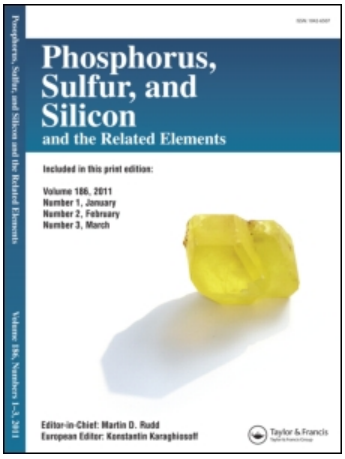

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Solvent Free Synthesis of Coumarins

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SOLVENT FREE SYNTHESIS OF COUMARINS

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An efficient synthesis of 3-substituted coumarins under solventless system is described.

Keywords: Coumarin; β-ketoesters; piperidine; solventless system

Coumarins are very well known natural products and many such compounds exhibited high levels of biological activity.[1] Coumarins are also used as additives to food and cosmetics,[2] optical brightening agents[3] and dispersed flurescent and laser dyes.[4] In addition some coumarins are of much interest as a result of their toxcicity,[5] carcinogenity,[6] and photodynamic effects.[7]

More than 100 years ago Knoevenagel described the solution phase condensation of 2-hydroxybenzaldehyde and malonic acid to afford 3-carboxycoumarins.[8] Although several methods have been reported for the synthesis of coumarins,[9] the Knoevenagel reaction has kept its importance and originality.[10] Recently several methods based on a solid phase synthesis utilizing the Kneovenagel condensation for the preparation of coumarins have been reported.[11] These methods have their own merits and disadvantages, therefore introduction of efficient and new methods based on green methodology is still in demand.

The ability of inorganic solid supports to enhance the reaction rates is well known for several types of organic reactions,[12] and the use of them has been the main research topics of several laboratories, including ours.[13] Resently we have reported the montmorilonite K-10 catalyzed

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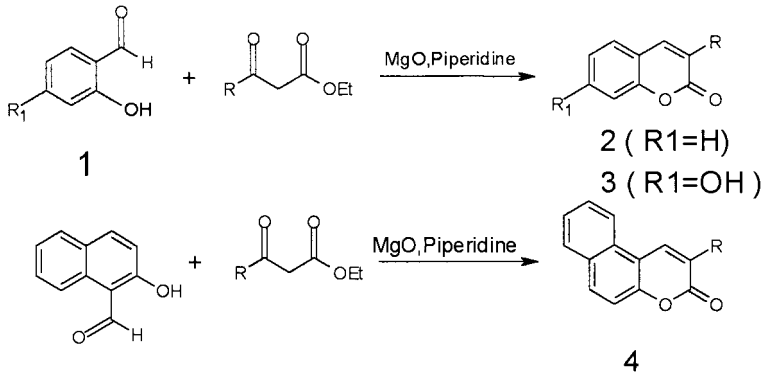
Knoevenagel condensation in solventless system.[14] Armed with these experiments we report herein the Knoevenagel type condensation of salisylaldehyds **1** and 2-hydroxy-1-naphtaldehyde with a variety of β-ketoesters supported onto MgO in α solventless system for the rapid one-pot synthesis of 3-substituted coumarins. It is noteworthy to mention that addition of piperidine enhanced the rate of reaction drastically. Use of base as a catalyst in Kneovenagel condensation has been previously noticed.[15]

Thus salisylaldehyde and its derivatives **1** as well as 2-hydroxy-1-naphtaldehyde were reacted with β-ketoesters to afford a variety of coumarins **2**, **3**, **4** (Scheme 1).



SCHEME 1

In conclusion this method describes a noticeable improvement in reaction condition for the synthesis of substituted coumarins via the Knoevenagel condensation and takes advantages of the reaction under solvent free condition. As shown in Table I the time of reaction is

TABLE I Physical Properties and Yields of the Prepared Compounds

Entry	Product	R	Reaction time (min)	m.p. (°C)	Yield (%)	Cryst. solvent
1	3a	CO2Et	6	173–5	75	H2O/EtOH
2	3b	CO2Me	5.5	265–7	78	H2O/EtOH
3	3c	CN	5.5	249–51	82	H2O/EtOH
4	2a	COMe	1	115–8	85	CHCl3/EtOH
5	2b	CO2Et	1	94–7	81	CHCl3/EtOH
6	4a	CO2Et	1	110–2	86	CHCl3/EtOH
7	4b	CO2Me	0.5	168–70	82	CHCl3/EtOH
8	4c	CN	0.5	292–5	88	CHCl3/EtOH
9	4d	COMe	0.5	192–5	92	CHCl3/EtOH
10	4e	COPh	0.5	212–5	90	CHCl3/EtOH

reduced to a few minutes or even a few seconds. These reaction times in some cases are even better than those under microwave irradiation.[10b] The reactions can be run safely in an efficient hood and the work-up procedure is reduced to the filteration and crystallization from suitable solvent.

EXPERIMENTAL

The reactions were carried out in an efficient hood. The melting points (uncorrected) were measured with a Stuart Scientific apparatus. ^{1}H-NMR spectra were recorded on a 60 MHz Bruker spectrometer using TMS as an internal standard. IR spectra were measured on a Perkin-Elmer model 543.

GENERAL PROCEDURE

A mixture of the appropriate hydroxyaldehyde (2.9 mmol) and β-ketoester (3 mmol) were supported on MgO (1.8 g). A drop of piperidine was then added and this was grinded to make an intimate mixture. The progress of the reaction was monitored by TLC using (petroleum ether/Ethylacetate, 70/30%) as eluent. After the completion of the reaction, the residue was dissolved in hot EtOH and filtered off. The solvent was evaporated to dryness under reduced pressure and the crude residue was crystallized from a suitable solvent to afford the substituted coumarins. Melting points, yields, reaction times and crystallizing solvents were given in Table I.

Selected Spectroscopic Data for 3a

^{1}H NMR δ (DMSO d6): 1.52 (t, 3H, Me), 4.55 (q, 2H, OCH2), 7–7.8 (m, 3H, aromatic protons), 8.68 (s, 1H, olefinic CH), OH is unobserved; IR, ν (KBr disc): 1725, 1685, Up to 3000 cm^{-1} (OH broad).

Selected Spectroscopic Data for 3b

^{1}H NMR δ (DMSO d6): 3.8 (s, 3H, OMe), 6.9–7.7 (m, 3H, aromatic protons), 6.69 (s, 1H, olefinic CH), OH is unobserved, IR, ν (KBr disc): 1715, 1680, Up to 3000 cm^{-1} (OH, broad).

Selected Spectroscopic Data for 3c

^{1}H NMR δ (DMSO d6): 6.9–7.9 (m, 3H, aromatic protons), 8.81 (s, 1H, olefinic CH), OH is unobserved, IR, ν (KBr disc): 2230, 1685, Up to 3000 cm^{-1} (OH, broad).

Selected Spectroscopic Data for 2a

^{1}H NMR δ (CDCl3): 2.85 (s, 3H, Me), 7.3–7.85 (m, 4H, aromatic protons), 8.62 (s, 1H, olefinic CH), IR, ν (KBr disc): 1750, 1680 cm^{-1}.

Selected Spectroscopic Data for 2b

^{1}H NMR δ (CDCl3): 1.52 (t, 3H, Me), 4.55 (q, 2H, OCH2), 7.4–7.9 (m, 4H, aromatic protons), 8.62 (s, 1H, olefinic CH); IR, ν (KBr disc): 1790, 1650 cm^{-1}.

Selected Spectroscopic Data for 4a

^{1}H NMR δ (CDCl3): 1.48 (t, 3H, Me), 4.45 (q, 2H, OCH2), 7.4–8.3 (m, 6H, aromatic protons); 9.32 (s, 1H, olefinic CH),); IR, ν (KBr disc): 1745, 1680 cm^{-1}.

Selected Spectroscopic Data for 4b

^{1}H NMR δ (CDCl3): 4.1 (s, 3H, OMe), 7.4–8.4 (m, 6H, aromatic protons), 9.4 (s, 1H, olefinic CH); IR, ν (KBr disc): 1730, 1685 cm^{-1}.

Selected Spectroscopic Data for 4c

^{1}H NMR δ (CDCl3): 7.4–8.5 (m, 6H, aromatic protons), 9.4 (s, 1H, olefinic CH),); IR, ν (KBr disc): 2245, 1675 cm^{-1}.

Selected Spectroscopic Data for 4d

^{1}H NMR δ (CDCl3): 2.75 (s, 3H, Me), 7.4–8.5 (m, 6H, aromatic protons), 9.4 (s, 1H, olefinic CH); IR, ν (KBr disc): 1735, 1675 cm^{-1}.

Selected Spectroscopic Data for 4e

^{1}H NMR δ (CDCl3): 7.1–8.5 (m, 6H, aromatic protons), 9.3 (s, 1H, olefinic CH); IR, ν (KBr disc): 1710, 1625 cm^{-1}.

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