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A novel light induced Knoevenagel condensation of Meldrum's acid with aromatic aldehydes in aqueous ethanol

Somnath Ghosh *, Jhantu Das, Subhagata Chattopadhyay

Department of Chemistry, Jadavpur University, Kolkata 700 032, India

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ABSTRACT

A highly efficient environment-friendly photochemical methodology has been developed for the condensation of Meldrum's acid with aromatic aldehydes in water–ethanol solution *sans* any catalyst, support or promoter.

The use of Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione), prepared by Meldrum[1] in 1908, as an active methylene compound was utilized after about 40 years of its preparation, when Davidson[2] in 1948 correctly assigned its structure along with the position of acidic hydrogen onto the central carbon atom. Interestingly, its high acidity is still an attractive area of study as evidenced by the recent works of Fillion et al.[3] It is well known that Meldrum's acid can undergo Knoevenagel condensation with aldehydes and ketones (as imines) in an efficient fashion and excellent reviews[4] have been published. The various condensing agents that have been employed are sodium hydroxide,[5] pyridine,[2,6] piperidine/glacial acetic acid,[7] metal salts[8,9] ionic liquid,[10] triethyl ammonium formate,[11] piperidinium acetate,[12] anhydrous zinc chloride,[13] neutral alumina,[14] kaolin,[15] and clays[16] in different solvents[17] such as DMF or DMSO and under varied experimental conditions like microwave irradiation,[18] ultrasound exposure,[7] and melt reaction,[19] and also in solid phase.[20] Additionally, uncatalyzed reactions in water/water-surfactant[21] have also been reported. It is noteworthy to observe that all these protocols have been accomplished under thermal reaction conditions and disposal of toxic solvents and catalysts often pose a problem.

In order to perform organic reactions in environment-friendly conditions, photochemical reactions particularly using visible light are an attractive area of study and more so, if these reactions are done in water or water–ethanol mixtures; and generally considered as a clean and green procedure.[22,23] Our enduring interest in the realm of photochemical reactions[24] has prompted us to envisage a hitherto unknown visible light induced uncatalyzed and unsupported photochemical Knoevenagel condensation of the title compound with various aromatic aldehydes in water–ethanol mixture (1:1 v/v) and also under microwave condition over neutral alumina (Scheme 1) and we wish to report here our observations.

The photochemical reactions were found to be very clean and the products were obtained in extremely pure crystalline states with an average yield of 76–92%. In general, the products were isolated by simple filtration and needs no further crystallization. On the other hand, the microwave assisted reaction, accomplished in an average time period of 30–150 s in the temperature range of 81–181 °C, products were isolated by column chromatography and required further crystallization from appropriate solvents with yield varying from 55% to 78%; and the results of these experiments are given in Table 1. It appears that the microwave reactions are better than the light induced reactions, but so far as the isolation and purity of the products (**3**) are concerned, the photochemical reactions are more efficient though, the time required is more than the microwave assisted reactions.

Furthermore, by this novel photochemical methodology, coumarin-3-carboxylic acid, a potent bioactive substance,[25] useful as a fluorescent probe[26,27] and triplet sensitizer,[28,29] has been synthesized in almost analytically pure form and in amazingly high yield (Scheme 2).

In conclusion, we have developed a potentially efficient, absolutely clean and very high yielding eco-friendly methodology[30] in neutral aqueous ethanol solution for the condensation of Meldrum's acid with aromatic aldehydes devoid of any unwarranted

* Corresponding author. Tel.: +91 033 2414 6223; fax: +91 033 2414 6223.
E-mail address: ghoshsn@yahoo.com (S. Ghosh).

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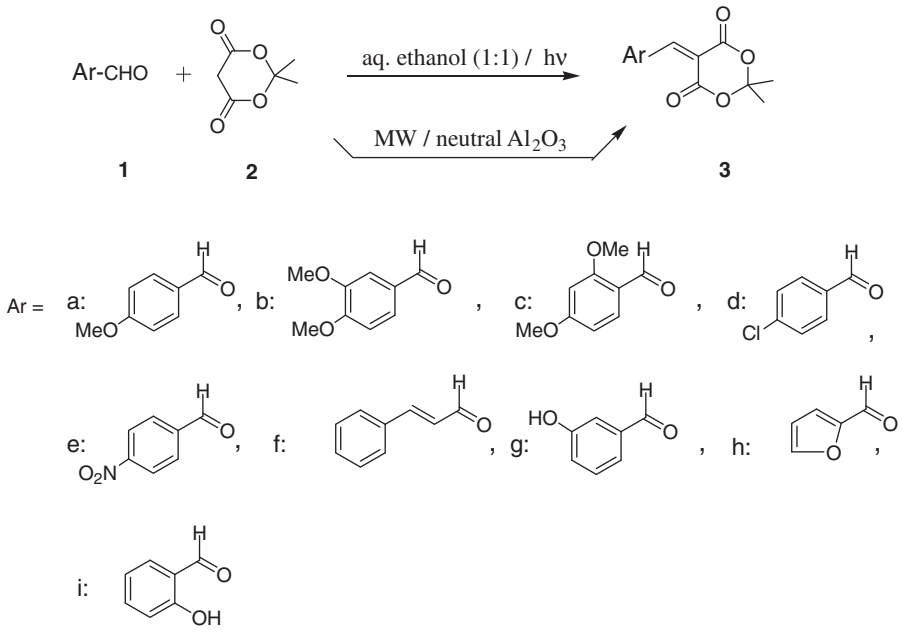


Scheme 1. Photochemical Knoevenagel condensation between aromatic aldehydes and Meldrum's acid.

Table 1
Results of Photochemical Knoevenagel condensation of aromatic aldehydes and Meldrum's acid

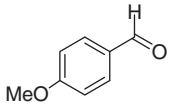
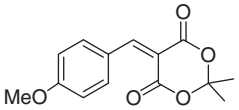
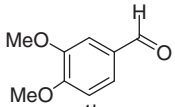
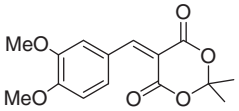
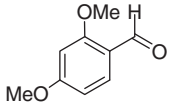
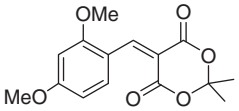
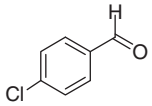
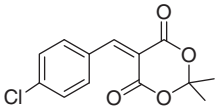
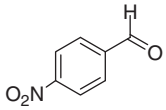
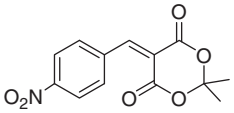
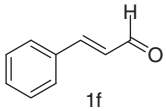
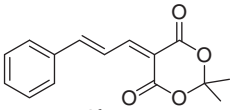
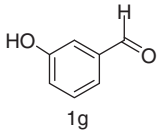
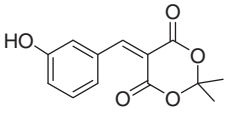
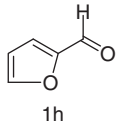
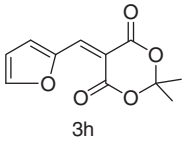
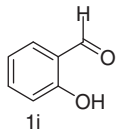
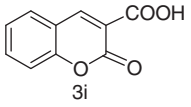
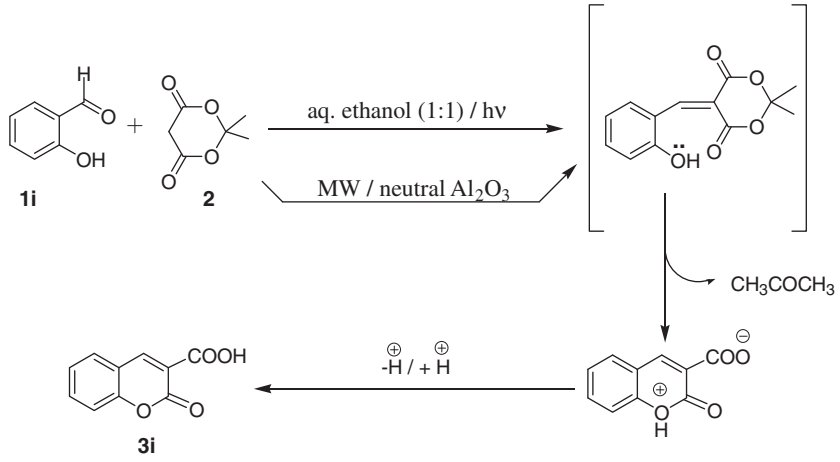
Entry	Substrate	Product[a]	Yield[b] (%) [lit.[18c] yield (%)]	Mp (°C)	Time (min)
1	 1a	 3a	*A* (*hv*): 92 *B* (MW): 74[90]	127	15
2	 1b	 3b	*A* (*hv*): 88 *B* (MW): 77[99]	171	10
3	 1c	 3c	*A* (*hv*): 88 *B* (MW): 67	140	15
4	 1d	 3d	*A* (*hv*): 90 *B* (MW): 56[91]	156	15
5	 1e	 3e	*A* (*hv*): 76 *B* (MW): 55[83]	217–18	10
6	 1f	 3f	*A* (*hv*): 89 *B* (MW): 75	109	15
7	 1g	 3g	*A* (*hv*): 79 *B* (MW): 58	170–71	20

Table 1 (*continued*)

Entry	Substrate	Product[a]	Yield[b] (%) [lit.[18c] yield (%)]	Mp (°C)	Time (min)
8	 1h	 3h	*A* (*hv*): 87 *B* (MW): 78[89]	91–92	15
9	 1i	 3i	*A* (*hv*): 89 *B* (MW): 56	192	20

[a] All products were characterized by their satisfactory spectral data and also by comparison with literature data (vide Supplementary data).
[b] Yield refers to combined amounts of first and second crops of products obtained either from aqueous ethanol (Method A) or after chromatography (Method B).



Scheme 2. Photochemical Knoevenagel condensation of salicylaldehyde and Meldrum's acid.

side reactions such as Norrish Type I cleavage in the absence of any catalyst, support or promoter and may be considered as an excellent improvement over the existing methods.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.123.

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30. *Method A*: An equimolar quantity of Meldrum's acid (**2**) (10 mmol) and different aromatic aldehydes (**1a**–**i**) were taken in aqueous-ethanol mixture (20 mL, 1:1 proportion) and irradiated with a 150 W tungsten lamp (Philips India Ltd.). The reaction time varied on an average from 10 to 20 min for different aromatic aldehydes (monitored by TLC after 5 min interval). Upon

completion of the reaction, the reaction mixture was cooled and the crystalline product (**3a–i**) so obtained was filtered, washed, with water and dried in vacuo. The Knoevenagel condensation products were isolated in high yields in essentially pure form.

Method B: Aromatic aldehydes (**1a–i**) (10 mmol), Meldrum's acid (**2**) (10 mmol) and neutral alumina (2 g) were mixed well with the help of a mortar pestle and the mixture was subjected to microwave irradiation (2450 MHz) at temperatures 81 °C (for 30 s, entries 2 and 3), 103 °C for 1 min 10 s, entry 8), 131 °C (for 50 s, entries 1 and 6), 142 °C (for 1 min, entry 9),154 °C (for 1 min 20 s, entry 7), 181 °C (for 2 min 30 s, entries 4 and 5), and the condensation product (**3a–i**) were isolated by a column filtration over silica gel (petroleum ether, 60–80 °C and ethyl acetate, 10–40% v/v) in pure form.

5-(2,4-Dimethoxy-benzylidene)-2,2-dimethyl-[1,3] dioxane-4,6-dione (**3c**): Yellow shining flakes, Yield: 88% (*hv*), mp 140 °C; IR (KBr) ν_{max} 2998, 2943, 2835, 1750, 1728, 1604, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 22 °C) δ 8.86 (s, 1H), 8.43 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 9.0 Hz, 1H), 6.42 (s, 1H), 3.90 (s, 6H), 1.79 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 22 °C) δ 166.6, 164.0, 162.7, 160.8, 152.1, 135.5, 114.6, 110.2, 105.7, 103.8, 97.5, 55.8, 55.6, 27.4 ppm. Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.52; H, 5.42.