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Solid Phase Synthesis of Imines via Mechanochemistry and Screening for their Antifungal Activity

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ABSTRACT

Aim: To develop facile synthetic techniques for the preparation of imines, a series of imines were synthesized via mechanochemistry.

Introduction: Imines are important in biological and medicinal chemistry because along with anti-bacterial action they also exhibit anti-parasitic and anti-cancer properties.

Methodology: Present synthetic technique complies with principles of Green chemistry. During the screening of synthesized imines for their antifungal activity, some compounds showed better action against fungi when compared with standard.

Result: Herein imines were synthesized by implying mechanical force and were monitored and screened by spectroscopic techniques. Green chemistry pertains across the life span of chemical products which provides simple methods and highly efficient products with excellent yields in a shorter period.

Conclusion: Adopted mechanochemical technique found to be safer for a chemist, yields maximum yield without the use of catalysts. Such type of techniques provides certain advantages like Short reaction time, increased safety, economic.

Key Words: Schiff bases, Imines, Mechanochemistry, Organic solid phase synthesis, Green chemistry, Antifungal activity

INTRODUCTION

An amine is a nitrogen derivative of either ketone or aldehyde in which the acyl (c=o) group is reformed as the imine (C=N-R) group.[2] It is generally formed by condensation of ketone or an aldehyde with a primary amine. Imines that possess aryl substituents are significantly stable and more readily synthesized as compared to alkyl substituents, which is relatively unstable. Aromatic Schiff bases are effective conjugation and are more stable.[1]

Schiff bases formation is a very important reaction in biological chemistry as they play an imperative role in living organisms such as decarboxylation, transamination and C-C bond cleavage. Hence, they are used in the biosynthesis of hormones, neurotransmitters and pigments. Schiff bases containing contributor atoms can take part in the chilation of the transition of metal ions. Schiff bases are widely studied and research of this compound imparts the following properties: anti-parasitic, bactericidal and anticancer agents.

Green chemistry is the design of compound products and processes that trim down or eliminate the use or generation of harmful substances. Green chemistry is also recognized as sustainable chemistry. Green chemistry applies across the life span of chemical products, including its blueprint, manufacturing, use and ultimate disposal[3]. It provides certain advantages like Short reaction time, increased safety, economic and prevention of pollution.

This is the primary cause for the rediscovery of mechanochemistry. Mechanochemistry is a division of chemical and physiochemical changes of substances of all states of agglomeration due to the influences of mechanical energy such as milling, grinding, shearing and scratching. [4,6]

The novel, high performance, low-cost materials and faster decomposition of synthesis are reasons for the burgeoning of mechanochemistry subject[7]. It is used for the manufacturing of intermetallic products and alloys in metallurgy, amalgamated and complex oxides for materials, nanocrystalline

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substances, for production of fertilizers, building materials, pigments, etc. and hence it is the topic of choice of researchers for the synthesis of organic molecules.[5,8]

MATERIALS AND METHODS-

All the required chemicals and reagents were acquired from commercial sources (SD Fine Chemicals, India; Aldrich, United States; Merck; Germany) and used without purification. Solvents incorporated in the work were freshly distilled and used. The purification of products was performed by recrystallization with a suitable solvent system. For induction of mechanical force- mortal pestle and Coslab made mechanical mill was used. Melting points was determined on Equip-Tronics EQ 730 Digital Melting Point apparatus. Spectra of IR have been recorded on Perkin Elmer (Spectrum Two) FTIR spectrophotometer. The purity of the product was checked using the TLC technique; spots were developed by exposure to iodine vapours and UV cabinets. Ultraviolet spectra were taken on Agilent Technologies Cary 60UV-Vis Spectrophotometer. Mass spectra were recorded in the QP-2010 PLUS GC-MS system. Nuclear Magnetic Resonance spectra were recorded with AVANCE 300MHz, using $CDCl_3$

Experimental

All the synthetic procedures were performed by grinding together 10 mmol of the pure primary amine with 10 mmol of the pure substituted aldehyde in a mortar and mechanical ball mill room temperature (Scheme 1-5).[12-14] Some mixtures liquefied intermediately on mixing, but most of these could be run without melting at lower temperatures.[9] The completion of the reactions was checked by a permanent change in colour of the product and confirmed by TLC, generally, it changes from white to yellow/ orange. (Product of schemes 2 and 3 were kept further at room temperature in dark for 24hr. to ensure the proper uniform colour appearance of the product.) The water produced in the reaction was removed at 80 ^{0}C under a vacuum and recrystallized with a suitable solvent. The TLC was carried out by using combinations of mobile phases, reported in table 3(Reaction Parameters). The percentage yield was reported in table 1(Physiochemical and analytical characterization of synthesized compounds). Chemical analysis was carried out by IR and NMR spectroscopy which gave the expected peaks and signals. Thin-layer chromatography and comparison of melting points with literature data confirmed the purity of the products.

Biological activity studies- antifungal activity.[10,11]

The antifungal activity was performed by using the cup plate method. By pouring 10-15 ml of the base layer medium into each sterilized petri-dish, the bottom layer was obtained and was kept at room temperature. The subculture which is over nightly grown was mixed with seed layer medium, about 10-15 ml, was transferred over the base layer and again allowed to attain room temperature.

The cups for the study were made by cork borer. After the addition of test compounds solutions (Scheme 1-5) to the cups, plates were incubated at 37^{0}C for 48 hours. Inhibitory action was measured in mm, repeated three times to confirm the findings and the average of the readings was taken into consideration and reported as the mean of readings in table 4. (Biological screening for antifungal activity of synthesized Imine compounds)

The two fungi, C. Albicans and A.niger were collected and used in the fungicidal bioassays, using 100 µg/ml and 150 µg/ml concentrations of each imines (Scheme 1-5) using Fluconazole as reference standard and dimethylformamide (DMF) as a control for the activity. All the compounds show moderate inhibitory activity, the data of antifungal screening is given in Table 4(Biological screening for antifungal activity of synthesized Imine compounds.).

RESULT AND DISCUSSION

A Novel series of imines were synthesized using a nonconventional method i.e. Mechanochemistry. Selected aromatic primary amines were ground or milled with corresponding aromatic aldehydes and ketones with constant rpm at room temperature, finally at a definite time; the colour of reactant changes from original to else.

Spectroscopic data reveals that the imines show stretching bands of Ar-H, C-N at the region of 3500-3200 and 2985-2833.24 cm^{-1} respectively. The 1H NMR spectra showed in each case the signal at δ= 7.94-7.17 ppm attributes to aromatic protons and at δ= 4.62-4.57 ppm due to ch3 proton. Besides this C13 NMR spectra are shown in each case of carbon of C=O and C=N at δ=201.11-180.85, and 155.28-174.94 ppm. The aromatic and CH2 carbon resonated at δ=163.93-112.86 and 56.69-44.35 ppm respectively. Spectral characteristics of synthesized compounds were summarized in table 2 (Spectral characteristics of the synthesized compound). The elemental (C, H, N, O) analyses were found within the limit of theoretical values, reported in table 1. The synthesized compound complies with the spectroscopic studies. Among the different reactants used in synthesis, scheme 2 shows maximum yield with a short duration of the reaction. Other compound yields more than the traditional route of synthesis in slighter time.

Among synthesized compounds 4-({(1Z)-[4(dimethylamino) phenyl]methylene}amino)benzoic acid shows better fungicidal action compared with a standard against C. Albicans species, while 4-{[(1E)-(4-hydroxy-3methyoxyphenyl) methylene]amino}benzoic acid shows improved action against both i.e. C. Albicans and A. Niger. Other all synthe-

sized compounds (scheme 3-5) shows comparative antifungal action.

CONCLUSION

The result obtained directed that herein reported methods are more convenient and reactions can be carried out in superior yield, shorter reaction period and gentle conditions and safer to the analyst, Compared with conventional techniques. Herein developed green procedure can be adopted for other organic or medicinal synthesis. The synthesized compound exhibit superior fungicidal action against C. Albicans and A. Niger

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Individual author's contribution:

1. Bendale Atul R.: Planning and conceived of the presented idea
2. Sethiya Jigar: Developed the theory and performed the reactions
3. Narkhede Sushil P.: Contributed to the interpretation of the results
4. Jadhav Anil G.: Directed the project
   All authors discussed the results and contributed to the final manuscript

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Table 1: Physiochemical and analytical characterisation of synthesized compounds.(Scheme 1-5)

Scheme no.	Empirical formula	Molecular weigh	MP., oC	Yield, %	Calculated, %			
					C	H	O	N
1	$C_{15}H_{13}NO_4$	271.27	152-154	93.72	66.41	4.83	23.59	5.16
2	$C_{16}H_{16}N_2O_2$	268.31	149-151	95.31	71.62	6.01	11.93	10.44
3	$C_{21}H_{15}NO_3$	329.34	175-177	91.07	76.58	4.59	14.57	4.25
4	$C_{17}H_{17}NO_4$	299.32	165-167	83.33	68.21	5.72	21.38	4.68
5	$C_{18}H_{20}N_2O_2$	296.36	162-164	81.87	72.95	6.80	10.80	9.45

Table 2: Spectral characteristics of synthesized compound. (Scheme 1-5)

Scheme no.	FT-IR, v,cm^{-1}	^{1}H-NMR ($CDCl_3$), δ ppm	M/e
1	1616.24 (C=N), 3068 (Ar-H), 3436.4 (O-H), 1618.0(C=O), 1572.4(O-C), 1498.9 (Ar-C),	6.81 - 7.82 (m, 12H), 8.49 (s, 1H), 11.61 (s, 1 H); 201.11-180.85 (C=O),163-112.86(CH_2)	269.084 (0.061), 271.084 (100), 272.081(8.36533), 272.088 (16.22359) 272.089 (15.237), 272.091 (0.14952)

Table 2: *(Continued)*

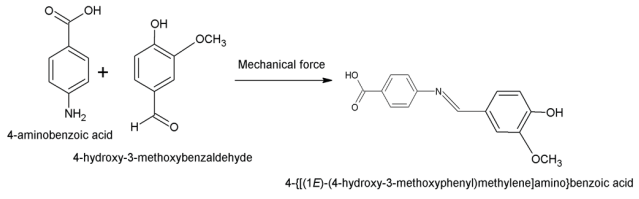
2	1614.09 (C=O), 3070.6 (Ar-H), 1620.0 (C=N), 3265 (N),3127.9 (O-H)	2.65 (s, 3H), 6.90 -7.85 (m, 8H), 8.66 (s, 1H), 13.01 (s, 1H); 13C, 168.1937(C=O)	231.6 (0.765), 266.121 (0.63), 268.23 (100), 270.39(18.40)
3	1731 (C=O), 1614.31 (C=N), 3384.84 (O-H), 3035 (Ar-H)	6.41 - 7.68 (m, 8H), 8.84 (s, 1H), 10.25 (s, 1H), 10.70 (s, 1H);186.76(C=O)	302.82(0.965), 327.105 (0.310), 329.1(100), 330.109 (22.82), 331.11 (2.45)
4	1591 Ar- C=N, 3439.7(O-H), 3068.2 (Ar-OH), 1620.0 (C=O), 1488.6 (Ar-C), ;	7.78-7.68(m, 2H, Ar-H), 10.67(s, 1H, NH) 194.325(C=O)	279.23(0.56), 297.11(0.29), 299.11 (100), 300.19 (18.38), 301.12 (1.59)
5	3035.75 (Ar-OH),3383.32(O-H), 1681.82(C=O),1741.02(C=N), 2941.24 (CH_2)	205.34(C=O),7.27 - 7.93 (m, 12H), 9.73 (s, 1H), 12.18 (s, 1 H);	291.52 (0.219), 294.152 (0.65), 297.152(100), 297.156 (19.46), 298.19 (1.789)

Table 3: Reaction Parameters

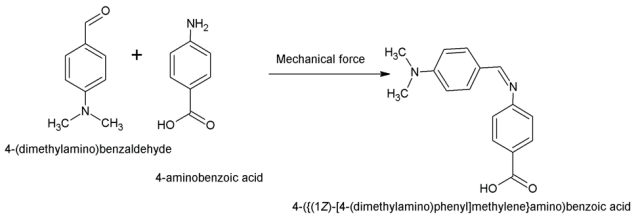
Scheme	Grinding time (min)	Mobile phase	Rf Value	Colour of product
1	12	Benzene : Ethyl Acetate (70 : 30)	0.68	Pale yellow
2	9	Benzene : Ethyl Acetate (70 : 30)	0.60	orange
3	15	Benzene : Ethyl Acetate (70 : 30)	0.55	Yellow
4	20	Chloroform : Methanol : Acetic Acid (90 : 10 : 1)	0.74	Orange to brown
5	20	Chloroform : Methanol : Ethyl Acetate (70 : 20 : 10)	0.72	Yellow

Table 4: Biological screening for antifungal activity of synthesized Imine compounds.

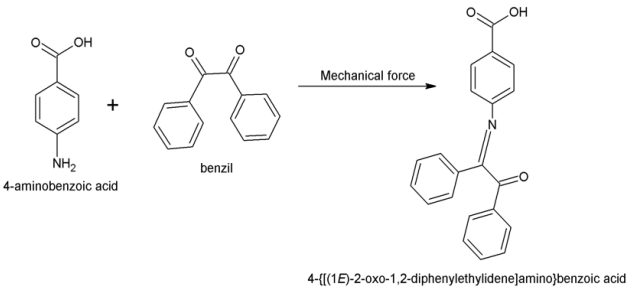
Compound	Bacteria and fungi along with zone of inhibition(mm)	
	C. Albicans	A. Niger
Scheme 1	19.5	18.2
Scheme 2	20.1	17.2
Scheme 3	16.7	16.4
Scheme 4	17.8	17.5
Scheme 5	17.5	17.0
Std. Fluconazole	19.2	17.7



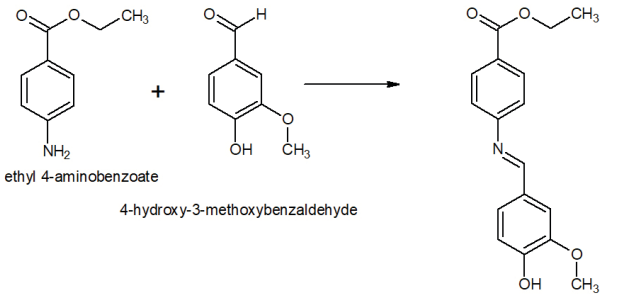
Scheme 1: Synthesis of 4-{[(1E)-(4-hydroxy-3methyoxyphenyl)methylene]amino}benzoic acid.



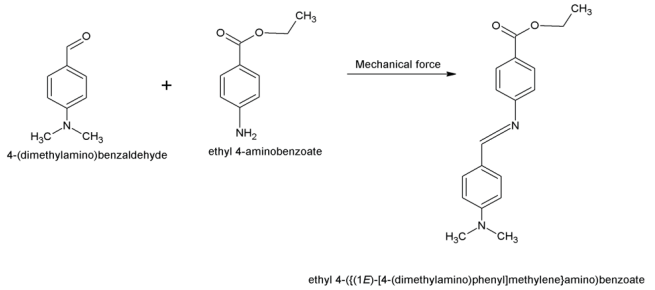
Scheme 2: Synthesis of 4-({(1Z)-[4(dimethylamino)phenyl] methylene}amino)benzoic acid.



Scheme 3: Synthesis of 4{[(1E)-2-oxo1,2-diphenylethylidene] amino}benzoic acid.



Scheme 4: Synthesis of ethyl 4-{[(1E)-(4-hydroxy-3meth0xy-phenyl) methylene] amino} benzoate.



Scheme 5: Synthesis of ethyl4-({(1E)-[4(dimethylamino)phenyl]methylene}amino)benzoate.