1,3-Dibromo-5,5-dimethylhydantoin (DBDMH): An Efficient and Reusable Catalyst for the Synthesis of α-hydroxyphosphonates

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Abstract

We have described that 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) is an inexpensive, efficient and mild catalyst for the synthesis of α-hydroxyphosphonate derivatives by the reaction of various aryl or heteroaryl aldehydes with triethylphosphite at room temperature. This method affords the α-hydroxyphosphonates in short reaction times, under solvent-free conditions and in high yield.

Keywords: 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH), α-hydroxyphosphonates, catalysis

INTRODUCTION

α-Hydroxyphosphonates acts as inhibitor of a diverse group of enzymes including renin,[1a,b] FPTase,[1c] HIV protease[1d] and EPSP synthase.[1e] α-Hydroxyphosphonates has antibacterial activities with the quinoline nucleus.[2]

α-hydroxyphosphonates has many synthetic applications in the field of organic chemistry. It serves as an attractive precursors for the synthesis of other α-substituted phosphonates and phosphonic acids, such as α-aminophosphonates, α-aminophosphonic acids which have broad spectrum of medicinal applications.[3] It has also been used for the synthesis of 1,2-diketones,[4] α-halophosphonates, halosubstituted alkenes and alkynes,[5] α-ketophosphonates.[6] Recently α-hydroxy allylic phosphonates were used in the synthesis of (-)-Enterolactone and cyclopentenones.[7]

The synthesis of α-hydroxyalkylphosphonates has been extensively studied and described in the literature. Searching common databases gives many papers devoted to the preparation of a broad spectrum of α-hydroxyalkylphosphonates. However, most of them are just obvious modifications of the old method described for the first time in 1950[8] by Abramov[9] and independently by Pudovik[10] and Fields.[11] This method is based on the reaction of aldehydes or ketones with dialkyl phosphonates, in the presence of basic catalyst (sodium alkoxides were applied by Abramov and Pudovik, and triethylamine by Fields)

The addition of base is essential for the Abramov reaction, since the reaction between dialkyl phosphonates and aldehydes or ketones does not start spontaneously because: (i) the phosphonate is too weakly acidic to activate the aldehyde or ketone, and (ii) the aldehyde (or ketone) is too weakly basic to activate the dialkyl phosphonates.

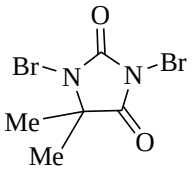
Many other bases were used for this reaction such as triethyl amine,[12a] ethyl magnesium bromide,[12b] caesium fluoride,[12c] potassium fluoride on alumina,[12d] MgO,[12e] tetramethyl guanidine,[12f] DBU.[12g]

The use of base for the activation of dialkyl phosphonates causes two main problems. The first problem is the reversibility of the reaction[13] especially when a high temperature is necessary to distill the products. The second problem is a well-known phosphonate–phosphate rearrangement, which gives the alkyl phosphates instead of the desired 1-hydroxyalkylphosphonates.[14] This problem exists especially when a strong base is applied as the catalyst in the Abramov reaction. Additionally, the anions of dialkyl phosphonates, obvious ambident nucleophiles, can react by their electron pair located on the phosphorus

atom, as well as by those located on the oxygen, for example, when silver dialkyl phosphonates react with some halides, the alkylation on oxygen is observed predominantly.[15] The basic catalyst could also cause the well-known Aldol reaction, and the products of the Aldol reaction could react with dialkyl phosphonates to give a complex reaction mixture.

Asymmetric synthesis of α-hydroxy phosphonates has also been carried out under basic condition by the reaction of aldehydes or ketones with either chiral dialkyl phosphonates or in the presence of a chiral catalyst.[16-23]

Specific objectives of our current research program include the development of new synthetic methodologies using DBDMH. Literature survey reveals that DBDMH is an efficient, non-toxic, cheap, and environmentally benign catalyst discussed as follows:



From dimethylhydantoin DBDMH is derived. DBDMH is five membered heterocycle which had been known as a bromination agent,[24] but it has recently gained special attention as an efficient homogeneous catalyst in organic transformations.[25]

DBDMH is an N-halo reagent which has found widespread applications in industrial processes due to its economic advantages. DBDMH is a well known brominating and oxidating agent that has recently gained special attention as a highly efficient, commercially available and inexpensive homogeneous catalyst.[26] However, in the following of our interest on the application of N-halo reagents in organic synthesis.[27-30]

Knowing all these aspects herein we want to report an efficient method for the synthesis of α-hydroxyalkylphosphonates using homogeneous catalyst like 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH).

RESULT AND DISCUSSION:

In the preparation of α-hydroxyphosphonates we have used an efficient catalyst and the best experimental reaction conditions; in this regard we have determined that the reaction of **1a** compound with triethyl phosphite under solvent-free conditions at room temperature is the standard model reaction. We screened a number of different catalysts, such as *p*-toluene sulphonic acid (*p*-TSA), acidic alumina, Zinc chloride ($ZnCl_2$), Cadmium Chloride ($CdCl_2$), Ferric Chloride ($FeCl_3$), sulphamic acid, and DBDMH and the results are formulated in Table 1. DBDMH provided the best results, yielding 98% of product yield within 1 min (Table 1, Entry 5).

Table 1: Screening of Catalysts[a]

Entry	Catalyst	Time (min)	Yield[b] (%)
1	Acidic alumina	76	77[c]
2	*p*-TSA	56	55
3	$CdCl_2$	58	43
4	$FeCl_3$	62	35

5	DBDMH	1	98
6	$ZnCl_2$	62	23
7	Sulphamic acid	57	76

[a]*Reaction Conditions:* 1a (10 mmol), triethyl phosphite (15 mmol), Catalyst (10 mol%), solvent-free at rt. [b]Isolated yields. [c]Catalyst (mg).

To evaluate the effect of solvent, various solvents such as water, dichloromethane, tetrahydrofuran, toluene, and ethanol were used for the standard model reaction. Predictably, it was observed that the use of solvent retarded the reaction rate and afforded the desired product in much lower yields. (Table 2, Entry 2-5). When water is used as the solvent no product was observed (Table 2, Entry 1).

Table 2: Screening of Solvents[a]

Entry	Solvents	Time (hr)	Yield[b] (%)
1	Water	21	No reaction
2	Dichloromethane	24	10
3	Tetrahydrofuran	24	10
4	Toluene	24	15
5	Ethanol	24	20

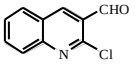
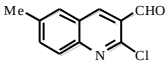
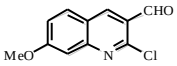
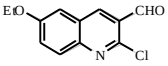
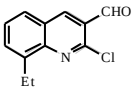
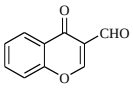
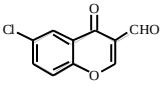
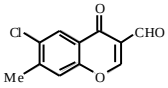
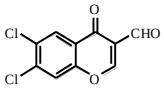
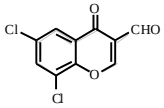
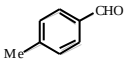
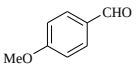
[a]*Reaction Conditions:* 1a (10 mmol), triethyl phosphite (15 mmol), DBDMH (10 mol%), solvent (10 mL) at rt. [b]Isolated yields.

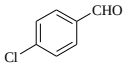
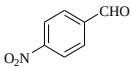
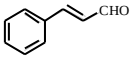
To establish generality with respect to the reaction of carbonyl compounds; triethyl phosphite was treated with various aldehydes and ketones under the influence of DBDMH (Table 3). It was observed that substituted 2-chloroquinoline-3-carbaldehydes reacted faster than other aldehydes, providing excellent yields 90-98% (Table 3, Entry 1-5). The substituted 4-oxo-4*H*-chromene-3-carbaldehydes formed the corresponding hydroxy phosphonates in 10-12 min in good yields 83-90% (Table 3, Entry 6-10). In comparison with these results, aryl aldehydes formed their respective hydroxyphosphonates, requiring longer time, but also if good yields (80-90%, Table 3, Entry 11-17). In case of cinnamaldehyde, the addition of triethyl phosphite selectively occurs at the carbonyl carbon (Table 3, Entry 18). Unfortunately the reaction of aliphatic aldehydes and aliphatic or aromatic ketones does not show any conversion after 24 hrs, even on increasing the concentration of DBDMH (Table 3, Entry 19-22).

In case of aryl aldehydes, electron donating substituents resulted in longer reaction times whereas electron withdrawing substituents requires shorter time for the complete reaction (Table 3, Entry 12-17). However, no significant substituent effect was found in case of heteroaryl aldehydes.

With the optimized conditions, we have carried out the reaction of various aryl and heteroaryl aldehydes 1a-r with triethyl phosphite. The corresponding α-hydroxyphosphonates 2a-r were formed in excellent yields (Table 3).

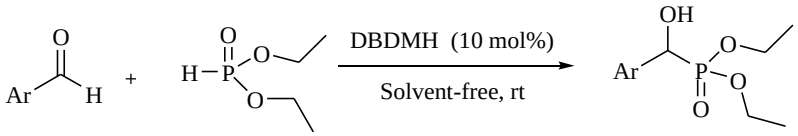
Table 3: Characterization data of α-hydroxyphosphonates 3[a]

Entry	Compound	Aldehyde/Ketone	Time (min)	Yield (%)[b]	M.P. (°C)	
					Found	Literature
1	2a		5	98	123-125	124-126[4]
2	2b		6	94	144-146	145-147[4]
3	2c		5	92	155-157	154-156[4]
4	2d		5	97	162-164	168-170[4]
5	2e		7	90	144-146	145-147[4]
6	2f		10	88	168-170	172[33b]
7	2g		12	87	178-180	180[33b]
8	2h		10	90	176-178	178[33b]
9	2i		10	85	222-224	220[33b]
10	2j		12	83	191-193	190[33b]
11	2k		15	90	75-77	75-77[19]
12	2l		20	84	97-99	94-95[19]
13	2m		25	80	121-123	120-121[19]
14	2n		20	82	95-97	97-98.5[19]

15	2o		12	88	65-67	67-68[19]
16	2p		15	83	73-75	74-75[19]
17	2q		10	90	86-88	87-88[19]
18	2r		40	80	105-107	105-106[19]
19	2s		24[c]	No reaction	-	-
20	2t		24[c]	No reaction	-	-
21	2u		24[c]	No reaction	-	-
22	2v		24[c]	No reaction	-	-

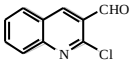
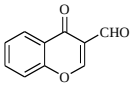
[a]*Reaction Conditions: 1* (10 mmol), triethyl phosphite (15 mmol), DBDMH (10 mol%), solvent-free at rt. [b]Isolated yields. [c]Time in hr.

We also examined the reaction of diethyl phosphonate with three principal aldehydes (Scheme 1, Table 4) by applying the same experimental conditions. Only the benzaldehyde gives their hydroxyphosphonate in trace amount, whereas heteroaryl aldehydes do not show any conversion after 24 hr.



Scheme 1: Reaction of aldehyde with diethyl phosphite

Table 4: Synthesis of α-hydroxyphosphonates using dialkyl phosphonates[a]

Entry	Aldehyde	Time (h)	Yield[b] (%)
1		24	No reaction
2		24	No reaction
3		24	6

[a]*Reaction Conditions:* Aldehyde (10 mmol), diethyl phosphonate (15 mmol), DBDMH (10 mol%), solvent-free at rt. [b]Isolated yields.

In order to show the merit of DBDMH in comparison with the other catalyst used for the similar reaction, a side by side comparison was run with some of the more common catalysts used for this chemistry. The results are presented in Table 5. It is evident from these results, DBDMH was found to be an effective catalyst for the synthesis of α-hydroxyphosphonates.

Table 5: Comparison with reported procedure

Entry	Catalyst	Catalyst Conc.	Solvent/ Medium	Temp (^oC)	Time	Yield[e] (%)	Reference
1	TMSCl	1 eq.	-	120	8 hr	92[a]	6
2	Guanidine·HCl	5 mol%	H_2O	50	2 hr	95[b]	28
3	HCl·Et_2O	1 eq.	DCM	-10	1 hr	74[a]	22
4	TMSCl	1 eq.	$LiClO_4$·Et_2O	rt	5 min	98[a]	27
5	DBDMH	20 mol%	-	rt	15 min	90[a]	Present
6	TMSCl	2 eq.	Toluene	Reflux	20 min	76[c]	4
7	DBDMH	20 mol%	-	rt	5 min	92[c]	Present
8	TMSCl	2 eq.	MW/150W	-	10 min	85[d]	33b
9	DBDMH	20 mol%	-	rt	10 min	88[d]	Present

[a]Reaction of benzaldehyde with triethyl phosphite. [b]Reaction of benzaldehyde with trimethyl phosphite. [c]Reaction 2-chloroquinoline-3-carbaldehyde with triethyl phosphite. [d]Reaction of 4-oxo-4H-chromene-3-carbaldehyde with triethyl phosphite. [e]Isolated yields based upon starting aldehyde.

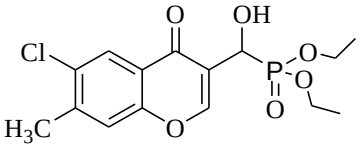
EXPERIMENTAL SECTION

All the melting points were determined in open capillaries in a paraffin bath and are uncorrected. ^{1}H NMR spectra were recorded on Mercury Plus Varian in DMSO-d_6 at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using electrospray ionization technique. The progress of the reactions was monitored by TLC.

General Procedure

A mixture of aldehyde (10 mmol), diethyl phosphonate (15 mmol) and DBDMH (10 mol%) was stirred magnetically at room temperature. 20 mL ice cold water was added to the reaction mixture after 24 hr. The crude product was extracted by chloroform and purified by column chromatography on silica gel by petroleum ether: ethyl acetate (8:2) as an eluent. Only the benzaldehyde forms their hydroxy phosphonate in 6% yield.

Spectral Analysis



*Diethyl (6-chloro-7-methyl-4-oxo-4H-chromen-3-yl)(hydroxy)methylphosphonate (**2h**)*

IR (KBr, cm^{-1}): 3250 (O-H), 1690 (C=O), 1210 (P=O), 1020 (P-O-C).

^{1}H NMR (DMSO-d_6, 400 MHz, δ_{ppm}): 1.11 (t, 3H, *J* = 7.2 Hz, CH_3), 1.19 (t, 3H, *J* = 7.2, CH_3), 2.4 (s, 3H, Ar-CH_3), 3.93-3.99 (m, 2H, O-CH_2), 4.01-4.08 (m, 2H, O-CH_2), 5.16 (dd, 1H, *J* = 12.4, 6.8 Hz, P-CH), 6.27 (brs, 1H, OH), 7.73 (s, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 8.31 (d, 1H, *J* = 3.6 Hz, Ar-H).

ES-MS: m/z 361(M+1).

CONCLUSION

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) is a readily available, inexpensive, and efficient catalyst for the synthesis of variety of α-hydroxyphosphonate derivatives. The remarkable advantages offered by this method are solvent-free reaction conditions, room temperature reactions, short reaction times, ease of product isolations, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of α-hydroxyphosphonates.

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