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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL N-(4-(PYRROLIDIN-1-YL)BENZYLIDENE)-ARYLAMINE AND DIETHYL (ARYLAMINO)(4-(PYRROLIDIN-1-YL)PHENYL)METHYL PHOSPHONATE

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Abstract:
In this work we have synthesis Schiff bases and α-amino phosphonates by conventional and non-conventional methods. The one pot synthesis of α-amino phosphonates were also carried out by both the methods.

Keywords: Schiff base, α-amino phosphonates and Sonication

Introduction:

α-aminophosphonates are structural analogues of the natural α-amino acids [1]. They have been reported as peptidomimetics [2], enzyme inhibitors [3,12-14], herbicidals [4], serine hydrolase inhibitors[5], UDP-galactopyranosemutase inhibitors[6], antimicrobial[7-9,15], antioxidant[10], antiviral[11], antiproliferative[15] in the literature.

Kabachnik-Fields reaction is the most useful method for the synthesis of α-amino phosphonates. Recently "one pot" three component synthesis of α-amino phosphontes starting from aldehydes, amines and dialkyl or trialkylphosphites has been reported using various catalysts such as boric acid [16], silica sulfuric acid[17], oxalic acid[18], magnesium perchlorate [19], titanium dioxide [20], thamine hydrochloride (VB1) [21], zirconium (IV) compounds [22], ethyl ammonium nitrate (EAN) [15]. Synthesis of α-amino phosphonates through "one pot" three component reaction under solvent and catalyst free condition are reported in literature [23], along with this combination of catalyst and ultrasonication [21,24] or microwave [8,25] irradiation leads to strong acceleration.

We report the synthesis of α-amino phosphonates by conventional and nonconventional method.

Result and Discussion :

Imines(Schiff base) (Scheme 1) were synthesized by conventional and non-conventional way. Under the conventional condition the time and energy requirement was more with 58 to 63 % yield. To overcome these limitations we have tried to synthesis the compounds by using sonication technique. The reaction of 4-(pyrrolidin-1-yl)benzaldehyde(1) and anisaldehyde (2a) has been taken as model, so from table 1, it was observed that there was a effect on reaction and the yield is increase from 65 to 76 % with decrease in the time.

In scheme 2, α-amino phosphonates was synthesized by conventional way, again the same limitation of less yield, more time and energy requirement was observed, to overcome these limitation, we have tried to synthesis the compound by sonication technique in presence

of solvent (ethanol) and solvent free condition. (Table 2). It was observed that in presence of solvent, reaction take place in less time and give good yield, this is because of more solubility of imine in ethanol.

As observed from literature *Dake s. a. et al* [15], *Mandhane p. g. et al* [21], *Tibhe g. d. et al* [25], *Rao A. J. et al* [8] reported the one pot three component syntheses of α-amino phosphonates. So we extended the reaction towards this. In scheme 3, α-amino phosphonates were synthesized by one pot three component reaction by convention and non-conventional route. Reaction between 4-(pyrrolidin-1-yl)benzaldehyde(1) , anisaldehyde (2a) and triethylphosphite was taken as model. So from table 3, an observable ultrasound effect was seen on the reaction. There was increase in yield 60 to 75%. The scope of all the reaction was studied for both electron donating and electron withdrawing substituents in aromatic amine part.

In overall, time requirement and yield of product is much improved in case sonicated one pot synthesis.

Antimicrobial activity of synthesized compounds was taken against *Pseudomonas aeruginosa (ATCC27853), Staphylococcus aureus (ATCC 25923), E. Coli (ATCC 25922)* and *Candila sp.,* the results was mentioned in table 4, only 3a shows activity against *E. Coli (ATCC 25922)* .

Conclusion:

In all the scheme non-conventional method offer advantages over conventional methods. The one pot synthesis provide advantages viz. short time span, easy workup, good yield, no need of inorganic catalyst.

Spectral Data:

1-(4-(pyrrolidin-1-yl)phenyl)-N-(o-olyl)methanimine (3e):

H^1 NMR (400 MHz DMSO):ð 2.03(t, 4H, CH_2) ; 2.35(s, 3H Ar-CH_3) ; 3.36(t, 4H , N-CH_2) ; 6.59(d, 2H, *J*= 8.92Hz, Ar-H) ; 6.89-7.24 (m, 4H, Ar-H) ; 7.77 (d, 2H, *J*=8.12Hz, Ar-H) ; 8.19 (s, 1H, imine proton) ; Mass (m/z) : 265 (M+1).

N-(2-methoxyphenyl)-1-(4-(pyrrolidin-1-yl)phenyl)methanimine (3c):

H^1 NMR (400 MHz DMSO):ð 1.99 (t, 4H, CH_2) ; 3.33 (t, 4H, N-CH_2) ; 3.85(s, 3H, OCH_3) ; 6.55(d, 2H, *J*=8.8Hz, Ar-H) ; 6.89-7.13(m, 4H, Ar-H) ; 7.75-7.77 (m, 2H, Ar-H) ; 8.19(s, 1H, imine proton) ; Mass (m/z) : 281 (M+1).

Diethyl(((4-fluorophenyl)amino)(4-(pyrrolidin-1-yl)phenyl)methyl)phosphonate (4f) :-

H^1 NMR (400 MHz DMSO): ð 1.14 (t, 3H, -O-CH_2-$\underline{CH_3}$) ; 1.29 (t, 3H, -O-CH_2-$\underline{CH_3}$) ; 1.97 (t, 4H, -CH_2) ; 3.23 (t, 4H, N-CH_2) ; 3.62-3.72 (m, 3H, -O-$\underline{CH_2}$-CH_3) ; 3.88-4.15(m, 3H, -O-$\underline{CH_2}$-CH_3) ; 4.54 (d, 1H, NH) ; 4.59 (d, 1H, -NH-$\underline{CH}$-P=O) ; 6.49-6.55 (m, 4H, Ar-H) ; 6.49-6.55 (m, 4H, Ar-H) ; 6.76-6.80 (m, 2H, Ar-H) ; 7.24-7.27 (m, 2H, Ar-H); Mass (m/z) : 407(M+1).

Experimental Section:

Melting points were recorded by open capillary method and are uncorrected. Bandelinsoncrex (with a frequency of 40 kHz and power 110W) ulrasonic bath was used for ultrasonic irradiation. IR spectra were recorded in KBr disc on Shimadzu IR Affinity 1 spectrophotometer. H^1 NMR were recorded on a Varian As 400 MHz spectrophotometer in $CDCl_3$/ DMSO d_6, chemical shift are in ppm relative to TMS. Mass spectra were taken on a Macro mass Spectrometer (Waters) by electrospray method (Es).

General procedure for synthesis of imines 3a-3j:

Method A:

To a solution of 4-(pyrrolidin-1-yl)benzaldehyde(1) (0.010mole) in 50mL ethanol, various aromatic amines (2) (0.015 mole)was added. The reaction mixture was made acidic by adding 1-2 drops of glacial acetic acid and refluxed for appropriate time (table 1). After completion of reaction as indicated by TLC, hexane: ethyl acetate(8:2), the solvent was removed by rotary evaporator, the residue was recrystalised from ethanol to give compound 3a-3j.

Method B:

To a solution of 4-(pyrrolidin-1-yl)benzaldehyde(1) (0.010mole) in 50mL ethanol, various aromatic amines (2) (0.015 mole)was added. The reaction mixture was made acidic by adding 1-2 drops of glacial acetic acid. The resulting reaction mixture was sonicated at 50^0C for the appropriate time (table1). After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the solvent was removed by rotary evaporator, the residue was recrystallized from ethanol to give compound 3a-3j.

General procedure for synthesis of α-amino phosphonates 4a-4j:

Method C :

To a solution of imine (3a-3j) (0.001 mole), in 10mL ethanol, triethylphosphite (0.002 mole) was added, the reaction mixture was made acidic by adding 1 drop of glacial acetic acid and stirred at 50^0C for the appropriate time (Table 2). After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the reaction mixture was poured in 50gm crushed ice, the resulting mixture was made alkaline by saturated aqueous sodium bicarbonate to give crude product, which on recrystallization from ethanol gives 4a-4j.

Method D :

To a solution of imine (3a-3j) (0.001 mole), in 10mL ethanol, triethylphosphite (0.002 mole) was added, the reaction mixture was made acidic by adding 1 drop of glacial acetic acid and sonicated at room temperature for appropriate time (table 2).After completion of reaction as indicated by TLC, hexane: ethyl acetate(8:2), the reaction mixture was poured in 50gm crushed ice, the resulting mixture was made alkaline by saturated aqueous sodium bicarbonate to give crude product, which on recrystalisation from ethanol gives 4a-4j.

Method E :

A mixture of imine (3a-3j) (0.001 mole) and triethylphosphite (0.003 mole) was sonicated for the appropriate time (table 2). After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the reaction mixture was poured in 50gm crushed ice, the resulting mixture was made alkaline by saturated aqueous sodium bicarbonate to give crude product, which on recrystallization from ethanol gives 4a-4j.

General procedure for one pot three component synthesis of α-amino phosphonates 4a-4j:

Method F :

To a solution of 4-(pyrrolidin-1-yl)benzaldehyde(1) (0.010mole) in 50mL ethanol, various aromatic amines (2) (0.015 mole)was added. The reaction mixture was made acidic by adding 1-2 drops of glacial acetic acid and refluxed for 30minutes, then triethylphosphite (0.02 mole) was added and the reaction mixture was stirred at 50^0 C for the time period mention in table 3. After completion of reaction as indicated by TLC, hexane: ethyl acetate (8:2), the reaction mixture was poured in 50gm crushed ice, the resulting mixture was made alkaline by saturated aqueous sodium bicarbonate to give crude product, which on recrystalisation from ethanol gives 4a-4j.

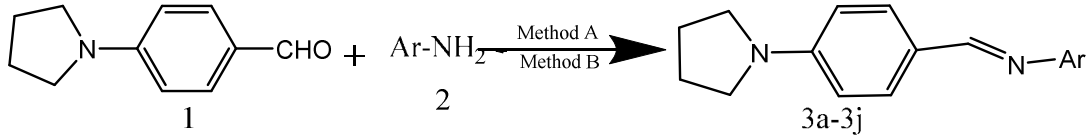
Method G:

To a solution of 4-(pyrrolidin-1-yl)benzaldehyde(1) (0.010mole) in 50mL ethanol, various aromatic amines (2) (0.015 mole)was added. The reaction mixture was made acidic by adding 1-2 drops of glacial acetic acid and sonicated at 50^0C for 15 minutes then triethylphosphite (0.02 mole) was added and the reaction mixture was sonicated for the mention time period (table 3). After completion of reaction as indicated by TLC, hexane: ethyl acetate(8:2), the reaction mixture was poured in crushed ice, the resulting mixture was made alkaline by saturated aqueous sodium bicarbonate to give crude product, which on recrystalisation from ethanol gives 4a-4j.

Antimicrobial activity:-

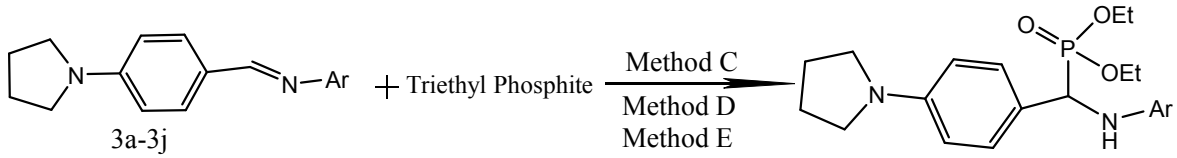
The compounds prepared were screened for antimicrobial activity against *Pseudomonas aeruginosa (ATCC27853), Staphylococcus aureus (ATCC 25923), E. Coli (ATCC 25922)* and *Candila sp.,* disc diffusion method. Each compounds was dissolved in DMSO to get concentration of 10mg/mL. Disc of Whatmann filter paper no41(6mm) were prepared , disc were placed on the surface of inoculated agar plate and 10µL of each dissolved compound was loaded on disc. The compound was allowed to diffuse for 10 minutes. DMSO was used as control. The petri dishes were incubated at 37^0C for 24 Hrs. Bioactivity was determined by measuring diameter of inhibition zone in mm.

Scheme 1



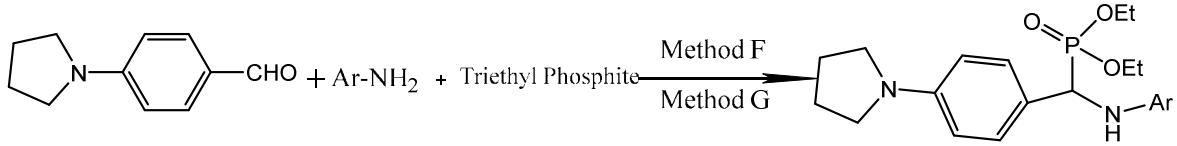
1 2 3a-3j

Scheme 2



3a-3j 4a-4j

Scheme 3



4a-4j

Table 1: synthesis of Schiff base (imine) 3a-3j

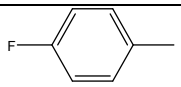
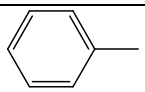
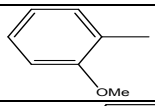
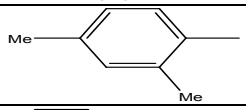
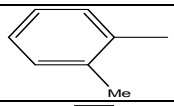
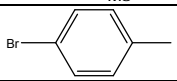
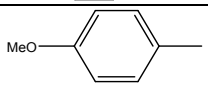
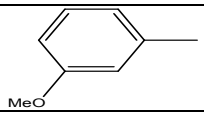
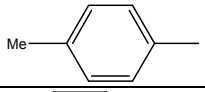
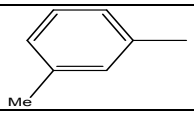
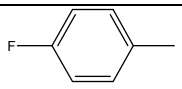
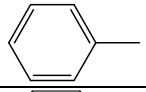
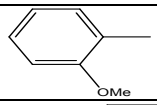
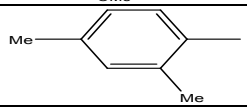
product	Ar	Time (min)		Yield %		M.Pt. ^{0}C
		Method A	Method B	Method A	Method B	
3a		180	100	63	76	150-151
3b		200	120	58	69	140-141
3c		220	110	61	70	117-118
3d		200	110	60	70	125-127
3e		240	130	59	72	98-100
3f		170	90	64	75	125-128
3g		210	120	61	74	120-121
3h		200	130	60	68	114-116
3i		220	110	58	65	119-120
3j		210	120	59	66	118-121

Table 2: synthesis of α-amino phosphonates 4a-4j from 3a-3j

product	Ar	Time (min)		Yield %			M.Pt. ^{0}C
		Method C	Method D and E	Method C	Method D	Method E	
4a		120	90	72	85	83	118-120
4b		140	100	68	80	76	135-138
4c		130	100	65	81	74	120-123
4d		140	110	68	83	79	118-121

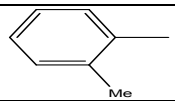
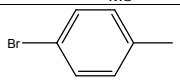
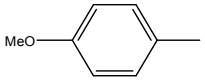
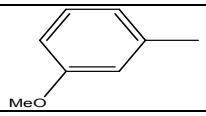
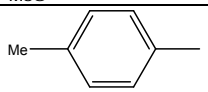
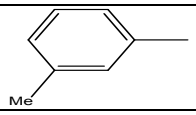
4e		150	110	65	80	72	102-104
4f		120	90	65	80	70	119-123
4g		150	120	63	82	70	129-130
4h		140	100	64	81	73	121-122
4i		140	110	62	80	71	127-130
4j		150	120	60	80	74	129-131

Table 3: one pot synthesis of aminophosphonates 4a-4j

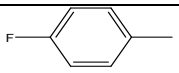
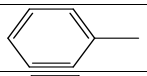
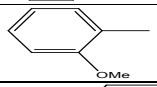
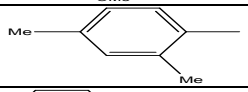
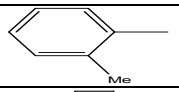
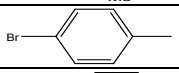
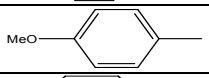
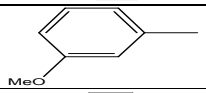
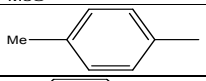
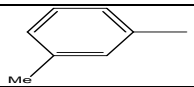
product	Ar	Time (min)		yield %	
		Method F	Method G	Method F	Method G
4a		180	100	65	80
4b		190	120	63	78
4c		200	120	64	75
4d		200	130	60	74
4e		210	130	61	75
4f		180	100	64	74
4g		200	110	60	75
4h		220	110	59	71
4i		240	130	64	70
4j		240	120	62	70

Table 4 : Anti-microbial evaluation of Synthesized compounds

Compounds	*Pseudomonas aeruginosa (ATCC27853)*	*Staphylococcus aureus (ATCC 25923)*	*E. Coli (ATCC 25922)*	*Candilasp*
3a	10mm	16mm	14mm	10mm
3b	10mm	--	--	--
3c	--	--	--	--
3d	--	--	--	12mm
3e	--	14mm	--	--
3f	12mm	10mm	10mm	--
3g	--	--	--	--
3h	10mm	10mm	12mm	10mm
3i	12mm	12mm	10mm	--
3j	14mm	10mm	12mm	--
Nystatin	--	--	--	23mm
Gentamycin	24mm	21mm	27mm	--

Compound 4a-4j does not give significant activity.

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