid (25 mol%) and the reaction mixture was exposed to ultra-wave sonication at room temperature. The completion of reaction was monitored on TLC. After the completion of reaction the resulting product poured on crushed ice. The products were filtered, dried and recrystallized using alcohol. All the products were confirmed by their spectral analysis.

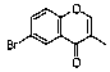
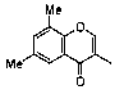
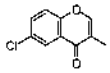
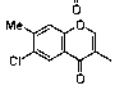
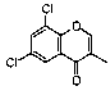
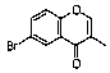
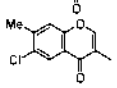
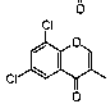
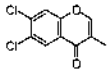
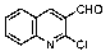
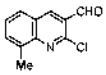
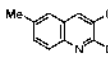
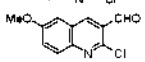
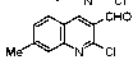
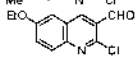
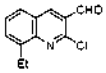


Scheme 1. Reaction Scheme.

RESULTS AND DISCUSSION

The original work of α-hydroxy phosphonates (Abramov reaction) involved the heating of an aldehyde or a ketone with trialkylphosphite at 70 ~ 100 °C for several hours in a sealed tube.[25] We attempted a reaction in solvent-free medium. For experimental setup initially we carried out a model reaction of benzaldehyde (1 mmol), triethyl phosphite (1.25 mmol) without catalyst at room temperature and we found that the reaction takes about 120 min. with 45% yield. We added a minimum amount of catalyst (5 mol%) to promote the reaction at room temperature with stirring in a sealed tube and the progress of reaction was monitored on TLC and the reaction requires about 100 min. with yield (50%). The results obtained with 5 mol% to 50 mol% catalytic amount of sulphamic acid were shown in (*Table* 2). *Table* 2 shows more reaction time required for 5 mol% catalyst. As we increase the catalyst proportion about 25 mol% yields were good but above 25 mol% catalyst there was no significant change in yields and reaction time. In search of better reaction condition, we carried out same model reaction using ultrasound irradiation with same proportion of reactant and catalyst at room temperature and we observed that the reaction time decreased dramtically (27 min.) with predominant yield. We performed an experiment with three various derivatives of aromatic aldehydes (*Table* 1, entry 3a, 3b, 3d). The comparative data for room temperature reaction and ultrasound irradiation is illustrated in *Table* 3. *Table* 3 clearly indicates the role of ultrasound irradiation in the synthesis of α-hydroxy phosphonates (*Scheme* 1). The proposed mechanism of the reaction was shown in the *scheme* 2. Reaction workup was very easy due to high solubility of catalyst in aqueous media. Overall the main importance of work is linked to green chemistry by avoiding use of hazardous solvents reported in previous literature methods. Com-

Table 1. α-hydroxyphosphonates Obtained from the Abramov reaction using Sulphamic acid (25 mol%) as a catalyst (3a-3v).

Entry	R	R'	Reaction Time (min.)	Yield (%)	M.P. (°C)[a]
3a		Et	27	98	78-80
3b		Et	30	92	92-94
3c		Et	35	95	126-128
3d		Et	20	89	62-64
3e		Et	60	85	127-129
3f		Me	2	85	200-202
3g		Me	1	86	204-206
3h		Me	3	80	190-192
3i		Me	1	83	210-212
3j		Me	2	82	203-205
3k		Me	1	78	189-191
3l		Et	1	83	166-168
3m		Et	2	79	180-182
3n		Et	1	81	186-188
3o		Et	1	80	220-222
3p		Et	1	88	124-126
3q		Et	4	83	146-148
3r		Et	4	81	140-142
3s		Et	5	84	171-173
3t		Et	4	87	154-156
3u		Et	5	89	168-170
3v		Et	5	80	144-146

[a]All physical constants of synthesized compounds compared with lit. Physical constants.

pounds (3a-3v) including hetro-arylaldehydes were used for all derivatization (*Table* 1) and time required for aromatic aldehydes were (27 ~ 60 min.) where as the hetro- arylaldehydes required much less time (1 min. ~ 5 min.). The entries in *Table* 1 (3f-3v) give quite interesting results with respect to time. On the basis of reaction time we conclude that the hetro-arylaldehydes gives rapid reaction with the exception of 3-pyridyl aldehydes (3e) over aromatic aldehydes. This methodology developed was clean. ecofriendly. costless, simple for synthesis of α-hydroxy phosphonates.

Table 2. Optimization of the Sulphamic acid catalyst for the benzaldehyde derivative (*Table* 1, Entry 3a) at room temperature.

Entry	Catalyst (mol%.)	Time (min.)	Yield (%)
1	-	120	45
2	5	100	50
3	10	100	50
4	15	100	55
5	20	100	60
6	25	100	65
7	30	100	65
8	40	100	65
9	50	100	65

Entry [2-9] compounds was isolated after the same reaction time.

CONCLUSION

In conclusion. we developed a green. efficient. cost-effective and solvent-free method for the synthesis of α-hydroxy phosphonates using ultrasound irradiation.

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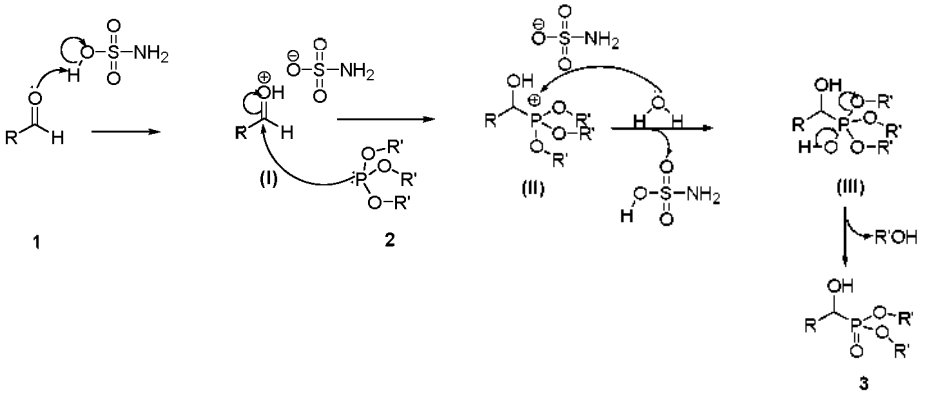
Table 3. Comparison data of room temperature condition and ultrasound irradiation using sulphamic acid (25 mol%) as a catalyst.

Entry	R	R`	Room temperature		Ultrasound irradiation	
			Time (min.)	Yield (%)[a]	Time (min.)	Yield (%)[a]
3a	H	Et	100	65	27	92
3b	4-Me	Et	100	60	30	88
3d	4-Cl	Et	80	65	20	90

[a] Isolated yields.



Scheme 2. Reaction mechanism.

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27. (**3a**): IR (KBr), cm^{-1}: 3425 (-OH), 1220 (-P = O), 1025 (P-O-C), ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.10 (t, 3H, O-CH_2-CH_3), 1.20 (t, 3H, O-CH_2-CH_3), 4.2 (m, 4H, O-CH_2-CH_3 and O-CH_2-CH_3); 4.5 (d, 1H, *J* = 12 Hz, -CH-OH), 6.00 (bs, 1H, -OH), 7.10-7.40 (m, 5H, Ar-H), ES-MS: *m/z* 245 (m+H). (**3c**) IR (KBr) cm^{-1}: 3425 (-OH), 1230 (-P = O), 1025 (P-O-C). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.21 (t, 3H, O-CH_2-CH_3), 1.27 (t, 3H, O-CH_2-CH_3), 3.80 (s, 3H, Ar-O-CH_3), 4.0 (m, 4H, O-CH_2-CH_3 and O-CH_2-CH_3), 4.90 (d, 1H, *J* = 12 Hz, Ar-CH), 6.9 (d, 2H, *J* = 8 Hz, Ar-H), 7.40 (dd, 2H, *J* = 8 Hz, Ar-H). MS: *m/z* 275 (m+H); (**3d**): IR (KBr), cm^{-1}: 3420(-OH), 1030 (P-O-C), ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.15 (t, 3H, O-CH_2-CH_3), 1.17 (t, 3H, O-CH_2-CH_3), 4.10 (m, 4H, O-CH_2-CH_3 and O-CH_2-CH_3); 4.60 (d, 1H, *J* = 12 Hz, -CH-OH), 5.90 (bs, 1H, -OH), 7.40 (d, 2H, *J* = 8Hz, Ar.H), 7.60 (d, 2H, *J* = 8 Hz, Ar.H), ES-MS: *m/z* 279(m+H); (**3p**): IR (KBr) cm^{-1}: 3246 (-OH),1218 (-P = O), 1033 (-P-O-C). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.2 (t, 3H, O-CH_2-CH_3), 1.3 (t, 3H, O-CH_2-CH_3), 4.0 (m, 4H, O-CH_2-CH_3 and O-CH_2-CH_3), 5.6 (d, 1H, *J* = 24 Hz, Ar-CH-P = O), 7.5 (t, 1H, Ar-H), 7.7 (t, 1H, Ar-H), 7.8 (d, 1H, *J* = 8 Hz, Ar-H), 8.0 (d, 1H, *J* = 8 Hz, Ar-H), 8.6 (s, 1H, Ar-H). MS: *m/z* 330 (m+H); (**3q**): IR (KBr), cm^{-1}: 3278 (-OH); 1218 (-P = O); 1037 (-P-O-C). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.2 (t, 3H, O-CH_2-CH_3); 1.3 (t, 3H, O-CH_2-CH_3); 2.4 (s, 1H, -CH-OH); 2.5 (s, 3H, Ar- CH_3); 4.1 (q, 2H, O-CH_2-CH_3); 4.2 (q, 2H, O-CH_2-CH_3); 5.6 (d, 1H, *J* = 12 Hz, -CH-P = O); 7.5 (s, 1H, Ar-H); 7.6 (d, 1H, *J* = 8 Hz, Ar-H); 7.9 (d, 1H, *J* = 8 Hz, Ar-H); 8.5 (s, 1H, Ar-H,). ES-MS: *m/z* 344 (m+H) (**3r**): IR (KBr) cm^{-1}: 3240 (-OH); 1215 (-P = O); 1037 (-P-O-C). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.2 (t, 3H, O-CH_2-CH_3); 1.3 (t, 3H, O-CH_2-CH_3); 2.4 (s, 1H, -CH-OH); 2.7 (s, 3H, Ar- CH_3); 4.2 (q, 2H, O-CH_2-CH_3); 4.3 (q, 2H, O-CH_2-CH_3); 5.6 (d, 1H, *J* = 24 Hz, -CH-P=O); 7.4 (t, 1H, Ar-H); 7.6 (d, 1H , *J*= 8 Hz, Ar-H); 7.7 (d, 1H , *J* = 8 Hz, Ar-H); 8.5 (s, 1H, Ar-H). ES-MS: *m/z* 344 (m+H) (**3s**): IR (KBr) cm^{-1}: 3269 (-OH); 1218 (-P = O); 1033 (-P-O-C). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.2 (t, 3H, O-CH_2-CH_3); 1.3 (t, 3H, O-CH_2-CH_3); 2.6 (s, 1H, -CH-OH); 3.8

(s, 3H, Ar-O-CH_3); 4.1 (q, 2H, O-CH_2-CH_3); 4.2 (q, 2H, O-CH_2-CH_3); 5.6 (d, 1H, J = 24 Hz, -CH-P = O); 7.0 (s, 1H, Ar- H); 7.4 (d, 1H , J = 8 Hz, Ar-H); 7.9 (d, 1H , J = 8 Hz, Ar-H); 8.5 (s, 1H, Ar-H). ES-MS: *m/z* 360 (m+H) (**3t**): IR (KBr) cm^{-1}: 3269 (-OH); 1218 (-P = O); 1033 (-P-O-C). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.2 (t, 3H, O-CH_2-CH_3); 1.3 (t, 3H, O-CH_2-CH_3); 2.7 (s, 1H, -CH-OH); 3.9 (s, 3H, Ar-OCH_3); 4.1 (q, 2H, O-CH_2-CH_3); 4.2 (q, 2H, O-CH_2-CH_3); 5.6 (d, 1H, J = 24 Hz, -CH-P = O); 7.2 (d, 1H, J = 8 Hz, Ar-H); 7.3 (s, 1H, Ar-H), 7.7 (d, 1H , J = 8 Hz, Ar-H); 8.5 (s, 1H, Ar-H). ES-MS: *m/z* 343.9 (m+H).