

Non-conventional Synthesis of Aminophosphonates

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Abstract: A series of α -aminophosphonates have been synthesized from pyrazole imines and triethyl phosphite by both conventional and under microwave irradiation (MWI) conditions. The results showed the beneficial effect of the microwave irradiation on reaction which helps in shortening of the reaction time as well as smooth increase in the yield of products..

Keywords: aminophosphonates, pyrazole, MWI, non-conventional reaction

I. INTRODUCTION

In the recent years, α -aminophosphonates have received enormous attention because they are considered to be structural analogues of the corresponding α -amino acids and transition state mimics of peptide hydrolysis [1]. The use of α -aminoalkyl phosphonates as enzyme inhibitors [2], antibiotics and pharmacological agents [3], herbicides [4], and haptens of catalytic antibodies [5] are well documented. Due to their structural analogy to α -amino acids, they may function as inhibitors of enzymes involved in the metabolism of proteins and amino acids. For example, the phosphonic analogue of phenylalanine is an inhibitor of phenylalanyl-tRNA-synthetase [6]; phosphonodipeptide alafosfalin is an antimicrobial agent [7].

Literature search revealed that there are various catalytic as well as non-catalytic methods available for the synthesis of α -aminophosphonates [8]. Of these methods, the nucleophilic addition of phosphites to imines, catalyzed by a base or an acid, is the most convenient [9]. Lewis acids such as SnCl_2 , SnCl_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, ZnCl_2 , and MgBr_2 have been used [10].

II. EXPERIMENTAL

Materials and Methods

The ^1H , ^{13}C NMR spectra were obtained on BRUKER DRX-250 AVANCE instruments with CDCl_3 as a solvent. IR spectra were recorded on Shimadzu IR-460 spectrometer. Elemental analyses were performed using a Heraeus CHN Rapid analyzer. Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus.

Procedure for synthesis of α -aminophosphonates (3a):

i) By conventional method:

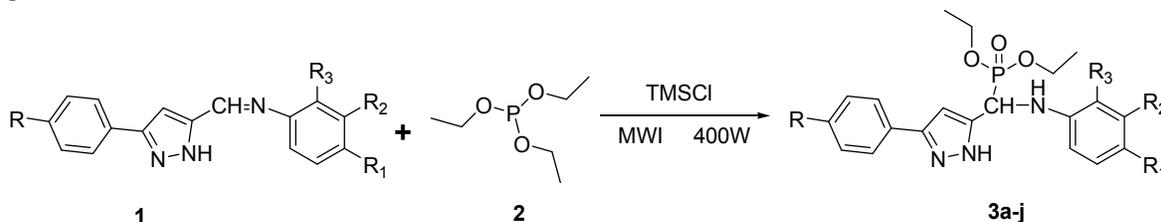
Mixture of an imine (1a) (1 mmol) and triethylphosphite (2 mmol) in 10 ml acetonitrile was refluxed in an oil-bath. To this mixture, trimethylsilyl chloride (2 mmol) was added under refluxing condition. Progress of the reaction was monitored on TLC. After completion of reaction (20 min.), the mixture was concentrated on rotavapor under reduced pressure to obtain solid residue which was decomposed with water. Thus, obtained solid was filtered, washed with hexane and dried under vacuum.

ii) Under microwave irradiation (MWI):

Mixture of an imine (1a) (1 mmol) and triethylphosphite (2 mmol) in a round bottom flask was taken and trimethyl silyl chloride (2 mmol) was added to it. The reaction mixture was then irradiated under MWI at 400W. Progress of reaction



was monitored on TLC. After completion of reaction (2 min.), the reaction mixture was quenched by water. The separated white solid was filtered and dried under vacuum.



Reaction Scheme 1

Table 1: Non-conventional synthesis of aminophosphonates (3a)

Sr. No.	R	R ₁	R ₂	R ₃	Yield (%)				M.P. (°C)
					Con.	Time (min.)	MWI	Time (min.)	
3a	H	H	H	H	57	20	75	2	172-174
3b	H	F	F	H	35	18	81	3	162-164
3c	H	F	F	F	54	16	84	3	-----*
3d	H	F	H	F	57	15	80	5	-----*
3e	CH ₃	F	H	F	67	10	85	3	90-92
3f	CH ₃	F	F	H	63	14	90	3	168-170
3g	CH ₃	F	F	F	71	13	77	3	148-150
3h	NO ₂	F	H	F	69	24	88	4	96- 98
3i	NO ₂	F	F	H	74	21	91	4	118-120
3j	NO ₂	F	F	F	76	18	78	5	130-132

*Oily liquid; Con.- Conventional; MWI – Microwave irradiation

III. RESULTS AND DISCUSSION

With aim of developing an improved methodologies for development of novel pyrazole derivatives, a model reaction between an imine (1a) and triethylphosphite in presence of trimethyl silyl chloride under both conventional and non-conventional method has been studied. Under conventional condition the reaction yield 57% of the target compound (3a) in 20 min have been achieved. Similarly, to gauge the effect of non-conventional microwave irradiation (MWI) on the model reaction was conducted under MWI. The effect of MWI on the model reaction showed and improved yield of target compound (3a) to 75% within 2 min. This clearly indicate beneficial effect of microwave irradiation (MWI) on model reaction.

This model reaction was extended to various imines (2a-2j) to judge the applicability of reaction to them. It was observed that under MWI, overall yield of the respective target compounds (3a-3j) has improved drastically (77-91%) within short period of time (3-5 min). M.P. of all the synthesized compounds were recorded and compared with the literature values which were in good agreement with literature values. Also, different analytical techniques like IR, NMR and Mass spectrometry were studied to establish the structures of synthesized compounds.

IV. CONCLUSION

An atom efficient and green synthesis of α -aminophosphonates have been achieved by using microwave irradiation method (MWI).

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