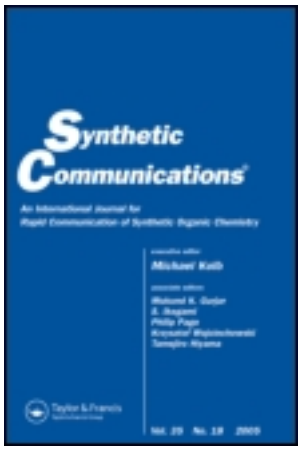

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KNOEVENAGEL CONDENSATION OF ALDEHYDES WITH CYCLIC ACTIVE METHYLENE COMPOUNDS IN WATER

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ABSTRACT

A new route of Knoevenagel condensation of aromatic aldehydes with Meldrum's acid, barbituric acid and dimedone in the presence of cetyltrimethyl ammonium bromide at room temperature in water is described.

The increased attention of the public is a driving force of searching environmentally friendly chemical processes. In the last decade, there was increased recognition that organic reactions carried out in aqueous media may offer advantages over those occurring in organic solvents.[1] We concentrate our attention on using water instead of organic solvent in chemical processes. The Knoevenagel reaction is a common synthetic method for forming carbon–carbon bonds. It had been found that the Knoevenagel condensation reaction of aromatic aldehydes with malononitrile or ethyl cyanoacetate occurred in water.[2] Our purpose is to broaden the scope of the

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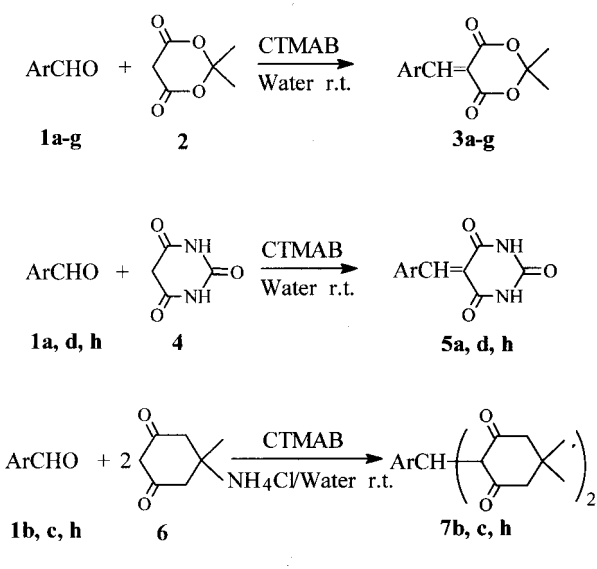
Knoevenagel reaction performed in water. The products of Knoevenagel condensation reaction of aldehydes with cyclic active methylene compounds are very useful reagents.[3] Here we now report the Knoevenagel reaction of aromatic aldehydes **1** with Meldrum's acid, **2** barbituric acid **4** and dimedone **6** in the presence of cetyltrimethyl ammonium bromide (CTMAB) at room temperature in water (Scheme 1).



a=C_6H_5, **b**=4-$NO_2C_6H_4$, **c**=4-$CH_3OC_6H_4$, **d**=4-$(CH_3)_2NC_6H_4$, **e**=4-HOC_6H_4,

f=4-HO-3$CH_3OC_6H_3$, **g**=3,4-O-CH_2-OC_6H_3, **h**=4-ClC_6H_4

Scheme 1.

Surfactants play an important role in the Knoevenagel condensation reaction in water. The relationship between the structure of the surfactant and efficiency of the reaction is investigated. As a model reaction we examined a stirred mixture of benzaldehyde (5 mmol), Meldrum's acid (5 mmol), the surfactant (0.5 mmol), and water (30 mL) at room temperature. The results are listed in Table 1.

A plausible explanation of the role of the surfactants is that the surfactants form micelles in water. Molecules of starting material aggregate to the hydrocarbon chain of the micelle and the reaction is facilitated by the hydrophobic environment. CTMAB is the most efficient agent among the

Table 1. Effect of Surfactant on the Knoevenagel Reaction of Benzaldehyde with Meldrum's Acid to give Arylidene Meldrum's Acid **3a**

Surfactant	Reaction Time (h)	Yield (%) **3a**
$(C_4H_9)_4NBr$	2	69
$C_6H_5CH_2N(C_2H_5)_3Cl$	2	71
$C_{16}H_{33}N(CH_3)_3Br$	2	76
$C_{12}H_{26}NaO_4S$	2	65

surfactants which shows that the presence of short-chain alkyl groups attached to the nitrogen seem to decrease the efficiency of adsorption of the organic molecules. The dominant factor will always be the length of the primary hydrophobic chain. The results also exhibits that cationic surfactants ($R_4N^+X^-$) are more efficient than anionic surfactant (RSO_4Na) for the Knoevenagel condensation reaction in water.

At first we hope to get arylidene dimedone from the reaction of p-nitrobenzaldehyde (**b**) (5 mmol) with dimedone (**6**) (5 mmol) in the presence of CTMAB in water, but only the 1.8-xanthenedione (**7b**), in 38% yield, was obtained. The yield of compound **7b** was 92% when two equivalents of dimedone (**6**) was used. It is interesting that the condensation reaction of p-nitrobenzaldehyde (**b**) with dimedone (**6**) occurs in water only, whereas the reaction with other aromatic aldehydes does not occur. However, when NH_2Cl is added to water containing surfactant, the condensation reaction of aromatic aldehydes with dimedone gives 1.8-xanthenediones (**7**) easily. We also examine the reaction of benzaldehyde (**a**) with two equivalents of Meldrum's acid (**2**) or barbituric acid (**4**) in water, in which the products still were arylidene Meldrum's acid (**3a**) or arylidene barbituric acid (**5a**), in 92% or 89% yield respectively. The experiment shows that Michael adducts, excess (**2**) or (**4**) attacking at the initial Knoevenagel products, are not formed. The different results of the reaction of aromatic aldehydes with Meldrum's acid (**2**), barbituric acid (**4**) and dimedone (**6**) may be related to the electron-withdrawing effect of the ester and amide group weaker than that of carbonyl group, so that arylidene Meldrum's acid (**3a–g**) or arylidene barbituric acid (**5a,d,h**) are not reactive enough to carry out Michael addition.

The experiments show that the order of reactivity of cyclic active methylene compounds for the Knoevenagel reaction in water is barbituric acid (**4**) > Meldrum's acid (**2**) > dimedone (**6**). The difference of reaction rate of dimedone (**6**) with barbituric acid (**4**) and Meldrum's acid (**2**) may ascribe to dimedone very easily transforming into the enol form strongly solvated by

water. The hydrophilicity of solvated dimedone increases, therefore the very low concentration of dimedone adsorbed on the micelle slows the reaction with the aldehydes collected on micelle by hydrophobic effect.

EXPERIMENTAL

Melting points are uncorrected. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai physical instrument factory (SPOIF), China. IR spectra were measured in KBr on PE-580B spectrometer. ^{1}H NMR spectra were recorded at Bruker AC-100SC, using $CDCl_3$ as solvent and TMS as internal reference.

General Procedure

A: Preparation of Arylidene Meldrum's Acid (**3a–g**) or Arylidene Barbituric Acid (**5a,d,h**)

The mixture of aromatic aldehydes (**1**) (5 mmol), Meldrum's acid (**2**) (5 mmol) or barbituric acid (**4**) (5 mmol) and cetyltrimethyl ammonium bromide 0.18 g (0.5 mmol) in 30 mL distilled water is stirred at room temperature for 2 h or 0.5 h (see Table 2). The precipitate is allowed to

Table 2. Knoevenagel Condensation of Aromatic Aldehydes (**1**) with Cyclic Active Methylene Compounds (**2,4,6**) in the Presence of CTMAB in Water

Product	Ar	Cyclic Active Methylene Compound	Reaction Time (h)	Yield (%)
3a	C_6H_5	Meldrum's acid **(2)**	2	76
3b	4-$NO_2C_6H_4$	Meldrum's acid **(2)**	2	85
3c	4-$CH_3OC_6H_4$	Meldrum's acid **(2)**	2	78
3d	4-$(CH_3)_2NC_6H_4$	Meldrum's acid **(2)**	2	69
3e	4-HOC_6H_4	Meldrum's acid **(2)**	2	98
3f	4-HO–3$CH_3OC_6H_3$	Meldrum's acid **(2)**	2	72
3g	3,4-O–CH_2–OC_6H_3	Meldrum's acid **(2)**	2	83
5a	C_6H_5	Barbituric acid (**4**)	0.5	76
5d	4-$(CH_3)_2NC_6H_4$	Barbituric acid (**4**)	0.5	79
5h	4-ClC_6H_4	Barbituric acid (**4**)	0.5	82
7b	4-$NO_2C_6H_4$	Dimedone (**6**)	24	92
7c	4-$CH_3OC_6H_4$	Dimedone (**6**)	24	51
7h	4-ClC_6H_4	Dimedone (**6**)	24	78

stand overnight, collected by suction filtration, washed with petroleum ether and water, and finally dried at room temperature. The crude product is recrystallized by 95% EtOH or 75% EtOH.

B: Preparation of 1.8-Xanthenedione (**7b,c,h**)

The mixture of aromatic aldehydes (**1**) (5 mmol), dimedone (**6**) (10 mmol), NH_4Cl 0.54 g (10 mmol) and CTMAB 0.18 g (0.5 mmol) in 30 mL distilled water is stirred at room temperature for 24 h. The precipitate is allowed to stand overnight, collected by suction filtration, washed with Petroleum ether and water, finally dried at room temperature. The crude product is purified by recrystallization from 95% EtOH.

3a: m.p. 84.5–85.0°C, (lit. (4) 85.0°C). IR: (KBr) 1776, 1738, 1605, 1385, 1233, 818.

3b: m.p. 213.5–214.5°C, (lit. (4) 217.0°C). IR: (KBr) 1758, 1728, 1600, 1367, 1231, 831.

3c: m.p. 122.0–123.0°C, (lit. (4) 126.0°C). IR: (KBr) 1747, 1714, 1574, 1389, 1234, 836.

3d: m.p. 174.0–175.0°C, (lit. (4) 175.0°C). IR: (KBr) 1730, 1698, 1611, 1399, 1262, 819.

3e: m.p. 200.0–201.0°C, (lit. (4) 195.0°C). IR: (KBr) 3280, 1750, 1695, 1585, 1450, 1270, 840.

3f: m.p. 135.5–136.5°C, (lit. (4) 136.0–138.0°C). IR: (KBr) 3343, 1740, 1700, 1586, 1469, 1244, 811.

3g: m.p. 172.0–173.0°C, (lit. (5) 167.0–169.0°C). IR: (KBr) 1740, 1710, 1561, 1382, 1248, 814.

5a: m.p. 248.5–249.5°C, (lit. (6) 256.0°C). IR: (KBr) 3211, 1700, 1624.

5d: m.p. 266.0–267.0°C, (lit. (7) 264.0°C). IR: (KBr) 3180, 3064, 1732, 1660, 1614.

5h: m.p. 271.0–272.0°C, (lit. (8) 271.0°C). IR: (KBr) 3211, 3084, 1753, 1702, 1674.

7b: m.p. 187.5–188.5°C, (lit. (9) 183.0°C). IR: (KBr) 3318, 1721, 1634, 1302, 1186.

^{1}H NMR: δ 1.1 (s, 6H), 1.2 (s, 6H), 2.3 (s, 4H), 2.4 (s, 4H), 5.5 (s, 1H), 7.0 (d, 2H, $J = 8.7$ Hz), 8.1 (d, 2H, $J = 8.7$ Hz), 11.9 (s, 1.3H).

7c: m.p. 125.5–126.5°C, IR: (KBr) 3424, 1790, 1590, 1303, 1165.

^{1}H NMR: δ 1.1 (s, 12H), 2.5 (s, 8H), 3.8 (s, 3H), 5.3 (s, 1H), 6.8 (d, 2H, $J = 9.0$ Hz), 7.0 (d, 2H, $J = 9.0$ Hz), 11.8 (s, 1.1H).

7h: m.p. 145.5–146.5°C, (lit. (9) 140.0–142.0°C). IR: (KBr) 3431, 1720, 1592, 1302, 1121.

^{1}H NMR: δ 1.0 (s, 6H), 1.2 (s, 6H), 2.3 (s, 4H), 2.4 (s, 4H), 5.5 (s, 1H), 6.8 (d, 2H, $J = 8.5$ Hz), 7.4 (d, 2H, $J = 8.5$ Hz), 11.9 (s, 2H).

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