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Ultrasound promoted synthesis of some novel α-aminophosphonates of fluorinated pyrazole imines as antimicrobial agents.

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ABSTRACT

A series of α-aminophosphonates (**2a-j**) have been synthesized from fluorinated pyrazole imines (**1a-j**) and triethyl phosphite using conc. H_2SO_4 as a catalyst by both conventional and under ultrasound irradiation conditions. The results showed the useful effect of the ultrasound irradiation on reaction which helps in shortening of the reaction period time as well as increasein the yield of products. The title compounds were characterized by mass, IR and ^{1}HNMR spectra.The synthesized compounds were evaluated for their antimicrobial and antifungal activity against Gram +ve and Gram-ve microorganisms. Some of compounds show moderate activity against standard drugs.

Keywords: -aminophosphonates, pyrazole imines, ultrasonication.

INTRODUCTION

α-aminophosphonatesis an important class of biologically active compounds those find applications in synthetic organic chemistry and medicinal chemistry [1]. α- aminophosphonates have already been found to actherbicides [2], enzyme inhibitors [3],peptidemimics [4], antibiotics and pharmaceutical agents [5]. □-aminophosphonates are generally prepared by the addition of phosphorus nucleophiles toimines 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. The development of new fluorinating agents and advancement in organofluorine chemistry has eminently increased the potential for synthesis of novel fluorinated drugs and fluorine-containing compounds with applications in medicinal chemistry. In a survey it was believed that around 1500 drugs containing fluorine were under different stages of development, apart from 220 fluorinated drugs available in 1990. These accounts for 20% of pharmaceuticals in the market are fluorine containing, including half of the top 10 drugs sold in 2005. Fluorine-containing drugs are used in medicine as anaesthetics (eg Halothane, isoflurane etc.), antibiotics (eg Fluoroquinolones, Ciprofloxacin), anti-cancer and anti-inflammatory agents (eg Niflumic acid), psychopharmaceuticals (eg. Fluoxetine and citalopram) and in many other applications [7].Fluorine substitution has profound effects on the properties of these organic compounds. The mode of action of such fluorinated compounds is believed to be achieved due to very high electronegativity and a small size of fluorine which can modify electron distribution in the molecule, affecting its absorption, distribution and metabolism [8].

Generally, three major reasons were attributed for the ever increasing role of these fluoro-organic compounds in medicinal chemistry (a) the fluoro-organic compounds have inherent biological activity (b) the introduction of fluorine in biologically active compound improve its pharmacological activity and (c) due to ‘patent-jumping’ huge demand for these molecules [9].

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.These act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them already commercialized. In this context, the therapeutic potential for modified α- aminophosphonates with

improved pharmacokinetic properties, potency or spectrum, and lower side effects, prompted us to start a synthetic program to explore new pyrazole-aminophosphonate conjugates. We focused on pyrazole and its derivatives because it is an important class of compounds and attracted widespread attention due to their pharmacological properties, being reported to have a large spectrum of biological effects, especially analgesic, anticancer and anti-inflammatory properties.

Ultrasounds promoted reactions are well known in literature and proceed through the formation and adiabatic collapse of cavitation bubbles [10]. 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-d6 on a Varian – mercury at 300 MHz using TMS as an internal standard. Mass spectra were taken on Water-Micromass Quattro-II spectrometer.

Experimental Work

Procedure for synthesis of fluorinated pyrazolyl α-aminophosphonates (2a):

By conventional method:

General procedure for the synthesis ofdiethyl (4-fluorophenylamino)(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylphosphonate (2a): A mixture of imine **1a** (0.30gm, 0.00070mol) and triethyl phosphite (0.233gm, 0.00140mol) in 10 ml ethanol was stirred on magnetic stirrer and catalytic amount of Conc. H_2SO_4 was added to the solution. Progress of 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. The solid thus obtained was filtered, washed with hexane and dried. The product was recrystallized from ethanol. The compounds **2(a-j)**were prepared by following the general procedure. Physical data are recorded in **Table 1**. Their structures have been confirmed by IR, ^{1}H NMR and Mass spectra.

Under Ultrasonication:

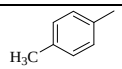
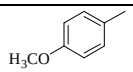
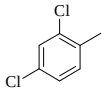
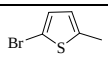
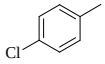
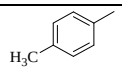
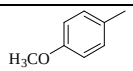
A mixture of imine **1a** (0.30gm, 0.00070mol), triethyl phosphite (0.233gm, 0.00140mol) was takenin a round bottom flask. The catalytic amount of Conc. H_2SO_4 was added to the solution. The reaction mixture was then irradiated under ultrasonication condition.Progress of reaction was monitored on TLC. After completion of reaction (3 min.), the reactionmixture was quenched by water. The separated white solid was filtered and dried under vacuum.

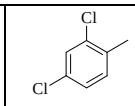
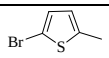
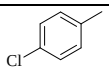
The product was recrystallized from ethanol. The compounds **2(a-j)**were prepared by following the general procedure. Physical data are recorded in **Table 1**. Their structures have been confirmed by IR, ^{1}H NMR and Mass spectra.

2a: m.p. 244-246 ^oC; IR (cm^{-1}):1244 (P=O), 1614 (C=N), 3290 (NH);^{1}H NMR($CDCl_3$)δ ppm: 1.160(t, 3H,-CH_2CH_3), 1.267(t, 3H, -CH_2CH_3), 3.877(t, 3H, Ar-OCH_3), 3.898-4.229(m, 4H, 2×-CH_2-), 4.357-4.408(m, 1H, C-H), 4.788-4.888(m, 1H, N-H), 6.411-6.455(m, 2H, Ar-H), 6.776-6.805(m, 2H, Ar-H),6.989-7.018(d, 2H, Ar-H), 7.291-7.294(d, 1H, Ar-H), 7.402-7.455(m, 2H, Ar-H), 7.598-7.628(m, 2H, Ar-H), 7.712-7.741(m, 2H, Ar-H), 8.291(s, 1H, Pyrazole-H).

ES-MS(m/z): 510 (M+1).

Table 1: Physical data of compounds 2(a-j)

						Conventional Method		Ultrasonication Method	
Compd.	Ar	R_1	R_2	R_3	M.P. (^oC)	Time (min)	Yield (%)	Time (min)	Yield (%)
2a		H	H	F	244-246	20	62	3	80
2b		H	H	F	206-208	20	70	3	78
2c		H	H	F	212-214	20	68	4	72
2d		H	H	F	236-238	20	64	5	70
2e		H	H	F	168-170	20	67	3	78
2f		F	H	F	196-198	20	62	3	68
2g		F	H	F	210-212	20	72	4	82

2h		F	H	F	214-216	20	74	6	78
2i		F	H	F	220-222	20	70	5	75
2j		F	H	F	240-242	20	68	4	80

Antimicrobial Activity

Compounds **2(a-j)**werescreened for their in vitro antimicrobial activity against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus albus, Staphylococcus aureus, Klebsiella pnuemoniae,Pseudomonas sp.*using Ciprofloxacin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using Fluconazole as standard drug. All the tests were evaluated at 100 µg/ml concentration. The culture media was Muller hinton agar. The zone of inhibition was measured in mm after 24 hr. of incubation at 37^{o}C. All the compounds show good to moderate antibacterial activity against above mentioned bacterial species.DMSO is used as control.Antimicrobial data is given in **Table 2.**

Table 2: Antimicrobial dataof compounds 2(a-j)

Disc Diffusion Method

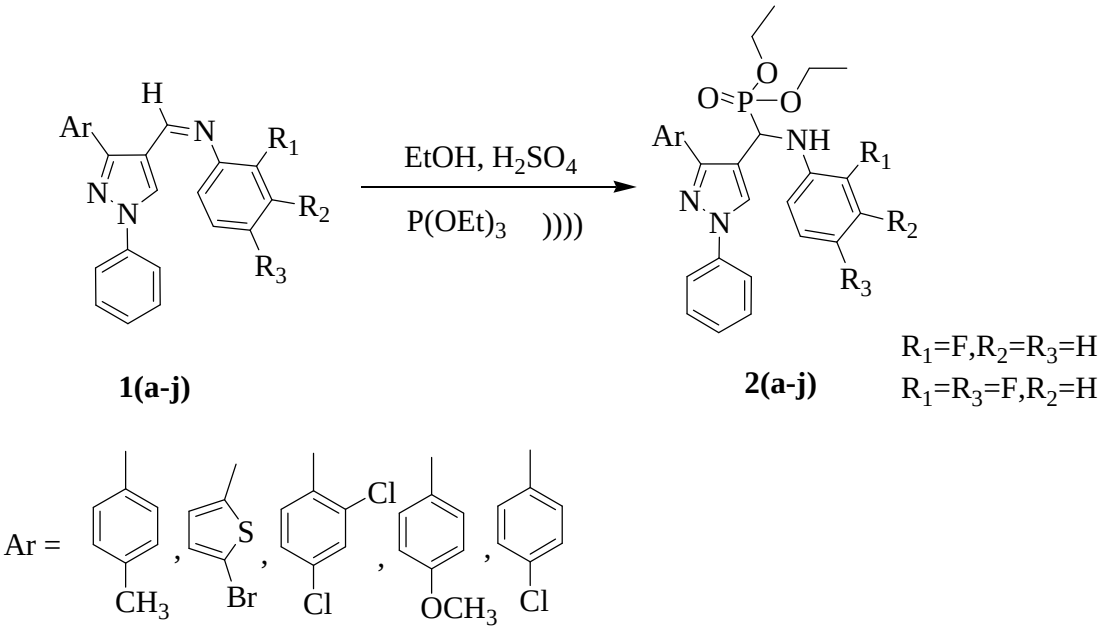
Sr. No.	Compound No.	**Inhibition Zone Diameter (mm)**					
		Candida sp.	*S. aureus*	*S. albus*	*Klebsiella pnuemoniae*	*E. coli*	*Pseudomonas sp.*
1.	2a	----	2	7	7	5	4
2.	2b	----	2	1	6	8	5
3.	2c	----	4	6	6		8
4.	2d	----	19	16	18	15	17
5.	2e		12	13	8	8	9
6.	2f	----	15	15	5	7	7
7.	2g	----	12	8	12	10	5
8.	2h	----	10	4	7	4	4
9.	2i	----	8	7	5	7	9
10.	2j	----	7	5	8	9	5

11.	Control	8	3	3	4	6	10
12.	Ciprofloxacin	---	20	22	22	21	23
13.	Fluconazole	23	---	---	---	---	---

RESULTS AND DISCUSSION

In continuation of our work [11], 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 yield. In the first step, the required fluorine containing imines of pyrazole (**1a-j**) were synthesized bycondensing different substituted fluoro anilines with pyrazole aldehydes. These fluoro anilineswere smoothly condensed with 4-formyl pyrazoles in alcohol to get the title compounds in betteryields (63-90%). In second step these imines or schiff bases were reacted with triethyl phosphite in ethanol solvent and Conc. H_2SO_4 at room temperature

(Scheme1).



Scheme 1

Under these conventional conditions, the formation of the target compounds was observed in poor to moderate yields (62-74%) indicating the limitations of conventional processes. To

overcome the drawbacks of such conventional processes, we tried to develop an alternate route to synthesize □-aminophosphonates by using ultrasound technique.

For this purpose, we investigated the effect of ultrasonic irradiation on this condensation reaction insolvent-free conditions. The reaction of *(E)*-4-fluoro-*N*-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)benzenamine(**2a**) and triethyl phosphite in presence of Conc. H_2SO_4 (see Scheme 1) hasbeen chosen as a model reaction. It was observed from table that there was remarkableultrasound effect on this solvent free reaction. There was substantial increase in yield from 72 to82% under ultrasonication over conventional reaction conditions (Table 1, entry 2a). In the caseof ultrasound-promoted solvent-free protocol, the target product was afforded in maximum yieldof 82% within dramatically shortened time at room temperature for comp. 2g(Table 1, entry 2g).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 waterfollowed 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.

CONCLUSION

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

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