

**A HIGH-SPEED AND ECO-FRIENDLY CATALYTIC SYSTEM FOR KNOEVENAGEL
CONDENSATION OF ALDEHYDES WITH MALONONITRILE AND ETHYL
CYANOACETATE IN AQUEOUS MEDIA**

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Abstract- Knoevenagel condensation of several aromatic and heteroaromatic aldehydes with ethyl cyanoacetate and malononitrile was carried out in water: ethanol mixture in the presence of catalytic amounts of potassium hydroxide or sodium hydroxide at 50-60°C. The new technique provide numerous common electron-poor alkenes with high-speed and the products do not require purifying workup.

KEYWORDS

Knoevenagel condensation, malononitrile, ethyl cyanoacetate, aldehydes .

INTRODUCTION

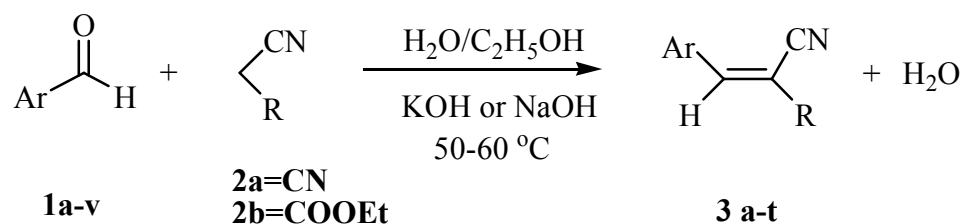
Knoevenagel condensation is one of the most important C–C bond forming reactions.^I It is widely used in the synthesis of important intermediates or end-products for perfumes,^{II, III} pharmaceuticals^{IV} and calcium antagonists^V and polymers.^{VI} The reaction is catalyzed by bases, acids or catalysts containing acid–base sites.^{VII} Bases such as ammonia, primary amine, secondary amine and their salts and Lewis acids such as CuCl₂,^{VIII} ZnCl₂^{IX} and SmI₃^X are some examples that have been employed in Knoevenagel condensation. Many modifications have been made to this process in recent years using Lewis acid catalysis,^{XI} ionic liquids,^{XII} microwave irradiation,^{XIII} quaternary ammonium salts,^{XIV} heterogeneous catalysts,^{XV} and organo-base mediation.^{XVI} However, in many of these methods relatively harsh conditions are required, expensive reagents are involved, or a combination of several additives is employed. Aprotic solvent with several unfavourable properties such as dimethylsulfoxide, is necessary to act as both solvent and oxidant. The use of environment ally benign solvents like water and solvent-free reactions represent very powerful green chemical technology procedures from both the economical and synthetic point of view. They not only reduce the burden of organic solvent disposal, but also enhance the rate of many organic reactions.^{XVII}

In fact, as clearly stated by R. A. Sheldon, it is generally recognized that “the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water”.^{XVIII} The use of water as the reaction medium represents a remarkable benefit since this green solvent is highly polar and therefore immiscible with most organic compounds thus separation of the organic materials is

easy. A further advantage is that many organic reactions like the aldol condensation, the benzoin condensation, the Diels-Alder cycloaddition and cyclocondensation reactions exhibit rate enhancement in water.^{XIX} In our continued interest, in Knoevenagel condensations and its application in the synthesis of heterocyclic compounds,^{XX} we report here, a high speed and very simple method for the condensation of various aromatic and heteroaromatic aldehydes with malononitrile, in mixture of water and ethanol at 50-60°C temperature .

RESULTS DISCUSSION

We first examined the reaction between aromatic aldehydes such as benzaldehyde with malononitrile in water by using catalytic amounts of potassium hydroxide or sodium hydroxide, formation of only small quantities of **3a** was detected and most of the starting materials were recovered. Optimum results were obtained when reactions were conducted in the solvent of water and ethanol at 50-60 °C (**Scheme 1**).



Scheme 1

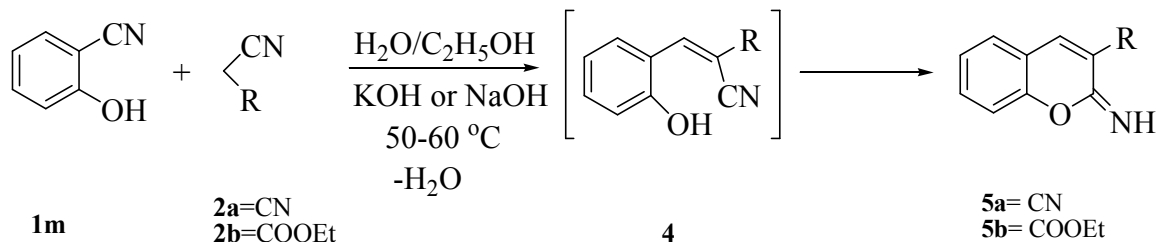
The experimental procedure is simple: To a magnetically hot solution (50-60°C) of malononitrile **2a** (132 mg, 2 mmol) and a catalytic amounts of potassium hydroxide or sodium hydroxide (5 mg) in water (20 ml) and ethanol (5ml) was added benzaldehyde **1a** (212 mg, 2 mmol) rapidly and all at once. A yellow precipitate of 2-benzylidene-malononitrile was formed instantly. The solid produced was isolated by simple filtration and do not require further purification. The product **3a** (301 mg, 98%) was identified by spectroscopic measurements and by comparison with an authentic samples. Under the same conditions other aldehydes reacted in similar manner with malononitrile producing 90-98% yields of their respective products (R=CN).

The generality of the method was demonstrated by subjecting mixtures of the same aldehydes and ethyl cyanoacetate to similar reaction conditions. In each case, single geometric isomers were obtained in high yields as shown in Table 1 (R=CO₂Et). The infrared spectra of compounds **3** revealed a band at 2210-2220 cm⁻¹ which is due to the cyano group and a strong band in the carbonyl region at 1715-1720cm⁻¹ cm⁻¹, arising from ester group in the ethyl alkylidene cyanoacetates.

Table 1: Knoevenagel condensation of aromatic aldehydes with malononitrile and ethyl cyanoacetate catalyzed by KOH or NaOH.

Com. No.	Ar	R	Conditions of Ref. reaction [Catalyst, Time, Yield (Ref.)]	In the presence of KOH or NaOH			KOH (Ref)
				Time (sec)	Yield (%)	M. P. (°C)	
3a	C ₆ H ₅	CN	MgO, methanol, heating, 0.5h, 90% (XXI)	20	98	82-8	(XXII)
3b	C ₆ H ₅	CO ₂ Et	MgO, methanol, heating, 0.5h, 90% (XXI)	40	92	48-50	(XXIII)
3c	4-MeC ₆ H ₅	CN	MgO/ZrO ₂ , Solvent free, 20min, 82%(XXIV)	45	94	128-130	(XXII)
3d	4-MeC ₆ H ₅	CO ₂ Et	MgO/ZrO ₂ , Solvent free, 20min, 84%(XXIV)	60	92	93	(XXII)
3e	4-MeOC ₆ H ₄	CN	MgBr ₂ .OEt ₂ , THF, 1-2h, 95% (XXV)	45	90	113-115	(XXII)
3f	4-MeOC ₆ H ₄	CO ₂ Et	MgBr ₂ .OEt ₂ , THF, 1-2h, 95% (XXV)	60	88	85	(XXIII)
3g	4-HOC ₆ H ₄	CN	Piperidine, ethanol, heating, 0.5h, 90%(XXVI)	30	95	186-189	(XXVI)
3h	4-Me ₂ NC ₆ H ₄	CN	Xonotlite/K t-butoxide, 1h, 87% (XXVII)	120	87	183-184	(XXVIII)
3i	4-Me ₂ NC ₆ H ₄	CO ₂ Et	Xonotlite/K -t-butoxide, 1h, 5% (XXVII)	150	85	128	(XXVIII)
3j	4-FC ₆ H ₄	CO ₂ Et	MgO/ZrO ₂ , Solvent free, 20min, 95% (XXIV)	30	92	123	(XXIX)
3k	4-ClC ₆ H ₄	CN	K ₃ PO ₄ , ethanol, heating, 0.5h, 97% (XXX)	30	97	156-58	(XXX)
3l	4-ClC ₆ H ₄	CO ₂ Et	MgO/ZrO ₂ , Solvent free, , 1.5h, 65% (XXIV)	45	95	93	(XXVIII)
3m	4-BrC ₆ H ₄	CN	MgO/ZrO ₂ , Solvent free, 20min, 97% (XXIV)	30	92	62-164	(XXVIII)
3n	4-BrC ₆ H ₄	CO ₂ Et	MgO/ZrO ₂ , Solvent free, , 1.5h, 89% (XXIV)	45	96	97-98	(XXVIII)
3o	4-O ₂ NC ₆ H ₄	CN	K ₃ PO ₄ , ethanol, heating, 0.5h, 95% (XXXI)	15	95	158-160	(XXVIII)
3p	4-O ₂ NC ₆ H ₄	O ₂ Et	MgO/ZrO ₂ , Solvent free, , 1.5h, 88% (XXIV)	30	94	170	(XXVIII)
3q	2-furyl	CN	MgO, methanol, heating, 0.5h, 80% (XXI)	120	92	71-73	(XXXII)
3r	2-furyl	CO ₂ Et	MgO, methanol, heating, 0.5h, 79% (XXI)	150	90	93-94	(XXXII)
3s	2-thienyl	CN	MgBr ₂ .OEt ₂ , THF, 1-2h, 93% (XXV)	120	94	93-95	(XXV)
3t	2-thienyl		MgBr ₂ .OEt ₂ , THF, 1-2h, 93% (XXV)	150	92	96-97	(XXV)
5a	2-HOC ₆ H ₄	CO ₂ Et CN	Piperidine, ethanol, heating, 0.5h, 88% (XXXIII)	120	89	164	(XXXIII)
5b	2-HOC ₆ H ₄	CO ₂ Et	Piperidine, ethanol, heating, 1h, 85% (XXXIII)	180	85	136	(XXXIII)

In the reaction of 2-hydroxybenzaldehyde **1m** with malononitrole and ethyl cyanoacetate, the first formed Knoevenagel products underwent cyclisation as a result of nucleophilic attack by the hydroxyl group on the cyano group. Thus 2-imino-2H-1-benzopyran-3-carbonitrile **5a** and 2-imino-2H-1-benzopyran-3-carboxylate **5b** were formed in excellent yields (**Scheme 2**).



Scheme 2

The mechanism of the Knoevenagel condensation involves abstraction of one of the active methylene protons by a base, followed by attack of the resulting anion on the carbonyl carbon of the benzaldehyde. The resulting O^- abstracts a hydrogen atom from the base. Elimination of a molecule of water results in the formation of a system of extended conjugation.

We have demonstrated a very simple and highly efficient method for the condensation of aromatic aldehydes with active methylene compounds such as malononitrole and ethyl cyanoacetate to give Knoevenagel products. On the other hand this method is very simple and the reaction conditions are mild, environmentally benign and more importantly shorten experimental time and in addition high yield of the final products and do not require purifying workup.

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