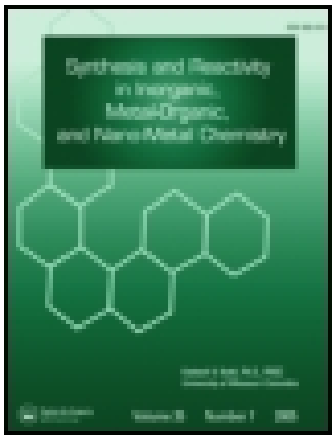

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Sulfamic acid supported magnetic $Fe3O_4$ nanoparticles catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones

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Sulfamic acid supported magnetic Fe_3O_4 nanoparticles catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones

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Abstract: Sulfamic acid supported on magnetic Fe_3O_4 nanoparticles catalyzed the condensation reaction of aldehydes, 1,3-dicarbonyl compounds, and urea or thiourea in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones under solvent-free conditions. This method offers several advantages including high yield, short reaction time, ease of separation, and recyclability of the magnetic catalyst.

Keywords: Magnetic, Fe_3O_4 nanoparticles, acylation, Biginelli reaction, Dihydropyrimidin-2(1*H*)-one/thione

Introduction

Dihydropyrimidin-2(1*H*)-one/thione and their derivatives have attracted great attention due to their pharmacological and therapeutic properties such as antibacterialï antihypertensive and calcium channel blocker activity as well as behaving as neuropeptide antagonists. [1]

The Biginelli reaction has received renewed interest because it is suitable for the generation of DHPM libraries in combinatorial chemistry. [2]

In order to improve the efficiency of the Biginelli reaction several catalysts such as sulfonic acid functionalized silica, [3] ion exchange resins, [4] Zieglerï Natta, [5] TMSCl/NaI, [6] $FeCl_3/Si(OEt)_4$, [7] Biocatalysts, [8] imidazolium-tagged recyclable iron [9] have been developed.

The design and preparation of the stable magnetic solid acid catalysts in harsh catalytic conditions is often a big challenge for chemists and is less advanced than the research in other solid acid catalysts. [10]

Recently, Clark et.al investigated effects of catalytic and solvent on the Biginelli Reaction. They elucidated that the diketoï enol tautomerisation equilibrium of the dicarbonyl reactant dictates the yield of the reaction. Whereas the solvent is responsible for the tautomerisation equilibrium position, the catalyst only serves to eliminate kinetic control from the reaction. Generally, to preserve reaction efficiency and improve sustainability, bio-derivable *p*-cymene was found to be a useful solvent. The metalï enolate intermediate that results from the application of a Lewis acidic catalyst often cited as promoting the reaction appears to hinder the reaction. In this instance, a Brønsted acidic solvent can be used to return greater reactivity to the dicarbonyl reagent.[12]

The demand for an environmentally benign procedure with heterogeneous and reusable catalyst prompted us to develop a safe alternate method for the synthesis dihydropyrimidin-2(1*H*)-ones/thiones derivatives in the presence of Sulfamic acid supported magnetic Fe_3O_4 nanoparticles as a solid heterogeneous acid catalyst.

Furthermore, in our work we applied a method based on magnetic nanoparticles facilitates the separation of solid catalyst after catalyzing one-pot reactions.

Experimental

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. Products were characterized by comparison physical data with known samples and spectroscopic data (FT-IR, ^{1}H NMR and ^{13}C NMR). The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO. FT-IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus.

Preparation of the magnetic Fe_3O_4 nanoparticles (MNPs):

Preparation of the magnetic Fe_3O_4 nanoparticles (MNPs) Naked Fe_3O_4 nanoparticles were prepared by co precipitation of Fe^{3+} and Fe^{2+} ions with a molar ratio of 2:1. Typically, $FeCl_3 \cdot 6H_2O$ (0.0216 mol) and $FeCl_2 \cdot 4H_2O$(0.0108 mol) were dissolved in 100mL deionized water at 85 ^{0}C vigorous mechanical stirring. Then, 10mL of 25% NH_4OH was quickly injected into the reaction mixture in one portion. The addition of the base to the Fe^{2+}/Fe^{3+} salt solution resulted in the formation of the black precipitate of MNPs. The reaction continued for another 1 h. The black precipitate was washed with distilled water through magnetic decantation.

Preparation of MNPs coated by (3-aminopropyl)- triethoxysilane:

The obtained MNPs powder (1.5 g) was dispersed in 250mL ethanol/water (volume ratio, 1:1) solution by sonication for30 min, and then APTES (99%, 2.5 mL) was added to the mixture. After mechanical agitation under N_2 atmosphere at 40 ŭC for 4 h, the suspended substance was separated with centrifugation. The settled product was re-dispersed in ethanol by sonication and then was isolated with magnetic decantation for 5 times. The precipitated product (APTESï MNPs) was dried at room temperature under vacuum.

Preparation of sulfamic acid-functionalized magnetic Fe_3O_4 nanoparticles (SA-MNPs):

The APTESï MNPs (500 mg) were dispersed in dry CH_2Cl_2 (3 mL) by ultrasonic bath for 10 min. Subsequently, chlorosulfuric acid (0.8 mL) was added dropwise over a period of 30 min at room temperature. Hydrogen chloride gas evolved from the reaction vessel immediately. Then, the as prepared functionalized MNPs nanoparticles were separated by magnetic decantation and washed three times with dry CH_2Cl_2 to remove the unattached substrates(Scheme 2).

General procedure for the synthesis of 3,4- dihydropyrimidin-2(1H)-ones/ thiones:

A stirred mixture of arylaldehyde (1 mmol), 1,3-dicarbonyl compounds (1.2 mmol), urea or thiourea (1.5 mmol), and sulfamic acid-functionalized magnetic Fe_3O_4 nanoparticles (25 mg) was reacted in an oil bath at 100 ^oC for the appropriated times (Tables 1). Completion of the reaction was indicated by TLC. After the reaction was completed, the catalyst was separated by an external magnet and reused for the next experiment. the crude solid product was solved in ethylacetate, and filtered for separation of the catalyst. The catalyst was washed four times with ethyl acetate, and then recovered catalyst was dried in oven at 100 ^oC for 2 h. The filtrate organic solution was concentrated. The solid product was purified by recrystallization procedure in

aqueous EtOH. All the products were characterized by comparison of their spectroscopic and physical data with the authentic samples. Spectral data for selected compound: 5-Methoxycarbony-6-methyl-4-(benzo[d][1,3]dioxol-5-yl)-3,4-dihydro-pyrimidin-2-one

Pale yellow solid; mp 196ï 198 ^{o}C; IR (KBr): 3367, 3220, 3012, 2952, 1712, 1692, 1644, 1488, 1459, 1436, 1231, 1099 cm^{-1}; 1H NMR (500MHz, DMSO-d_6): δ =2.25 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 5.06 (d, 1H, *J* = 3.2 Hz, CH), 5.98 (s, 2H, CH_2), 6.67ï 6.85 (m, 3H, ArH), 7.68 (s, 1H, NH), 9.19 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): d18.5, 51.1, 53.9, 99.5, 101.3, 107.0, 108.4, 119.6, 139.1, 146.7, 147.7, 148.9, 152.4, 166.2 ppm.

5-Ethoxycarbony-6-methyl-4-(4- nitrophenyl)-3,4-dihydro-pyrimidin-2-thione

Pale purple solid; mp 234ï 235 ^{o}C; IR (KBr) 3324, 3173, 2918, 1679, 1655, 1576, 1522, 1466, 1350, 1201, 1176, 1123 cm^{-1}; ^{1}H NMR (500MHz,DMSO-d_6): δ = 1.10 (t, 3H, *J* = 7.1 Hz, CH_3), 2.31 (s, 3H, CH_3), 4.02(q, 2H, *J* =7.1 Hz, CH2), 5.31 (d, 1H, *J*= 3.5 Hz, CH), 7.48 (d, 2H,*J* = 8.7 Hz, ArH), 8.23 (d, 2H, J¼8.7 Hz, ArH), 9.76 (d, 1H, *J* = 1.2 Hz,NH), 10.49 (s, 1H, NH) ppm; ^{13}C NMR (125MHz, DMSO-d_6): d 14.7,17.7, 54.1, 60.3, 100.2, 124.5, 128.3, 146.4, 147.5, 150.86, 165.3,174.9 ppm.

Result and Discussion

Sulfamic acid supported on magnetic Fe_3O_4 nanoparticles has proved to be efficient catalyst for the Biginelli condensation in a more efficiency way that minimizes the time, temperature, and amount of catalyst, the reaction of benzaldehyde, ethyl acetoacetate, and urea was selected as model to investigate the effects of the catalyst at different reaction temperatures and different amounts of catalysts, SA-MNPs. The best result was obtained by carrying out the reaction with

1.0:1.2:1.5 molar ratios of aldehyde, 1,3-dicarbonyl compounds, urea or thiourea, and 120 mg of SA-MNPs at 100 ^{o}C.

The suggested mechanism of this transformation is shown in Scheme 2. The first step in the mechanism is the condensation between the aldehyde and urea or thiourea, with some similarities to the Mannich Condensation. The acyl imine intermediate generated acts as an electrophile for the nucleophilic addition of the keto enol ether, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea or thiourea to give the cyclized Biginelli product.

Conclusion

We have developed a green and straightforward protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones using sulfamic acid supported on magnetic Fe_3O_4 nanoparticles is an efficient and heterogeneous catalyst from condensation reaction of aldehydes, 1,3-dicarbonyl compounds, and urea or thiourea under thermal solvent-free conditions. The catalyst can be recovered from reaction mixtures by applying an external magnetic field.

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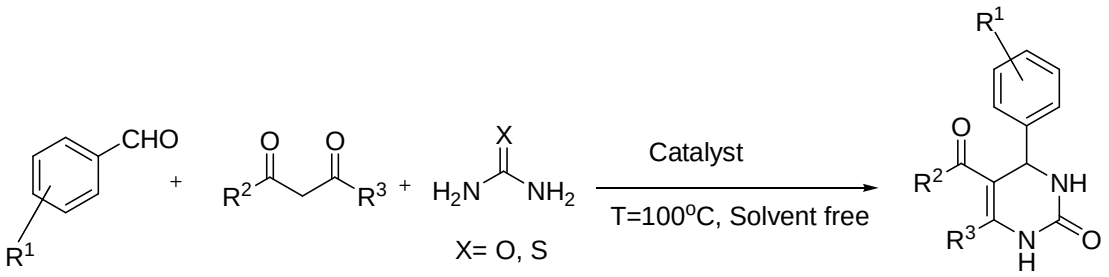
Table 1: Sulfamic acid supported on magnetic Fe_3O_4 nanoparticles catalyzed synthesis of 3,4 dihydropyrimidin2(1*H*)-ones/ thiones under solvent free conditions

Entry	R^1	X	R^2	R^3	Yield(%)	M.P(^oC)
1	H	O	C_2H_5O	CH_3	89	205-206 [203-204][12]
2	4-Cl	O	C_2H_5O	CH_3	90	215-216 [214-215] [12]
3	4-NO_2	O	C_2H_5O	CH_3	85	104-105 [207-208] [12]
4	4-CH_3O	O	C_2H_5O	CH_3	92	201-203 [200-202] [12]
5	H	O	CH_3O	CH_3	83	210-212 [209-210] [12]
6	4-NO_2	O	CH_3O	CH_3	88	230-233 [234-236] [12]
7	4-OH	O	CH_3O	CH_3	86	225-227 [227-229] [12]
8	4-CH_3O	O	CH_3O	CH_3	90	190-192 [191-193] [12]
9	H	O	CH_3	CH_3	82	264-265 [260-262] [13]

10	4-CH_3O	O	CH_3	CH_3	80	201-202 [200-202] [13]
11	4-CH_3	O	CH_3	CH_3	89	256-257 [258-260] [13]
12	4-Cl	O	CH_3	CH_3	88	258-260 [258-260] [13]
13	2-Cl	O	CH_3	CH_3	90	282-283 [280-282] [13]
14	4-F	O	CH_3	CH_3	84	260-261 [262-263] [13]
15	4-OH	O	CH_3	CH_3	86	236-238 [235-237] [13]
16	H	S	C_2H_5O	CH_3	78	205-207 [206-207] [13]
17	3-Cl	S	C_2H_5O	CH_3	75	194-196 [196-198] [13]
18	4-NO_2	S	C_2H_5O	CH_3	80	108-109 [108-110] [13]
19	3-CH_3O	S	C_2H_5O	CH_3	80	152-154 [150-152] [13]
20	4-OH	S	C_2H_5O	CH_3	79	195-197 [194-196] [13]
21	H	S	CH_3O	CH_3	84	220-222

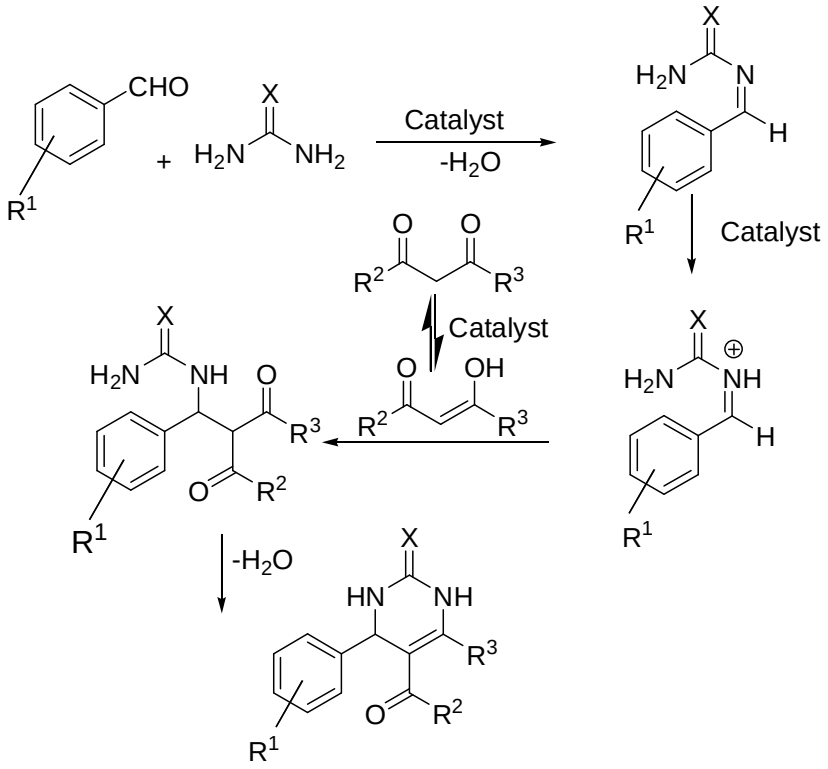
						[221-223] [13]
22	3-NO_2	S	CH_3O	CH_3	85	238-240 [237-239] [13]
23	4-OH	S	CH_3O	CH_3	82	225-227 [226-228] [13]
24	4-$(Me)_2N$	S	CH_3O	CH_3	80	154-156 [152-154] [13]

[a]Yields refer to the isolated pure products



R^2= OCH_3, OEt, Me
R^3= , Me, OCH_3, OEt, Et

Scheme 1: synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones



Scheme 2: The suggested mechanism for preparation of of 3,4- dihydropyrimidin-2(1H)-ones/ thiones