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Synthesis of and characterization of α- aminophosphonates of fluorinated pyrazole imines using triethyl phosphite and TMSCl

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ABSTRACT

*A series of α-aminophosphonates (**5a-j**) have been synthesized from fluorinated pyrazole imines (**3a-j**) and triethyl phosphite using TMSCl as a catalyst by both conventional and under ultrasound irradiation conditions. The results showed the beneficial effect of the ultrasound irradiation on reaction which helps in shortening of the reaction time as well as smooth increase in the yield of products. The title compounds were characterized by physicospectral techniques like mass, IR and NMR spectra.*

Keywords: α-aminophosphonates, pyrazole imines, TMSCl, ultrasonication.

INTRODUCTION

α-aminophosphonates constitute an important class of biologically active compounds those find applications in synthetic organic chemistry and medicinal chemistry [1]. These include peptide mimics [2], enzyme inhibitors [3], herbicides [4], antibiotics and pharmaceutical agents [5]. α-aminophosphonates are, in general, prepared by the addition of phosphorus nucleophiles to imines in presence of either a base or an acid, known as Kabachnik-Fields reaction [6].

Fluorinated chemicals and building blocks are of growing importance with applications in diverse fields, particularly in medicine and agrochemicals. Fluorine-containing drugs are used in medicine as anesthetics (ex. Halothane, isoflurane etc.), antibiotics (ex. Fluoroquinolones, Ciprofloxacin), anti-cancer and anti-inflammatory agents (ex. Niflumic acid), psychopharmaceuticals (ex. Fluoxetine and citalopram) and in many other applications [7].

Fluorine substitutions in the organic molecules have profound effects on the properties of such organic compounds. The very high electronegativity of fluorine can modify electron distribution in the molecule, affecting its absorption, distribution and metabolism.

Ultrasound promoted reactions are well known in literature and proceed through the formation and adiabatic collapse of cavitation bubbles [8]. Ultrasound provides an alternative source of energy for organic reactions which are accomplished by heating. Many homogeneous as well as heterogeneous reactions which can be conducted smoothly by sonication to provide improved yields and increased selectivities.

MATERIALS AND METHODS

All the melting points were determined on a Veego apparatus in open capillaries and are uncorrected. The purity of compounds was checked by TLC on silica gel 'G' coated aluminium plates. Ultrasound reactions were carried out on ultrasonic bath (with a frequency of 33 KHz). IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Brucker DRX-300 at 200 MHz using TMS as an internal standard. Mass spectra were taken on Water-Micromass Quattro-II spectrometer.

Procedure for synthesis of fluorinated pyrazolyl α-aminophosphonates (5a):
By conventional method:
Mixture of imine N-((1, 3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine (3a) (1 mmol) and triethylphosphite (2 mmol) in 10 ml acetonitrile was refluxed in an oil-bath. To this mixture, chloro(trimethyl)silane (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 rotary-evaporator under reduced pressure to obtain solid residue which was decomposed with water. Thus obtained solid was filtered, washed with hexane and dried under vacuum.

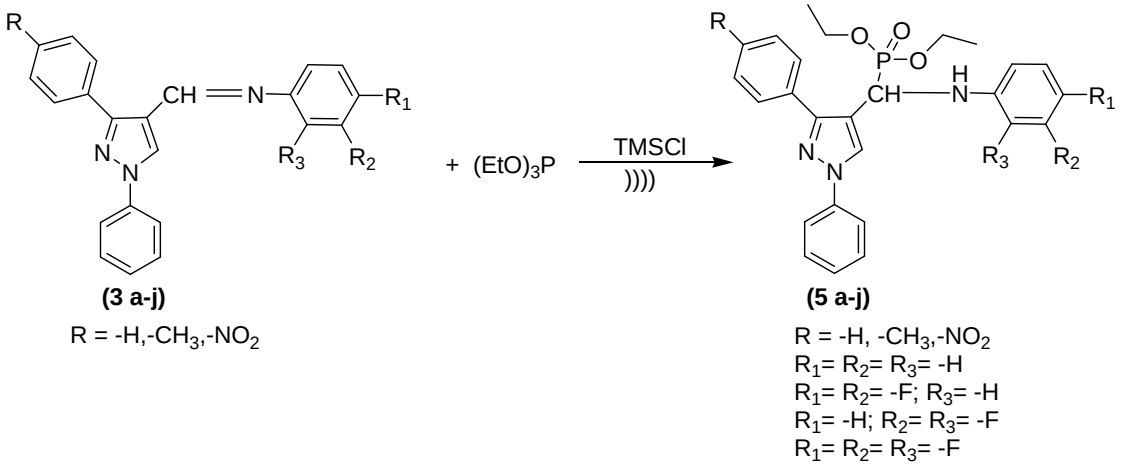
Under Ultrasonication:
Mixture of imine N-((1, 3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine (3a) (1 mmol) and triethylphosphite (2 mmol) in a round bottom flask was taken and chloro(trimethyl)silane (2 mmol) was added to it. The reaction mixture was then irradiated under ultrasonication condition. Progress of reaction was monitored on TLC. After completion of reaction (3 min.), the reaction mixture was quenched by water. The separated white solid was filtered and dried under vacuum.

RESULTS AND DISCUSSION

In continuation of our work [9], to develop environmentally benign and green protocols for the synthesis of heterocyclic molecules, herein, we developed a one pot, mild and efficient method for the synthesis of α-aminophosphonates of pyrazolyl imines using ultrasound irradiation in higher yields.

In the first step, the required fluorine containing imines of pyrazole (**3a-j**) were synthesized by condensing different substituted fluoro anilines with pyrazole aldehydes. These fluoro anilines were smoothly condensed with 4-formyl pyrazoles in alcohol to get the title compounds in better yields (81-96%) [10]. In second step these imines or schiff bases were reacted with triethyl

phosphite in acetonitrile solvent and trimethyl silyl chloride (TMSCl) at reflux temperature (Scheme 1).



Scheme 1

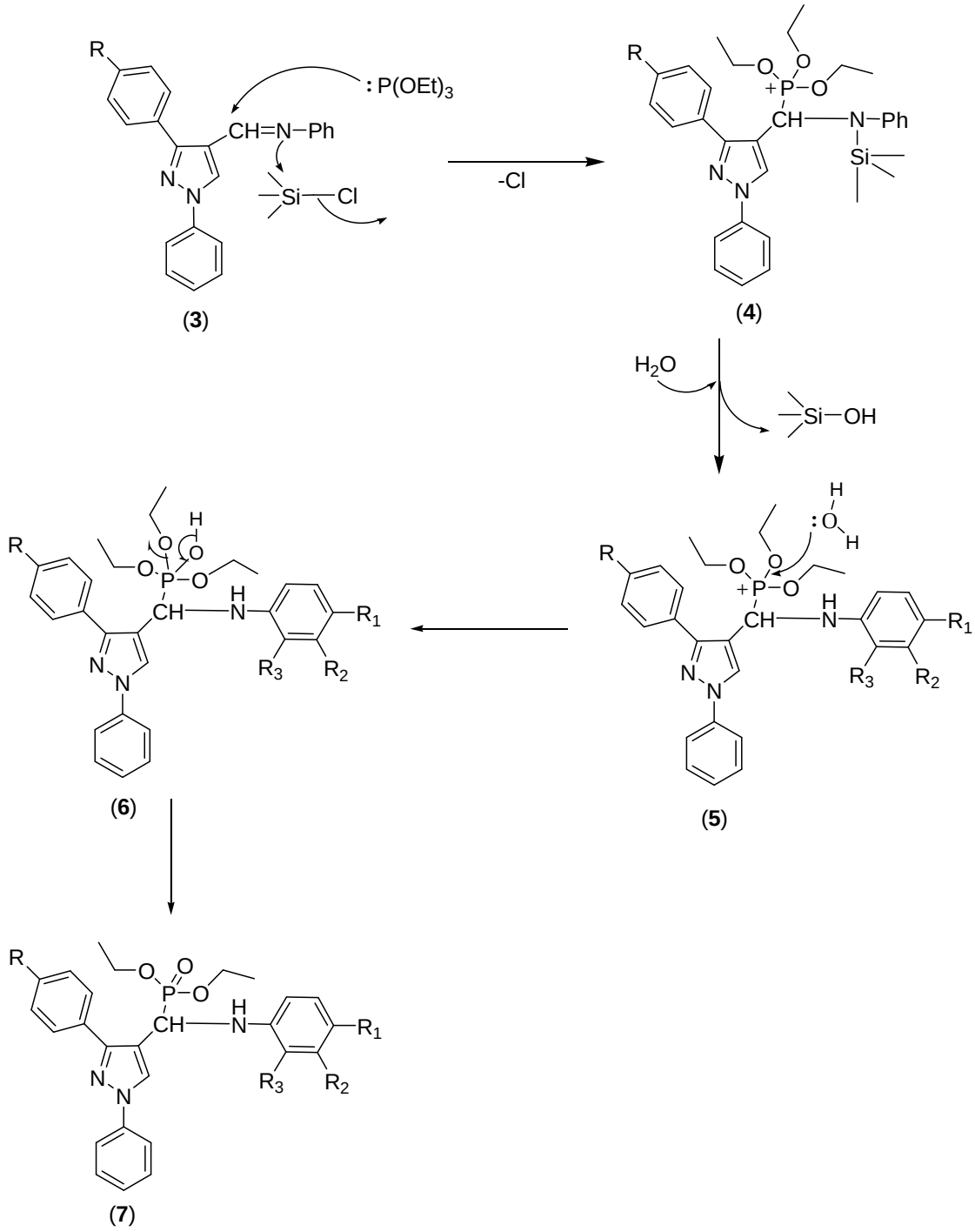
Under these conventional conditions, the formation of the target compounds was observed in poor to moderate yields (35-74%) indicating the limitations of conventional processes. To overcome the drawbacks of such conventional processes, we tried to develop an alternate route to synthesize α-aminophosphonates by using ultrasound technique.

Table 1: Ultrasound promoted synthesis of α-aminophosphonates using TMSCl 5(a-j).

Sr. No.	R	R_1	R_2	R_3	Yield (%)[a]				M. P. (°C)
					Con.	Time (min)	US	Time (min)	
5a	H	H	H	H	57	20	83	3	172-174
5b	H	F	F	H	35	18	77	3	162-164
5c	H	F	F	F	54	16	81	4	-------*
5d	H	F	H	F	57	15	94	5	-------*
5e	CH_3	F	H	F	67	10	86	5	90-92
5f	CH_3	F	F	H	63	14	91	4	168-170
5g	CH_3	F	F	F	71	13	85	5	148-150
5h	NO_2	F	H	F	69	24	87	4	96-98
5i	NO_2	F	F	H	74	21	90	4	118-120
5j	NO_2	F	F	F	76	18	88	6	130-132

[a] *-Isolated yield; Con.- Conventional; US- Ultrasonication*
** Compounds obtained as semi-solids*

For this purpose, we investigated the effect of ultrasonic irradiation on this condensation reaction under solvent-free conditions. The reaction of N-((1, 3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine (**3a**) and triethyl phosphite in presence of TMSCl (see Scheme 1) has been chosen as a model reaction. It was observed from table that there was remarkable ultrasound effect on this solvent free reaction. There was substantial increase in yield from 57 to 82% under ultrasonication over conventional reaction conditions (Table 1, entry 5a). In the case of ultrasound-promoted solvent-free protocol, the target product was afforded in maximum yield of 94% within dramatically shortened time at room temperature for comp. 3d (Table 1, entry 5d).



Scheme 2

All the reactions were carried out within short period of time (3-6 min) and in excellent yields. The pure products were obtained after the reaction by quenching the reaction mixture in water followed by filtration without further purification thereby reducing cost of purification.

In order to gauge the scope of the reaction, various imines bearing electron donating as well as electron with-drawing substituents were studied. It was found that the reaction undergo well in all cases effectively within 3-6 min. affording the corresponding products.

The effect of catalyst concentration was also studied. It was revealed from observation that increasing catalyst concentration up to 2 mmol increases yield of product. Further increase in concentration of catalyst didn't affect appreciably on yield of model reaction up to 4 mmol. The catalyst concentration of 2mmol was appropriate for all reactions (Table 2).

Table 2: Effect of catalyst concentration on model reaction under US.

Sr. No.	Catalyst Concentration (mmol)	Yield (%) [a]
1	1	75
2	2	83
3	3	82
4	4	82

[a] *-Isolated yield;*

A plausible mechanism for the formation of α-aminophosphonates is outlined in Scheme 2. The mechanism of the reaction is believed to be following the path of activation of imine (**3**) by trimethyl silyl chloride (TMSCl) in the first step. This facilitates nucleophilic addition of the triethyl phosphite to the polar C-N bond of imine to give phosphonium salt (**4**) as an intermediate. In final step, this phosphonium salt get decomposed by water liberating product (**7**) through intermediates (**5**) & (**6**). (Scheme 2)

CONCLUSION

In the present work, a simple one-pot procedure was developed for the synthesis of fluorine containing α-aminophosphonates using ultrasonication reaction. The non-conventional method offer advantages over conventional process viz., short time span to complete reaction, easy work procedure and excellent yields.

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