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Sillica-supported sulfuric acid as heterogeneous, reusable and efficient catalyst for the multi-component synthesis of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate derivatives under solvent free condition

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ABSTRACT

Sillica-supported sulfuric acid was used as heterogeneous, reusable and efficient catalyst for the synthesis of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates by using multi-component reaction of dialkylacetylene dicarboxylate, amines and formaldehyde. These reactions were carried out under solvent free condition at 70 °C. The great advantage of these catalysts is ease of handling. Sillica-supported sulfuric acid can use and remove by filtration. With this method some advantages are such as, no special handling necessity of catalyst, easy monitoring of reaction progress, convenient workup procedure and high yields in short reaction times.

Keywords: *sillica-supported sulfuric acid, diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates, solvent free, multi-component reaction.*

1. INTRODUCTION

In the recent years, notable attention has been focused on solid acid catalysts in organic synthesis. Many of them are reusable, easy to separation from liquid products, high stability, grater selectivity and less harm to environment [1,2]. Currently the study of reactions by heterogeneous catalysts has become an active part of ongoing research due to several advantages such as simplified isolation, recyclability, easy of recovery, and have eco-friendly and economic advantages [3]. Lately, sillica-supported sulfuric acid (H_2SO_4. SiO_2) because of their ease of preparation, efficiency, and reusability, have gained considerable attention and have been used in many organic transformations such as transamidation [4], synthesis of dipyrromethanes [5], oxathioacetalization of aldehydes [6] and hydration of ethane [7] under solvent-free conditions.

Multi-component reactions (MCRs) are a powerful and flexible strategy for the rapid synthesis of diverse heterocyclic compounds. MCRs, combines at least three simple components, produce final products contain almost all portions of substrates, generating almost no by-products that makes MCRs an extremely ideal and eco-friendly reaction system [8-10].

Moreover, MCRs have advantages such as operational simplicity, decrease in the number of workup and purification processes, special synthetic yield and frequently with high stereoselectivity. Therefore, MCRs have been paid much attention in various research fields, such as discovery of lead compounds in medicinal chemistry, or combinatorial chemistry [11-13].

Pyrimidines are one of the most common *N*-heteroaromatic compounds containing two nitrogen atoms has widely appearing in nature as substituted and ring fused compounds. Specifically, tetrahydropyrimidines has gained great importance medicinal chemistry. Tetrahydropyrimidine derivatives possess numerous types of interesting pharmacological activities such as antiviral, antimicrobial, anti-inflammatory, anti-mycobacterial, anticancer and muscarinic agonist [14-21].

However, for the synthesis of polysubstituted-1,2,3,6-tetrahydropyrimidines some of the methods have been reported [22-27], which have several limitations such as use of toxic organic solvents, costly catalysts, existence of transition metals, difficult work up, time-consuming reaction and low yield. To avoid these limitations, we have investigated for a new catalyst (H_2SO_4. SiO_2) for the synthesis of polysubstituted-1,2,3,6-tetrahydropyrimidines. And to the best of our knowledge there are no reports on the use of this catalyst for the synthesis of polysubstituted-1,2,3,6-tetrahydropyrimidines (**4a-r**) *via* multi-component reaction of dialkylacetylene dicarboxylate (**1a**, **1b**), amines (**2a-i**) and formaldehyde (**3**).

2. EXPERIMENTAL SECTION

2.1. General. Melting points were measured on a Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Brucker FT-IR Tensor 27 infrared spectrophotometer. ^{1}H NMR and spectra were recorded on a Avance III 400 MHz Bruker spectrometer. ^{13}C NMR spectra were recorded on the same instruments at 100 MHz using TMS as an internal standard respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

2.2. General procedure for preparation of H_2SO_4. SiO_2. To a slurry of silica gel (10 g, 200 mesh) in dry diethyl ether (50 mL) was added commercially available concentrated H_2SO_4 (3 mL) with shaking for 5 min. The solvent was evaporated under reduced pressure resulting in free flowing H_2SO_4. SiO_2, which was then dried at 110 °C for 3 h [5].

2.3. General procedure for the preparation of dimethyl/ethyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-

dicarboxylate derivatives (4a-r). A mixture of dialkylacetylene dicarboxylate (**1a**, **1b**) (1 mmol), aromatic amine (**2a-i**) (2 mmol), formaldehyde (**3**) (2 mmol, aqueous solution 37%) and H_2SO_4. SiO_2 (50 mol%) were stirred for the appropriate time at 70 °C (Table 2) (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as an eluent). After completion of the reaction, the reaction mixture was dissolved in ethanol. The catalyst was removed by simple filtration. Ethanol was concentrated and the product was obtained.

*Diethyl 1,3-bis(4-chlorophenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4d)***

Oil; IR (KBr, *v* max/cm^{-1}): 1734, 1715 (C=O), 1574 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 7.21 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 8.1 Hz, 2H), 4.88 (s, 2H), 4.17 (s, 2H), 4.05-3.97 (q, *J* = 7.3 Hz, 2H), 3.85-3.78 (q, *J* = 7.3 Hz, 2H), 1.18 (t, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.12, 163.84, 146.40, 146.11, 145.92, 141.94, 132.36, 129.58, 125.21, 118.27, 117.15, 99.79, 68.57, 54.29, 52.94, 47.35, 14.28, 13.31. Anal. calcd. For $C_{22}H_{22}Cl_2N_2O_4$: C, 58.81; H, 4.94; N, 6.23 %. Found: C, 58.87; H, 4.99; N, 6.27 %.

*Dimethyl 1,3-di-p-tolyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4g)***

Oil; IR (KBr, *v* max/cm^{-1}): 1734, 1715 (C=O), 1561 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 7.11 (d, *J* = 8.3 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 4.91 (s, 2H), 4.19 (s, 2H), 4.12 (s, 3H), 3.91 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 164.89, 163.15, 146.23, 145.78, 140.89, 135.35, 129.45, 124.59, 117.17, 98.78, 78.95, 68.14, 60.89, 59.58, 47.12, 20.58, 20.04. Anal. calcd. For $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36 %. Found: C, 69.61; H, 6.45; N, 7.47 %.

*Diethyl 1,3-di-p-tolyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4h)***

Oil; IR (KBr, *v* max/cm^{-1}): 1734, 1696 (C=O), 1590 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.90 (s, 2H), 4.19 (s, 2H), 4.14-4.08 (q, *J* = 7.2 Hz, 2H), 3.98-3.92 (q, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 2.20 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 164.74, 163.02, 146.12, 145.78, 140.74, 135.32, 129.39, 124.45, 117.25, 117.01, 98.69, 78.94, 67.96, 60.78, 59.35, 47.06, 20.37, 19.98, 13.94, 13.19. Anal. calcd. For $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86 %. Found: C, 70.66; H, 6.99; N, 6.95 %.

*Dimethyl 1,3-bis(4-hydroxyphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4i)***

Oil; IR (KBr, *v* max/cm^{-1}): 3376 (broad pick, OH), 1734, 1699 (C=O), 1577 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 9.47 (s, 1H, OH), 6.99 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 2H), 4.09 (s, 2H), 3.96 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.2174, 164.12, 148.01, 146.28, 143.21, 142.56, 139.45, 129.42, 125.75, 117.68, 116.12, 98.97, 78.21, 69.21, 60.15, 58.06. Anal. calcd. For $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29 %. Found: C, 62.66; H, 5.37; N, 7.41 %.

*Diethyl 1,3-bis(4-hydroxyphenyl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4j)***

Oil; IR (KBr, *v* max/cm^{-1}): 3376 (broad pick, OH), 1728, 1664 (C=O), 1580 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 9.68 (s, 1H, OH), 7.01 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 2H), 5.01 (s, 2H), 4.18 (s, 2H), 4.22-4.16 (q, *J* = 7.2 Hz, 2H), 3.88-3.82 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.18, 164.04, 148.92, 146.12, 143.21, 141.36, 137.67, 129.47, 125.78, 117.01, 116.58, 99.02, 78.03, 68.98, 62.35, 59.89, 14.94, 13.89. Anal. calcd. For $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79 %. Found: C, 64.21; H, 6.01; N, 6.92 %.

*Dimethyl 1,3-di(naphthalen-1-yl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4n)***

Cream powders; IR (KBr, *v* max/cm^{-1}): 1734, 1718 (C=O), 1571 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 6.93-6.11 (m, 8H), 6.01 (d, *J* = 8.2 Hz, 2H), 4.93 (s, 2H), 4.01 (s, 2H), 4.02 (s, 3H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.21, 164.23, 146.14, 145.02, 141.98, 136.12, 135.97, 135.01, 133.25, 131.22, 129.58, 128.25, 127.99, 127.26, 125.98, 125.15, 124.79, 124.21, 122.16, 121.85, 117.14, 116.25, 115.38, 98.15, 78.39, 67.14, 60.01, 59.06. Anal. calcd. For. $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.35; N, 6.19 %. Found: C, 74.47; H, 5.48; N, 6.34 %.

*Diethyl 1,3-di(naphthalen-1-yl)-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4o)***

Yellow powder; IR (KBr, *v* max/cm^{-1}): 1734, 1718 (C=O), 1577 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.93-6.66 (m, 10H), 4.78 (s, 2H), 4.47 (s, 2H), 4.08-4.02 (q, *J* = 7.2 Hz, 2H), 3.76-3.70 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.99, 164.11, 147.12, 145.91, 141.26, 138.81, 137.92, 137.02, 136.05, 134.79, 133.35, 132.03, 130.89, 129.95, 127.70, 127.11, 123.89, 121.91, 120.17, 116.53, 116.04, 115.82, 114.88, 98.17, 79.62, 70.06, 59.73, 56.52, 14.70, 14.18. Anal. calcd. For $C_{30}H_{28}N_2O_4$: C, 74.98; H, 5.87; N, 5.83 %. Found: C, 75.15; H, 6.02; N, 6.01 %.

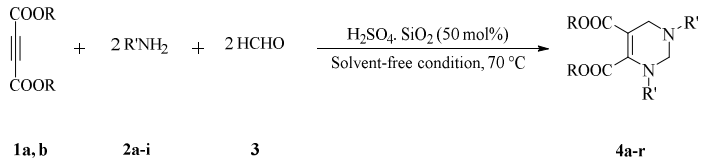
*Diethyl 1,3-dimethyl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate **(4q)***

Oil; IR (KBr, *v* max/cm^{-1}): 1734, 1680 (C=O), 1587 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 4.10-4.01 (q, *J* = 7.1 Hz, 2H), 3.95-3.90 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 2H), 3.49 (s, 2H), 2.87 (s, 3H), 2.47 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 164.89, 164.14, 159.58, 90.98, 68.28, 61.15, 59.87, 50.37, 47.02, 14.26, 13.37. Anal. calcd. For $C_{12}H_{20}N_2O_4$: C, 56.23; H, 7.87; N, 10.93 %. Found: C, 56.29; H, 7.93; N, 10.98 %.

3. RESULTS SECTION

In continuation of our previous works on environmentally friendly multi-component reactions [28-31], we have synthesized a series of dimethyl/ethyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate derivatives (**4a-r**) *via* multi-component reaction

of dialkylacetylene dicarboxylate (**1a**, **1b**), amines (**2a-i**) and formaldehyde (**3**) in presence of H_2SO_4. SiO_2 under solvent-free condition at 70 °C (Scheme 1).



1a, b **2a-i** **3** **4a-r**

Scheme 1. Synthesis of dimethyl/ethyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate derivatives (**4a-r**).

In order to optimize the reaction conditions, initially we used multi-component reaction of dimethylacetylene dicarboxylate **1a**, aniline **2a** and formaldehyde **3**, using different amounts of H_2SO_4. SiO_2 in solvent-free condition at 70 °C as model reactions for preparing compound **4a**. The results are shown in Table 1 (entry 1-3). The best results in terms of reaction time and yield of desired product **4a** were obtained when the reaction was carried out in the presence of 50 mol% H_2SO_4. SiO_2.

We also optimized the temperature of reaction. The best results were obtained when the reactions were carried out at 70 °C. The results are shown in Table 1 (entry 4-6).

We also attempted to reuse the catalyst. After each cycle, the catalyst was recovered by simple filtration, washed with hot ethanol, dried and reused directly in the next cycle. As shown in the Table 1 (entry 7-9) after the four cycle the catalyst was still highly efficient.

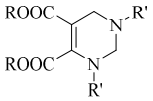
Up to this point, we decided to apply this method for synthesis of dimethyl/ethyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate derivatives (**4a-r**) *via* multi-component reaction of dialkylacetylene dicarboxylate (**1a**, **1b**), amines (**2a-i**) and formaldehyde (**3**) in presence of H_2SO_4. SiO_2 under solvent-free condition at 70 °C (Table 2).

Table 1. Optimization of the model reaction between dimethylacetylene dicarboxylate **1a**, aniline **2a** and formaldehyde **3**.

Entry	Catalyst (mol %)	Temperature	Time (min)	Yield (%)
1	H_2SO_4. SiO_2	70 °C	10	90
2	H_2SO_4. SiO_2	70 °C	5	93
3	H_2SO_4. SiO_2	70 °C	7	92
4	H_2SO_4. SiO_2	60 °C	10	91
5	H_2SO_4. SiO_2	70 °C	5	93
6	H_2SO_4. SiO_2	80 °C	7	92
7[a]	H_2SO_4. SiO_2	70 °C	8	91
8[b]	H_2SO_4. SiO_2	70 °C	12	89
9[c]	H_2SO_4. SiO_2	70 °C	15	88

a: first cycle; b: second cycle; c: third cycle.

Table 2. Multi-component reaction of dialkylacetylene dicarboxylate (**1a**, **1b**), amines (**2a-i**) and formaldehyde (**3**).



4a-r

Compd. No.	R	R'	Time (min)	Yield (%)	M. P. observed (°C)	M. P. reported (°C)
4a	Me	C_6H_5	5	93	Oil	Oil [23]
4b	Et	C_6H_5	5	92	86-88	85-86 [23]
4c	Me	4-Cl-C_6H_4	4	93	Oil	Viscous [26]
4d	Et	4-Cl-C_6H_4	5	93	Oil	———
4e	Me	4-Br-C_6H_4	5	93	153-155	152-153 [26]
4f	Et	4-Br-C_6H_4	5	93	149-151	143-145 [25]
4g	Me	4-CH_3-C_6H_4	7	92	Oil	———
4h	Et	4-CH_3-C_6H_4	8	91	Oil	Oil [23]
4i	Me	4-OH-C_6H_4	10	92	Oil	———
4j	Et	4-OH-C_6H_4	10	91	Oil	———
4k	Et	4-CH_3O-C_6H_4	10	93	117-119	114–116 [25]
4l	Me	C_6H_4-CH_2	10	91	Oil	Oil [23]
4m	Et	C_6H_4-CH_2	12	90	Oil	Oil [23]
4n	Me	$C_{10}H_7$	10	93	167-169	———
4o	Et	$C_{10}H_7$	10	92	173-175	———
4p	Me	CH_3	10	91	Oil	Viscous [26]
4q	Et	CH_3	10	90	Oil	———
4r	Et	n-C_4H_9	12	92	Oil	Oil [23]

$C_{10}H_7$-NH_2: 1-naphthyl amine

4. CONCLUSIONS

In this study, new applications of H_2SO_4-SiO_2 as inexpensive, nontoxic, reusable and environmentally catalyst, for the synthesis of dimethyl/ethyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate derivatives *via* multi-

component reaction of dialkylacetylene dicarboxylate amines and formaldehyde under solvent-free condition at 70 °C are explained. H_2SO_4-SiO_2 offers a simple, novel, and convenient method for this reaction. High yields, short reaction time, easy work-up and reusability of the catalyst are advantages of this procedure.

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6. ACKNOWLEDGEMENTS

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