

# Structurally complexes aromatic aldehydes on Knoevenagel condensation catalyzed by Chitosan hydrogel beads

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## Abstract

Knoevenagel condensation has been widely studied for reaction model in C–C bond formation. The design of recyclable and eco-friendly catalysts is an essential task in modern-day chemistry. It is known that Chitosan clearly have the capability of support metal for catalytic applications. In this communication, the catalyst properties of Chitosan on Knoevenagel condensation involving bulky and heteroaromatic aldehydes have been extended. Moreover, steric hindrance and electronic effects have been also studied in correlation with reaction time.

## Keywords

Knoevenagel condensation, chitosan, organocatalyst, hydrogel

## Introduction

Chitosan is a heteropolymer constituted by glucosamine and *N*-acetylglucosamine units. This biopolymer has been widely applied in biomedical fields, for example, free amino groups of chitosan can be modified by different functional groups for, drug,<sup>1</sup> gene<sup>2</sup> and DNA delivery<sup>3</sup> or more recently therapy photogenic,<sup>4</sup> among others. In some applied industrial specifications Chitosan proves to be very useful for waste water treatment, cosmetic or different alimentary process by using their biocompatible, biodegradable and antimicrobial properties.

Nowadays, the synthesis of applicable products in everyday life is an increasing research topic. Knoevenagel condensation presents a broad range of applications in synthesis of multiple substances involving domino reactions to obtain five- and six-membered heterocycles such as polysubstituted pyrrolidines, dihydrothiophenes and 1,4-dihydropyridines.<sup>5</sup> Chitosan has been employed as support of metallic catalysts in hydrogenation of ethyl cinnamate, Suzuki cross coupling or to transform nitriles into amides.<sup>6</sup> Very recently, this polymer has been used in several reactions (*e.g.* aldol,

Henry or Michael reactions) as heterogeneous catalyst using simple aldehydes.<sup>7</sup> Other interesting applications involve the synthesis of heterocycles such as pyrimidino-benzothiazole.<sup>8</sup>

In this communication, we synthesized new Knoevenagel switchable products from malononitrile and highly modified aldehydes owning different steric hindrance and electronic effects. The heterogeneous chitosan catalyst role has been studied to improve on conversion, time and yields compared with non-catalyzed reactions.

## **Experimental Methods**

All chemicals were purchased and used without further purification. Evaporations were conducted under reduced pressure. TLC was performed on silica gel plates (DC-Alufolien F254, E. Merck). All compounds obtained were synthesized following the general procedure. Detection of compounds was accomplished with UV light (254 nm) and by charring with H<sub>2</sub>SO<sub>4</sub> and characterization by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy and Mass spectrometry.

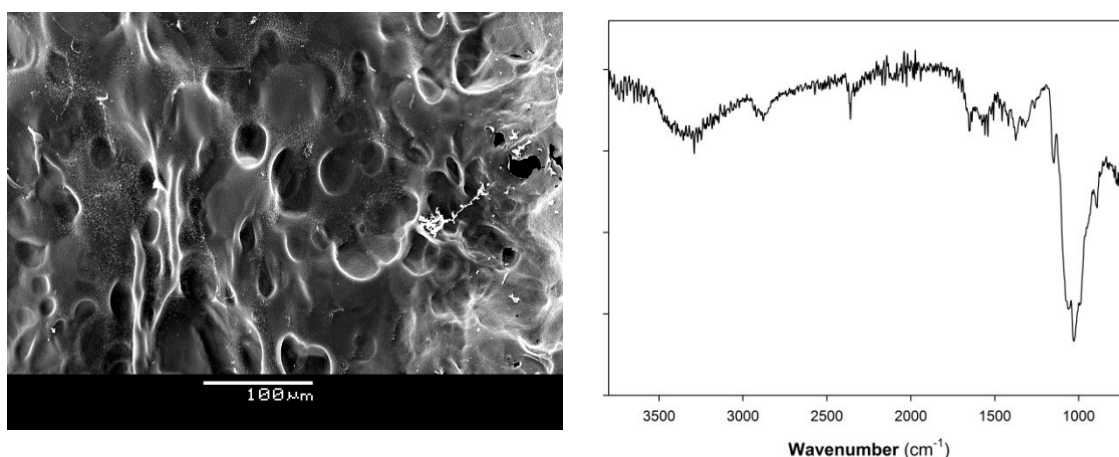
### *General Procedure to obtain Knoevenagel malononitrile products.*

To a solution of aromatic aldehyde (1 equiv.) in DMSO (1.5 mL) was added malononitrile (1.1 equiv.) and 10 chitosan hydrogel beads. The heterogeneous mixture was leaved at room temperature until the reaction was completed monitoring by TLC. Then, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and filtered off. To resulting solution was added H<sub>2</sub>O (2.5 mL) and washed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure to give the corresponding malononitrile in high yields.

## **Results and discussion**

Chitosan hydrogel beads with a diameter of 3 mm and pore size of 29.5 × 40.2 μm were prepared by alkaline coagulation. Characterization of beads by FTIR and SEM is shown in Figure 1. IR spectrum shows the typical bands corresponding to chitosan backbone. Additionally, morphology of beads and catalytic properties proved to be pH-dependent. In this context, the most efficient catalyst was obtained at pH 7.0.

**Figure 1.** (a) Representative SEM images for catalyst (scale bar, 100  $\mu\text{m}$ ); (b) FTIR spectrum of dried chitosan beads

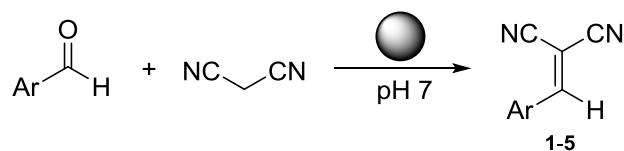


Following the general procedure, switchable-Knoevenagel products (**1-6**) by using malononitrile and different aromatic and heteroaromatic aldehydes were obtained in moderate to excellent yields (Scheme 1, Table 1). In all cases the conversion upper than 80 %. Necessarily, for an effective comparison of the results, reactions in absence of chitosan catalyst were carried out for each used aldehyde. Non-catalyzed reactions were considerably more slowly than those chitosan-catalyzed.

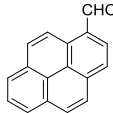
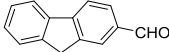
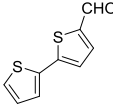
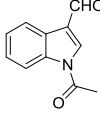
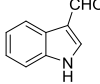
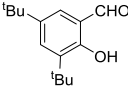
Reaction times were correlated with electronic effects on aromatic moiety. Thus, electron-donating groups (*e.g.* compound **5**) provide more reaction times than those with acceptor character (*e.g.* compound **4**). However, steric hindrance dominates the reaction times in pyrene derivatives (**1**). For compound **6**, an intramolecular cyclization thanks to hydroxyl groups occurs giving rise to 2-imine-2*H*-chromene.

In all malononitrile derivatives,  $^1\text{H}$  NMR spectra show a singlet in the range 8.90 (for compound **1**) to 7.76 ppm (for compound **3**) corresponding to olefinic H-2 proton.

**Scheme 1.** Knoevenagel condensation to obtain malononitrile derivatives (**1-5**)



**Table 1.**

Aldehyde	Product	t (days) <sup>a</sup>	Yield (%) <sup>b</sup>	Conversion (%) <sup>c</sup>
	1	9	12	86
	2	4	81	100
	3	3	82	97
	4	3	78	81
	5	6	89	100
	6	2	50	95

<sup>a</sup> Monitorized by TLC; <sup>b</sup> Calculated from isolated product; <sup>c</sup> Determined by <sup>1</sup>H NMR of the reaction crude

A singlet in compound **6** at 7.76 ppm was assigned to H-4 into chromene ring as well as singlets at 1.45 and 1.32 ppm identically to the value described in literature<sup>9</sup> for this compound.

## Conclusions

Chitosan hydrogel beads have been successfully prepared at pH 7.0 and characterized by using FTIR spectroscopy and SEM. The synthesis of Knoevenagel products (**1-6**) was carried out using chitosan beads as catalyst. Despite of steric hindrance and electronic effects the compounds were obtained with highly conversion and yields. Electronic effects have influence on reaction times, with electron-donating groups increasing this time contrarily to electron-withdrawing groups.

## Acknowledgements

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## References

1. Huang, W.; Wang, Y.; Zhang, S.; Huang, L.; Hua, D.; Zhu, X. *Macromolecules* **2013**, *46*, 814-818.
2. Sajomsang, W.; Gonil, P.; Ruktanonchai, U. R.; Petchsangai, M.; Opanasopit, P.; Puttipipatkachorn, S. *Carbohydr. Polym.* **2013**, *91*, 508-17
3. Mao, S.; Sun, W.; Kissel, T. *Adv. Drug Deliv. Rev.* **2010**, *62*, 12-27.
4. Chung, C.-W.; Chung, K.-D.; Jeong, Y.-I.; Kang, D. H. *Int. J. Nanomedicine* **2013**, *8*, 809-19.
5. Voskressensky, L. G.; Festa, A. A.; Varlamov, A. V. *Tetrahedron* **2014**, *70*, 551-572.
6. (a) Raspolli-Galletti, A. M.; Antonetti, C.; Bertoldo, M.; Piccinelli, F. *Appl. Catal. A.* **2013**, *468*, 95-101. (b) Nasir Baig, R. B.; Nadagouda, M. N.; Varma, R. S. *Green Chemistry* **2014**, *16*, 2122-2127.
7. Kühbeck, D.; Saidulu, G.; Reddy, K. R.; Diaz-Diaz, D. *Green Chemistry* **2012**, *14*, 378-392.
8. Sahu, P. K.; Sahu, P. K.; Gupta, S. K.; Agarwal, D. D. *Ind. Eng. Chem. Res.* **2014**, *53*, 2085-2091.
9. Li, W.; Liu, H.; Jiang, X.; Wang, J. *ACS Catal.* **2012**, *2*, 1535-1538.