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Alum Catalysed Simple and Efficient Synthesis of α-hydrxyphosphonates from 2-Chloroquinoline-3-carbaldehydes

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ABSTRACT

Alum ($KAl(SO_4)_2.12H_2O$) is an inexpensive, efficient, non-toxic and mild catalyst for the synthesis of α-hydroxyphosphonates from 2-chloroquinoline-3-carbaldehyde and triethylphosphite under the influence of ultrasound irradiation in solvent free condition. The remarkable advantages of this method are the simple experimental procedures, shorter reaction times, high yields of product and green aspects by avoiding toxic catalysts and solvents. All the synthesized compounds were characterized by IR, ^{1}HNMR and Mass spectroscopy.

Keywords:
α-hydroxyphosphonates, 2-chloroquinoline-3-carbaldehyde, alum, ultrasound irradiation, triethylphosphite.

Introduction:

Quinoline ring system represents a very important and major class of heterocyclic compounds and is used as a key intermediate for many pharmacologically important compounds.[1-2] The derivatives of quinoline exhibits physiological and biological activities such as antimalarial,[3-5] anti-inflammatory,[6-7] antitumor,[8-9] DNA binding capacity,[10] antibacterial,[11] antimicrobial,[12-14] anticancer[15-16] anti-tuberculosis[17] antihistamine,[18] antifungal,[19] anti-HIV,[20] antihypertensive[21] and antiparasitic properties.[22] Also quinoline is used in the study of bioorganic and bioorganometallic processes.[23] Quinolines such as 2-chloroquinoline-3-carbaldehyde occupy a prominent position as they are key intermediates for further annelation and for various functional group interconversions.[24-25]

Phosphonic acids and their phosphonate derivatives are of great interest in organic chemistry due to their biological activity.[26] Some vinyl phosphates have been reported as potent inhibitors of phosphatase[27] and phosphodiesterase.[28]

There are only a few reports on the synthesis and bioactivity of C"P bonds which have been found to have insecticidal[29] and antifungal[30] activities. Also α-hydroxyphosphonates[31] and α-aminophosphonates are important biologically active compounds.[32-33] α-hydroxyphosphonates may serve as precursors for the synthesis of α-aminophosphonates which are analogs of amino acids. synthesis of α-halo substituted alkenes and alkynes, which are important intermediate in organic synthesis.[34-35]

A number of synthetic methods for the preparation of α-hydroxyphosphonates have been reported during the past two decades.[36-37] In the literature, α-hydroxyphosphonates have been prepared using: quinine catalyst in toluene as solvent,[38] DBU or n-BuLi in THF,[39] HCl: ether media in DCM,[40] $LiClO_4$: diethyl ether solution in the presence of trimethylsilyl chloride (TMSCl),[37] toluene and $Ti(OiPr)_4$,[41] hydroxy phosphorylation of aldehydes catalyzed by guanidine hydrochloride in water,[42] BF_3.etherate and $AlCl_3$,[43] and TFA or TfOH.[44]

At present, with the development in the fields of synthetic and catalytic chemistry, researchers have started to develop environmentally benign processes to avoid or minimize the harmful effects.

The application of solvent-free reaction conditions in organic chemistry has been explored extensively within the last decade. It has been demonstrated to be an efficient technique for various organic reactions. Solvent-free conditions often lead to a remarkable decrease in reaction time, increased yields, easier workup, enhancement of regio and stereo selectivity of reaction matches with the green chemistry protocol.[45] Ultrasound irradiation has been established as an important technique in synthetic organic chemistry.

It has been used as an efficient heating source for the organic reactions. Shorter reaction time is the main advantage of ultrasound assisted reactions. Simple experimental procedure, very high yields, increased selectivities and clean reaction of many ultrasound induced organic transformations offers additional convenience in the field of synthetic organic chemistry.[46-47]

Alum ($KAl(SO_4)_2.12H_2O$) were found to be effective in the synthesis of cis-isoquinolic acids,[48] mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones,[49] dihydropyrimidines via Biginelli reaction,[50] coumarins,[51] 1,3,4-oxadiazoles,[52] dibenzoxanthenes,[53] 1,5-benzodiazepines,[54] trisubstituted imidazoles[55] 2-arylbenzothiazoles and 2-arylbenzoxazoles.[56] However, there are no any reports of the use of alum as a catalyst for the synthesis of α-hydroxyphosphonates. Hence, we wish to report solvent-free synthesis of α-hydroxyphosphonates using cost- effective alum catalyst in ultrasound irradiation. Hence, we exploited such efficient catalyst for synthesis of α-hydroxy phosphonates.

Result 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.[57] We have earlier reported the synthesis of α-hydroxyphosphonates[58-59] from 2-chloroquinolin-3-carbaldehyde at reflux

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temperature in toluene while at reflux temperature, TMSCl was added and at room temperature without solvent;. To add TMSCl at the reflux temperature is not ecofriendly because it emits gases during addition. Azizi et al.[37] reported that for the same system at room temperature costly moisture sensitive reagents such as $LiClO_4$ and diethyl ether media could be used.

In search of better reaction condition, we carried out the reaction using 2-chloroquinolin-3-carbaldehyde, triethylphosphite and alum as catalyst under ultrasound irradiation with same proportion of reactant and catalyst at room temperature and we observed that the reaction time decreased (15 min.) with predominant yield. This clearly indicates the role of ultrasound irradiation in the synthesis of α-hydroxyphosphonates (Scheme-1, Table-1).

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. Here we have synthesized eight compounds by applying the same procedure and obtained each in quantitative yield. All the synthesized compounds are characterized by spectral analysis, physical constants, and compared with their authentic.

Experimental:

2-Chloroquinoline-3-carbaldehydes were prepared in the laboratory by the reported method. Triethylphosphite was procured from Lancaster; Alum, and *N,N*-dimethylformamide (DMF) were procured from S.D. Fine-chem.

All melting points were determined in open capillaries on Kumar's melting point apparatus. The products were characterized by their spectral data. ^{1}H NMR spectra were recorded on Varian Gemini in $CDCl_3$ at 400 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quatrro-II using electrospray Ionization technique, showing (m+1) peak as a molecular ion peak. The test for the purity of products and the progress of the reactions was accomplished by TLC on Merck silica gel plates.

General procedure

(2a) Diethyl (2-chloro-quinolin-3-yl)(hydroxy) methylphosphonate:

To the mixture of 2-chloroquinoline-3-carbaldehyde (0.95 gm, 5 mmol), triethylphosphite (1.66 gm, 10 mmol), and alum catalytic amount were added 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. (1.58 gm, yield 97%, m.p. 124"126 ^{0}C).

IR (KBr), cm^{-1}: 3246 (-OH); 1218 (-P=O); 1033 (-P-O-C).

^{1}H NMR ($CDCl_3$), δ ppm: 1.2 (t, 3H, O-CH_2-CH_3); 1.3 (t, 3H, O-CH_2-CH_3); 2.0 (s, 1H, -CH-OH); 4.0 (m, 4H, O-CH_2-CH_3 and O-CH_2-CH_3); 5.6 (d, 1H, -CH-P=O); 7.5 (t, 1H, Ar"H, C_6); 7.7 (t, 1H, Ar-H, C_7); 7.8 (d,1H, Ar-H,' C_5); 8.0 (d, 1H, Ar-H, C_8); 8.6 (s, 1H, Ar-H, C_4).

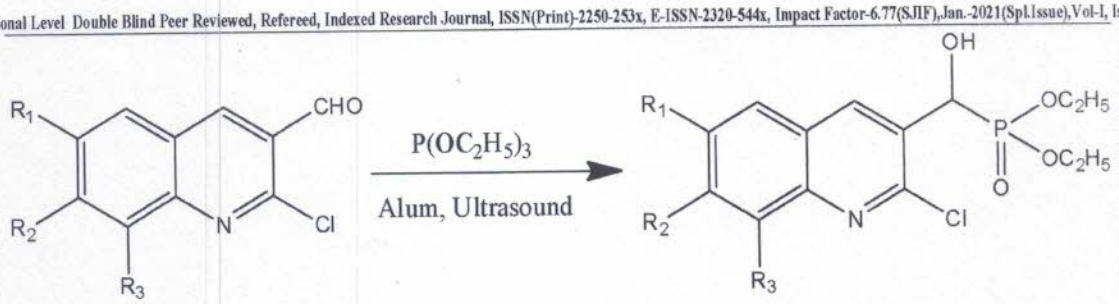
ES MS: m/z 330 (m+1) and 331.9 (m+3).

Diethyl (2-chloro-8-methylquinolin-3-yl)(hydroxy)methylphosphonate (2c).
IR (KBr) cm^{-1}: 3240 (-OH); 1215 (-P=O); 1037 (-P-O-C).

^{1}H NMR (CDCl3), 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, CH-P=O); 7.4 (t, 1H, Ar-H,C6); 7.6 (d, 1H, Ar-H, C5); 7.7 (d, 1H, Ar-H, C7); 8.5 (s, 1H, Ar-H, C4).

ES-MS: m/z 344 (m+1)

Scheme 1. Alum catalyzed synthesis of α-hydroxyphosphonates under ultrasound.



1a-g **2a-g**

Table 1. Alum facilitated synthesis of α-hydroxyphosphonates.

Entry	R_1	R_2	R_3	Time (min)	Yield (%)	MP (^{0}C)
2a	H	H	H	15	97	124–126
2b	CH_3	H	H	15	95	145–147
2c	H	CH_3	H	20	96	126–128
2d	H	H	CH_3	15	96	141–143
2e	OCH_3	H	H	15	95	170–172
2f	H	OCH_3	H	15	97	154–156
2g	OC_2H_5	H	H	15	96	168–170
2h	H	H	C_2H_5	20	96	145–147

Conclusion:

In conclusion, a new methodology was developed for the synthesis of α-hydroxyphosphonates 2a-h from 2-chloroquinoline-3-carbaldehydes 1a-h using triethylphohphite in the presence of alum as catalyst under ultrasound irradiation at room temperature in quqntative yield. The remarkable advantages of this method are the simple experimental procedures, shorter reaction times, high yields of product and green aspects by avoiding toxic catalysts and solvents. It may be useful for combinatorial chemistry.

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