

A Novel Polymeric Catalyst for One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones via Biginelli Reaction

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Abstract:

Poly(2-acrylamido-2-methyl propane sulphonic acid) crosslinked with *N,N'*-methylene bisacrylamide catalyses efficiently the three component condensation reaction of an aromatic aldehyde, β -ketoester and urea in refluxing ethanol to afford the corresponding dihydropyrimidinones in high yield.

Keywords: Biginelli reaction, three-component reaction, polymeric catalyst

1. Introduction

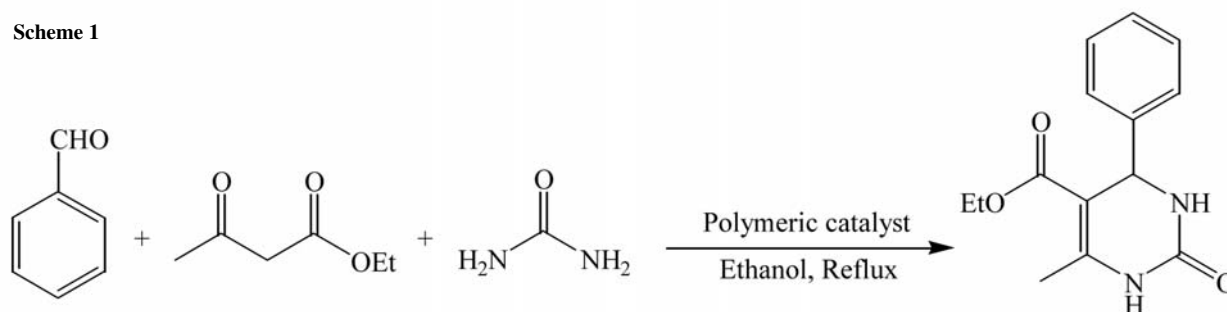
Dihydropyrimidinones that were first synthesized by Pietro Biginelli in 1893 have attracted considerable interest because of their pharmacological and therapeutic properties.^{1–7} Several functionalized derivatives are used as calcium channel modulators and anti hypertensive α_{1a} -antagonists.^{5–8} Batzlladin B, an alkaloid containing the dihydropyrimidine-5-carboxylate unit, that has been isolated from marine sources, was found to be potent HIV-gp-120-CD4 inhibitor.² Biginelli synthesized dihydropyrimidinones through one-pot three-component condensation of β -ketoesters, aldehydes and urea in refluxing ethanol containing a catalytic amount of HCl.^{1,9} However, this reaction proceeds with low yields particularly in the case of substituted aromatic aldehydes. This has led to the development of more complex multi step strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot Biginelli protocol.^{10–12}

Recently there was considerable activity aiming to improve the efficiency of the Biginelli synthesis. Many catalysts have been investigated.^{13–39} In spite of their potential utility some of these methods involve strongly aci-

dic conditions, long reaction times, high temperature and unsatisfactory yields. Therefore, the discovery of new catalyst for the preparation of 3,4-dihydropyrimidin-2-ones under mild conditions is of prime importance.

Polymer supported reagents have been in use since the 1946, and have been the subject of many review articles.^{40–41} Synthesis using these reagents is attractive and suitable for parallel synthesis because the reactions often proceed with high yields, and the workup involves simple filtration and evaporation of the solvent. Polymeric reagents can also be used in flow systems.⁴² Moreover the reactions using polymer-supported reagents were carried out with the reagents in “T-bags” so that when each particular reaction was completed the “T-bag” was simply removed and washed.⁴³ Therefore it is reasonable to assume that polymeric reagents will be employed with increasing regularity to conduct one- to multistage synthetic sequences. To facilitate this use, the technique requires rapid development, in particular in the following areas: (1) The search for new functionalized polymers, and (2) The development of new solid supports with properties specifically optimized for the synthetic procedure. Two approaches exist for the preparation of functional polymers, the poly-

Scheme 1



merization or copolymerization of monomers which carry the desired functionality, and the chemical modification of performed polymers.⁴¹

With these in mind, during the course of systematic study on the development of supported reagents and catalysts for the organic transformation,⁴⁴ we decided to investigate poly(2-acrylamido-2-methyl propane sulphonic acid) (AMPS) crosslinked with *N,N'*-methylene bisacrylamide (MBA) as a novel catalyst for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. This reaction proceeds in ethanol at reflux temperature for 12–36 h with one-pot protocol, simple workup, and with excellent yields for substituted aromatic aldehydes. The overall reaction is best formulated as shown in the Scheme 1.

2. Results and Discussion

Crosslinked poly(AMPS) was prepared by polymerization of the monomer in water, in the presence of a crosslinking agent (MBA) and a free radical initiator (ammonium persulphate). A proposed mechanism is outlined in Scheme 2.

The persulphate initiator is decomposed under heating to generate sulphate anion-radical. As a consequence, polymerization of AMPS is radically initiated. Since a crosslinking agent, e.g. MBA, is presented in the system, the polymer comprises a three dimensional crosslinked structure. Infrared spectroscopy was carried out to confirm the chemical structure of the polymer (Figure 1). The band observed at 1654 cm^{-1} can be attributed to the C=O stretching in the amide functional groups, whereas the broad band at $3200\text{--}3500\text{ cm}^{-1}$ is due to the O–H stretching of sulphonate groups.

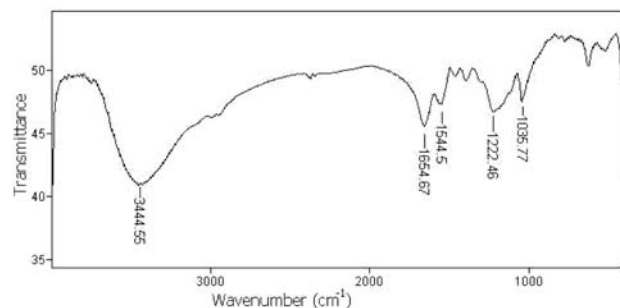
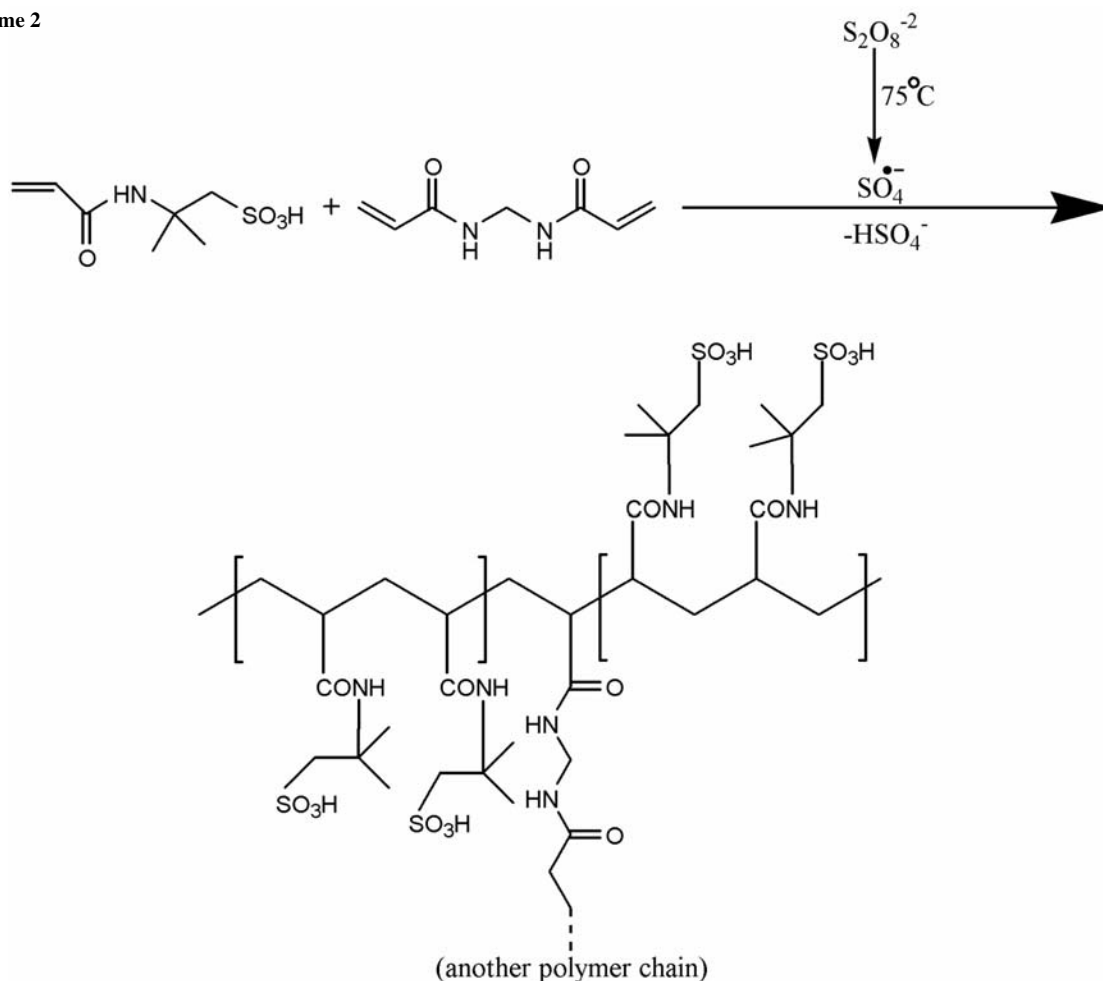


Figure 1. FTIR spectrum of the catalyst.

Scheme 2



Poly(AMPS) crosslinked with MBA catalyses efficiently the three component condensation reaction of an aromatic aldehyde, β -ketoester and urea in refluxing ethanol to afford the corresponding dihydropyrimidinones (Scheme 1). Electron deficient aromatic aldehydes give high yields. The workup involved simple filtration of heterogeneous catalyst and removal of the solvent followed by purification of the residue using crystallization with hot ethanol. The results are summarized in Table 1.

Table 1: Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones using a polymeric catalyst

Entry	Aldehyde (RCHO)	Time (h)	Yield (%)
1	R = Phenyl-	24	65
2	4-Cl-C ₆ H ₄ -	24	76
3	4-F-C ₆ H ₄ -	12	95
4	4-NO ₂ -C ₆ H ₄ -	12	90
5	4-Me-C ₆ H ₄ -	36	51
6	3-NO ₂ -C ₆ H ₄ -	24	85
7	2-NO ₂ -C ₆ H ₄ -	24	65
8	PhCH=CH-	12	71
9	4-HO-C ₆ H ₄ -	36	20

^a All yields refer to pure isolated products, characterized by mp, IR and ¹H-NMR.

Poly(AMPS) crosslinked with MBA after using as catalyst for Biginelli condensation can be recovered. In a typical procedure catalyst after the first use for the reaction was recovered by washing with hot ethanol and water (2 × 15 mL) followed by drying at 100 °C for 24 h. The second and third runs according to this procedure showed no considerable decrease in the reaction yield. In conclusion this polymeric reagent can be used as an efficient and recoverable catalyst for condensation of aromatic aldehydes with ethylacetoacetate and urea. High yields, easy work-up and reusability of the catalyst are the most significant aspects of this method.

3. Experimental

All products are known compounds and were characterized by comparison of their physical and spectroscopic data with those of authentic samples. IR and ¹H-NMR spectra were recorded on Perkin Elmer 781 and Bruker DPX500 instruments.

3.1. General Procedure for Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones

A solution of ethylacetoacetate (2 mmol), aromatic aldehyde (2 mmol) and urea (4 mmol) in ethanol (3 mL) was heated under reflux in the presence of polymeric reagent (0.1 g) for specified time given in Table 1. The progress of the reaction was monitored by TLC. After the completion of the reaction, appropriate amounts of hot et-

hanol was added and the catalyst separated by filtration. The filtrate was concentrated in vacuo to remove the ethanol. The residue was washed with cold water and crystallized from hot ethanol to afford the pure products.

3.2. Preparation of the Polymeric Catalyst

N,N'-methylene bisacrylamide (MBA, 2 g) as a crosslinker was added to the mixture of 2-acrylamido-2-methylpropane sulphonic acid (AMPS) (8 g) in 20 mL distilled water. The solution was added to a three-neck reactor equipped with a mechanical stirrer (Heidolph RZR 2021, three blade propeller type). The reactor was immersed in a thermostated water bath at 75 °C. An inert gas (nitrogen) was gently bubbled into the reactor to remove the oxygen. After 15 min, the initiator solution (0.15 g ammonium persulphate in 2 mL H₂O) was added to the mixture, and the mixture was allowed to stir (200 rpm) for 20 min. To remove water, the resultant polymer was poured to excess methanol and remained for 48 h. After that, methanol was decanted and the product scissored to small pieces. Finally, the polymer was dried in oven. To remove probably unreacted monomer, 1 g of polymer was added to 300 mL distilled water and the mixture allowed to stir gently for 72 h. Then the polymer was filtered and dried as mentioned above. After grinding, the powdered polymer was stored away from moisture, heat and light. The IR spectrum of the polymer showed the characteristic absorption of acid (O-H) groups at 3444 cm⁻¹ and carbonyl groups at 1654 cm⁻¹ (Figure 1).

4. Conclusion

Poly(2-acrylamido-2-methylpropane sulphonic acid) (AMPS) crosslinked with *N,N'*-methylene bisacrylamide (MBA) is presented as an effective heterogeneous catalyst for Biginelli condensation of aromatic aldehydes with ethylacetoacetate and urea in ethanol as solvent. The green and mild reaction conditions, high yields, low cost, and easy preparation and handling of the polymeric catalyst (as a bench-top catalyst) are the main advantages of the presented method. Also the work-up is reduced to a mere filtration and evaporation of the solvent. Finally, this polymeric catalyst can be recovered by washing with aqueous solution and used again at least three times with negligible loss in its activity.

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Povzetek

Polimerizirana 2-akrilamido-2-metilpropansulfonska kislina, zamrežena z *N,N'*-metilen bisakrilamidom, je bila uporabljena kot učinkovit katalizator v trikomponentni reakciji kondenzacije med aromatskimi aldehydi, β -ketoestrom in ureo pri refluxu etanola. Pri reakciji z visokimi izkoristki nastanejo ustrezni dihidropirimidoni.