

Cellulose sulphuric acid as a biodegradable and reusable catalyst for the Knoevenagel condensation

Short Communication

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Abstract: A green, mild and efficient method for Knoevenagel condensation of 3-formylchromone/2-chloroquinoline-3-carbaldehyde with active methylene compounds such as Meldrum's acid/ethyl cyanoacetate using biosupported cellulose sulphuric acid (CSA) in the solid-state by grinding under solvent-free condition has been developed. This method provides several advantages including environmental friendliness, short reaction times, high yields and a simple work-up procedure. Moreover, the CSA was successfully reused for four cycles without significant loss of activity.

Keywords: Knoevenagel reaction • Cellulose sulphuric acid • Grinding • 3-formylchromone • Meldrum's acid

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1. Introduction

The grinding method has gained increasing use in organic synthesis. Compared with traditional methods, many organic reactions occur more efficiently in the solid-state than in solution and in many cases even more selectively, because molecules in the crystals are arranged tightly and regularly [1]. Furthermore, solid-state reactions have many advantages: little pollution, low cost, and simplicity in progress and handling. A large number of organic reactions can be carried out simply and in high yield under mild conditions by this method [2]. Therefore, we focus on developing a novel procedure involving a solid-state reaction performed by grinding.

Knoevenagel condensations are useful and widely employed reactions for carbon-carbon bond formation in organic synthesis [3]. The Knoevenagel condensation reactions are classically catalyzed by base in liquid-phase systems; various catalysts are known to effect the reaction with different aldehydes and active methylene groups.

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is an active methylene compound having a rigid cyclic structure with high acidity ($pK_a = 4.9$), which readily hydrolyzes [4]. Recently, there have been several literature methods reported for Knoevenagel condensations of aldehydes with Meldrum's acid [5].

In this work we introduced the quinoline nucleus for Knoevenagel condensation since quinoline possesses diverse biological and physiological activities, including *anti-malarial*, *anti-tuberculosis*, receptor antagonists and *anti-cancer* [6].

Compounds having a chromone moiety are synthetically versatile molecules with a reactive carbonyl group. They have considerable significance for their biological activities [7] and for their reactivity towards nucleophiles, which allow the syntheses of a wide variety of heterocycles. The substrate, 3-formylchromone [4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde] has three active sites: an α , β -unsaturated carbonyl group, a carbon-carbon double bond and a formyl group. Of these, the formyl group has the highest reactivity towards active methylene compounds. The condensation reactions of

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3-formylchromone with active methylene compounds are well known [8]. It is well known that 2,2-dimethyl-5-[(4-oxo-4*H*-chromen-3-yl)methylene]-1,3-dioxane-4,6-diones are generally synthesized by condensation of 3-formylchromones with Meldrum's acid in presence of alumina under microwave irradiation [9a] and ethyl 3-(2-chloroquinolin-3-yl)-2-cyanoacrylates are synthesized by condensation of 2-chloroquinoline-3-carbaldehydes with ethyl cyanoacetate catalyzed by DBU (1,8-diazabicycloundec-7-ene) under sonication [9b].

Biopolymers, especially 'cellulose' and its derivatives [10] have some unique properties, which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Among others, they are extremely inert, inexpensive, biodegradable and environmentally benign which allows various reaction conditions to be employed. Cellulose is the most abundant renewable natural material in the world. It has been widely studied during the past decades because it is both biodegradable and a renewable resource.

Recently, several synthetically useful organic transformations using bio-supported, biodegradable and recyclable cellulose sulphuric acid (CSA) as a catalyst have been reported in the literature [11].

2. Experimental procedure

Melting points were obtained on a melting point apparatus with capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR Spectrophotometer using

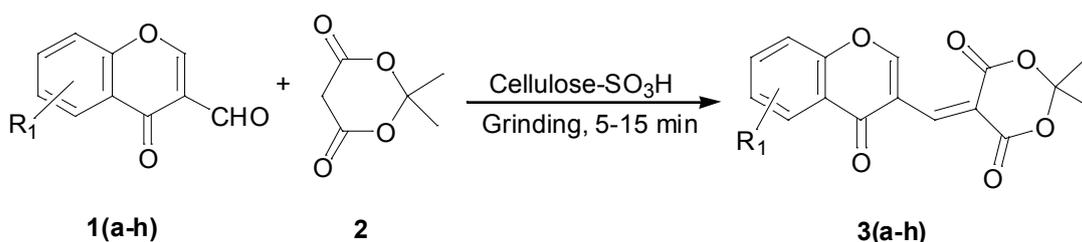
KBr discs. ¹H NMR spectra were recorded with a Varian 300 MHz spectrometer in CDCl₃ with TMS as an internal standard. The preparation of cellulose sulphuric acid (CSA) by the dropwise addition of chlorosulfonic acid to DEAE cellulose (Merck) suspended in hexane has been carried out as previously described [12].

2.1. General procedure for Knoevenagel condensations

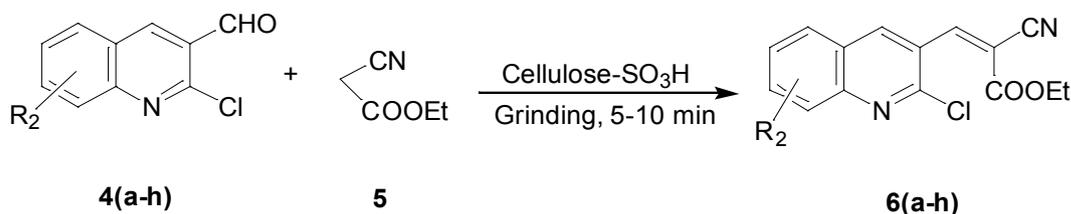
A mixture of heteroaromatic aldehyde (1 mmol), active methylene compound (1 mmol) and CSA (0.5 g) were ground at room temperature with a mortar and pestle. The reactions were monitored by thin layer chromatography (TLC). After completion of reaction, the product was extracted with dichloromethane (2×20 mL) and the insoluble CSA directly recycled in subsequent runs. The organic layer was washed by brine (2×10 mL), dried over Na₂SO₄ and the solvent removed by rotary evaporation under reduced pressure. The crude product was recrystallized from ethanol to afford pure corresponding compounds in high yield.

2.2. Spectral data

Compound (Table 2, **3h**): IR (KBr, cm⁻¹): 3061, 2992, 1730, 1669, 1372, 1296, 797. ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 1.9 (6H, s, 2×CH₃), 7.2-8.2 (3H, m, aromatic), 8.6 (1H, s, olefinic), 9.6 (1H, s, C₂-H of chromone moiety). EIMS (m/z, %) = 319 [M+1].



Scheme 1. Synthesis of 2,2-dimethyl-5-[(4-oxo-4*H*-chromen-3-yl)methylene]-1,3-dioxane-4,6-dione derivatives



Scheme 2. Synthesis of ethyl 3-(2-chloroquinolin-3-yl)-2-cyanoacrylate derivatives

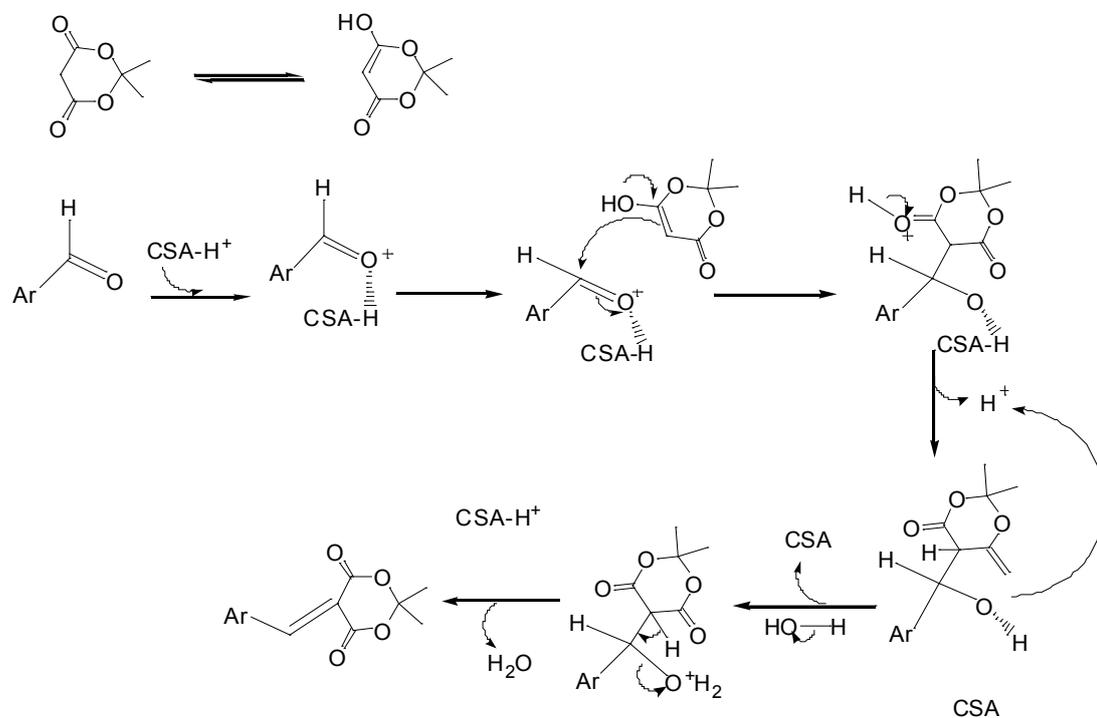


Figure 1. Proposed reaction mechanism (Scheme 1)

Table 1. Effect of proportion of CSA for the synthesis of 2,2-dimethyl-5-[(4-oxo-4H-chromen-3-yl) methylene]-1,3-dioxane-4,6-dione^a [Table 2, entry 3a] from 1 mmol each of Meldrum's acid and aldehyde

Entry	CSA (g)	Time (min)	Yield (%) ^b
1	0.1	15	84
2	0.2	15	87
3	0.3	10	89
4	0.4	10	91
5	0.5	10	93
6	0.6	10	93

^aReaction condition: 1a (1 mmol), 2 (1 mmol) grinding at room temperature;

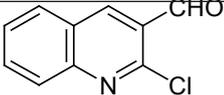
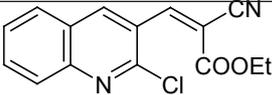
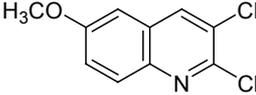
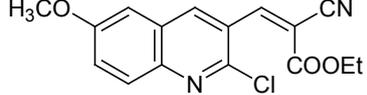
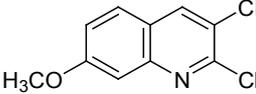
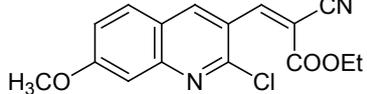
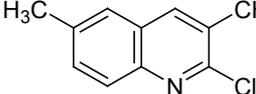
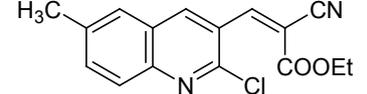
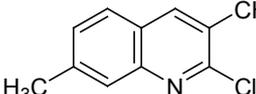
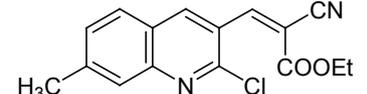
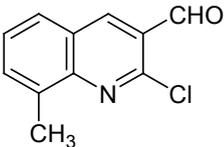
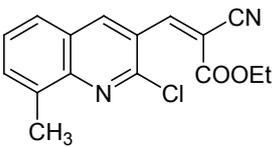
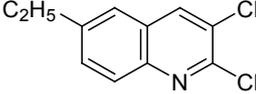
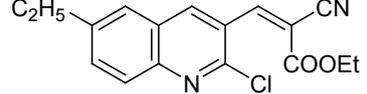
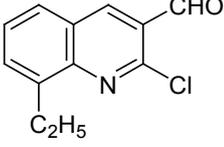
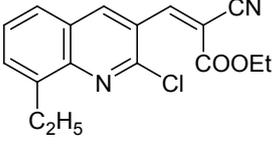
^bIsolated yield.

Table 2. Cellulose sulphuric acid catalyzed Knoevenagel reaction by grinding at room temperature (Scheme 1)

Entry	Aldehyde	Product	Time (min)	Yield (%) ^a	M.P. (°C)	
					Found	Literature [9a]
3a			10	93	181-183	182
3b			5	92	197-199	198
3c			10	87	184-186	186
3d			10	91	178-180	180
3e			15	89	198-200	200
3f			10	92	240-242	242
3g			5	95	202-204	205
3h			5	96	200-202	-

^aIsolated yield based upon starting aldehyde.

Table 3. Cellulose sulphuric acid catalyzed Knoevenagel reaction by grinding at room temperature (Scheme 2)

Entry	Aldehyde	Product	Time (min)	Yield (%) ^a	M. P. (°C)	
					Found	Literature [9b]
6a			5	91	161-163	160-162
6b			5	94	142-144	144-146
6c			10	89	155-157	155-157
6d			10	90	148-150	150-152
6e			10	89	146-148	146-148
6f			10	92	160-162	162-164
6g			5	87	170-172	168-170
6h			5	89	164-166	165-167

^aIsolated yield based upon starting aldehyde.**Table 4.** Recycling of CSA for the synthesis of 2,2-dimethyl-5-[(4-oxo-4H-chromen-3-yl)methylene]-1,3-dioxane-4,6-dione^a [Table 2, entry 3a]

Entry	1	2	3	4	5
Cycle ^b	Fresh	First reuse	Second reuse	Third reuse	Fourth reuse
Yield (%) ^c	93	91	89	88	88

^aReaction condition: 1a (1 mmol), 2 (1 mmol) and CSA (0.5 g) grinding at room temperature;^bReaction time 10 min;^cIsolated yield.

3. Results and Discussion

In continuation of our research work on Knoevenagel condensations [9,13] and on development of the novel synthetic methodologies [14], herein, we report a simple, efficient and safe methodology for the Knoevenagel condensation in the presence of CSA under grinding condition. The synthetic route is shown in Schemes 1 and 2.

In order to optimize the reaction conditions, the reaction of 3-formylchromone **1a** with Meldrum's acid **2** was selected as a model to investigate the effect of varying proportions of catalyst on the yield. The best results were obtained by carrying out the reaction with 1:1 mol ratio of 3-formylchromone: Meldrum's acid and 0.5 g of CSA under solvent-free conditions by grinding at room temperature. Under these conditions (Table 2, entry **3a**) was obtained 93% yield within 10 min. Encouraged by the results obtained with this model reaction, different heteroaromatic aldehydes containing electron-withdrawing or electron-donating compounds were reacted with both Meldrum's acid and ethyl cyanoacetate. They all gave the expected products with high yields in short reaction times.

To determine the appropriate ratio of the CSA, we investigated the model reaction at different proportions including 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 g (Table 1). The Knoevenagel product formed in 84%, 87%, 89%, 91%, 93% and 93% yield, respectively, indicating that 0.5 g of CSA is sufficient for the condensation of 1 mmol of each substrate pair (Table 1, entry **5**).

We have developed a newer route for the Knoevenagel condensation of 3-formylchromone/2-chloroquinoline-3-carbaldehyde with active methylene compounds such as Meldrum's acid/ethyl cyanoacetate in presence of CSA under solvent-free condition by grinding at room temperature (Table 2 and 3). All the reactions were carried out at room temperature by

grinding, *i.e.*, using mild reaction conditions. In this methodology, condensation reactions were completed in a short reaction time (5-15 min) and with excellent yields (87-96%). Thus, this is an excellent method for the Knoevenagel condensation.

Further investigation of the ability to recycle the catalyst is important for potential large-scale and/or industrial operations. Therefore, the recovery and reusability of CSA was examined. The catalyst can be separated and reused after extracting the desired product. The reusability of the catalyst was investigated in the model reaction. The results illustrated in Table 4 showed that the catalyst could be used at least four times without significant loss of activity.

The proposed mechanism of this reaction (Scheme 1) is as shown in Fig. 1.

4. Conclusions

In conclusion, we have reported a new and effective methodology for the Knoevenagel reaction via the condensation of substituted heteroaromatic aldehydes with active methylene compounds such as Meldrum's acid and ethyl cyanoacetate in the presence of CSA under solvent-free conditions by grinding at room temperature. The remarkable merits offered by this methodology are mild reaction conditions, cleaner reactions, short reaction times, simple work-up procedures and excellent yields. Additionally, the CSA was successfully reused for four cycles without significant loss of activity which makes the reaction convenient and environmentally benign.

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References

- [1] K. Tanaka, F. Toda, *Chem. Rev.* 100, 1025 (2000)
- [2] (a) F. Toda, K. Tanaka, K. Hamai, *J. Chem. Soc. Perkin Trans. 1*, 3207 (1990); (b) K. Tanaka, S. Kishigami, F. Toda, *J. Org. Chem.* 56, 4333 (1991); (c) M. Veit, U. Hoffmann, *Chemie-Ingenieur-Technik* 68, 1279 (1996); (d) F. Toda, T. Suzuki, S. Higa, *J. Chem. Soc. Perkin Trans. 1*, 3521 (1998)
- [3] G. Jones, *Organic reactions* 15, 204 (1967)
- [4] H. McNab, *Chem. Soc. Rev.* 7, 345 (1978)
- [5] (a) S. Daqing, W. Yucheng, L. Zaisheng, D. Guiyuan, *Synth. Commun.* 30, 713 (2000); (b) Z. Ren, W. Cao, W. Tong, X. Jing, *Synth. Commun.* 32, 1947 (2002); (c) S. Aimin, W. Xiaobing, S.L. Kit, *Tetrahedron Lett.* 44, 1755 (2003); (d) U.V. Desai, D.M. Pore, R.B. Mane, S.B. Solabannavao, P.P. Wadgaonkar, *Synth. Commun.* 34, 25 (2004)

- [6] (a) R.G. Ridley, *Nature* 415, 686 (2002); (b) V.R. Solomon, W. Haq, K. Srivastava, S.K. Puri, S.B. Katti, *J. Med. Chem.*, 50, 394 (2007); (c) P. Jasinski et al., *Invest. New Drugs* 26, 223 (2008)
- [7] W.H. Gerwick, A. Lopez, G.D. Van Duyne, J. Clardy, W. Ortiz, A. Buez, *Tetrahedron Lett.* 270, 1986 (1979)
- [8] (a) J. Prousek, *Colt. Czech. Chem. Commun.* 58, 3014 (1993); (b) G.V.S. Rama Sarma, V.M. Reddy, *Ind. J. Hetero. Chem.* 3, 111 (1993)
- [9] (a) S.S. Shindalkar, B.R. Madje, M.S. Shingare, *Ind. J. Chem. Sec. B* 45, 2571 (2006); (b) G. K. Kakade, B. R. Madje, R. U. Pokalwar, M.N. Ware, M.S. Shingare, *Ind. J. Hetero. Chem.* 17, 379 (2008)
- [10] D. Klemm, B. Heublein, H.P. Fink, A. Bohn, *Angew Chem. Int. Ed.* 44, 3358 (2005)
- [11] (a) S. Ahmad, M. Ali, *Appl. Catal. A* 331, 149 (2007); (b) J.V. Madhav, Y.T. Reddy, P.N. Reddy, M.N. Reddy, S. Kumar, P.A. Crooks, B. Rajitha, *J. Mol. Cat. A: Chem.* 304, 85 (2009); (c) S. Ahmad, R. Abbas, B. Zahra, *Catal. Comm.* 9, 13 (2008); (d) A. Shaabani, A. Rahmati, Z. Badri, *Catal. Commun.* 9, 13 (2008)
- [12] S. Ahmad, M. Ali, R. Jafar, S. Ebrahim, *Chem. Pharm. Bull.* 55, 957 (2007)
- [13] (a) R.V. Hangarge, S.A. Sonwane, D.V. Jarikote, M.S. Shingare, *Green Chem.* 3, 310 (2001); (b) R.V. Hangarge, D.V. Jarikote, M.S. Shingare, *Green Chem.* 4, 266 (2002); (c) S.S. Shindalkar, B.R. Madje, M.S. Shingare, *Ind. J. Chem.* 44B, 1519 (2005); (d) S.S. Shindalkar, B.R. Madje, M.S. Shingare, *J. Korean Chem. Soc.* 49, 377 (2005)
- [14] (a) S.A. Sadaphal, K.F. Shelke, S.S. Sonar, M.S. Shingare, *Cent. Eur. J. Chem.* 6, 622 (2008); (b) S.B. Sapkal, K.F. Shelke, B.B. Shingate, M.S. Shingare, *Tetrahedron Lett.* 50, 1754 (2009); (c) K.F. Shelke, S.B. Sapkal, M.S. Shingare, *Chine. Chem. Lett.* 20, 283 (2009); (d) K.F. Shelke, S.B. Sapkal, A.H. Kategaonkar, B.B. Shingate, M.S. Shingare, *S. Afr. J. Chem.* 62, 109 (2009); (e) K.F. Shelke, S.B. Sapkal, N.V. Shitole, B.B. Shingate, M.S. Shingare, *Org. Commun.* 2, 72 (2009); (f) K.F. Shelke, S.B. Sapkal, S.S. Sonar, B.R. Madje, B.B. Shingate, M.S. Shingare, *Bull. Korean Chem. Soc.* 30, 1057 (2009)