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Research Article

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Trizma: Efficient catalyst and reactant in Knoevenagel condensation reaction under conventional heat and microwave irradiation conditions

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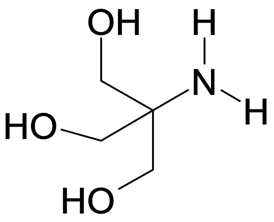
ABSTRACT

*Knoevenagel condensation of several aromatic aldehydes **1** with different active methylene compounds **2** under conventional heat condition was efficiently mediated by TRIZMA as a benign catalyst to afford the corresponding arylidenes **3** in excellent yield. In the same reaction the yield has dramatically reduced when microwave irradiation was employed under nitrogen while when the irradiation has carried out in presence of oxygen air TRIZMA showed an extraordinary reactivity and N1-(1,1-diethylpropyl)-N2-(1-ethyl-1-hydroxymethylpropyl) ethanediamide **4** was obtained instead.*

Keywords: Trizma, Knoevenagel condensation, microwave irradiation, carbonyl compounds.

INTRODUCTION

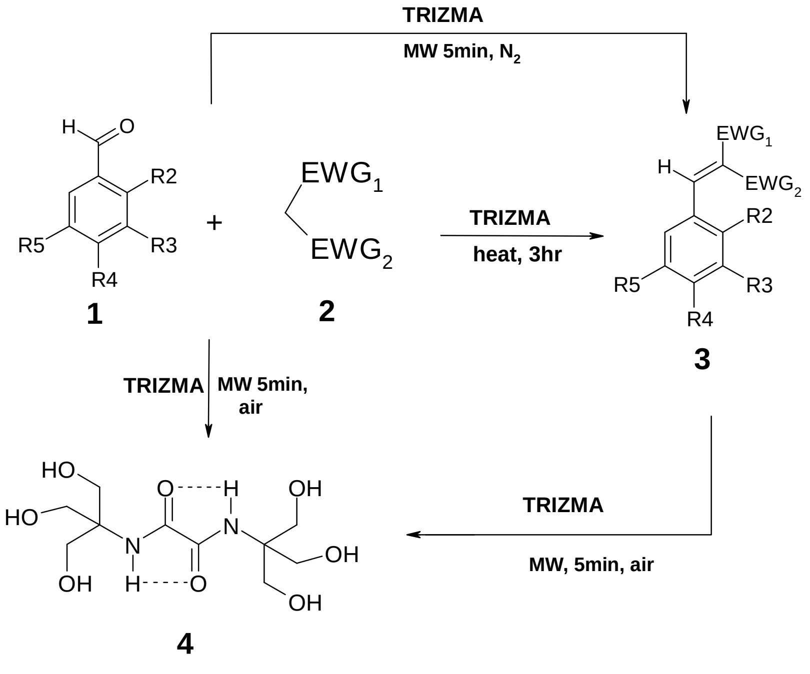
There have been a number of reports on the condensation of carbonyl substrates with a variety of active methylene compounds using traditional bases, inorganic catalysts both under conventional as well as microwave heating conditions [1-12]. Other Lewis bases and acids have also been reported as catalysts in the Knoevenagel condensation, including $ZnCl_2$ [13], ZnO and MgO [14], Al_2O_3 [15], KF–Al_2O_3 [16], $AlPO_4$–Al_2O_3 [17], CdI_2 [18], $TiCl_4$ [19], Ni-SiO_2 [20], synthetic phosphate ($Na_2CaP_2O_7$, $Ca_2P_2O_7$ [21] and $K_2NiP_2O_7$ [22]) and natural phosphate {(NP)/KF or NP/$NaNO_3$} [23]. In addition, other modified inorganic solids [24-26], resins [27] phase-transfer agents [28], ionic liquid [29, 30], LDH-F hydrotalcite [31], cation-exchanged zeolites [32], and mesoporous materials [32], and MCM-41 [33] have been introduced as new catalysts. Nevertheless, most of these known methods suffer from significant limitations, which include toxic reagents, harsh reaction conditions, low yields or long reaction times. In addition, the use of such bases/acids and solvents in large scale Knoevenagel reactions has led to environmental problems, *i.e.* the necessity to dispose of huge amounts of organic waste due to the formation of undesirable side products resulting from polymerisation, bis-addition and self condensation; in addition to the total dissolved salts formed during the neutralization of the base or acid catalysts. Only a few sustainable procedures, particularly with basic heterogeneous catalyst, were reported [34-37]. However, no reaction utilizing Trizma as catalyst has been reported for carbon-carbon condensation.



TRIZMA

TRIZMA is extensively used in biochemistry and molecular biology [38]. This, and its low cost, makes TRIZMA one of the most common buffers used in chemistry/biochemistry lab. [39-43].

Further to our strategy on employing primary amino alcohols in three components condensation reactions with aldehydes and acidic methylene containing compounds aiming to synthesize biologically active compounds of alcoholic hydroacridines [44-46] and alcoholic-amino cyclohexene derivatives [47], we found tris-amino alcohol (TRIZMA) did not give the expected corresponding product; instead it behaved as an excellent mild catalyst. Thus, the reaction of TRIZMA with aromatic aldehydes and several beta-dicarbonyl compounds under conventional heat afforded numerous C-C bond formations of arylidenes **3** which are widely employed in organic synthesis [48]. By contrast, when we employed microwave protocol with the same reaction in presence of air, TRIZMA showed an extraordinary reaction where the polyol diamide (**4**) was obtained (Scheme 1). When the irradiation reaction was carried out under nitrogen, the corresponding arylidenes **3** were obtained in low yield (see table 1).



For EWG_1, EWG_2, R2, R3, R4 and R5 see table 1.

(Scheme 1)

EXPERIMENTAL SECTION

All glass apparatus were oven dried prior to use. All chemicals used were purchased from Aldrich Chemical Co. All solvents were distilled by standard techniques prior to use. Where stated, reactions were performed under an inert atmosphere of nitrogen. Melting points were determined on a Thermonik Campbell melting point apparatus and were uncorrected. All microwave irradiation reactions were conducted by using CEM Discover S-Class microwave reactor (single mode reactor, method: dynamic mode at power 300 W). The microwave reactor is equipped with fiber optic temperature control.

*General synthetic method of **3a-r** under conventional heat:*
A mixture of 1mmol of aromatic aldehyde **1** and 1mmol of the appropriate active methylene compounds **2** along with 1mmol TRIZMA in 50ml ethanol were heated at 80°C for 3 hours. The reaction was monitored by TLC. On completion the solid arylidenes **3a-r** were obtained on cooling and filtered off. All products were crystallized from ethanol in an excellent yield (see table 1). A sample of single crystal for x-ray purpose was prepared by slow evaporation of a diluted ethanolic solution of the product over two days.

*General synthetic method of **3a-r** under microwave irradiation in presence of nitrogen:*
A mixture of an equamolar ration of aldehydes **1**, acidic methylene containing compounds **2** and TRIZMA in ethanol was kept under nitrogen in a sealed container and irradiated by microwave 300W for 5 minutes at intervals every 30 seconds. The corresponding arylidenes **3a-r** were collected on cooling and recrystallized from ethanol in low yield.

*General synthetic method of **4** under microwave irradiation:*
1- A mixture of 1mmol of aromatic aldehyde **1** and 1mmol of the appropriate active methylenes **2** along with 1mmol TRIZMA in 20 ml ethanol were irradiated in presence of air under microwave at 300 W for 5 min. The reaction was monitored by TLC. On completion the solid N1-(1,1-diethylpropyl)-N2-(1-ethyl-1-hydroxymethylpropyl)ethanediamide **4** was obtained on cooling and was filtered off. The product was crystallized from ethanol. A sample of single crystal for x-ray purpose was prepared by slow evaporation of a diluted ethanolic solution of the product over two days

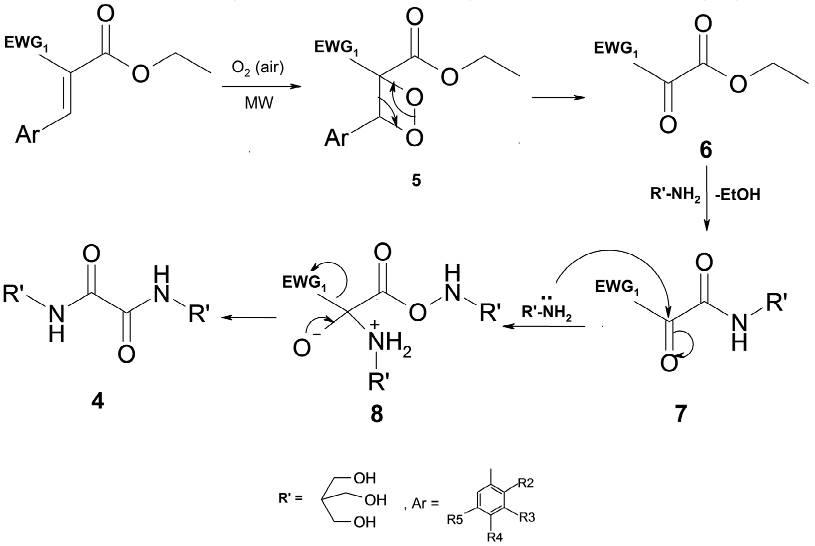
2- A mixture of 1mmol arylidene **3a** and 1mmol TRIZMA in 20 ml ethanol were irradiated in presence of air under microwave at 300W for 5 min with intervals every 30 seconds. The reaction was monitored by TLC. On completion the solid N1-(1,1-diethylpropyl)-N2-(1-ethyl-1-hydroxymethylpropyl)ethanediamide **4** was obtained on cooling and was filtered off. The product was crystallized from ethanol. A sample of single crystal for x-ray purpose was prepared by slow evaporation of a diluted ethanolic solution of the product over three days.

RESULTS AND DISCUSSION

Reaction of the active methylenes compounds **2** such as ethyl acetoacetate, ethylcyanoacetate and malononitrile with different aromatic aldehydes **1** in presence of tris-amino alcohol (TRIZMA) under conventional heat afforded the corresponding arylidenes **3a-r** in an excellent yield (Scheme 1). The reaction proceeded via Knoevenagel condensation mechanism. Same reaction when carried out under microwave irradiation in open air for few minutes revealed the unexpected product *N*1-(1,1-diethylpropyl)-*N*2-(1-ethyl-1-hydroxymethylpropyl)ethanediamide (**4**). When the reaction has carried out in absence of oxygen under microwave irradiation the corresponding arylidenes **3a-r** were revealed instead.

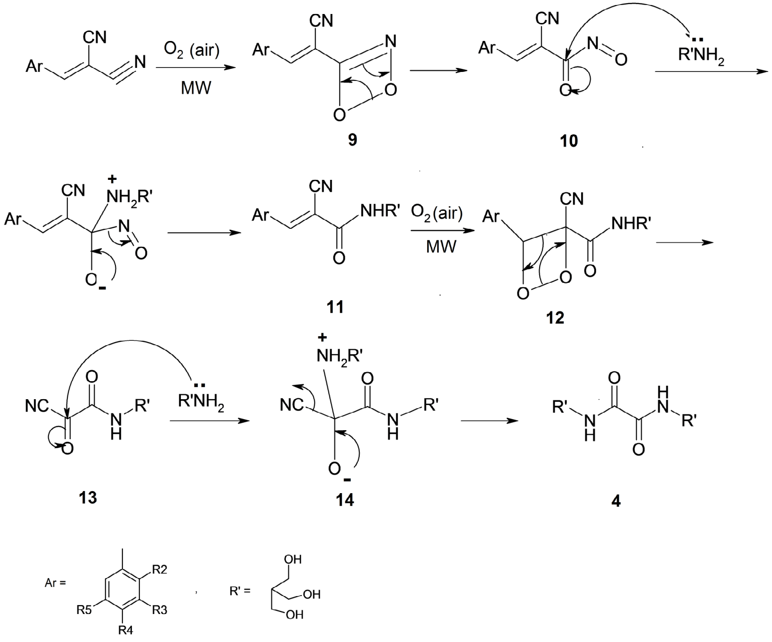
The physical and spectral properties of all products were in accordance with the reported data [49-55]. The formation of **4** was rationalized through two mechanisms (Schemes 2, 3) depending on the type of active methylene derivatives. So, when ethylacetoacetate or ethylcyanoacetate were employed, the formation of **4** might have been constructed via the oxidation of the corresponding arylidenes **3** which might have been obtained in situ under irradiation in oxygen air to form the unstable intermediate **5** which was ultimately arranged into the stable di-carbonyl compound **6.** Reaction of the latter with **TRIZMA** might have formed the mono amide **7** by eliminating ethanol**.** Nucleophilic reaction of **7** with another molecule of TRIZMA could have led ultimately to the polyol-diamide **4** via **8 (Scheme 2)**.

Formation mechanism of 4 from the arylidenes of either Ethyl acetoacetate or ethylcyanoacetate:



(Scheme 2)

Formation mechanism of 4 from the arylidenes of Malononitrile:



(Scheme 3)

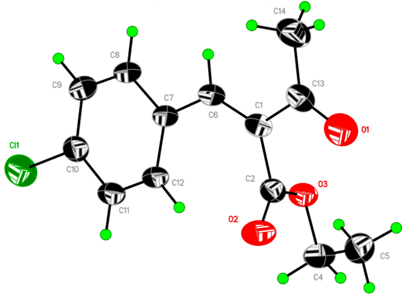


Figure 1: X-ray crystallography of 3a

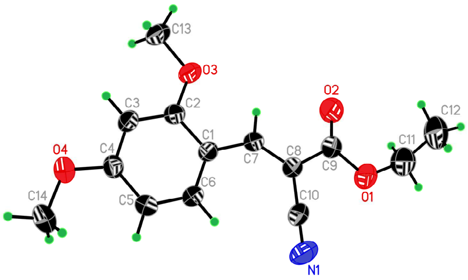


Figure 2: X-ray crystallography of 3i

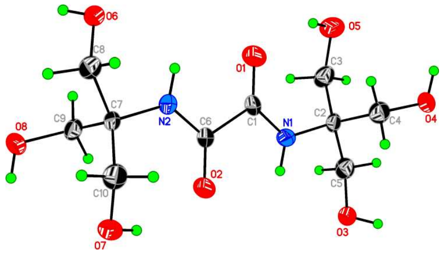


Figure 3: X-ray crystallography 4

Table 1: Knoevenagel condensation products 3a-r mediated by TRIZMA

Product	EWG_1	EWG_2	R2	R3	R4	R5	Yield (%)		m.p. °C	Reference
							Y^*	Z^*		
3a	CH_3CO	COOEt	H	H	Cl	H	91	27	100	48
3b	CH_3CO	COOEt	H	H	NO_2	H	94	22	160	51
3c	CN	COOt	H	H	H	H	92	38	52-54	46
3d	CN	COOEt	H	H	Cl	H	97	29	92-94	46
3e	CN	COOEt	H	H	OMe	H	93	34	86-88	46
3f	CN	COOEt	H	H	Me	H	92	24	90-92	46
3g	CN	COOEt	H	H	NO_2	H	97	31	170-172	46
3h	CN	COOEt	H	H	OH	H	89	39	171-172	46
3i	CN	COOEt	H	H	$(Me)_2N$	H	91	18	125-127	46
3j	CN	COOEt	H	OMe	OMe	H	90	21	139	47
3k	CN	COOEt	H	$-O-CH_2-O-$		H	93	28	108	47
3l	CN	COOEt	OMe	H	OMe	H	92	23	138	52
3m	CN	CN	H	H	NO_2	H	97	31	161-162	46
3n	CN	CN	Cl	H	H	H	98	27	96	47
3o	CN	CN	H	$-O-CH_2-O-$		H	96	32	200	47
3p	CN	CN	H	H	Me	H	91	30	135	47
3q	CN	CN	OMe	H	OMe	H	92	21	136	49
3r	CN	CN	H	OMe	OMe	H	93	18	140	50

Y^*: The reaction has carried out under conventional heat (at 80°C for 3hrs).
Z^*: The reaction has carried out under microwave irradiation in presence of nitrogen for 5 mins.

In order to confirm this mechanism we have reacted TRIZMA with the synthesized arylidene **3** in a separate reaction under same reaction condition (microwave irradiation in air for 5 minutes). The product was exactly identical with **4**. When malononitrile was irradiated under microwave in air with aromatic aldehydes, product **4** might have been obtained via the oxidation of one of the cyano group in the corresponding arylidenes **3** which might have been obtained in situ to form the nitroso ketone **10** via the unstable intermediate **9**. Nucleophilic reaction of **10** with TRIZMA might have afforded the mono-amide **11** which in turn might have undergone further oxidation under irradiation condition to form the di-carbonyl **13**. Further nucleophilic reaction of **13** with another molecule of TRIZMA could have led to the formation of **4** via the intermediate **14** (Scheme 3). The suggested mechanisms in schemes 1 and 2 were confirmed when TRIZMA was allowed to react with active methylene compounds **1** under nitrogen in sealed container and exposed to microwave irradiation, the corresponding arylidenes **3** were obtained. The x-ray crystallography of arylidenes **3a, 3i** and the di-amide **4** are illustrated in figures 1,2 and 3 respectively.

The crystal packing of **4** showed an inter- and intra-molecular hydrogen bonding across amide groups and adjacent molecules (Fig. 3).

CONCLUSION

In this study we reported that the TRIZMA was an efficient and benign catalyst in synthesis of arylidenes in high yield via Knoevenagel condensation under conventional heat while the use of microwave irradiation in presence of air afforded an unexpected product of polyol-dioxamide **4** in excellent yield. In absence of air, the reaction under microwave irradiation afforded the corresponding arylidenes in low yield indicating that the formation of **4** is a result of the function of oxidation competition.

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