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Uncatalysed Knoevenagel condensation in aqueous medium at room temperature

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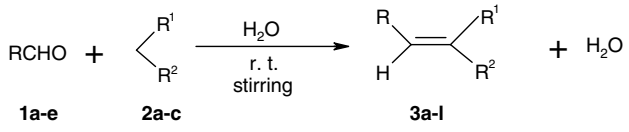
Abstract—Knoevenagel condensation of various aromatic and heteroaromatic aldehydes with active methylene compounds like malononitrile, ethyl cyanoacetamide, ethyl cyanoacetate, barbituric acids, Meldrum's acid, dimedone and pyrazolone proceeds smoothly with stirring in an aqueous medium. The reactions occur at room temperature giving excellent yields of the products. The work-up procedure is very simple and the products do not require further purification.

The Knoevenagel condensation of aldehydes with active methylene compounds is an important and widely employed method for carbon–carbon bond formation in organic synthesis[1] with numerous applications in the synthesis of fine chemicals,[2] hetero Diels–Alder reactions[3] and in synthesis of carbocyclic as well as heterocyclic[4] compounds of biological significance. The reactions are usually catalysed by bases[5] such as amines, ammonia or sodium ethoxide in organic solvents. Lewis acids,[6] surfactants,[7] zeolites[8] and heterogeneous catalysts[9] have also been employed to catalyse the reactions. Similarly, the use of ionic liquids[10] pave a new path for such organic synthesis. The use of environmentally benign solvents like water[11] 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. Therefore, efforts have been made to perform the Knoevenagel condensation in aqueous medium as well as in the absence of solvents[12] which are usually catalysed by Lewis acids,[12a] or base[12e,f] and require drastic conditions.[12b–d] Some of these reactions are performed on solid supports, promoted by infrared,[13a] ultrasound or microwave[13b,c] heating.

In our continued interest,[14] in Knoevenagel condensations and its application in the synthesis of bioactive molecules, we report here, a very simple and highly efficient method for the condensation of various aromatic and heteroaromatic aldehydes **1** with several active methylene compounds **2**, for example, malononitriles, ethyl cyanoacetamide, ethyl cyanoacetate, barbituric acids, Meldrum's acid, dimedone and pyrazolone in water at room temperature with stirring (Scheme 1). It was exciting to observe that, except in a few cases, all the reactions occurred rapidly and were complete in just a few minutes giving excellent yields of the Knoevenagel products **3**.

The experimental procedure is simple: to a stirred solution of malononitrile **2a** (132 mg, 2 mmol) in water (8 ml) was added benzaldehyde **1a** (212 mg, 2 mmol) rapidly and all at once. After 5 min, the solid produced was isolated by simple filtration and dried. The solid product **3a** (292 mg, 95%) was identified by spectroscopic measurements and by comparison with an authentic samples needed no further purification. Similarly, utilising the aldehydes **1a–e** and active methylene compounds **2a–c**, compounds **3b–i** were synthesised and characterised (Table 1).



Scheme 1.

Keywords: Knoevenagel condensation; Barbituric acid; Meldrum's acid; Malononitrile; Aqueous medium; Uncatalysed reaction.
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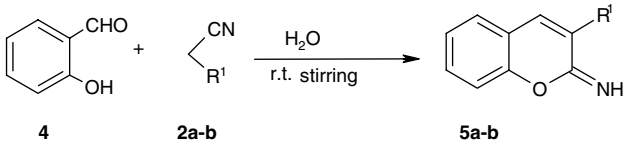
Table 1. Reaction time, yields and melting points of the product **3**

Product	R	R^1	R^2	Time (min)	Yield (%)	Mp (°C)
3a	C_6H_5	CN	CN	5	95	82[1a]
3b	*p*-ClC_6H_4	CN	CN	3	92	162[15a]
3c	*p*-HO–C_6H_4	CN	CN	5	90	188[15b]
3d	(*E*)-PhCH=CH	CN	CN	8	85	128[15c]
3e	2-Furyl	CN	CN	30	84	72[15d]
3f	2-Furyl	CO_2Et	CN	60	90	94[15d]
3g	*p*-ClC_6H_4	$CONH_2$	CN	60	85	210[15e]
3h	*p*-HO–C_6H_4	$CONH_2$	CN	60	90	246[15f]
3i	(*E*)-PhCH=CH	$CONH_2$	CN	20	90	143[6]

In the reaction of *o*-hydroxybenzaldehyde **4** with **2a**–**b**, the first formed Knoevenagel products underwent cyclisation as a result of nucleophilic attack by the hydroxy group on the cyano group. Thus 2-imino-2*H*-1-benzopyran-3-carbonitrile **5a** and 2-imino-2*H*-1-benzopyran-3-carboxylate **5b** were formed in excellent yields. However, the reaction of ethyl cyanoacetate **2b** with **4** required an elevated temperature (60 °C) and product



4 **2a-b** **5a-b**

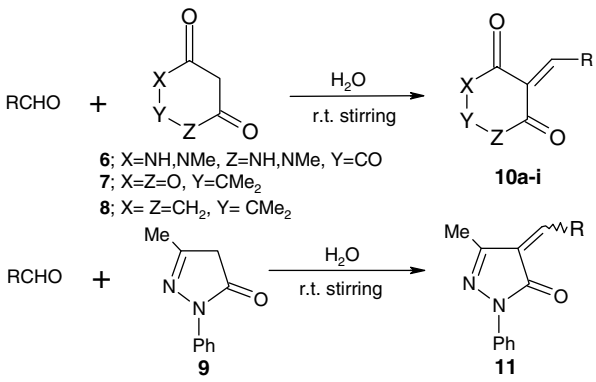
Scheme 2.

Table 2. Reaction time, yields and melting points of the product **5**

Product	R^1	Reaction time (min)	Yield (%)	Mp (°C)
5a	CN	20	88	164[6]
5b	CO_2Et	30	85	136[6]

5b was obtained on cooling the reaction mixture (Scheme 2 and Table 2).

The reaction was further explored using aromatic aldehydes with various heterocyclic and carbocyclic compounds having an active methylene site, for example, barbituric acids **6**, Meldrum's acid **7** and also with dimedone **8** and pyrazolone **9** (Scheme 3). We obtained



Scheme 3.

Table 3. Reaction time, yields and melting points of the products **10** and **11**

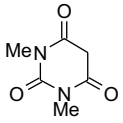
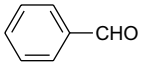
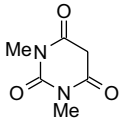
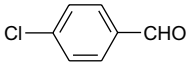
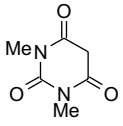
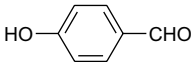
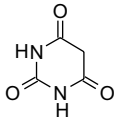
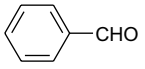
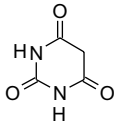
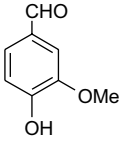
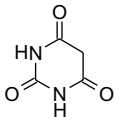
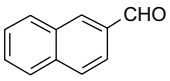
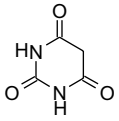
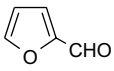
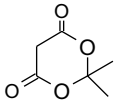
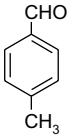
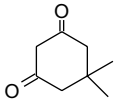
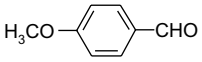
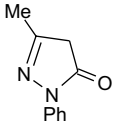
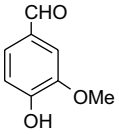
Produts	**6/7/8/9**	RCHO	Time (min)	Yield (%)	Mp (°C)
10a			5	98	159–160
10b			5	94	154–156
10c			8	90	297–298
10d			2	96	256–258[16]
10e			30	as	310–312

Table 3 (*continued*)

Produts	6/7/8/9	RCHO	Time (min)	Yield (%)	Mp (°C)
10f			15	87	268[17](dec)
10g			30	80	264[17]
10h			60	60	149–152
10i			30	60	127–129
11			2	94	139–141

excellent results in all cases and our observations are recorded in Table 3.

In conclusion, we have demonstrated a very simple and highly efficient method for the condensation of aromatic and heteroaromatic aldehydes with various active methylene compounds to give Knoevenagel products in excellent yields. We suggest that the present method may displace all other methods that use various organic solvents, catalysts and that are performed at high temperature.

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