Research Article

Microwave Assisted Synthesis and Antituberculosis Activities of some Novel Heteroarylidene Nitriles by Knoevenagel Condensation

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ABSTRACT

An operationally/efficient simple route for preparation of biologically active 3-(heteroaryl)-2-(aryl) prop-2-ene nitrile and 2-(heteroaryl)-2-yl methylene-malononitrile derivatives has been reported. The target compounds were characterized by IR, NMR and MASS. There *in-vitro* antituberculosis activity was evaluated by Microplate Alamar Blue Assay (MABA). All the target compounds exhibited good activities against tuberculosis species. The manuscript entails a diverse library of some novel Knoevenagel condensation products. The products serve as precursors for preparation of several multifunctionalized pharmacophores.

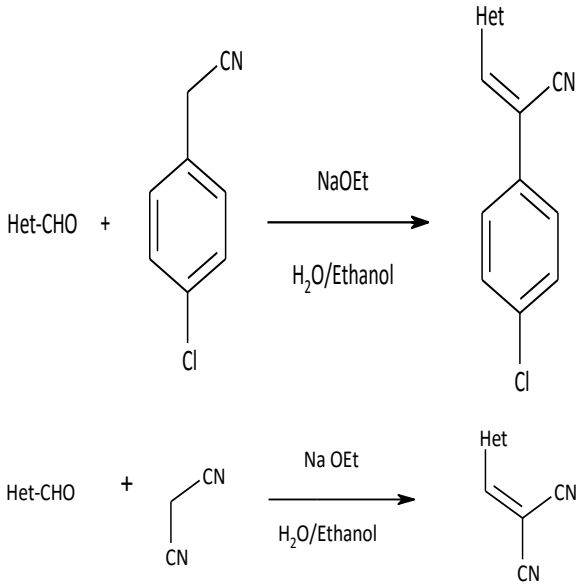
Keywords: Knoevenagel condensation, 3-(heteroaryl)-2-(aryl) prop-2-enenitriles**,** 2-(heteroaryl)-2-yl methylene-malononitrile derivatives, antituberculosic activity.

INTRODUCTION

Organic reactions under solvent-free[1,2] and aqueous[3-5] conditions have increasingly attracted chemists' interests, particularly from the viewpoint of green chemistry.[6-8] As an important carbon-carbon bond forming reaction, Knoevenagel condensation has been extensively studied. The efficient preparation of heterocycles is an important field of synthetic organic chemistry since most heterocycles exhibit biological activities and are therefore of great interest for the development of new drugs, diagnostics, and agrochemicals.

Over the past decade, Knoevenagel condensation has captivated research community by providing admirable contribution as a peculiar precursor for delving out diverse molecular entities. In accordance with this view, a simple, efficient, and practical method is being reported for the Knoevenagel condensation between active methylene compounds with heteroaromatic aldehydes in excellent yields using water as a solvent.[9-13] The Knoevenagel condensation is one of the most important, significant and widely used methods for the formation of carbon-carbon bonds.[14,17] The structurally simple compound produced after the Knoevenagel condensation between the several active methylenes and the aldehydes has accessed wide array of biological applications. The present concern for the environment demands the development of environmentally benign and economic processes in organic synthesis, wherein even less hazardous byproducts are not desirable.

In our continued interest, the Knoevenagel condensations and its applications in the synthesis of biologically active heterocyclic compounds, we expect that the synthesized products will be of significant biological activity, a high speed and very simple method for the condensation of various heteroaromatic aldehydes with 4-chloro benzyl cyanide or malononitrile, in mixture of water and ethanol at 50-60°C temperature (Scheme-1).



Scheme-1

MATERIALS AND METHODS

The reagent grade chemicals were obtained from commercial sources and used without further purification. Purity of synthesized compounds has been checked by thin layer chromatography.

Melting points were determined by open capillary method and are uncorrected.

Infrared spectra were recorded as on a Perkin-Elmer FTIR spectrometer and results are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra was recorded on Bruker avon 300MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are expressed as δ values (ppm).

Experimental Procedure

General procedure for the Knoevenagel condensation of Heteroaldehydes with Phenyl Acetonitrile and Malononitrile

In a clean round bottomed flask, a mixture of 4-Cl benzyl cyanide or malononitrile (1mmol) and heteroaryl aldehyde (1mmol) was stirred in presence of catalytic amount of sodium ethoxide by using water as a solvent at room temperature till the completion of reaction as monitored by TLC. The crude product was filtered off, washed with water. The solid was dried and recrystallized from ethanol to obtain desired product in purest form.

Spectral data of selected compounds

2-(4-Chlorophenyl)-3-(thiophen-2-yl) prop-2-enenitrile (1)

IR (KBr) ν_{max}:. 3083, 3035, 2205, 1898, 1486 cm^{-1};

^{1}H NMR ($CDCl_3$, 300 MHz): δ7.14-7.26(m,1H), 7.37-7.384(d,2H),7.389-7.412(m,1H),7.549-7.555(d,2H), 7.571-7.583(m,1H),7.630-7.669(m,1H)ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 107.18, 117.95, 127.02, 128.07, 129.43, 130.58, 132.56, 132.87, 134.60, 135.07, 137.83 ppm.

2-(4-chlorophenyl)-3-(furan-2-yl) prop-2-enenitrile (2)

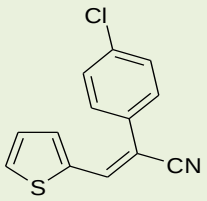
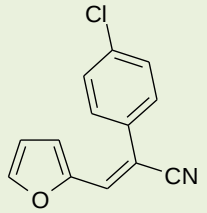
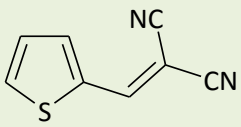
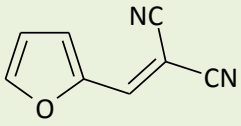
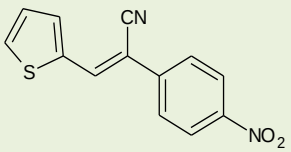
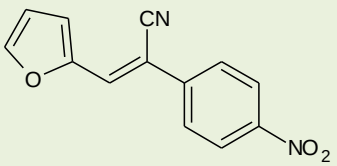
IR (KBr) ν_{max}:. 3100, 3022, 2221, 1670, 1404, 1318, 1231 cm^{-1}.

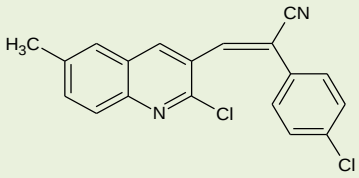
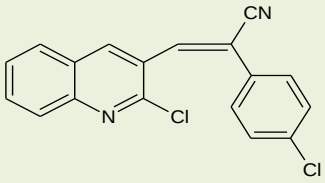
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.263-7.286(t, 1H), 7.809-7.818(d,1H,), 7.877-7.891(d, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ 126.48, 129.15, 132.06, 138.58, 139.30, 156.74 ppm.

The following table represents the list of synthesized 3-(heteroaryl)-2-(aryl) prop-2-enenitriles, 2-(heteroaryl)-2-yl methylene-malononitrile derivatives and their physical data.

Table 1: Physical Data of Synthesized Compounds

Entry	Product	Mol. Formula	Time in seconds	Colour	Yield (%)
1.		$C_{13}H_8ClNS$	10	Dark Orange	90
2.		$C_{13}H_8ClNO$	15	Dark Brown	80
3.		$C_8H_4N_2S$	10	Pale Yellow	90
4.		$C_8H_4N_2O$	20	Dark Orange	85
5.		$C_{13}H_8N_2O_2S$	20	Yellow orange	91
6.		$C_{13}H_8N_2O_3$	35	Dark Brown	80

7.		$C_{19}H_{12}Cl_2N_2$	30	Pale Yellow	90
8.		$C_{18}H_{10}Cl_2N_3$	25	Yellow orange	90

Anti-TB Results

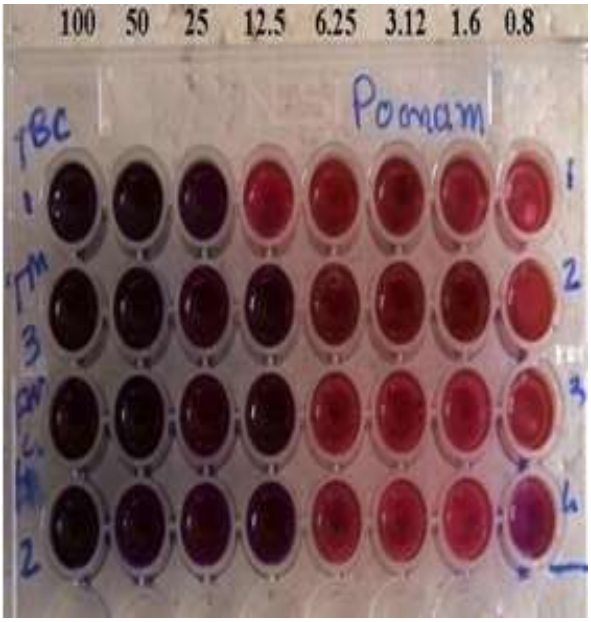
S. No.	Samples	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1	TBC-1	S	S	S	R	R	R	R	R
2	TM-3	S	S	S	S	R	R	R	R
3	FM-4	S	S	S	S	R	R	R	R
4	FBC-2	S	S	S	S	R	R	R	R

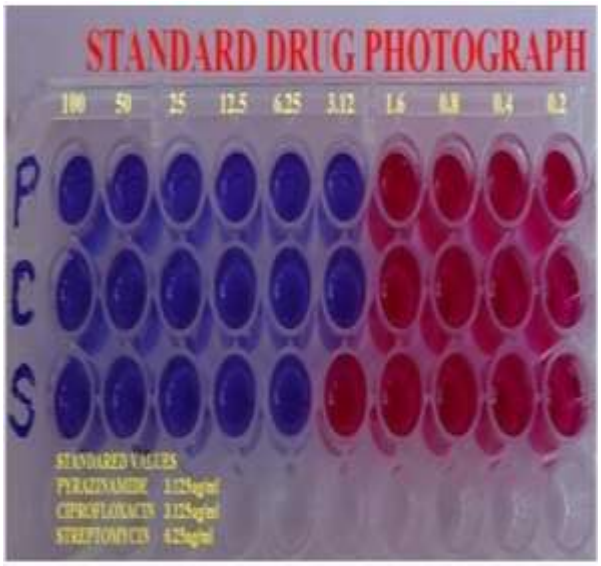
Anti-TB activity study using Alamar Blue Dye

1) The anti mycobacterial activity of compounds were assessed against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA).
2) This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with propotional and BACTEC radiometric method.
3) Briefly, 200µl of sterile deionzed water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation.
4) The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate.
5) The final drug concentrations tested were 100 to 0.2 µg/ml.
6) Plates were covered and sealed with parafilm and incubated at 37°C for five days.
7) After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs.
8) A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth.
9) The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

RESULTS AND DISCUSSION

The synthesis of 3-(heteroaryl)-2-(aryl) prop-2-enenitriles and 2-(heteroaryl)-2-yl methylene-malononitrile derivatives was achieved by modified conventional method. These moieties were prepared using freshly prepared sodium ethoxide with short period of time at room temperature in good yields of 80-90% with high purity. The investigation of antituberculosic activity revealed that all of the tested compounds showed good antituberculosic activity as compared with standard drugs.





Note: S – Sensitive; R - Resistant

Strain used: ***M.tuberculosis*** (H37 RV strain) : ATCC No-27294.

Here are the ***standard values*** for the Anti-TB test which was performed.

Pyrazinamide- 3.125µg/ml

Streptomycin- 6.25µg/ml

Ciprofloxacin-3.125µg/ml

CONCLUSION

In conclusion, we have developed a quick, clean, a novel, practically efficient solvent free protocol and simple method for the synthesis of 3-(heteroaryl)-2-(aryl) prop-2-enenitriles and 2-(heteroaryl)-2-yl methylene-malononitrile derivatives by condensation of heteroaryl aldehyde (1mmol) with substituted benzyl cyanide or malononitrile (1mmol) respectively in presence of catalytic amount of sodium ethoxide using water-ethanol as a solvent. The NaOEt catalyst efficiently promotes the reaction in a comparatively lesser reaction time. The protocol advertizes the use of benzyl cyanide (phenyl acetonitrile) in multicomponent synthetic strategies to delve out several stringent molecular entities of biological and pharmaceutical importance. The present protocol offers several advantages such as solvent free condition, operational simplicity, short reaction time, easy work up and easy purification of products simply by recrystallization.

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