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Sulfated Zirconia-Catalyzed Synthesis of 3,4-Dihydro-pyrimidin-2(1H)-ones (DHPMs) Under Solventless Conditions: Competitive Multicomponent Biginelli *vs*. Hantzsch Reactions

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Abstract: The catalytic ability of ZrO_2/SO_4^{2-} to promote solventless three-component condensation reactions of a diversity of aromatic aldehydes, urea or thoiurea and ethyl acetoacetate was studied. Products resulting from Hantzsch and/or Biginelli multi-component reactions are obtained in the presence of solid acid catalysts using the same reactants but different temperature conditions. The sulfated zirconia catalyst can be recovered and recycled in subsequent reactions with a gradual decrease of activity.

Keywords: Biginelli reaction, Hantzsch reaction , multicomponent reactions, 1,4-dihydropyridines, dihydropyrimidinones, solventless reactions.

Introduction

Acid-catalysed transformations are common in bond-making and breaking reactions in Organic Chemistry. These reactions are most often conducted in solution and involve heating a mixture of reagents containing a catalytic amount of mineral or classic Lewis acids [1]. The replacement of these acids has been a focal point of research and development for a long time. The applications of solid

acids such as natural and modified clay minerals [2], zeolites and zeotype materials [3] as efficient catalysts in organic transformations have been widely studied. Aside the fact that they have excellent activity and selectivity, even on industrial scales, and in most cases these substances can be recovered from reaction mixtures and reused with good results [4], these solid acids are important from an environmental point of view because they produce less hazardous by-products. In this context, solid sulfated zirconia [5] have been used, due to their acidic and shape-selective nature, for performing the synthesis of heterocycles [6,7], acylation of aromatics ketones [8] and stereocontrolled glycosidations [9], synthesis of aromatic gem-dihalides [10], acylation of crown ethers [11], and chemoselective synthesis of acylals from aromatic aldehydes and their deprotections [12]. It is also known that in many cases organic reactions under solvent free conditions occur more efficiently and more selectively than do their solutions counterparts [13].

In 1893 Biginelli reported the first synthesis of 3,4-dihydropyrimidin-(1H)-ones by a very simple one-pot condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solution using a catalytic amount of acid [14]. The dihydropyrimidinone core and its derivatives form an important class of compounds, as it is present in a large family of natural products with broad biological activities as antihypertensive, antiviral, antitumor and anti-inflammatory agents and as calcium channel blockers [15]. Attempts to synthesize these moieties by the Biginelli reaction over various heterogeneous catalysts such as KSF [16], silica sulfuric acid [17] and more recently, the Lewis acids cerium (III) and indium(III) chloride [18], $CuCl_2H_2O/CuSO_4{\cdot}5H_2O$ [19] and ferric chloride/tetraethyl orthosilicate system are reported [20]. Recently, sulfated zirconia and sulfated zirconia modified with metals have been used in organic transformations to obtain 3,4-dihydropyrimidin-2(1H)-ones, bis-(indoyl)methane derivatives, 2,3-dihydro-1H-1,5-benzodiazepines, diaryl sulfoxides, coumarins, diphenylureas and protected carbonyl compounds and ZrO_2/pillared clay has been reported to be an efficient catalyst for solventless synthesis of dihydropyrimidinones [21].

Hantzsch heterocyclic derivatives have been also obtained since the last century. This one pot reaction occurs in a similar way to Biginelli´s, but it involves the use of ammonia in ethanol under reflux [22] or solvent-free conditions [23] Hantzsch derivatives as well as Biginelli condensation products have been studied due to their potent biological activities, but Hantzsch-type dihydropyridines in particular are used are hypotensive agents for the treatment of cardiovascular disorders [24].

Some publications have proven the existence of a competition between the obtention of 1,4-dihydropyridines (DHPs) and 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) under infrared radiation and solventless conditions [25] or microwave heating [26]. These one pot condensation reactions in the presence of acid solids have enabled us to achieve a simple green route for the preparation of DHPs; in connection with our interest in the novel use of sulfated zirconia as a catalyst in solvent free organic reactions, we report herein the synthesis of DHPMs via a clean, single-step, high yield cyclo-condensation reaction of aromatic aldehydes, ethyl acetoacetate and urea or thiourea under solvent-free conditions using sulfated zirconia as catalyst. Products resulting from competitive Biginelli and Hantzsch pathways are obtained, depending on the reaction temperature. Reusability of the catalyst, ease of separation of pure products, selectivity and high yields in comparison to the classical Biginelli reaction are some of the unique features of this process.

Results and Discussion

The sulfated zirconia catalyst was prepared by the reaction of zirconium isopropoxide with sulfuric acid in isopropanol. The product, obtained as a viscous solution, was first heated at 80°C to evaporate excess alcohol and then calcinated in air at 600°C, to give a white solid, identified as the target compound.

Figure 1 shows the results obtained after X-ray diffraction characterization of sulfated zirconia; the diffractogram pattern corresponds to sulfated zirconia samples where a tetragonal phase was found in all the samples given by reflections in 2θ = 30.18° (relative intensity is 100) as well as peaks 34.616°, 35.283°, 50.214°, 50.770°, 59.291°, 60.187° and 63.724°. (ICSD collection code: 066787).

Figure 1. Diffraction pattern of sulfated zirconia

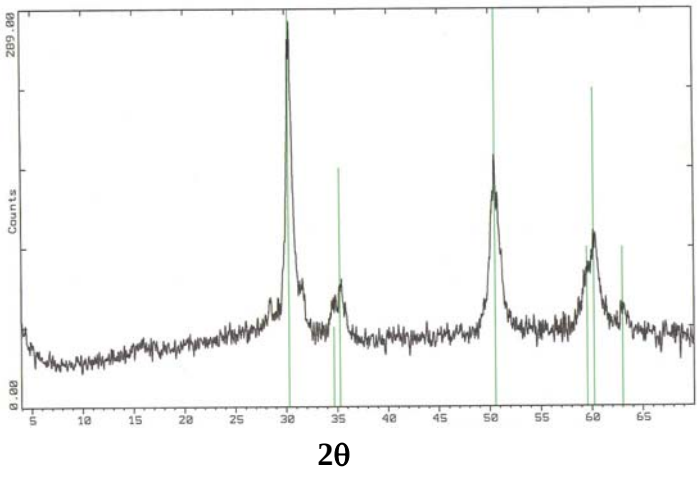
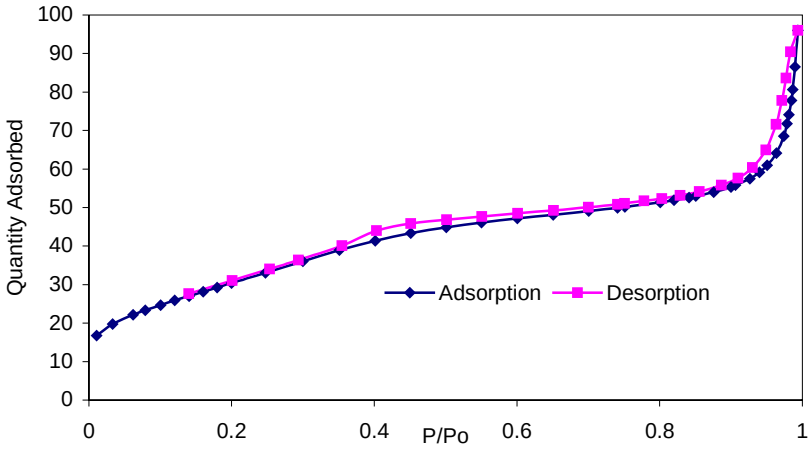


Figure 2 presents the results obtained by means of adsorption-desorption of nitrogen that gave an isotherm plot type IV of BET classification (Brunauer Emett and Teller theory); the isotherm hysteresis loop indicated a uniform pore size distribution.

Figure 2. Nitrogen adsorption-desorption plot of sulfated zirconia



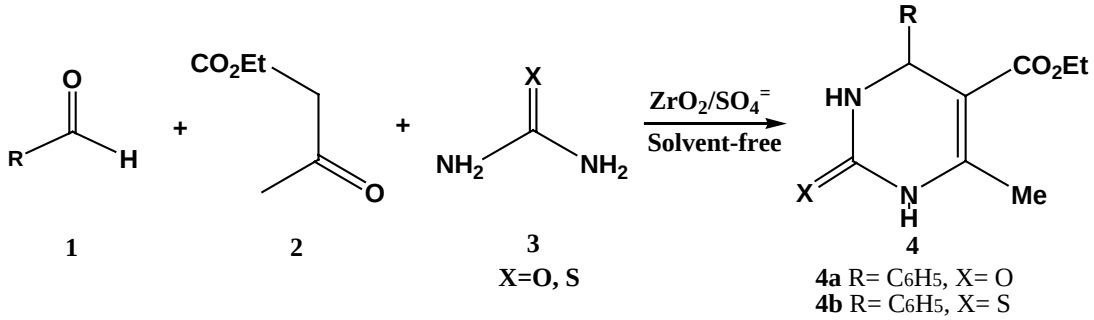
The data for BET specific surface-area, pore volume and pore size values are shown in Table 1. The TPD curve consisted of a wide high temperature desorption peak (at 600 °C) and the number of acid sites was measured by integration of the peak area. The acidity result was 340.72 μmole $NH_3 \cdot g^{-1}$.

Table 1. Sulfated zirconia textural features

Surface area	105.73 $m^2 \cdot g^{-1}$
Pore volume	0.12 $mL \cdot g^{-1}$
Pore size	42.79 Å

The basic scheme of the Biginelli reactions using sulfated zirconia as acid catalyst is shown in Scheme 1.

Scheme 1



1 **2** **3** **4**

X=O, S

4a R= C_6H_5, X= O
4b R= C_6H_5, X= S

Table 2 shows the different aldehydes used in solvent-free Biginelli reactions at 60°C in the presence of a catalytic amount of sulfated zirconia during a 4 hr reaction. We report isolated yields. The product's characteristics have been reported in the literature [20-22, 25, 27-32]. Some solvents were also used to test Biginelli reactions over sulfated zirconia at 60°C. No Hantzsch reaction products were observed.

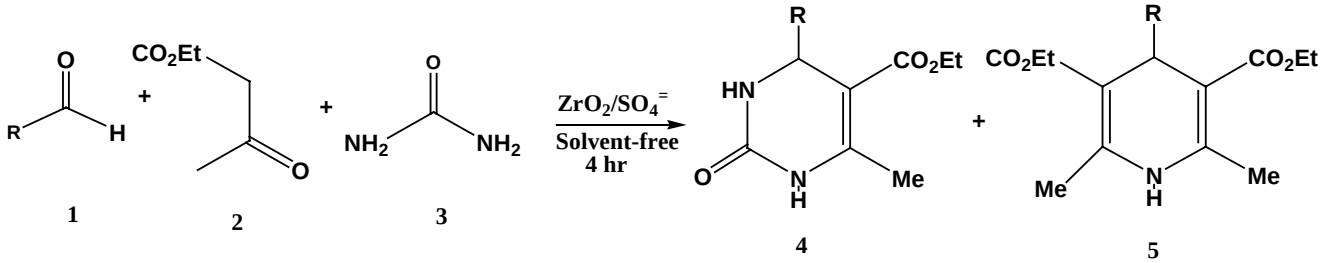
Table 2

Entry	R	X	4 Yield (%)
1	C_6H_5	O	94
2	2-$(CH_3)C_6H_4$	O	80
3	4-$(CH_3)C_6H_4$	O	80
4	5-(CH_3)-2-Furyl	O	83
5	C_6H_5	S	98
6	2-$(CH_3)C_6H_4$	S	90
7	4-$(CH_3)C_6H_4$	S	86
8	4-$(OCH_3)C_6H_4$	S	98
9	2-Furyl	S	88

When the solvent free reactions were carried out at 80°C in the presence of sulfated zirconia, only traces of Hantzsch product were obtained. A temperature increase, however, favored the

decomposition of urea into ammonia, thus promoting Hantzsch's reaction and allowing a competitive reaction leading to Biginelli **4** and Hantzsch **5** condensation products to take place (Scheme 2).

Scheme 2



1 2 3 4 5

5a R= C_6H_5

Table 3 shows the different aldehydes used in a one-step solvent-free reaction at 100°C and 150°C in the presence of a catalytic amount of sulfated zirconia during a 4 hr reaction. In all cases urea was used.

Table 3

Entry	R	Yield (%)			
		4	5	4	5
		100°C		150°C	
1	C_6H_5	84	10	52	41
2	2-(CH_3)C_6H_4	78	16	35	16
3	4-(CH_3)C_6H_4	71	6	42	51
4	5-(CH_3)-2-Furyl	50	32	25	64
5	2-Furyl	59	20	34	63
6	2-(OCH_3)C_6H_4	70	21	22	57
7	4-(OCH_3)C_6H_4	57	5	57	37

* Isolated yields of products 4 and 5 are reported.

To examine the reuse of the catalyst the sulfated zirconia was recovered by filtration and washed with acetone prior to drying. Reactivation was performed by heating the product in air at 500 °C. The XRD pattern of the materials thus recovered and reactivated were typical of sulfated zirconia, with the exception that there was an increase in the intensity of the peak at 2θ = 28° that is associated with the presence of the monoclinic phase. Recently, Sticher *et al*. reported that in a fixed-bed flow reactor at 300 °C monoclinic sulfated zirconia showed lesser catalytic activity in n-butane isomerizations as compared to the tetragonal phase [33]. Our results indicate that as the number of reactivation cycles increases, so does the presence of the monoclinic phase, which makes the material proportionally less catalytically active. Our results using benzaldehyde reflected such a decrease of the catalytic activity at 60 °C, whereby an 87% yield of the Biginelli condensation product was obtained in the first cycle and a 52% one in the second.

Conclusions

Sulfated zirconia proved to be an efficient acid catalyst replacement for common acid substances in multicomponent reactions under solventless conditions. Advantages of the technique described were easy recovery of the catalyst and the good yields of Biginelli and obtained, depending on the reaction temperarture. An increase of the latter typically increased the amounts of the 1,4-dihydropyridines (Hantzsch products) in most cases.

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Experimental

General

The reaction products were analyzed by means of a Hewlett Packard GC/MS system 6890/5973 gas chromatograph equipped with an HP-5 column, 70-280 °C (10 °C/min), inj. 250 ºC, det. 280 °C; the detector was set in the Chemical Ionization mode using methane as reactive gas. Powder X-ray diffraction (XRD) patterns were obtained with a Siemens instrument using Cu Kα radiation. Nitrogen adsorption/desorption isotherms were plotted at -196 °C on a Micromeritics ASAP 2020 equipment. Temperature programmed desorption (TPD) measurements were acquired on a Micromeritics TPD/TPR 2900 instrument (sample was activated at 370 °C for 10 min in flowing He (10 mL/min) and then, saturation of ammonia at 100 °C (20% NH_3 in He) and desorption at 10 °C/min to 600 °C. IR spectra were recorded on a Perkin-Elmer FT-IR system/GX spectrometer. ^{1}H- and ^{13}C-NMR were measured on a Bruker Avance DMX-500 spectrometer with tetramethylsilane as internal standard.

Procedure for the preparation of sulfated zirconia catalysts.

Sulfuric acid (98 % wt, 1 mL) was mixed with deionized water (3.5 mL). Zirconium isopropoxide (70% wt in 1-propanol, 20 mL) was further diluted with 1-propanol (30.5 mL). The acid solution was dropwise added to the alkoxide solution under vigorous stirring, until a viscous solution was obtained. The gel was heated at 80°C to evaporate excess alcohol. After, the dry gel was calcinated at 600°C for 7 h in air, leading to a white solid, identified as sulfated zirconia.

General procedure for the synthesis of DHPs (**4**) *and DHMPs* (**5**).

Ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and amine (urea or thiourea, 1.5 mmol) were placed in a vial equipped with a magnetic stirrer and plastic cap. The mixture was heated at 60, 80, 100 and 150°C in the presence of sulfated zirconia (50 mg) for 4 h without solvent. After the reaction, the mixture was left at room temperature, then 1:1 methanol-dichloromethane (10 mL) was added and the

solid was recovered by filtration. The filtrate was evaporated under reduced pressure and products were purified by silica gel column chromatography. For entry 1, Table 3, ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol) and urea (1.5 mmol), in this order, were mixed at 100 °C for 4 h with sulfated zirconia (50 mg). The results are summarized in Tables 2 and 3. All products were identified by comparison of their corresponding melting points, mass spectra data and ^{1}H-NMR spectra as follows:

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**): Yield 84%; m.p. 205-206 °C (lit. [25] 206-207°C); GC-MSD for $C_{14}H_{16}N_2O_3$ (m.w.: 260 g/mol): $[M+1]^+$=261, $[M+29]^+$= 289, $[M+41]^+$=301; IR (cm^{-1}): 3238, 3117, 2980, 1722, 1697, 1644, 1462, 1419, 1383, 1367, 1340, 1313, 1289, 1272, 1217, 1180, 1087, 1027, 956, 879, 824, 756, 697, 661; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.77 (br, 1H, N<u>H</u>), 7.27-7.32 (m, 5H, Ar-<u>H</u>), 5.62 (br, 1H, N<u>H</u>), 5.41 (s, 1H, C<u>H</u>-Ph), 4.04-4.11 (m, 2H, -C<u>H</u>$_2$-CH$_3$), 2.35 (s, 3H, -C<u>H</u>$_3$), 1.16 (t, 3H, *J*= 7.1 Hz, -CH$_2$-C<u>H</u>$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 165.47, 153.05, 146.96, 144.00, 128.05, 127.14, 126.25, 100.22, 59.32, 54.66, 17.99, 13.76.

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4b**). Yield 98%; m.p. 202-204°C (lit. [32] m.p. 205-206°C); GC-MSD for $C_{14}H_{16}N_2O_2S$ (m.w.: 276g/mol): $[M+1]^+$=277, $[M+29]^+$= 305, $[M+41]^+$=317; IR (cm^{-1}): 3324, 3169, 3102, 2981, 2234, 2001, 1666, 1572, 1495, 1464, 1449, 1425, 1388, 1344,1326, 1302, 1263, 1192, 1175, 1117, 1027, 1003, 963, 916, 871, 836, 822, 781, 758, 722, 692, 651,615; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 9,68 (br, 1H, N<u>H</u>), 9,06 (br, 1H, N<u>H</u>), 7.27-7.31 (m, 5H, Ar-<u>H</u>), 5.33 (s, 1H, C<u>H</u>-Ph), 4.04-4.09 (m, 2H, -C<u>H</u>$_2$-CH$_3$), 2.36 (s, 3H, -C<u>H</u>$_3$), 1.16 (t, 3H, *J*= 6.97 Hz, -CH$_2$-C<u>H</u>$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 174.09, 164.99, 143.93, 142.92, 127.82, 127.11, 126.23, 101.11, 59.26, 54.56, 17.14, 13.48.

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**5a**): Yield 10%; m.p. 154-155 °C (lit. [25] m.p. 156-157 °C); GC-MSD for $C_{19}H_{23}NO_4$ (m.w.: 229 g/mol): $[M+1]^+$=330, $[M+29]^+$= 358, $[M+41]^+$=370; IR (cm^{-1}): 3340, 3061, 2982, 1725, 1685, 1648, 1621, 1560, 1486, 1474, 1453, 1372, 1322, 1299, 1247, 1207, 1167, 1143, 1122, 1091, 1032, 1019, 916, 882, 843, 827, 777, 766, 737, 702, 679, 638, 619; ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 7.26-7.29 (m, 2H, Ar-<u>H</u>), 7.20 (t, 2H, *J*= 7.3 Hz, Ar-<u>H</u>), 7.11 (tt, 1H, J_1= 2.0, J_2= 7.3 Hz, Ar-<u>H</u>), 5.78 (br, 1H, N<u>H</u>), 4.99 (s, 1H, C<u>H</u>-Ph), 4.03-4.13 (m, 4H, -C<u>H</u>$_2$-CH$_3$), 2.32 (s, 6H, -C<u>H</u>$_3$), 1.22 (t, 6H, *J*= 7.2 Hz, -CH$_2$-C<u>H</u>$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 167.66, 147.76, 143.90, 127.70, 127.95, 126.06, 104.02, 59.60, 39.59, 19.45, 14.20.

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