ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formation of Substituted Propanenitrile during Biginelli Type Reaction of Tosyloxy Benzaldehyde with Malononitrile: Synthesis and Crystal Structure Determination.

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ABSTRACT

Reaction of active methylene compound with an aldehyde and thiourea under Biginelli conditions reported to yield dihydropyrimidine derivatives in good yield. Herein we report a special case wherein the isolated product was propanenitrile derivative resulting from Knoevenagel condensation of malononitrile with the aldehyde. The structure of the product was confirmed by single crystal X-ray diffraction studies.

Keywords: Biginelli type reaction; Knoevenagel condensation; Crystal structure; Spectral characterization.

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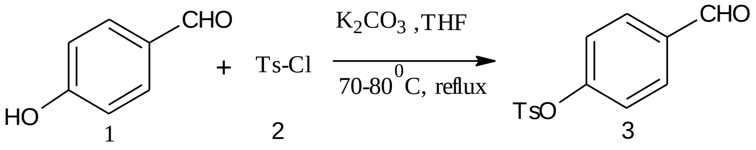
INTRODUCTION

There is an increasing interest in multicomponent reactions (MCR) in organic synthesis, owing to their speed and efficiency, and the large number of derivatives it can offer. MCRs give products containing scaffolds from each of the constituents used for the reaction in a single step [1]. Biginelli reaction is one such well known multicomponent reaction, reported long back [2]. The reaction reported was the cyclization of benzaldehyde, urea, and ethyl acetoacetate, in catalytic amounts of HCl under reflux conditions in ethanol medium. This reaction though not explored for several years, got interest during the last few decades of the 20th century and several workers synthesized numerous functionalised dihydropyrimidines by varying all the three constituent reagents. This resulted in renewed interest in the reaction, that produced a series of applications of such compounds, viz. antitumor, antiviral, antibacterial, and anti-inflammatory activities, to name a few [3-6]. The recent interest in multicomponent reactions and their role in green chemistry prompted us to look into these types of reactions for synthesis and to explore their biological potential [1]. In view of this, tosyloxy aldehyde is used as a reactant along with malononitrile and thiourea under the modified Biginelli reaction, where acid catalysis was avoided. The result of these studies is reported in this paper.

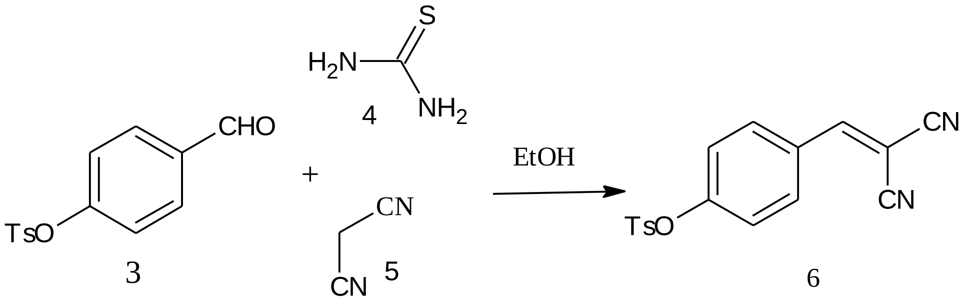
EXPERIMENTAL

As a part of synthesis of dihydropyrimidines, tosyloxy aldehyde was chosen as one of the scaffolds. This was prepared from hydroxy benzaldehyde (**Scheme 1**) by reacting it with tosyl chloride [7, 8].



Scheme 1

The tosyloxy aldehydes were reacted with thiourea, and malononitrile in modified Biginelli conditions (**Scheme 2**) without the aid of acid catalyst to get the expected pyrimidine as reported in literature [4]. The precipitate obtained by cooling the reaction mixture, was filtered and recrystallized using ethanol as a solvent. The product of the reaction was analyzed by FTIR and NMR spectroscopy. The product after analysis is proved to be due to the Knoevenagel condensation reaction of malononitrile with tosyloxy aldehyde. The added thiourea didn't involve in the condensation to form cyclized derivative but acted as a catalyst for the Knoevenagel condensation reaction as reported in the literature [6]. Further, single crystal of the compound was grown by slow evaporation technique to assign the structure of the compound unambiguously using acetone as the solvent.



Scheme 2

RESULTS AND DISCUSSION

The product obtained in the modified Biginelli reaction wherein acid catalyst is not used, failed to give cyclized product, and disproves the expectation that cyclization can happen even in the absence of acid if the active methylene compound used is malononitrile. Therefore based on the results obtained from this study, it is suggested that Biginelli reaction does need catalyst to undergo cyclization reaction. The product was isolated from the reaction mixture as papery off-white form as the reaction mixture is cooled down to room temperature. The melting point of the crystal is recorded and is found to be 144-46 °C. Single crystals for analysis were developed using slow solvent evaporation technique using acetone-water mixture as solvent.

The FTIR spectrum (**Figure 1**) of the compound 6 show characteristic absorption bands at 3058 cm^{-1} (aryl CH_3 str), 2900-3050 (Aryl CH str), 2229 cm^{-1} (CN str) and 1593 cm^{-1} (C=C str) the peaks associated with tosyl group corresponding to S=O str, and O=S=O asymmetric str, at around 1300-1050 cm^{-1}.

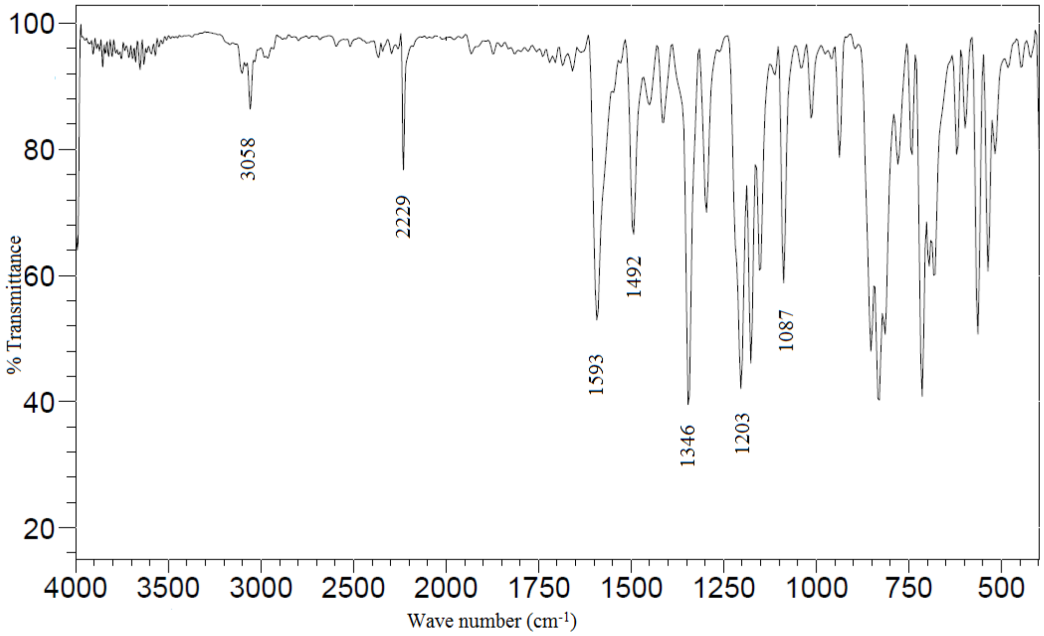


Figure 1: The FTIR spectrum of compound 6

The proton NMR spectrum of the product formed is shown in **Figure 2**. Thus, a singlet observed at δ 2.4 ppm integrating for three protons is due to CH_3 group, four doublets in the aromatic region correspond to 4 sets of chemically equivalent protons on the two benzene rings present, and a singlet at δ 8.5 is due to the presence of -C=CH proton.

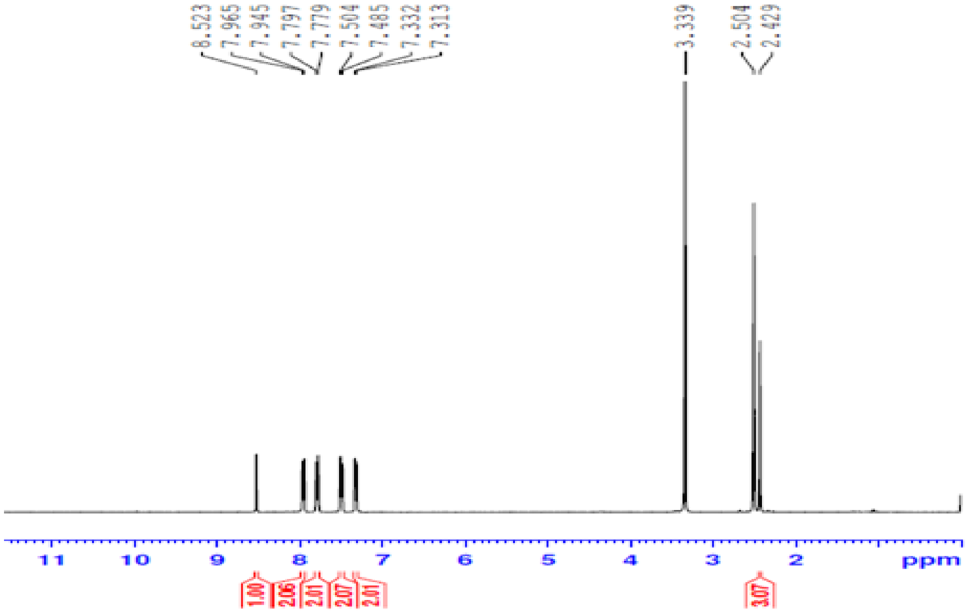


Figure 2: The NMR spectrum of compound 6

Single crystal X-ray analysis

Colourless, block shaped single crystal of the title compound (**6**), with dimensions of 0.49 mm × 0.34 mm × 0.16 mm was selected and mounted on a Bruker APEX-II CCD diffractometer [9] with a fine-focus sealed tube graphite-monochromated Mo *Kα* radiation (λ = 0.71073 Å) at 294 K in the range of 2.5≤ ϑ ≤ 30.0°. In the structure refinement, all H atoms were positioned geometrically with C—H bond length of 0.93 Å or 0.96 Å (methyl) and they are refined using a riding model with U_{iso}(H) = 1.2 or 1.5 × U_{eq}(C). A rotating group model was applied to the methyl groups. Experimental details (crystal data, data collection and structure refinement) are summarized in Table I. The crystallographic data has been deposited at the Cambridge Crystallographic Data Centre with CCDC No: 1029646 which contain the supplementary data for this paper.

The *ORTEP* diagram of the title compound, $C_{17}H_{12}N_2O_3S$, with atom labelling scheme drawn at 30% probability displacement ellipsoid is depicted in Figure 3. The dihedral angle between the mean plane of the two benzene (C1—C6 and C8—C13) rings is 15.19 (7) (7)^{0}. Both of these aromatic rings are connected *via* central C8—O3—S1(=O2)—C1 (torsion angle = 178.69 (10)^{0}) bridge. In the molecule, the terminal propanenitrile (N1/C16/C15/C14 and N2/C17/C15/C14) groups is co-planar to the bound benzene (C8—C13) ring with the interplanar angles of 4.78 (13)^{0} and 4.51 (13)^{0} respectively. In the crystal structure, the molecules are linked *via* C13—H13*A*···O1 and C14—H14*A*···O2 (Symmetry code: x, y+1, z and −x+1, y+1/2, −z+1/2) into a zig-zag chain propagating along the crystallographic axis *b* (Fig. 4). The bond length and bond angles are in normal range and agree with the literature values [10]. The crystal belongs to centrosymmetric space group; and such compounds may find application as optical materials [11-13].

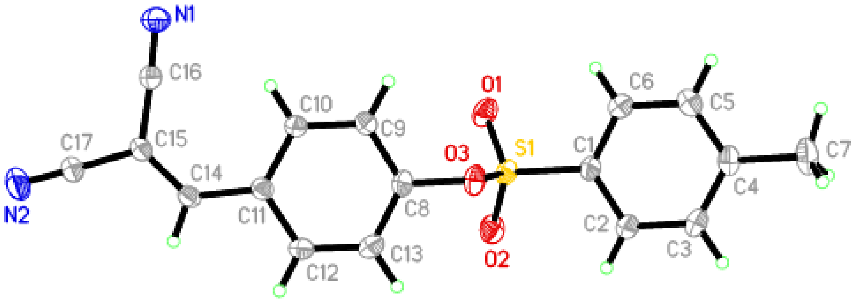


Figure 3: Molecular view of compound (6), showing 30% probability displacement ellipsoids and atom labelling scheme.

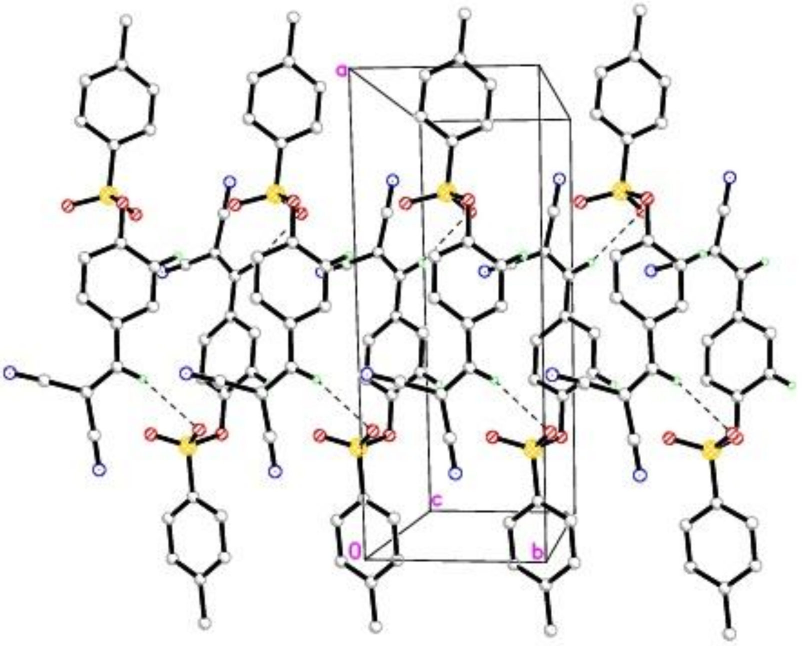


Figure 4: Crystal packing of the title compound (6), showing intermolecular C—H···O hydrogen bonding interactions as dotted lines. H atoms not involved in hydrogen bonding are omitted for clarity

Table I: Experimental details

Crystal data

$C_{17}H_{12}N_2O_3S$	V = 1546.31 (19) Å^3
M_r = 324.35	Z = 4
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 15.7796 (11) Å	μ = 0.23 mm^{-1}
b = 5.8373 (4) Å	T = 294 K
c = 17.1328 (12) Å	0.49 × 0.34 × 0.16 mm
β = 101.5217 (14)°	

Data collection

Bruker APEX-II CCD diffractometer	4513 independent reflections
Absorption correction: multi-scan (*SADABS*; Bruker, 2009)	3561 reflections with $I > 2\sigma(I)$
T_{min} = 0.898, T_{max} = 0.965	R_{int} = 0.027
16881 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039	0 restraints
$wR(F^2)$ = 0.117	H-atom parameters constrained
S = 1.05	$\Delta\rho_{max}$ = 0.29 e Å^{-3}
4513 reflections	$\Delta\rho_{min}$ = −0.26 e Å^{-3}
209 parameters	

CONCLUSION

Synthesis, physicochemical characterization, and single crystal XRD studies of the product of the modified Biginelli condition was carried out. We conclude that under mild condition and in the absence of acid catalyst, Knoevenagel condensation product was formed rather than expected pyrimidine derivative by cyclization with thiourea. In such reactions, thiourea is believed to act as a catalyst.

ACKNOWLEDGEMENT

Shubhalaxmi is thankful to Manipal University for fellowship under MU-structured PhD programme. We are also thankful to Central Instruments Facility, Manipal Institute of Technology, Manipal University for recording NMR spectrum. CSCK thanks Universiti Sains Malaysia (USM) for a postdoctoral research fellowship. The authors extend their appreciation to The Deanship of Scientific Research at King Saud University for the research group project No. RGP VPP-207.

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