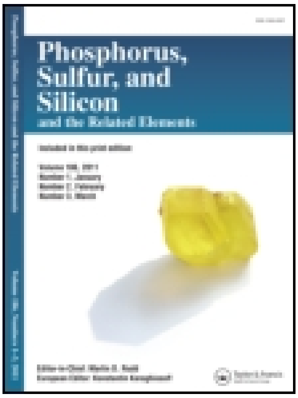

Phosphorus, Sulfur, and Silicon and the Related Elements

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The Efficient Synthesis of 3,4-Dihydropyrimidin-2-(1H)-Ones and Their Sulfur Derivatives with H_2SO_4 Immobilized on Activated Charcoal

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THE EFFICIENT SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2-(1*H*)-ONES AND THEIR SULFUR DERIVATIVES WITH H_2SO_4 IMMOBILIZED ON ACTIVATED CHARCOAL

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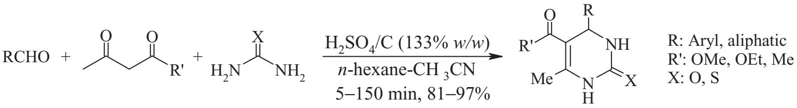
GRAPHICAL ABSTRACT



Abstract

Various 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs) and their sulfur derivatives were efficiently synthesized by a one-pot cyclocondensation reaction of aromatic and aliphatic aldehydes, β-dicarbonyl compounds and urea (or thiourea) in the presence of sulfuric acid immobilized on activated charcoal (133% w/w). The reactions were carried out in refluxing n-hexane-acetonitrile (2.5:0.5 mL) within 5–150 min to give 3,4-dihydropyrimidinones (or thiones) in high to excellent yields (81–97%).

Keywords 3,4-Dihydropyrimidin-2(1*H*)-one; activated charcoal; H_2SO_4; Biginelli synthesis

INTRODUCTION

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) and related compounds have attracted a great deal of attention in organic and medicinal chemistry.[1] This class of compounds possesses a broad range of biological activities including antiviral, antitumor, antibacterial, anti-inflammatory, antihypertensive, and potent calcium channel blockers.[2] The classical Biginelli synthesis of 3,4-dihydropyrimidinones was first reported in 1893 by a one-pot cyclocondensation reaction of β-dicarbonyl compounds, aromatic aldehydes and urea under strongly acidic conditions.[3] However, this reaction suffers from harsh reaction conditions, long reaction times and unsatisfactory yields. 3,4-Dihydropyrimidinones were also prepared by complex multi-step strategies with higher overall yields, whereas they lack the simplicity of one-pot protocol.[4] A literature review shows that numerous homogeneous as well as heterogeneous reagents have been devoted to a one-pot approach because of

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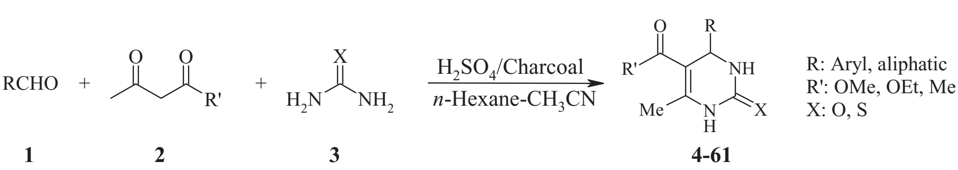
simplicity and high yields. $FeCl_3/Si(OEt)_4$,[5] $ZrCl_4$,[6] $ZrOCl_2\cdot8H_2O$,[7] $BiCl_3$,[8] $SnCl_2\cdot2H_2O$,[9] $InBr_3$,[10] $InCl_3$,[11] $LaCl_3\cdot7H_2O$,[12] $CeCl_3\cdot7H_2O$,[13] $CuCl_2\cdot2H_2O$,[14] $CaCl_2$,[15] $BF_3\cdot OEt_2$,[16] I_2,[17] $Mn(OAc)_3\cdot2H_2O$,[18] $NaIO_4$,[19] NH_4Cl,[20] $Cu(OTf)_2$,[21] $Bi(OTf)_3$,[22] $Fe(OTf)_3$ and $Fe(O_2CCF_3)$,[23] $Yb(OTf)_3$,[24] $B(OH)_3$,[25] $Al(HSO_4)_3$,[26] $NaHSO_4\cdot H_2O$,[27] H_2SO_4/SiO_2 or Al_2O_3,[28] silica sulfuric acid,[29] $MeSO_3H/Al_2O_3$,[30] sulfated zirconia,[31] *p*-TsOH,[32] montmorillonite KSF,[33] Envirocat EPZ10,[34] dodecylphosphonic acid,[35] $H_3PW_{12}O_{40}$,[36] $H_3PMo_{12}O_{40}$,[37] baker yeast,[38] and ionic liquid[39] are some of the reagents that have been used for synthesis of 3,4-dihydropyrimidinones.

On the other hand, solid supports have become popular and have been used for immobilization of various reagents. Heterogeneous catalyst/reagent systems derived by the immobilization method have been found a lot of benefits relative to the homogeneous ones. They have special characteristics such as ease of manipulation, rise in the selectivity of reactions, decrease in the waste production, ability to support moisture-sensitive reagents/catalysts, provide straightforward workup procedures and finally rendering more attractive synthetic processes from both the environmental and the economic point of view, in agreement with some parameters of the "ideal synthesis" presented by Wender.[40] Numerous articles have demonstrated the importance and applications of solid supports[41] as well as heterogeneous systems[42] in organic synthesis. In this context, activated charcoal, because of its high degree of micro-porosity (just one gram of activated carbon has a surface area in excess of 500 m^2 with 1500 m^2 being readily achievable), provides a high surface area and this situation makes it more desirable for academic and industrial applications.[43]

Recently, the immobilization of sulfuric acid on silica gel or alumina as an efficient heterogeneous acidic reagent has been reported by our research group for the synthesis of DHPMs and their sulfur analogs.[28] Therefore, to continue our research program and due to lack of information to investigate the influence of high micro-porosity of activated charcoal on Biginelli synthesis of DHPMs (or thiones), we decided to study the combination system of sulfuric acid and activated charcoal in catalysis of the titled reaction. Herein, we wish to introduce a fast and efficient protocol for synthesis of DHPMs as well as their sulfur analogs by a one-pot cyclocondensation reaction of aromatic and aliphatic aldehydes (**1**), *β*-dicarbonyl compounds (**2**), and urea (or thiourea) (**3**) with sulfuric acid immobilized on activated charcoal as a readily available heterogeneous acidic reagent in refluxing *n*-hexane-CH_3CN (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

Reaction conditions were preliminary optimized by the promotion of a one-pot cyclocondensation reaction of benzaldehyde, ethyl acetoacetate, and urea with the immobilized sulfuric acid on activated charcoal to afford 3,4-dihydropyrimidinone (**4**). The effect of various solvents, sulfuric acid alone and mass ratio of sulfuric acid to charcoal (*w/w*) were

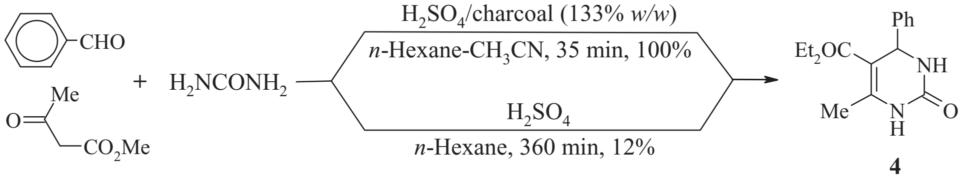
Table 1 Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (**4**) with H_2SO_4 immobilized on activated charcoal under different conditions[a]

Entry	H_2SO_4 (g)	Charcoal (g)	H_2SO_4/C (% *w/w*)	Solvent	Time (min)	Conversion[b] (%)
1	0.3	—	—	*n*-Hexane (3 mL)	360	12
2	0.3	0.3	100	CH_3CN (3 mL)	60	30
3	0.3	0.3	100	THF (3 mL)	60	20
4	0.3	0.3	100	H_2O (3 mL)	80	5
5	0.3	0.3	100	*n*-hexane (3 mL)	120	100
6	0.3	0.3	100	*n*-hexane-CH_3CN (2.5:0.5 mL)	90	100
7	0.2	0.3	67	*n*-hexane-CH_3CN (2.5:0.5 mL)	60	30
8	0.35	0.3	117	*n*-hexane-CH_3CN (2.5:0.5 mL)	45	100
9	0.4	0.3	133	*n*-hexane-CH_3CN (2.5:0.5 mL)	35	100
10	0.5	0.3	167	*n*-hexane-CH_3CN (2.5:0.5 mL)	30	100

[a] All reactions were carried out with 1 mmol of benzaldehyde in a molar ratio of aldehyde:ethyl acetoacetate:urea (1:1:1.2) under reflux conditions.

[b] Conversions less than 100% were determined on the basis of recovered aldehyde.

studied in Table 1. The results showed that in the case of sulfuric acid alone, the reaction remained incomplete after 360 min, with only 12% conversion, whereas the immobilization of sulfuric acid on activated charcoal dramatically accelerated the rate of reaction and consequently the reaction was completed within 30–120 min in refluxing *n*-hexane or a mixture of *n*-hexane-CH_3CN (Scheme 2). The results revealed that the reaction in a mixture of *n*-hexane-CH_3CN (2.5:0.5 mL) was faster than using *n*-hexane alone. Although the effect of mixing acetonitrile and *n*-hexane in promotion of the titled reaction is not clear, however, this could be due to less solubility of the produced dihydropyrimidinone (**4**) in *n*-hexane and more solubility of the reaction components in part of CH_3CN. Therefore, using H_2SO_4/charcoal system (133% *w/w*, easily available by mixing 0.4 g H_2SO_4 98% with 0.3 g activated charcoal) in refluxing *n*-hexane-CH_3CN (2.5:0.5 mL) is the optimum reaction conditions to afford the best yield of DHPM (**4**) from the reaction of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1.2 mmol) within 35 min (Table 1, entry 9).



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Scheme 2

The synthetic utility of H_2SO_4/charcoal system (133% *w/w*) was further studied by the reaction of various aromatic and aliphatic aldehydes, β-dicarbonyl compounds (ethyl/methyl acetoacetate and acetylacetone) and urea at the optimized conditions. Table 2 summarizes the results of this investigation. As it is observed, all reactions were carried out successfully in a mixture of *n*-hexane-CH_3CN (2.5: 0.5 mL) within 5–120 min to afford DHPMs (**4–28**) in high to excellent yields. Thiourea has also been used to provide

Table 2 Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones with H_2SO_4 immobilized on activated charcoal[a]

R	R’	X	DHPMs	Time (min)	Yield (%)[b]	M.p.(°C) Found	Reported
C_6H_5	OEt	O	**4**	35	95	202, 203	200–202[28]
2-ClC_6H_4	OEt	O	**5**	14	90	216, 217	215–218[30]
2,4-$Cl_2C_6H_3$	OEt	O	**6**	30	85	250, 251	249, 250[12b]
3-$NO_2C_6H_4$	OEt	O	**7**	5	92	226, 227	226, 227[30]
4-$NO_2C_6H_4$	OEt	O	**8**	17	88	208, 209	208–211[30]
4-MeC_6H_4	OEt	O	**9**	40	94	170, 171	170–172[19]
4-$MeOC_6H_4$	OEt	O	**10**	40	95	201, 202	200–201[30]
3-$MeOC_6H_4$	OEt	O	**11**	50	89	206, 207	207–208[11]
1-Naphthyl	OEt	O	**12**	40	92	246, 247	246–248[21]
CH_3	OEt	O	**13**	30	91	193, 194	194–195[10]
H	OEt	O	**14**	15	87	243, 244	242–244[10]
C_6H_5	OMe	O	**15**	60	95	210, 211	209–212[28]
2,4-$Cl_2C_6H_3$	OMe	O	**16**	70	91	253, 254	254–255[29]
3-$NO_2C_6H_4$	OMe	O	**17**	30	88	280, 281	279–280[20]
4-$NO_2C_6H_4$	OMe	O	**18**	10	94	234–236	235–237[28]
4-MeC_6H_4	OMe	O	**19**	120	93	203, 204	204–206[28]
4-$MeOC_6H_4$	OMe	O	**20**	50	87	193, 194	192–194[28]
3-$MeOC_6H_4$	OMe	O	**21**	40	85	171, 172	—
2-$MeOC_6H_4$	OMe	O	**22**	25	92	283–285	283–286[5]
4-OH-3-$MeOC_6H_3$	OMe	O	**23**	12	90	252–254	–
1-Naphthyl	OMe	O	**24**	120	92	235, 236	234–236[5]
CH_3	OMe	O	**25**	7	91	171, 172	—
4-MeC_6H_4	Me	O	**26**	120	95	227, 228	228–229[19]
2-$MeOC_6H_4$	Me	O	**27**	60	85	250, 251	—
CH_3	Me	O	**28**	10	90	182, 183	—

[a] All reactions were carried out with a molar ratio of aldehyde/β-dicarbonyl/urea (1:1:1.2) in the presence of H_2SO_4/charcoal (133% *w/w*) system under refluxing *n*-hexane-CH_3CN (2.5:0.5 mL).

[b] Yields refer to isolated pure products.

sulfur analogs of 3,4-dihydropyrimidinones. Similarly, the reaction of substituted aromatic and aliphatic aldehydes (1 mmol), β-dicarbonyl compounds (1 mmol) and thiourea (1.2 mmol) with the immobilized sulfuric acid on activated charcoal (133% *w/w*) in refluxing *n*-hexane-CH_3CN (2.5:0.5 mL) afforded 3,4-dihydropyrimidin-2(1*H*)-thiones (**29–61**) in high to excellent yields (Table 3).

The important aspect of sulfuric acid-activated charcoal system in synthesis of 3,4-dihydropyrimidinones (or thiones) is the tolerance of substituents including NO_2, Br, Cl, OH, OMe, and Me under the experimental conditions. In addition, aliphatic aldehydes such as HCHO and CH_3CHO as well as aromatic ones exhibited the high efficiency at this synthetic protocol that is known to be less reactive under conventional Biginelli reaction conditions (Table 2: DHPMs **13**, **14**, **25**, and **28**; Table 3: DHPMs **38**, **50**, and **61**). Moreover, in Tables 2 and 3, the influence of electron-donating and withdrawing groups of the aromatic rings on the rate of reactions is easily observed in the time of reactions. For example, Table 2 shows that in the case of substituted aromatic aldehydes, ethyl acetoacetate and urea, electron-withdrawing groups such as 3- or 4-NO_2 and 2,4-dichloro increase the rate of Biginelli cyclocondensation reaction and vice versa electron-donating groups such as 4-Me, 3-, or 4-OMe decrease the rate of reaction. Substituents such as hydrogen (in

Table 3 Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones with H_2SO_4 immobilized on activated charcoal[a]

R	R′	X	DHPMs	Time (min)	Yield (%)[b]	M.p.(°C) Found	Reported
C_6H_5	OEt	S	**29**	120	96	206–208	206, 207[28]
2,4-$Cl_2C_6H_3$	OEt	S	**30**	90	87	112–114	—
3-BrC_6H_4	OEt	S	**31**	50	90	170–172	—
4-$NO_2C_6H_4$	OEt	S	**32**	14	91	110, 111	109–111[39]
4-MeC_6H_4	OEt	S	**33**	130	97	192, 193	192–194[28]
2-$MeOC_6H_4$	OEt	S	**34**	35	90	199, 200	—
3-$MeOC_6H_4$	OEt	S	**35**	150	85	150–152	150–152[11]
3-OHC_6H_4	OEt	S	**36**	15	95	184, 185	184–186[28]
1-Naphthyl	OEt	S	**37**	140	88	199–201	—
CH_3	OEt	S	**38**	20	92	174–176	—
C_6H_5	OMe	S	**39**	120	82	227, 228	228–229[39]
3-BrC_6H_4	OMe	S	**40**	70	88	247, 248	—
3-$NO_2C_6H_4$	OMe	S	**41**	20	89	193, 194	—
3-$MeOC_6H_4$	OMe	S	**42**	130	90	211, 212	—
2-$MeOC_6H_4$	OMe	S	**43**	60	82	255–257	—
4-$MeOC_6H_3$	OMe	S	**44**	75	91	185, 186	185–186[39]
4-MeC_6H_3	OMe	S	**45**	130	92	165, 166	—
3-OHC_6H_3	OMe	S	**46**	30	96	222, 223	—
4-OHC_6H_3	OMe	S	**47**	15	89	244, 245	—
4-OH-3-$MeOC_6H_3$	OMe	S	**48**	30	86	257, 258	—
1-Naphthyl	OMe	S	**49**	120	81	254, 255	—
CH_3	OMe	S	**50**	10	90	198–200	—
C_6H_5	Me	S	**51**	150	96	219–221	220–222[39]
3-BrC_6H_4	Me	S	**52**	120	82	273, 274	—
4-$NO_2C_6H_4$	Me	S	**53**	25	87	256–258	—
3-$MeOC_6H_4$	Me	S	**54**	110	87	231–233	—
2-$MeOC_6H_4$	Me	S	**55**	25	95	192, 193	—
4-$MeOC_6H_3$	Me	S	**56**	75	90	182, 183	183–184[45]
4-MeC_6H_3	Me	s	**57**	120	92	228, 229	—
3-OHC_6H_3	Me	s	**58**	25	97	250, 251	—
4-OHC_6H_3	Me	s	**59**	8	88	252, 253	—
4-OH-3-$MeOC_6H_3$	Me	s	**60**	5	89	232–234	—
CH_3	Me	s	**61**	15	95	192–194	—

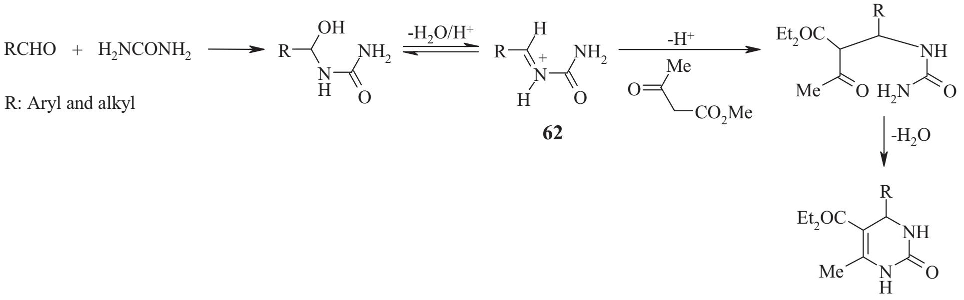
[a] All reactions were carried out with a molar ratio of aldehyde/β-dicarbonyl/thiourea (1:1:1.2) in the presence of H_2SO_4/charcoal (133% *w/w*) system under refluxing *n*-hexane-CH_3CN (2.5:0.5 mL).

[b] Yields refer to isolated pure products.

benzaldehyde) and benzene ring (in 1-naphthaldehyde) exhibit the efficiency of electron-donating groups similarly. In addition, the examinations with aliphatic aldehydes show more rates than aromatic ones in Biginelli synthetic reaction. The results of a comparable study in Tables 2 and 3 also show that the rate enhancement of 3,4-dihydropyrimidinones synthesis is generally higher than 2-thioxo derivatives when the same aldehydes and β-dicarbonyl compounds were used. This reveals that the nucleophilic activity of urea is higher than thiourea under the experimental conditions.

Reusability of the catalyst at this synthetic method was studied by recovering of charcoal immobilized sulfuric acid from the reaction mixture and then reusing it for the synthesis of 3,4-dihydropyrimidinones (**4**) from the reaction of benzaldehyde, ethyl acetoacetate, and urea in a mixture of *n*-hexane-CH_3CN. The results showed that due to liberation and consumption of some amount of sulfuric acid from the surface of charcoal in the reaction mixture, the regenerated system did not show the original activity. However, when the regenerated charcoal again is charged with sulfuric acid up to 133% *w/w*, the reagent system shows the primary catalytic activity in synthesis of 3,4-dihydropyrimidinone (**4**).

Kappe, in 1997 using spectroscopic methods,[44] demonstrated that the classical three-component Biginelli synthesis of 3,4-dihydropyrimidinone from the reaction of an aldehyde, ethyl acetoacetate, and urea in the presence of strong Brønsted acidic catalyst (HCl) exactly take places through the Folkers and Johnson proposed mechanism pathways involving acid-catalyzed formation of *N*-acyliminium ion precursor of type **62** from the preliminary condensation of an aldehyde and urea components as a key intermediate in the rate determining step. Although the exact mechanism of sulfuric acid immobilized on activated charcoal for the promotion of 3,4-dihydropyrimidinone synthesis is not clear, however, we think that due to closer characteristics of sulfuric acid to hydrochloric acid which was used in classical Biginelli reaction, the following mechanistic pathways could play a role in catalysis of the titled reaction (Scheme 3).



Scheme 3

As mentioned above, the promotion of 3,4-dihydropyrimidinone synthesis has been reported by modified sulfuric acid systems such as $NaHSO_4 \cdot H_2O$,[27] H_2SO_4 immobilized on SiO_2 or Al_2O_3,[28] and silica sulfuric acid.[29] So, in order to highlight the advantages of H_2SO_4/charcoal system (133% *w/w*), we compared some of our results with those of reported methods (Table 4). Comparison of the results shows that due to high microporosity and surface area of activated charcoal, the immobilization of sulfuric acid on charcoal exhibited the more rates and efficiency than the other protocols.

In summary, we have shown the high efficiency of sulfuric acid immobilized on activated charcoal (133% *w/w*) as an inexpensive and heterogeneous acidic reagent to promote the synthesis of DHPMs and their sulfur analogs in high to excellent yields. The reactions were carried out by a one-pot cyclocondensation reaction of aromatic and aliphatic aldehydes, β-dicarbonyl compounds and urea (or thiourea) in refluxing *n*-hexane-CH_3CN within 5–150 min. Therefore, the use of available low-cost reagents, synthesis of wide spectrum of 3,4-dihydropyrimidinones (or thiones) from aromatic aldehydes especially aliphatic ones, the tolerance of various functional groups and reusability of the recovered charcoal are the main advantages that make this protocol a useful addition to the present methodologies.

Table 4 Comparison of synthesis of 3,4-dihydropyrimidinones and 2-thione derivatives with H_2SO_4 immobilized on activated charcoal and other reported protocols

				H_2SO_4/Charcoal[a]		$NaHSO_4{\cdot}H_2O$[27]		H_2SO_4/SiO_2[28]		H_2SO_4/Al_2O_3[28]		$SiO_2\text{-}OSO_3H$[29]	
R	R′	X	DHPMs	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
C_6H_5	OEt	O	**4**	35	95	420	96	432	93	120	95	600	91
4-$MeOC_6H_4$	OEt	O	**10**	40	95	630	94	138	92	78	93	600	95
Me	OEt	O	**13**	30	91	—	—	—	—	—	—	—	—
C_6H_5	OMe	O	**15**	60	95	348	95	480	94	300	94	600	96
4-$NO_2C_6H_4$	OMe	O	**18**	10	94	240	96	138	95	96	95	600	95
C_6H_5	OEt	S	**29**	120	96	372	96	378	96	108	96	600	93
C_6H_5	Me	S	**51**	150	96	342	92	270	90	330	90	600	93
Me	Me	S	**61**	15	95	—	—	—	—	—	–	—	—

[a] The present protocol.

EXPERIMENTAL

General

All reagents and substrates were purchased from commercial sources with the best quality and they were used without further purification. Activated charcoal was obtained from Merck Company (Art No 102186). IR and $^1H/^{13}C$ NMR spectra were recorded on Thermo Nicolet Nexus 670 FT-IR and 300 MHz Bruker spectrometers, respectively (^1H at 300MHz; ^{13}C at 75MHz. The products were characterized by their spectra data and comparison with the reported data in literature. Melting points were recorded on a Philip Harris C4954718 apparatus. All yields refer to isolated pure products. Thin layer chromatography (TLC) was applied for the purity determination of substrates, products, and reaction monitoring over silica gel 60 F_{254} aluminum sheet.

Preparation of Sulfuric Acid Immobilized on Activated Charcoal (133% *w/w*)

To a round-bottom flask (5 mL) equipped with a magnetic stirrer, activated charcoal (0.3 g) and sulfuric acid (0.4 g, 98%) were added and the mixture was stirred vigorously for 3 min to afford sulfuric acid immobilized on activated charcoal (133% *w/w*). FT-IR (ν_{max}/cm^{-1}, KBr): 3400, 2610, 2488, 1713, 1633, 1286, 1176, 1069, 1008, 881, 851, 657, 578, 455. Figure S1 (Supplemental materials) shows the FT-IR spectrum of the catalyst.

General Procedure for Synthesis of DHPMs (Thiones) with Sulfuric Acid Immobilized on Activated Charcoal

In a round-bottom flask (10 mL) equipped with a magnetic stirrer and condenser, freshly prepared H_2SO_4/charcoal system (133% *w/w*), *n*-hexane (2.5 mL) and CH_3CN (0.5 mL) were added and the mixture was stirred for 1 min at room temperature. After addition of the aldehyde (1 mmol), β-dicarbonyl compound (1 mmol) and urea/thiourea (1.2 mmol) to the reaction mixture, stirring under reflux conditions was continued for the appropriate time (Tables 2 and 3). The progress of the reaction was monitored by TLC. When the reaction was complete, the mixture was cooled to room temperature and a sinter glass funnel removed the residue charcoal. To the filtrate, aqueous $NaHCO_3$ (10%, 5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent and recrystallization of the crude product in hot MeOH affords DHPMs or 2-thione (**4–61**) in 81–97% yield. Spectroscopic data for the previously prepared products are provided as supplementary data sheet.

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