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Greener acrylonitrile and bis-acrylonitrile synthesis by Knoevenagel condensation using ecofriendly catalyst

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Abstract: Acrylonitrile nucleus bearing heterocyclic compounds are present in various biologically active natural products and drugs. Various attempts made for the synthesis of acrylonitrile derivatives which exhibit biological activities like anticancer, antidepressant, anti arrhythmic agent, antifungal, uricosuric, vasodialator. Aqueous catalysis is an innovative task for the sustainable chemical industry. The use of bio-degradable catalysts from natural sources may lead to greener reactions. Herewith we described a greener route for the synthesis of a series of novel acrylonitrile derivatives employing a highly efficient and ecof-riendly Bael Fruit Extract(BFE) as a catalyst. This methodology offers diverse advantages such as mild reaction conditions, short reaction time, excellent yields, and operational simplicity that make it a useful and attractive option for the synthesis of the acrylonitrile derivatives by Knoevenagel condensation. The structures of synthesized novel acrylonitrile derivatives were deduced by their ^{1}H NMR, ^{13}CNMR, IR and mass spectra.

Keywords: Heterocyclic compounds, Acrylonitrile derivatives, Knoevenagel condensation, Pyri-dazine

Introduction

The majority of chemical operations relied on molecular solvents. Because of their widespread usage in the chemical industry and laboratories, molecular solvents may pollute the environment and harm organism and human health. To limit the generation of chemical waste, hazardous solvents and catalysts must be avoided. As people's awareness of the need for a cleaner environment grows, one of the most immediate concerns today is the development of non-hazardous synthetic techniques for organic transformations. In order to meet the requirements of a safe environment, the use of toxic chemicals and hazardous waste should be reduced using greener, more sustainable, at the same time more efficient, eco-friendly and inexpensive approaches[1]. One can achieve pure products with good yield by shifting to new procedures and eliminating the usage

of harmful materials and toxic solvents. To prevent the production of harmful byproducts, certain criteria should be taken into account while building new methods, including the use of acceptable reaction media, the conversion of all materials into products, the minimizing of energy requirements, and the use of renewable raw materials[2]. Various natural materials are used as solid supports as well as catalysts in a wide range of reactions that promote the formation of final products. Natural materials like clay, zeolites, enzymes and various plant materials like leaves, fruits and roots are used effectively in a variety of chemical transformations[3-4].

Nature has a wide variety of plants that are possessed with a number of chemical constituents that are both biologically and medicinally significant. Plant parts such as fruits, leaves, and roots have received increased attention due to their extensive use as effective medicines[5]. Researchers are attempting to use these significant characteristics of natural plants while developing new methods for organic transformations that can make the processes eco-friendly and meet the requirements for greener chemistry. In comparison to conventional methods, organic synthetic transformations using these natural materials have been found to be competent and characterized by simple workup, non-toxicity, less waste production and pure products. The use of constituents derived from natural resources has paved the way for the development of new eco-friendly and cost-effective methodologies. These processes are distinguished by simple workup, cleaner procedures and non-toxic waste materials, all of which meet the requirements for greener methods.

Acrylonitrile derivatives are important class of organic compounds with wide range of biological activities. Many of these molecules have antiproliferative[6], antifungal[7], antibacterial[8], antitubercular[9], antioxidative[10] properties. The structural framework of a number of significant drugs includes an acrylonitrile moiety. Some representative examples are given in figure1. Wittig[11] and Heck[12] reactions have previously been used to produce acrylonitrile derivatives. The Knoevenagel reaction is a simple and convenient method for synthesize acrylonitrile derivatives[13-14]. This reaction can be carried out utilizing a variety of catalysts like ionic liquids,15 organocatalysts,[16-18] nanocatalysts. MOFs [19-, 21] as well as metal catalysts [22,23] and silica supported acid catalyst[24.]

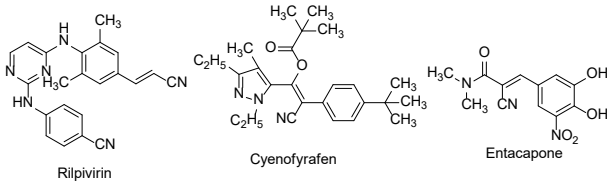

Figure 1

Results and discussion

Optimization Studies

Here, we describe an effective approach for synthesizing acrylonitrile derivatives at room temperature by using BFE as a catalyst. A model reaction of 4,4'-(pyridazine-3,6-diylbis(oxy) dibenzaldehyde (1 mmol) and malononitrile (2 mmol) using 3 mL BFE as the catalyst at room temperature was carried out in the presence of various organic solvents and the results are shown in Table 1. After two hours in aqueous medium, just 56% of the anticipated product was generated (Entry 1). When DCM or acetonitrile were used as the solvent, the reaction could not progress efficiently, and even an hour later, the yield remained poor (Entry 2, 3). Two polar protic solvents, ethanol and methanol, were shown to be efficient solvents for the synthesis. In the solvent methanol, product formed in 0.5 hours with a yield of 72% (entry 4), and in the solvent ethanol, a yield of 78% was attained (Entry5). However, there was a considerable improvement in the conversion of reactants into product after 30 minutes when ethanol and water were used as the solvent, with a product yield of 86% (Entry 6).

Table 1: Optimization of reaction conditions for the synthesis of bis acrylonitrile derivative[a]

Entry	Solvent	Time (min)	Yield (%)
1	H_2O	120	56
2	CH_2Cl_2	60	35
3	CH_3CN	60	48
4	CH_3OH	30	72
5	C_2H_5OH	30	78
6	**C_2H_5OH: H_2O**	**30**	**86**

[a]Conditions: 4,4'-(pyridazine-3,6-diylbis(oxy) dibenzaldehyde (1mmol), malononitrile (2 mmol), BFE (3 mL), solvent (3mL) at room temperature.

To assess the generality of this model reaction, we synthesized a number of acrylonitrile and bisacrylonitrile derivatives by reacting various active methylene compounds with various pyridazine-bearing aromatic aldehydes under optimum reaction conditions in the presence of the BFE as catalyst. The results are presented in Tables 2.

[a]Condition: Substituted aldehyde (1 mmol), active methylene compound (1 or 2 mmol), EtOH:H_2O (5 mL), BFE (3mL) at room temperature condition. b Isolated Yield.

Conclusion

We have used an environmentally benign method for the synthesis of acrylonitrile and bis acrylonitrile derivatives using BFE as a catalyst in ethanol water mixture at room temperature. High yield, simple work up procedure, efficient catalyst obtained from renewable resources and a short reaction time are some of the advantage of the present method.

Acknowledgement

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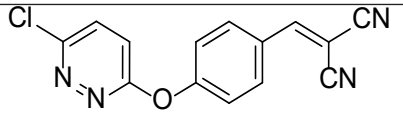
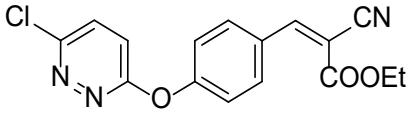
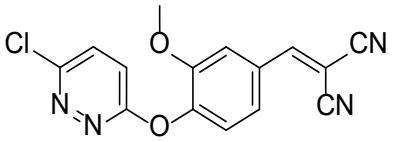
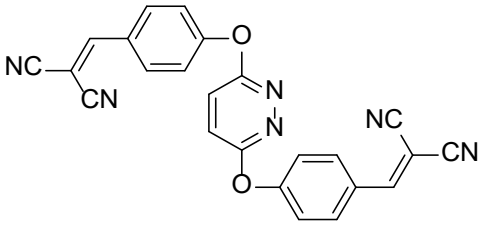
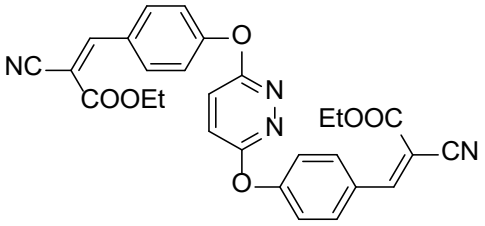
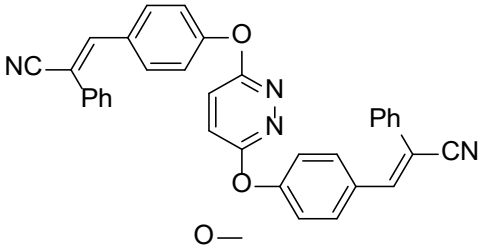
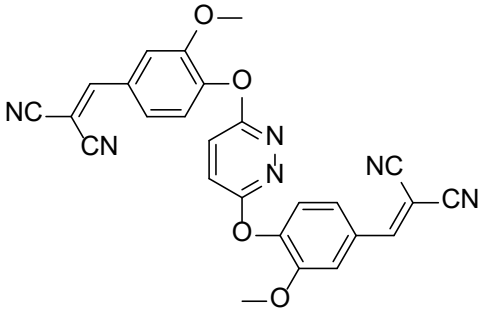
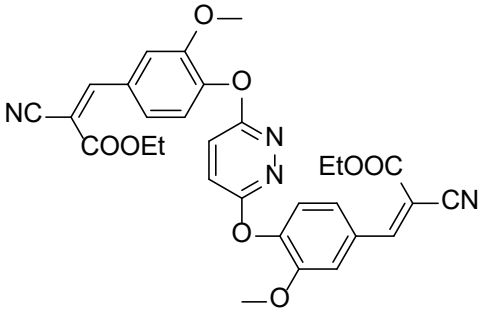
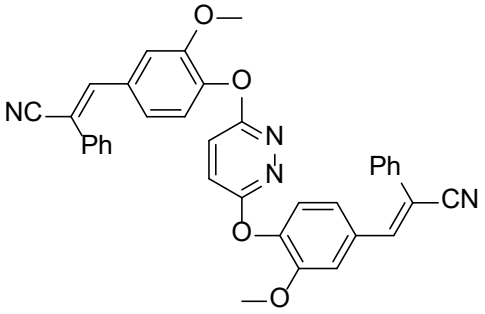
Materials and Methods

Table 2: Synthesis of acrylonitrile derivatives using BFE[a].

Entry	Product	Time	Yield (%)	M.P. (^{0}C)
4a		22	88	113-115
4b		27	83	130-132
4c		25	83	126-128
5a		40	85	182-190

5b		45	78	209-2011
5c		48	75	220-222
5d		45	80	210-212
5f		48	78	190-192
5g		50	75	225-227

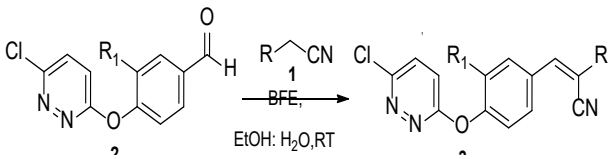
Experimental:

All the reagents were acquired from Spectrochem or Aldrich chemicals and did not further purified. Determined melting points are not corrected. ^{1}HNMR and ^{13}C NMR spectra were recorded on a Bruker Avance III Hd 500 MHz spectroophotometer**.** The Brucker (Impact II UHR-TOF) mass spectrometer was used to record the mass spectra. IR spectra were recorded on a Perkin Elmer spectrophotometer.

Method of Synthesis

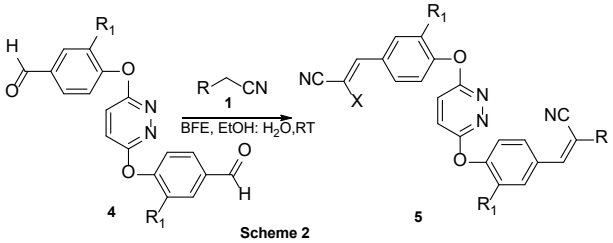
Synthesis of acrylonitrile derivatives : A

mixture of aromatic aldehyde (1 mmol) and active methylene compound (1 mmol) was stirred in 1:1 water: ethanol mixture (5 mL) in the presence of BFE (3 mL) at room temperature for an appropriate period of time (Table 2). After completion of reaction, product was separated (the reaction mass treated with water and filtered) and purified by recrystallization from ethylacetate to afford the corresponding acrylonitriles.



Synthesis of bis-acrylonitrile derivatives :

A mixture of aromatic bis-aldehyde (1 mmol) and active methylene compound (2 mmol) was stirred in 1:1 water: ethanol mixture (5 mL) in the presence of BFE (3 mL) at room temperature for an appropriate period of time (Table 2). After completion of reaction, product was separated (the reaction mass treated with water and filtered) and purified by recrystallization from ethylacetate to afford the corresponding bisacrylonitrile derivatives.



Scheme 2

General procedure for synthesis of catalyst:

The rind of bael fruits was obtained from the local area for this study. The dry rinds (100 g) were washed and dried in an oven. The dried rinds were broken into small pieces and thermally heated for 2 hours at 900 ^{0}C to produce white soft ash (4.8 g). The resulting ash was stirred in 25 mL of water for 1 hour. The mixture was then filtered to obtain a clear BFE extract.

Characterization: Synthesized acrylonitrile derivatives are characterized by ^{1}HNMR, ^{13}CNMR, IR and mass spectroscopic technique. Compound (4b) of the series is taken as the representative compound. In the ^{1}H NMR spectrum the characteristic signals due to each proton and functional groups with protons are well described on the basis of shielding and deshielding effect. From the ^{1}HNMR spectra it shows that the aromatic protons are comes in the region of 7.3-8.3 δppm in downfield region where as the methylene protons of ethoxy group attached to oxygen atoms is appear at 4.40 δppm. Absence of signal near 9.9 indicative absence of aldehyde proton. Vinylic proton is comes at 8.24 δppm. In the IR spectrum of compound, the band at 1723 & 2227 cm^{-1} shows CO of ester group & CN stretching respectively. All these spectrum data indicate formation of acrylonitrile derivative.

Ethyl 3-(4-((6-chloropyridazine-3-yl) oxy) phenyl)-2-cyanoacrylate (4b)

IR (ν max, cm^{-1}): 3064, 2223,1723,1593,1408, 841 ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H, CH), 8.08 (d, 2H, ArH), 7.57 (d, 1H, ArH), 7.36 (d, 2H, ArH), 7.25 (d, 1H, ArH), 4.40 (q, 2H, CH_2),1.41(t, 3H, CH_3) ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.32, 162.50, 156.76, 153.69, 152.96, 133.06, 131.94, 128.71, 121.73, 120.55, 115.53, 102.64, 62.82, 14.19 HRMS: m/z 330.0678 $(M+H)^+$.

2-(4-((6-chloropyridazine-3-yl) oxy)-3-methoxybenzylidene) malononitrile (4c)

IR (ν max, cm−1): 3060,2227,1573,1460, 850 ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H, CH), 7.73 (d, 1H, ArH), 7.54 (d, 1H, ArH), 7.44 (dd, 1H, ArH), 7.34 (d, 1H, ArH), 7.27 (d, 1H, ArH),

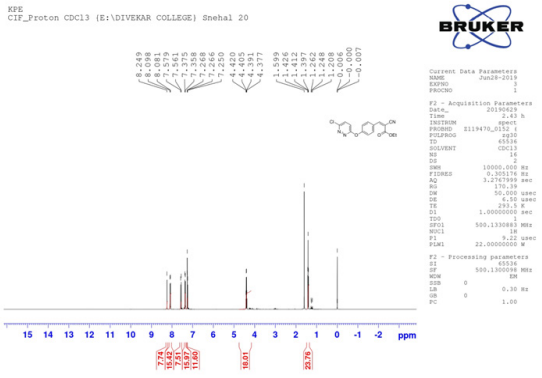
3.81 (s, 3H, CH_3) ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.06, 158.99, 152.66, 151.87, 146.89, 131.80, 129.47, 126.06, 123.61, 119.63, 113.68, 112.88, 82.51, 56.12 HRMS: m/z 313.0556 $(M+H)^+$.

2, 2'-(((pyridazine-3,6-diylbis(oxy)) bis(4,1-phenylene))bis(methanylylidene)) dimalononitrile (5a)

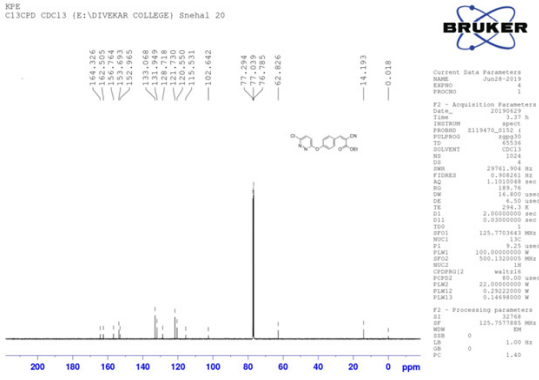
IR (ν max, cm^{-1}): 3062,2225,1570,1460, 852 ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (s, 2H, CH), 7.68 (d, 4H, ArH), 7.42 (d, 4H, ArH), 7.08 (d, 2H, ArH) ^{13}C-NMR (125 MHz, $CDCl_3$): δ 162.08, 161.86, 155.65, 130.54, 128.69, 120.72, 119.32, 114.16, 80.52 HRMS: m/z 417.7720 $(M+H)^+$.

2,2'-(((pyridazine-3,6-diylbis(oxy)) bis(3-methoxy-4,1-phenylene))bis (methanylylidene)) dimalononitrile (5d)

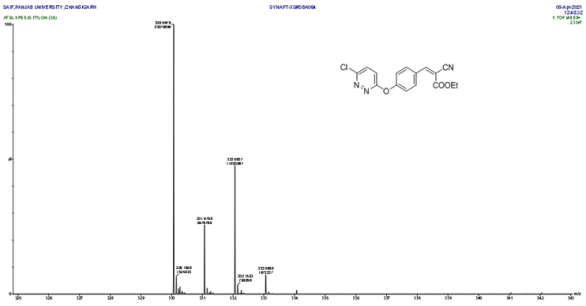
IR (ν max, cm^{-1}): 3066,2220,1570,1402,854 ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 2H, CH), 7.70 (d, 2H, ArH), 7.40 (dd, 2H,ArH), 7.31 (d, 2H,ArH), 7.10 (d, 2H,ArH), 3.83 (s, 6H, OCH_3) ^{13}C-NMR (125 MHz, $CDCl_3$): 160.08, 151.62, 150.87, 147.70, 128.54, 125.18, 123.58, 120.60, 113.72, 111.70, 82.40, 55.22 HRMS: m/z 477.5620 $(M+H)^+$.



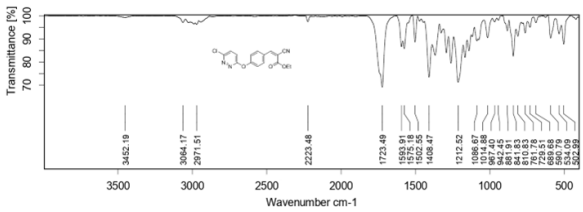
^{1}HNMR spectra of compound 3b



^{13}CNMR spectra of compound 3b



Mass spectra of compound 3b



Mass spectra of compound 3b

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