Solvent-free and aqueous Knoevenagel condensation of aromatic ketones with malononitrile

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Abstract

The microwave irradiation-assisted and thermal solvent-free Knoevenagel condensations of aromatic ketones with malononitrile catalyzed by NH_4OAc or silica gel, and the uncatalyzed Knoevenagel condensations in refluxing water have been investigated.
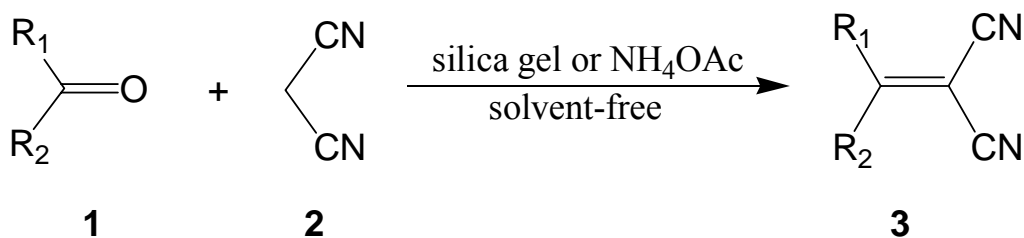
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Introduction

Organic reactions under solvent-free[1,2] and aqueous[3,4,5] conditions have increasingly attracted chemists' interests, particularly from the viewpoint of green chemistry.[6] As an important carbon-carbon bond forming reaction, Knoevenagel condensation has been extensively studied. Generally, this type of reaction is catalyzed by base or Lewis acid in the liquid-phase system. In recent years, chemists paid more and more attention to the clean synthesis of alkenes by Knoevenagel condensations. The Knoevenagel condensations between aldehydes and malononitrile in dry media catalyzed by $ZnCl_2$,[7] silica gel[8] and ammonium acetate (NH_4OAc)-basic alumina[9] have been reported. Recently Bigi's group described the same reactions which could proceed efficiently in water without any catalyst.[10] More recently, we found that aldehydes reacted with malononitrile efficiently in the absence of catalyst and solvent under microwave irradiation and thermal heating conditions.[11] However, much less work on the Knoevenagel condensation involving ketones has been done because ketones are generally very unreactive towards Knovenagel condensation. Little work has been reported on the Knovenagel reaction between ketones and malononitrile under solvent-free condition or in water. Herein we report our study on the Knoevenagel condensations of 9-fluorenone (**1a**), acetophenone (**1b**) and benzophenone (**1c**) with malononitrile (**2**) under solvent-free and aqueous conditions.

Results and Discussion

Microwave irradiation has been utilized as one of the most convenient and efficient ways to promote organic reactions.[12,13] We utilized the microwave irradiation technique to promote the solvent-free Knoevenagel condensation reactions of **1a-c** with **2** and found that the condensation reaction proceeded smoothly under microwave irradiation when catalyzed by either silica gel or NH_4OAc (Scheme 1).

1a, **3a**: R_1, R_2 = fluorenyl; **1b**, **3b**: R_1 = Ph, R_2 = CH_3; **1c**, **3c**: R_1 = R_2 = Ph

Scheme 1. Solvent-free Knoevenagel condensations of **1a-c** with **2** catalyzed by silica gel or NH_4OAc.

The yields of arylidenemalononitriles **3a-c** at different reaction time with irradiation power of 300 W catalyzed by silica gel and NH_4OAc are collected in Table 1 and Table 2, respectively.

Table 1. Yields of Knoevenagel condensations of **1a-c** with **2** catalyzed by silica gel at different reaction time with irradiation power of 300 W

Product	10 min	15 min	20 min	30 min
3a	71%	70%	76%	53%
3b	21%	46%	46%	24%
3c	4%	25%	29%	27%

Table 2. Yields of Knoevenagel condensations of **1a-c** with **2** catalyzed by NH_4OAc at different reaction time with irradiation power of 300 W

Product	1.5 min	2 min	3 min	4 min
3a	51%	74%	68%	66%
3b	60%	56%	47%	17%
3c	21%	41%	44%	44%

It can be seen from Table 1 and Table 2 that the Knoevenagel condensations of **1a-c** with **2** gave higher yields in shorter reaction time when catalyzed by NH_4OAc. Hence NH_4OAc is a more efficient catalyst than silica gel for the Knoevenagel condensation under microwave irradiation. Prolonged irradiation time decreased the product yield due to further side reactions.

The optimized reaction time for the microwave-irradiated solvent-free Knoevenagel condensations of **1a-c** with **2** with NH_4OAc and silica gel as the catalyst is 2 min and 20 min respectively. In contrast, conventional liquid-phase Knoevenagel reaction took much longer time. For example, β-alanine-catalyzed reaction of **1a** with **2** took 16 hr in refluxing benzene under a water separator,[14] while the NH_4OAc-catalyzed reaction of **1c** with **2** required about 12 hr in refluxing benzene with continuous removal of water.[15] The much shorter reaction time under our reaction conditions clearly indicates the advantage of the application of microwave irradiation to the solvent-free reaction. Among the studied ketones, **1a** was the most reactive one and afforded arylidenemalononitrile **3a** in the highest yield, meanwhile **1b** and **1c** gave arylidenemalononitriles **3b** and **3c** in moderate yields due to some side reactions for the former ketone and poor reactivity for the latter ketone.

Different irradiation powers varied between 80 W and 700 W and various catalysts were examined for the Knoevenagel condensation to find the optimal reaction conditions. It was found that the use of very low irradiation power required long reaction times and afforded the condensation products in low yields, while the application of very high irradiation power decreased the product yields due to the occurrence of side reactions even only after short microwave irradiation. Irradiation at 300 W gave the highest yields of products **3a-c**. Compared with NH_4OAc and silica gel, the use of Na_2CO_3, K_2CO_3, $NaHCO_3$, NaOH, NH_4Cl and piperidine as the catalyst for the Knoevenagel reactions of **1a-c** with **2** was ineffective. It should be noted that in the absence of any catalyst the condensation reaction failed to give the desired arylidenemalononitriles **3a-c**.

The Knoevenagel condensations of **1a-c** with **2** catalyzed by NH_4OAc could take place in the absence of any solvent by conventional thermal heating. The yields and reaction conditions for the neat Knoevenagel condensations are listed in Table 3. It was found that the reaction of **1a** with **2** occurred very fast and at lower temperature, reflecting its higher reactivity. The reason for the low yield in the case of **1b** is that more by-products were produced in the condensation reaction between **1b** and **2**.

Table 3. Yield of neat Knoevenagel condensations of **1a-c** with **2** catalyzed by NH_4OAc under thermal conditions

Product	3a	3b	3c
Reaction time	1 hr	1 hr	1 hr
Reaction temp	70 °C	100 °C	150 °C
Yield	91%	13%	52%

Since the solvent-free Knoevenagel condensation between ketones **1a-c** and **2** under microwave irradiation and thermal heating conditions afforded satisfactory results, we became interested in alternative method for the clean synthesis of arylidenemalononitriles. Inspired by the efficient uncatalyzed Knoevenagel condensation of aldehydes with **2** in water[10], we investigated the Knoevenagel condensation of ketones **1a-c** with **2** in water in the absence of any catalyst. To our delight, the uncatalyzed condensation of **1a-c** with **2** indeed occurred in

refluxing water (Table 4). The yield of **3a** is quite good, while that of **3c** is very low because of the relatively low reactivity of **1c** and formation of insoluble solid as the main product. The identity and reason for the formation of the insoluble solid are not clear now.

Table 4. Yields of the uncatalyzed Knoevenagel condensations of **1a-c** with **2** in refluxing water

Product	3a	3b	3c
Reaction time	10 hr	24 hr	24 hr
Yield	74%	45%	5%

In summary, we have investigated the microwave-assisted and thermal solvent-free Knoevenagel condensations of aromatic ketones with malononitrile catalyzed by NH_4OAc or silica gel, as well as the uncatalyzed Knoevenagel condensations in refluxing water. All these protocols are considered as environmentally benign procedures because harmful organic solvents were avoided during the reaction process.

Experimental Section

Solvent-free Knoevenagel condensation under microwave-irradiation conditions. One hundred miligrams of a chosen ketone (**1a, 1b** or **1c**) and equal molar equivalent of **2** and catalyst (equal molar equivalent of NH_4OAc or 300 mg of silica gel) were mixed thoroughly in a mortar. Then the reaction mixture was transferred to a pyrex test tube and subjected to microwave irradiation in a domestic Sanyo EM-350 microwave oven. The cooled reaction mixture was diluted with CH_2Cl_2 and filtered to remove the insoluble material. The filtrate was concentrated in vacuo and the crude product was purified by separation on a silica gel column with ethyl acetate-petroleum ether as the eluent or by recrystallization from ethanol to afford pure arylidenemalononitriles **3a-c**. The identities of compounds **3b** and **3c** were confirmed by comparison of their melting points and spectral data with those reported previously.[9,14-16]

Knoevenagel condensation under thermal-heating conditions. A mixture of a chosen ketone (**1a, 1b** or **1c**, 2 mmol) and **2** (2 mmol) together with equal molar equivalent of NH_4OAc or 5 mL of distilled water was mixed in a round-bottomed flask. The reaction mixture was heated in an oil bath at given temperature for the desired time. After cooling to room temperature, the reaction mixture (after filtration for the aqueous reactions) was isolated by separation on a silica gel column with ethyl acetate-petroleum ether as the eluent or by recrystallization from ethanol to afford pure arylidenemalononitriles **3a-c**.

Acknowledgments

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