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RESEARCH ARTICLE

SYNTHESIS OF *α*-CYANOACRYLATES THROUGH KNOEVENAGEL CONDENSATION UNDER SOLVENT FREE CONDITIONS AND THEIR ANTIMICROBIAL ACTIVITY

[1]Umair Ahmed Khan, [1]Imran Ali Hashmi, [2]Abdul Wahab, [2]Muneera Naz Baloch, [1]Shoaib Muhammad, [1]Syed Kashif Ali and [1,*]Firdous Imran Ali

[1]Department of Chemistry, University of Karachi, Karachi-75270, Pakistan
[2]Department of Microbiology, University of Karachi, Karachi-75270, Pakistan

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ABSTRACT

α-Cyanoacrylates were synthesized employing Knoevenagel condensation under solvent free conditions. The reactions with aromatic aldehydes were accomplished in exceptionally reduced time when instead of stirring, grinding of reaction mixture in a pestle and mortar was applied. To investigate the potential of these α-cyanoacrylates as antimicrobial agents these compounds have been tested against four bacterial strains *S. aureus*, *P. aeroginosa*, *S. typhi* and *M. luteus*. These compounds showed activity against *S. aureus*, *P. aeruginosa* and *S. typhi* while neither compound showed any activity against *M. luteus*.

INTRODUCTION

Recently, it was found that some α-cyanoacrylates prepared from Knoevenagel condensation are found to be biologically active against some strain of bacteria (Chin *et al*., 2006). Knoevenagel reaction is the condensation reaction between aldehydes and compounds containing active methylene to generate alkene. It was first discovered by Emil Knoevenagel in 1896 (Knoevenagel, 1894). Different catalysts for Knoevenagel condensation (KC) employed so far include triphenylphosphine and Potassium fluoride mixture (Sebti *et al*., 2002)carried out using bases or acids in the presence of organic solvents the mainly DMAP (Narsaiah *et al*., 2004). Generally KC reactions are catalyzed with weak organic bases like Pyridine (Li, 1999), pyrrolidine (Borhegyi, 2010) and tertiary amine. Several Inorganic salts such as $ZnCl_2$ (Shanthan Rao and Venkataratnam, 1991), Zinc acetate and zinc bromide are also employed (Jiang *et al*., 2009). Since then it has gained great importance in organic synthesis as one of the key C=C formation reaction. Such types of Alkenes formed through Knoevenagel condensation possess wide variety of biological applications. Some of derivatives form by KC are used for diagnosis of disease like Alzheimer with the assistance of molecular imaging techniques (Cragg, 2005). Also reported to be use for biomedical imaging (Haefner, 2003). It is also observed in reported literature that Carbon-Carbon double bond are responsible for enhancing the anti-parasitic activity (Mishra, 2011) so such types of compounds can be consider as a good contestant for Anti-microbial activities to. KC yields products specially benzyldienemalononitrile has gain a great interest since 1990s due to potent tyrosine kinase inhibitors (Cragg and Chem. 2005, 2005; Rey-Ladino, 2011). In view of above facts we planned to investigate antimicrobial potential of some synthesized tri-substituted alkenes or α-cyanoacrylates using Knoevenagel condensation under solvent free conditions. The synthesized compounds were tested against four bacterial strains including *S. aureus, P. aeroginosa, S. typhi,* and M. luteus to explore the antimicrobial potential of α-cyanoacrylates.

Corresponding author: Firdous Imran Ali,
Department of Chemistry, University of Karachi, Karachi-75270, Pakistan

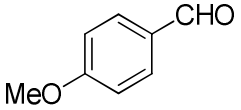
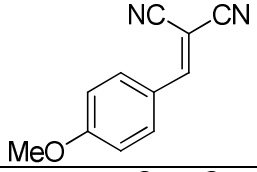
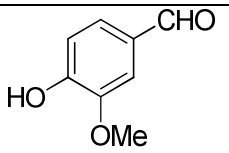
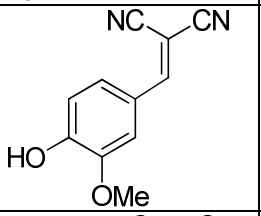
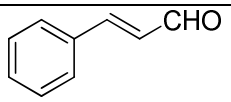
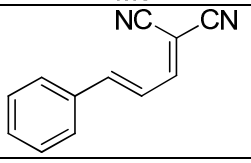
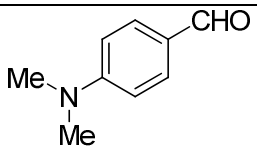
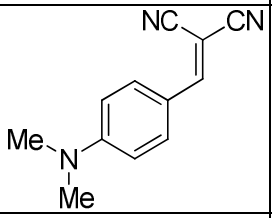
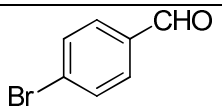
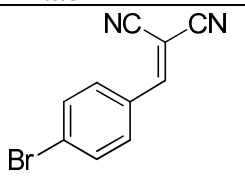
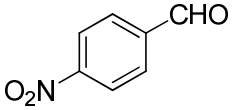
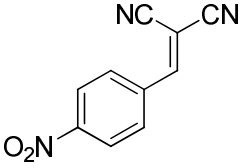
MATERIALS AND METHODS

Chemistry

All chemical were purchased from Sigma-Aldrich Company and verified via TLC and FT-IR techniques. TLC was performed by pre-coated aluminum plates, Kieselgel 60, F254, 0.25mm; e. Merck, Darmstadt, Germany. FT-IR was

performed on IRPrestige-21, Fourier Transformed Spectrophotometer by Shimadzu. Chromatograms were detected by UV 254nm and iodine tank. Melting points are aking in conventional paraffin baths. Room temperature was 20 to 30 ºC. Centrifuge process was done with Hettich Centrifuge D-78532.

Table 1. Synthesis of *α*-cyanoacrylates

Entry (Code)	Substrate	Product	Time (min)	Yield (%)	MP bsd. (ºC)	MP Lit. (ºC)
1 (T-4)			3	92	115-116	115-117 (Valizadeh and Gholipour, 2010)
2 (T-2)			2	97	134-135	135-137 (Gupta et al., 2009)
3 (T-7)			1	99	111	111-113 (Zhuo et al., 2011)
4 (T-3)			1	97	182	182-183 (Rong et al., 2006)
5 (T-1)			1	92	162	160.5-161.6 (Raposo et al., 2004)
6 (T-5)			1	99	163	161-163 (Shanthan Rao and Venkataratnam, 1991)

General Procedure for the synthesis of *α*-cyanoacrylates:
Previously reported method

Aromatic aldehyde (5mmol) were taken into a 50 ml two necked round bottom flask fitted with a sealed mechanical stirrer and protected by Calcium chloride guard-tube. 5 mmol of Malononitrileand 0.5 mmol Zinc Chloride was added to it. The mixture was then allowed to stir at room temperature for overnight. After completion of the reaction solid mass forms in the round bottom flask, which represents the termination of the reaction, further confirmed by TLC. The solid mass was then further washed with 5% aqueous ethanol then filtered the product under vacuum and dried well then further purified by Colum chromatography (*9:1*Hexane : Ethyl acetate)

Present method

Aromatic aldehyde (5mmol) were taken into a mortar. 5 mmol of Malononitrile and 0.5 mmol Zinc Chloride was added to it. The reaction mixture was then ground mechanically with pestle at room temperature. Within a few minutes solid mass was obtained, which represents the termination of the reaction. Completion of reaction was further confirmed by TLC. The solid mass was then further washed with 5% aqueous ethanol then filtered the product under vacuum and dried well then further purified by Colum chromatography (*9:1*Hexane : Ethyl acetate)

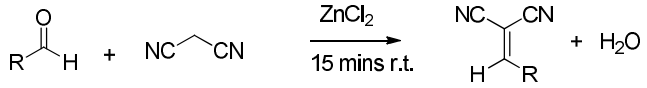
Antibacterial activity

Antibacterial activity of the α-cyanoacrylates was determined by agar well diffusion method according to National Committee for Clinical Laboratory Standards (NCCLS, 1993).

100 µl of freshly grown (4 - 8 hour) cultures of microorganisms were mixed in 1ml of 1% soft nutrient agar and spread onto the nutrient agar plates. Plates were allowed to solidify for 30 minutes. Wells were made using sterile borer. 100 µl of each tested compound (dissolved in 70 % DMSO) was transferred to wells and plates were incubated at 37 ^{o}C. Next day, results were recorded and antimicrobial activity was observed in the form of zone of inhibition around wells.

RESULTS

α-cyanoacrylates were prepared using Knoevenagel condensation. For the synthesis of α-cyanoacrylates, malononitrile was treated with different aromatic aldehydes containing electron donating and electron withdrawing groups at para-position in the presence of $ZnCl_2$ at room temperature **Scheme 1**. No solvent was used. Reaction completion was monitored through TLC (Hexane-ethylacetate; 9:1). Isolated yields and reaction conditions are depicted in Table 1.



Scheme 1. Synthesis of *α*-cyanoacrylates

Compounds	Zone of inhibition			
	S. aureus	*P. aeruginosa*	*S. typhi*	*M. luteus*
T-1	-	-	-	-
T-2	+	-	-	-
T- 3	+	+	-	-
T- 4	+	+	-	-
T- 5	+	+	-	-
T- 7	+	-	+	-

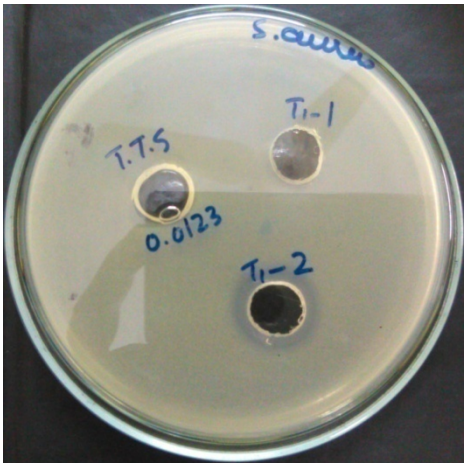


Figure 1. Antimicrobial activity of compound T-2 against *S. aureus*

All compounds were obtained in good yield in shortest time (Table-1). Characterization of all these compounds was carried out through comparison of spectral data including ^{1}H-NMR,^{13}C-NMR,FTIR, ESI-MS Positive Mode, with reported literature ().

DISCUSSION

Green chemistry is a topic of interest of the current era. Conducting organic reactions under solvent free conditions is not only environmentally benign it is also economical due to minimization of solvent used in the reaction beside reduced reaction times, good yields and ease of purification of products.

We herein report a green, efficient, simple and high yielding method for Knoevenagel condensation. All reactions completed within a few minutes and high yields (more than 90 %) obtained. Previously, the same method was reported (Jiang *et al*., 2009) at room temperature under stirring and reported to complete in 24 hours. We have conducted same reaction at room temperature but applying mechanical force through grinding reaction mixture in a pestle and mortar. This also suggests that reduced reaction times in solvent free conditions are because of small intermolecular distances and mechanical forces applied. Purification stage has also options whether to recrystalize by acetone/n-hexane or use of column chromatography depending upon solubility of the product. All yields of Knoevenagal condensation are obtained *via* later separation technique. Even most of the reactions just needed to wash out by cold chloroform, cold dichloromethane or cold ethyl acetate.

Results of antimicrobial activity

To check antimicrobial activity of the -cyanoacrylates four bacterial strains were used. It can be seen *α* in Table 2 that antimicrobial activity was observed against S. *aureus* and *P. aeruginosa*. All of the compounds except T-1 tested showed activity against *S. aureus*. Compound T-3, T-4 and T-5 showed activity against *P. aeruginosa*. Compound T-7 showed activity only against *S. typhi*. Previous studies have shown that the cyanoacrylates possess Staphylococcal activity against methicillin-resistant *S. aureus* (MRSA) (Jang *et al*., 2008).

Conclusion

In present research study we found antibacterial potential of some *α*-cyanoacrylates against tested bacterial cultures, however, further research work is needed to explore the spectrum of these compounds on pathogenic bacteria.

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