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The Condensation of Aromatic Aldehydes with Acidic Methylene Compounds in Water

Da Qing SHI[1,2,*], Jing CHEN[1], Qi Ya ZHUANG[1], Xiang Shan WANG[1], Hong Wen HU[2]

[1]Department of Chemistry, Xuzhou Normal University, Xuzhou 221009
[2]Department of Chemistry, Nanjing University, Nanjing 210093

Abstract: The condensation of aromatic aldehydes with acidic methylene compounds such as malononitrile, methyl cyanoacetate, cyanoacetamide, 5,5-dimethyl-1,3-cyclohexanedione, bartbituric acid and 2-thiobarbituric acid proceeded very efficiently in water in the presence of triethylbenzylammonium chloride (TEBA) and the products were isolated simply by filtration.

Keywords: Condensation, aromatic aldehyde, acidic methylene compound, water, green chemistry.

Knoevenagel condensation is one of the elemental reactions in organic chemistry. Traditionally, it was carried out in the presence of a base catalyst[1], *e.g.*, ammonia, amine and their salts. For its importance in organic synthesis, many catalysts such as aluminum oxide[2], xonotlite[3], $AlPO_4$-Al_2O_3[4], KF-Al_2O_3[5], K10-$ZnCl_2$[6], cadmium iodide[7] and KF-montmorillonite[8] have been reported as useful catalysts for Knoevenagel condensation. Generally this reaction is performed in organic solvent, such as benzene, ethanol and DMF, most of them are toxic. The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. As one of the most promising approaches, water is used as reaction medium. Breslow[9,10] showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in 1980s. Previously the scant solubility of the reactants was the main reason that ruled this solvent out from studies. Further reasons that make water unique among solvents are that it is cheap, not inflammable, and more important, nontoxic. In this paper we wish to report the condensation of aromatic aldehydes with acidic methylene compounds in water.

When aromatic aldehydes **1**, malononitrile or methyl cyanoacetate or cyanoacetamide **2** and TEBA were stirred at 70 ºC for 5 h in water, the desired substituted alkenes **3** were obtained in good yields (**Scheme 1**).

Table 1 summarized the results on this reaction. This protocol did not require the use of any organic solvent. In fact the substituted alkenes **3** were isolated in a

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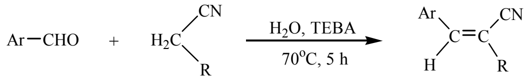
[*] E-mail: dqshi@xznu.edu.cn

practically pure form by simple filtration of the final aqueous mixture. The reactions occurred in a short time. The aqueous phase obtained after filtration can be reused as the reaction medium. The reuse of the aqueous medium was repeated four subsequent runs and the yields obtained were excellent. As an example, we report the results obtained in the reuse of the aqueous medium in the reaction of **1a** and **2a** in **Table 2**.

Scheme 1



1 **2** **3**

Table 1 The results on the reaction of aromatic aldehydes **1** and malonontrile or methyl cyanoacetate or cyanoacetamide **2**

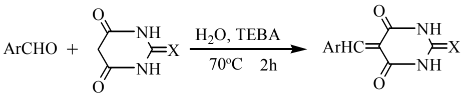
Entry	Ar	R	Yield(%)	mp (°C) (Lit.)
3a	4-ClC_6H_4	CN	90	156~158 (162~164[8])
3b	2-ClC_6H_4	CN	73	96~97 (95~96[8])
3c	4-$CH_3OC_6H_4$	CN	90	114~115 (114~115[8])
3d	3,4-$OCH_2OC_6H_3$	CN	95	201~202 (198~199[8])
3e	4-$CH_3C_6H_4$	CN	74	134~135 (136~137[8])
3f	2-$NO_2C_6H_4$	CN	90	138~139 (139~140[11])
3g[18]	4-$NO_2C_6H_4$	$COOCH_3$	98	177~178
3h[18]	2-ClC_6H_4	$COOCH_3$	90	109~111
3i[18]	4-ClC_6H_4	$COOCH_3$	92	126~127
3j[18]	2,4-$Cl_2C_6H_3$	$COOCH_3$	87	102~103
3k[18]	3-$NO_2C_6H_4$	$COOCH_3$	94	136~137
3l	2-$NO_2C_6H_4$	$COOCH_3$	94	142~143 (138~140[11])
3m	4-ClC_6H_4	$CONH_2$	71	207~208 (205~206[12])
3n	4-$NO_2C_6H_4$	$CONH_2$	81	231~232 (233~234[12])
3o	2-$NO_2C_6H_4$	$CONH_2$	78	168~170 (173~174[12])
3p	3-$NO_2C_6H_4$	$CONH_2$	84	157~158

Table 2 Yield of the reaction of **1a** and **2a** with the reusing water medium

Times	1	2	3	4	5
Yield **3a** (%)	90	90	93	93	93

Treatment of aromatic aldehydes **1** with barbituric acid **4i** or 2-thiobarbituric acid **4ii** under the same reaction conditions afforded 5-arylidenebarbituric acid **5i** or 5-arylidene- 2-thiobarbituric acid **5ii** (**Scheme 2**) and the results are summarized in **Table 3**.

Scheme 2



1 **4i-ii** **5i-ii**

i, X=O

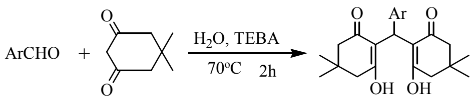
ii, X=S

However, treatment of aromatic aldehydes **1** with 5,5-dimethyl-1,3-cyclohexanedione **6** under the same reaction conditions Knoevenagel condensation and Michael addition have taken place and 2,2′-arylmethyl-enebis(3-hydroxyl-5,5-dimethyl-2-cyclohexene-1-one **7** are obtained in good yield (**Scheme 3**) and the results are summarized in **Table 4**.

Table 3 The results on the reaction of aromatic aldehydes **1** and barbituric acid or 2-thiobarbituric acid **4**

Entry	Ar	X	Yield (%)	mp (°C) (Lit.)
5a	4-ClC_6H_4	O	84	297~298 (290~293[13])
5b	4-$CH_3C_6H_4$	O	93	276~277 (278~280[14])
5c	4-$CH_3OC_6H_4$	O	97	296~298 (298~300[14])
5d[18]	4-OH-3-$CH_3OC_6H_3$	O	99	293~294
5e	3,4-$OCH_2OC_6H_3$	O	97	>350 (>350[14])
5f[18]	4-FC_6H_4	O	95	295~297
5g	2,4-$Cl_2C_6H_3$	O	96	268~369 (265~270[14])
5h	4-ClC_6H_4	S	98	291~292
5i	4-$CH_3C_6H_4$	S	98	>300(>300[15])
5j	4-$CH_3OC_6H_4$	S	98	>300(>300[15])
5k	3,4-$OCH_2OC_6H_3$	S	99	>300(>300[15])
5l[18]	4-FC_6H_4	S	99	217~218
5m[18]	2,4-$Cl_2C_6H_3$	S	98	264~265
5n[18]	4-OH-3-$CH_3OC_6H_3$	S	98	261~262

Scheme 3



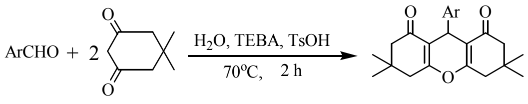
1 **6** **7**

Table 4 The results on the reaction of aromatic aldehydes **1** and 5,5-dimetyl-1,3-cyclohexanedione **6**

Entry	Ar	Yield (%)	mp (°C) (Lit.)
7a	4-ClC_6H_4	90	142~144 (140~142[16])
7b	4-$CH_3C_6H_4$	97	127~129 (126~128[16])
7c[18]	2-ClC_6H_4	84	197~199
7d[18]	2,4-$Cl_2C_6H_3$	85	188~190
7e[18]	4-$CH_3OC_6H_4$	91	142~143
7f	3,4-$OCH_2OC_6H_3$	93	168~169 (168~170[16])
7g	4-HO-3-$CH_3OC_6H_3$	97	190~192 (192~194[16])
7h	C_6H_5	90	190~191 (188~190[16])
7i	4-$NO_2C_6H_4$	92	188~190 (188~190[16])
7j[18]	4-FC_6H_4	91	187~189

On the other hand, the reaction of aromatic aldehydes **1** with 5, 5-dimethyl-1, 3-cyclohexanedione **6** and TsOH afforded 3, 3, 6, 6-tetramethyl-1, 8-dioxo-2, 3, 4, 4a, 5, 6, 7, 8, 9, 9a-decahydro-1*H*-xanthene **8** (**Scheme 4**).

Scheme 4



1 **6** **8**

Table 5 The results on the reaction of aromatic aldehydes **1** and 5,5-dimethyl-1,3-cyclohexamedione **6** and TsOH

Entry	Ar	Yield (%)	mp (°C) (Lit.)
8a	4-ClC$_6$H$_4$	99	231~233 (230~231[17])
8b	4-CH$_3$C$_6$H$_4$	98	216~218 (218~220[17])
8c	4-CH$_3$OC$_6$H$_4$	97	227~228 (224~226[17])
8d	C$_6$H$_5$	91	201~203 (198~200[17])
8e	4-NO$_2$C$_6$H$_4$	98	222~224 (222~224[17])
8f[18]	4-FC$_6$H$_5$	69	225~227

In conclusion we report the reaction of aromatic aldehydes and malonitrile, methylcyanoacetate, cyanoacetatmide, 5,5-dimethyl-1,3-cyclohexamedione, barbituric acid and 2-thiobarbubituric acid, which were carried out in water in the presence of TEBA. Compared to the classical Knoevenagel condensation, this method has the advantages of excellent yields, inexpensive reagents and highly environmentally friendly condition.

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