Facile Microwave-Promoted Knoevenagel Condensation and the Combination of Knoevenagel/ Michael addition Reaction in Aqueous Medium Containing Ionic Surfactant

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Abstract: A simple, efficient, environment-friendly and high yielding procedure is developed for the Knoevenagel condensation and the combination of Knoevenagel/ Michael addition reaction of various 1, 3-dicarbonyls and aryl aldehydes in an aqueous surfactant medium. The reaction can be dramatically improved under microwave-irradiation.

Keywords: 4-hydroxy coumarin, barbituric acid, dimedone, Knoevenagel condensation, microwave-irradiation, surfactant medium.

INTRODUCTION

Synthesis of heteroaromatic compounds has received increasing attention in organic chemistry, since a wide variety of such molecules shows potential biological and agrochemical activities [1]. Several reactions have been discovered, and their applications in organic chemistry have also been well documented in the literature. The most important ones include Diels-Alder reaction [2], Knoevenagel condensation reaction [3], Pd (0)-catalyzed insertion reaction [4], etc. Knoevenagel condensation reaction holds a prominent position in organic synthesis due to its numerous applications in elegant synthesis of fine chemicals and biologically important heterocycles, such as, xanthene [5], coumarin [6], dicoumarin [7] and their derivatives. They possess various biological properties including antibacterial, antiviral, antioxidant and anti-inflammatory activities [8]. In recent years, several new efficient methods have been developed including the use of catalysts, silica gel [9], Mn(III) [10], silica-ammonium acetate [11], DBU [12], $BiCl_3$ [13], $ZnCl_2$ [14], water/TEBA [15], microwave [16] and also solid phase reaction [17] . All these methods, however, suffer from drawbacks such as unsatisfactory yield, extended reaction time, elevated temperature, tedious work-up, and the use of anhydrous organic solvents and relatively expensive reagents.

One of the major drawbacks of conventional organic synthesis is the use of organic solvents. The most attractive alternative to organic solvents is water because of its easy availability, safe and environment friendly properties. In this endeavor, a number of reactions such as Diels-Alder [18], 1, 3-dipolar cycloaddition [19], oxidation [20], etc are performed successfully in water with the aid of surfactant, which helps in solubilizing the organic substrate in aqueous medium. In addition, reactions in aqueous surfactant medium illustrate activities and selectivity are not usually observed in water or even organic solvents [21].

However, to the best of our knowledge, reports related to the Knoevenagel condensation and the combination of Knoevenagel/Michael addition reaction in ionic surfactant medium promoted by microwave irradiation have not been published till date. We herein, report for the first time, one-pot protocol for the Knoevenagel condensation and the combination of Knoevenagel/Michael addition reaction in surfactant medium promoted by microwave-irradiation. Microwave activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions with a short reaction time and in high yields [22].

RESULT AND DISCUSSION

The reaction of dimedone (**1**), benzaldehyde (**2a**), in surfactant medium under microwave-irradiation has been considered as a standard model reaction. In order to optimize the reaction condition, we have screened a number of different surfactants on the model reaction. When the reaction was carried out in presence of only water under microwave-irradiation, it gave lower yield of the product even of the prolonged reaction time. However, when the same reaction was conducted under microwave- irradiation using CPC (cetylpyridinium chloride) or SDS (sodium dodecyl sulphate) as a surfactant, it gave better yields of product (Table **1** entry 2, 3), but the best result was achieved by using AOT (sodium *bis* -2-ethyl hexyl sulfosuccinate) as a surfactant under microwave-irradiation (Table **1**, entry 4). Ninety two percent of 2, $2^{/}$-arylmethylene *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) was obtained by simple recrystallization from ethanol. Among SDS, CPC and AOT, the latter accelerates the reaction better, presumably due to the stronger binding of the AOT with the substrate, which is expected to have more hydrocarbon content in the core region than SDS or CPC [23].

Moreover, we investigated the effects of different microwave power settings and temperature variations. It was observed that the irradiation at the lower power required longer reaction time, the excellent result was achieved at 150

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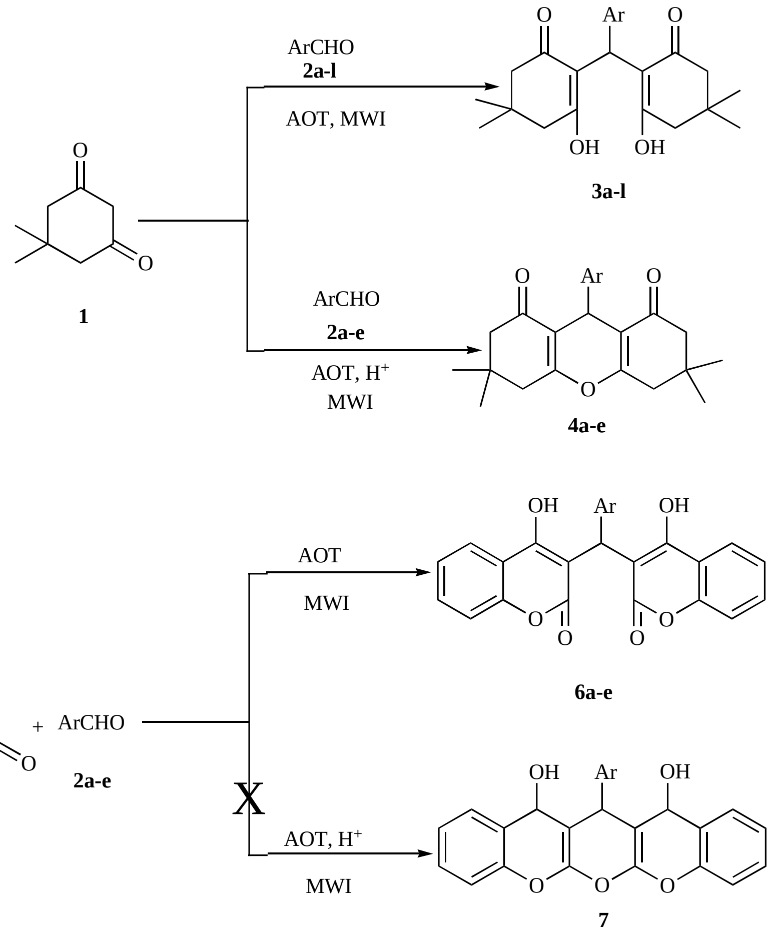
Table 1. Optimization of the Reaction Condition Under Microwave-Irradiation and Conventional Methods in Presence of Different Surfactants

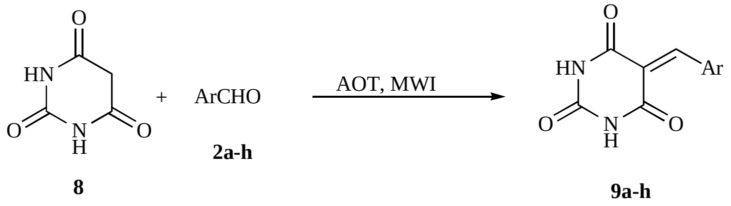
Microwave				Conventional		
Entry	**Surfactant**	**Time (min)**	**Yields (%)**	**Surfactant**	**Time (h)**	**Yields (%)**
1	Water	10	55	Water/TEBA	1.5	90 [Ref. No 15]
2	SDS	5	80	SDS	3	91 [Ref. No 24]
3	CPC	5	82	CPC	1.3	78 [present work]
4	AOT	5	92	AOT	1.3	82 [present work]

watt at 60 °C and further increasing the watt or temperature did not affect much.

After optimizing the condition, the generality of the method was examined by the reaction of several substituted aryl aldehydes with dimedone or 4-hydroxy coumarin, a series of differently substituted compounds (**3a-l**), (**6a-e**) were obtained in very good yields. These results are listed in (Table **2**). In the reaction of dimedone or 4-hydroxy coumarin with aryl aldehydes, the first formed Knoevenagel products underwent Michael addition to give corresponding products (**3a-l, 6a-e**). Furthermore, in case of dimedone if the reaction was carried out in presence of catalytic amount of sulfuric acid in a surfactant medium, it furnished cyclized products (**4a-e**). On the other hand, when 4-hydroxy coumarin (**5**) was treated with aryl aldehyde (**2**) and catalytic amount of conc. sulfuric acid, it afforded uncyclized product (**6**) rather than cyclized product (**7**). Encouraged by these results, we extend the scope of the present protocol for the condensation of



Scheme 1.



Scheme 2.

Table 2. Synthesis of Compounds 3, 4, 6 and 9 under Microwave Irradiation Conditions in Presence of AOT

Entry	Products	Ar	Time (min)	M.P. (^{o}C)	Yields (%)
1	**3a**	C_6H_5	5	198-200	92
2	**3b**	4-$OCH_3C_6H_4$	7	230-231	86
3	**3c**	3-$NO_2C_6H_4$	5	158-160	90
4	**3d**	4-FC_6H_4	5	119-120	89
5	**3e**	4-BrC_6H_4	5	220-222	91
6	**3f**	2-$CH_3C_6H_4$	6	156-158	85
7	**3g**	4-CNC_6H_4	6	210-212	88
8	**3h**	3-ClC_6H_4	7	175-176	89
9	**3i**	4-N $(CH_3)_2C_6H_4$	6	227-228	85
10	**3j**	4-$CH_3C_6H_4$	6	208-210	87
11	**3k**	4-$NO_2C_6H_4$	5	229-230	93
12	**3l**	4-ClC_6H_4	5	210-212	90
13	**4a**	C_6H_5	5	198-199	91
14	**4b**	4-$OCH_3C_6H_4$	5	230-231	88
15	**4c**	3-$NO_2C_6H_4$	7	165-166	86
16	**4d**	4-BrC_6H_4	6	208-210	89
17	**4e**	4-FC_6H_4	6	188-189	90
18	**6a**	C_6H_5	5	229-230	91
19	**6b**	4-$NO_2C_6H_4$	4	231-232	92
20	**6c**	4- $CH_3C_6H_4$	6	272-274	86
21	**6d**	4-$OCH_3C_6H_4$	7	246-247	87
22	**6e**	4-BrC_6H_4	5	258-260	90
23	**9a**	C_6H_5	5	263-264	90
24	**9b**	4-$CH_3C_6H_4$	5	276-277	89
25	**9c**	4-$NO_2C_6H_4$	4	274-275	90
26	**9d**	4-BrC_6H_4	5	246-247	90
27	**9e**	$C_{10}H_7$	6	284-286	90
28	**9f**	3-$NO_2C_6H_4$	5	254-255	89
29	**9g**	4-FC_6H_4	6	295-296	91
30	**9h**	2-$OCH_3C_6H_4$	6	267-268	88

various aryl aldehydes with barbituric acid and it afforded compounds (**9a-h)** in good to excellent yields. It is noteworthy to mention that various aryl aldehydes containing electron donating to electron withdrawing functional groups at different positions in the aromatic ring did not show any remarkable effect on this conversion because the desired products were obtained in high yields in a relatively short reaction time (Table **2**).

CONCLUSION

In conclusion, AOT mediated microwave-irradiation technique is an efficient method for Knoevenagel condensation reaction. Prominent advantages of this method are novelty, operational simplicity, short reaction time, easy product isolation and higher yields. We believe that this method is a useful addition to the present methodologies for the Knoevenagel condensation, as well as Knoevenagel condensation followed by Michael addition reaction.

EXPERIMENTAL

All the experiments were carried out in MATTHEWS, NC- MADE IN USA. MODEL-DISCOVER-S. MODEL NO-NP-1009, Microwaves Digester in closed vessel. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Spectrum BX FT-IR, Perkin Elmer (υ_{max} in cm^{-1}) on KBr disks. ^{1}H NMR and ^{13}C NMR (400 MHz and 100 MHz respectively) spectra were recorded on Bruker Avance II-400 spectrometer. Mass spectra were recorded on Waters 2695. CHN were recorded on CHN-OS analyzer (Perkin Elmer 2400, Series II). Silica gel G (E-mark, India) was used for TLC. Hexane refers to the fraction boiling between 60 and 80 ^{o}C.

General Procedure for the Synthesis of Compound 3a-l, 6a-e, 9a-h

Aryl aldehyde **2** (1 mmol) and 1, 3, dicarbonyl **1, 5** (2 mmol) and **8** (1 mmol) were added to an aqueous solution of AOT (15 mmol) successively and mixed thoroughly. The resulting mixture was irradiated under microwave at 150 watt and 60 ^{o}C until the TLC showed the dissappearance of the starting materials. On completion, the resulting mixture was cooled to room temperature, filtered and washed with water (3 × 5 ml). The residue obtained was recrystalized from ethanol to get pure crystalline products **(3a-l, 6a-e and 9a-h).**

Genaral Procedure for the Synthesis of Compound 4a-e

Aryl aldehyde **2a-e** (1.0 mmol), dimedone **1** (2.0 mmol) and catalytic amount of concentrated sulfuric acid were added to an aqueous solution of AOT (15 mmol) and mixed thoroughly. The resulting mixture was irridiated at 150 watt and 60 ^{o}C temperature for the time mentioned in Table **2**. The progress of the reaction was monitored by TLC and after completion, the resulting mixture was cooled to room temperature and filtered. The residue was washed with water (3 × 5 ml) and recrystalized from ethanol to get pure crystalline products (**4a-e**).

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

REFERENCES

[1] Scriven, F.V. *Comprehensive Heterocyclic Chemistry*, Ed.; Katrizky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Richard, J. K, Oxford, **1996**.

[2] Saito, A.; Yanai, H.; Taguchi, T. Bis-aluminated triflic amide promoted Diels–Alder reactions of α,β-unsaturated lactones. *Tetrahedron Lett*., **2004**, *45*, 9439-9442.

[3] Wang, G.W.; Cheng, B. Solvent-free and aqueous Knoevenagel condensation of aromatic ketones with malononitrile. *Arkivoc*., **2004**, *6*, 4-8.

[4] (a) Majundar, K. C.; Pal, A. K.;. Debnath, P. K.; Taher, A. Highly effective regioselective method for the synthesis of substituted coumarin- and quinolone-annulated heterocycles using a palladium(0)-catalyzed reaction. *Synthesis.,* **2007**, 1707-1711.(b)Majundar, K. C.; Debnath, P. K.; Taher, A.; Pal, A. K. Intramolecular cyclization reaction - Palladium(0)-catalyzed cyclization is more effective than tin hydride mediated reaction. *Can. J. Chem.*, **2008**, *86*, 325-332.

[5] Kumar, R.; Nandi, G.C.; Verma, R.K.; Singh, M.S. A facile approach for the synthesis of 14-aryl- or alkyl-14H-dibenzo[a,j]xanthenes under solvent-free condition *Tetrahedron Lett.*, **2010**, *51*, 442-445.

[6] Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. Neutral alumina catalysed synthesis of 3-nitro-1,2-dihydroquinolines and 3-nitrochromenes, under solvent-free conditions, *via* tandem process. *Green Chem.*, **2005**, *7*, 825-827.

[7] Patel, A. K.; Patel, N.H.; Patel, M.A.; Brahmbhatt, D.I. Synthesis, characterization and antimicrobial activity of some 4-aryl-2,6-di(coumarin-3-yl)pyridines. *Arkivoc*., **2010**, *9*, 28-38.

[8] Cabello, J.A.; Campelo, J.M.; Carcia, A.; Luna, D.; Marinas, J.M. Knoevenagel Condensation in the Heterogeneous Phase Using $AlP0_4$-Al_20_3 as a New Catalyst. *J. Org. Chem*., **1984**, *49*, 5195-5197.

[9] Maghadam, K.R.; Rouchi, S. Silica-bound benzoyl chloride mediated the solid-phase synthesis of 4H-3,1-benzoxazin-4-ones. *Beilstein Journal of organic chemistry*., **2009**, *5*, 1-4.

[10] Kantam, M. L.; Bharathi, B. Mn(III) salen catalyst for Knoevenagel condensation – a novel heterogeneous system. *Catalysis Lett.*, **1998**, *55*, 235-237.

[11] Gupta, R.; Gupta, M.; Paul, S.; Gupta, R. Silica supported smmonium scetate: An efficient and recyclable heterogeneous catalyst for Knoevenagel condensation between aldehydes or ketones and active methylene group in liquid phase *Bull. Korean Chem. Soc*., **2009**, *30*, 2419-2421.

[12] Kakadea, G.; Madjeb, B.; Warea, M.; Shingare, M. Phase transfer catalyzed one-pot synthesis of 14-aryl-14-H-dibenzo [a, j] xanthenes in aqueous medium. *Bull. Catal. Soc. India*. **2007**, *6*, 99-103.

[13] Prajapati, D.; Sandhu, J.S. Bismuth(III)chloride as a New Catalyst for Knoevenagel Condensation in the Absence of Solvent. *Chem. Lett*., **1992**, 1945-**1949**.

[14] Delgado, F.; Tamariz, J.; Zepeda, G.; Landa, M.; Miranda, R.; Garcia, J. Knoevenagel Condensation Catalyzed by a Mexican Bentonite Using Infrared Irradiation. *Synth. Commun.*, **1995**, *25*, 753-759.

[15] Shi. D.Q.; Chen, J.; Zhuang, Q.Y.; Wang, X. S.; Hu, H.W. The Condensation of Aromatic Aldehydes with Acidic Methylene Compounds in Water *Chineese Chemical Lett*., **2003**, *14*, 1242-1245.

[16] Naglaa, M.; Abd, El-R.; Ahmed, A. El-K.; Mohamed, F. M. Simplified approach to the uncatalyzed Knoevenagel condensation and Michael addition reactions in water using microwave irradiation. *Synth. Commun*., **2007**, *37*, 3961-3970.

[17] Hamper, B. C.; Kolodziej, S. A.; Scates, A. M. Knoevenagel condensation of unsymmetrical malonamic esters and malonates on a solid support. *Tetrahedrn Lett*., **1998**, *39*, 2047-2050.

[18] Otto, S.; Engberts, J. B. F. N. Reaction and synthesis in micellar media. *Ed.; Texter, J,* New York. **2005**.

[19] Wang, Q.; Chittabonia, S.; Hannah, N. B. Highlights in Organic Chemistry Advances in 1,3-Dipolar Cycloaddition Reaction of Azides and Alkynes - A Prototype of “Click” Chemistry. *Lett. Org. Chem.*, **2005**, *2*, 293-301.

[20] Sanchez, A.V.; Jose, G.A. Green oxidation of organic compounds: manganese sulphate/oxone/water. *J. Mex. Chem. Soc.,* **2007**, *51*, 213-216.

[21] (a) Bahrami, K.; Khodaei, M. M.; Nejati, A. Synthesis of 1,2-disubstituted benzimidazoles, 2-substituted benzimidazoles and 2-

substituted benzothiazoles in SDS micelles. *Green.Chem*., **2010**, *12*, 1237-1241. (b) Tandon, K.V.; Maurya, H.K. Water-promoted unprecedented chemoselective nucleophilic substitution reactions of 1,4-quinones with oxygen nucleophiles in aqueous micelles. *Tetrahedron Lett*., **2010**, *51,* 3843-3847.

[22] Loupy, E. A. *Microwave in Organic Synthesis*. Wiley, **2002**.

[23] Fendler, J. H.; Fendler, E. J.; *Catalysis in Micellar and Macromolecular System*. New York, **1975**.

[24] Liu, Li-B.; Jin, T-S.; Han, Li-S, Li, M.; Qi, N.; Li, T-S. The reaction of aromatic aldehyde and 1,3-cyclohexanedione in aqueous medium. *E-J. Chem.*, **2006**, *3*, 117-121.