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ARTICLE

An effective process for the synthesis of dihydropyridines via SO_4^{-2}/SnO_2-catalyzed Hantzsch reaction

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Abstract

Sulfated tin oxide (STO) was established as an admirable heterogeneous catalyst for the single-step synthesis of dihydropyridine derivatives via Hantzsch reaction. The synthetic method was mainly used in the presence of STO as a heterogeneous solid catalyst. STO-catalyzed Hantzsch reaction afforded good yields (90–94%) in acetonitrile at 80°C. The synthesized titled compounds were characterized and confirmed by High Resolution Mass Spectroscopy (HRMS), Fourier Tranform-Infrared (FTIR), ^{1}H and ^{13}C-NMR, and spectral data.

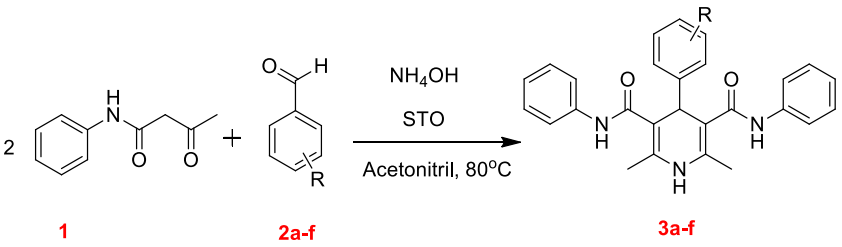
KEYWORDS

heterogeneous catalyst, shorter reaction times and high product yields, single-step reaction, STO

1 | INTRODUCTION

Sulfated tin oxide (STO) is an imported heterogeneous solid catalyst with both Brønsted and Lewis acid sites.[1–2] The STO catalyst has many advantages, such as easy preparation, nontoxic, low cost, highly selective, and environmentally benign with good yield, and it is stable in air, moisture, and heat.[3–6] STO has been explored significantly for its catalytical activity in various reactions, such as trans-esterification, dehydration, nitration, alkylation, condensation, pyrolysis, and polymerization.[7–10] The research reports that STO is a promising heterogeneous catalyst for the synthesis of important drug molecules such as 7-hydroxy-4-methyl coumarine, naphtha pyranopyrimidines, 2,4,5-Triaryl-1-H-imidazole and 7,8-Dihydro-2H-Chromen-5-ones, and pyrimidines.[11–15] It also plays a vital role in industrial applications, such as coal liquefaction, esterification of crude palm oil, and production of biodiesel.[16–17]

Dihydropyridines were first synthesized by Hantzsch.[18] Dihydropyridines have an appreciable role in natural products and biological activities,[19–22] such as a cerebral anti-ischemic, neuroprotectant, anticoagulatory, chemosensitizers, cardiovascular disorders, hypertension, nephroprotective in hypertensive types I and II for diabetic patients, and treatment of Alzheimer's disease.[23–27] Many methods were proposed for the synthesis of dihydropyridines using Lewis acid, Bronsted acid, biocatalysts, ionic liquids, and organocatalysts.[28–33] The commercial products of dihydropyridines, such as diludine, felodipine, amlodipine, nimodipin, nifedipine, nitredipin, nislodipin, nimopidipin, and Bay K 8644, were manufactured and are being used worldwide.[34–37] Many reports focus on the amendments of the Hantzsch process to increase the product yield and reduce the formation of byproducts and reaction time. The unsatisfactory points of these amendments are the usage of volatile organic solvents, longer time, and development of side products. Hence, this concept needs better diversity to create target libraries with selected building blocks for our various heterocyclic scaffolds. In this paper, we report a multicomponent simple process for the Hantzsch reaction process using a reusable solid STO catalyst for the preparation of target moiety. This process is capable of approaching target dihydropyridines with less reaction time and good yields.



SCHEME 1 STO-catalyzed synthesis of dihydropyridines

TABLE 1 Optimum reaction conditions of the synthesis of dihydropyridines for the compound **3a**

Entry	Compound no.	Catalyst	Amount	Solvent	Temp (°C)	Time (hr)	Yield (%)[a]
1	**3a**	—	—	H_2O	Room temp	12.0	[b]
2	**3a**	—	—	H_2O	80	12.0	25
3	**3a**	NaOH	1.0 (equiv.)	CH_3CN	Room temp	6.0	[c]
4	**3a**	$[Bmim]BF_4$	6 drops	H_2O	Room temp	10.0	[b]
5	**3a**	$[Bmim]BF_4$	6 drops	DCM	60	8.0	[b]
6	**3a**	$[Bmim]BF_4$	6 drops	CH_3CN	Room temp	10.0	[b]
7	**3a**	$[Bmim]BF_4$	6 drops	Ethanol	Room temp	5.0	[b]
8	**3a**	$[Bmim]BF_4$	6 drops	Ethanol	60	5.0	55
9	**3a**	$[Bmim]BF_4$	6 drops	CH_3CN	60	6.0	20
10	**3a**	STO	10.0 mg	CH_3CN	Room temp	5.0	[b]
11	**3a**	STO	20.0 mg	CH3CN	80	3.0	60
12	**3a**	STO	30.0 mg	CH_3CN	80	2.0	94
13	**3a**	STO	40.0 mg	CH_3CN	80	2.0	96

[a]Isolated yields.
[b]Products was not found.
[c]Trace.

2 | RESULTS AND DISCUSSION

In extension to our earlier effort towards finding new methods for construction of biologically active small heterocyclic molecules, STO was used as a recyclable solid catalyst.[38,39] Keeping these features in mind, we initially developed a model reaction of acetoacetanilide, ammonium hydroxide, and different aldehydes in the presence of STO (Scheme 1).

The reaction-optimized conditions were thoroughly studied with various solvents, catalyst reaction time, and yield of the product and were summarized in Table 1. First, the Hantzsch reaction (Scheme 1) for product **3a** was tried with catalyst-free water solvent at room temperature and 80°C (Table 1 entry 1–2), but this did not produce good results. In the same way, we tried with different catalysts such as NaOH and $[Bmim]BF_4$ in different mediums such as acetonitrile, water, dichloromethane, and ethanol, but the expected results were not produced, (Table 1 entries 3–9). Now, the same reaction was preceded with STO in CH_3CN medium at room temperature and 80°C, and the results are shown in Table 1 (entries 10–13). The catalyst was used in various amounts (20, 30, and 40 mg) for the synthesis of title compounds and resulted in optimum (60, 94, and 96%; Table 1 entries 11–13) product yields.

TABLE 2 Reusability of STO catalyst for compound **3a**

S. no	STO	Duration (hr)	Yield (%)[a]
1	Fresh	2.5	94
2	Second cycle	2.5	94
3	Third cycle	2.5	92
4	Fourth cycle	2.5	92
5	Fifth cycle	2.5	91

[a]Isolated yields.

The recycled STO catalyst was used for the second run and provided the product with 94% yield. The recovery and reuse process of STO was carried out for four more cycles, and the target product was yielded with no vanishing efficiency of the catalyst (Table 2).

TABLE 3 The synthesis of dihydropyridine derivatives (**3a-f**) with STO catalyst

S. no	Compound no.	Substituents	Duration (hr)	Yield (%)[a]
1	**3a**	H	2.5	94
2	**3b**	4-$N(CH_3)_2$	3.5	92
3	**3c**	4-Br	2.5	89
4	**3d**	2-NO_2	3.5	86
5	**3e**	4-OH	3.5	89
6	**3f**	4-OCH_3	3.0	91

[a]Isolated yields.

The definite contribution to the development of green strategy for the Hantzsch reaction was expected with an easy experimental setup, good yield of the product, green solvents, easy recovery, and a reusable catalyst. Under optimal reaction conditions, the derivatives of dihydropyridines (**3a-f**) have been synthesized using five various benzaldehyde substrates with appreciable yield. The dihydropyridine derivatives successfully precipitated even though they proceeded with a sterically hindered substrate (Table 3).

The STO-catalyzed Hantzsch reaction mechanism demonstrates how starting materials are converted to target molecules. The mechanism of this reaction proceeds through a Michael addition, followed by an intramolecular tandem sequence, that may take place in the formation of the final product (Mechanism).

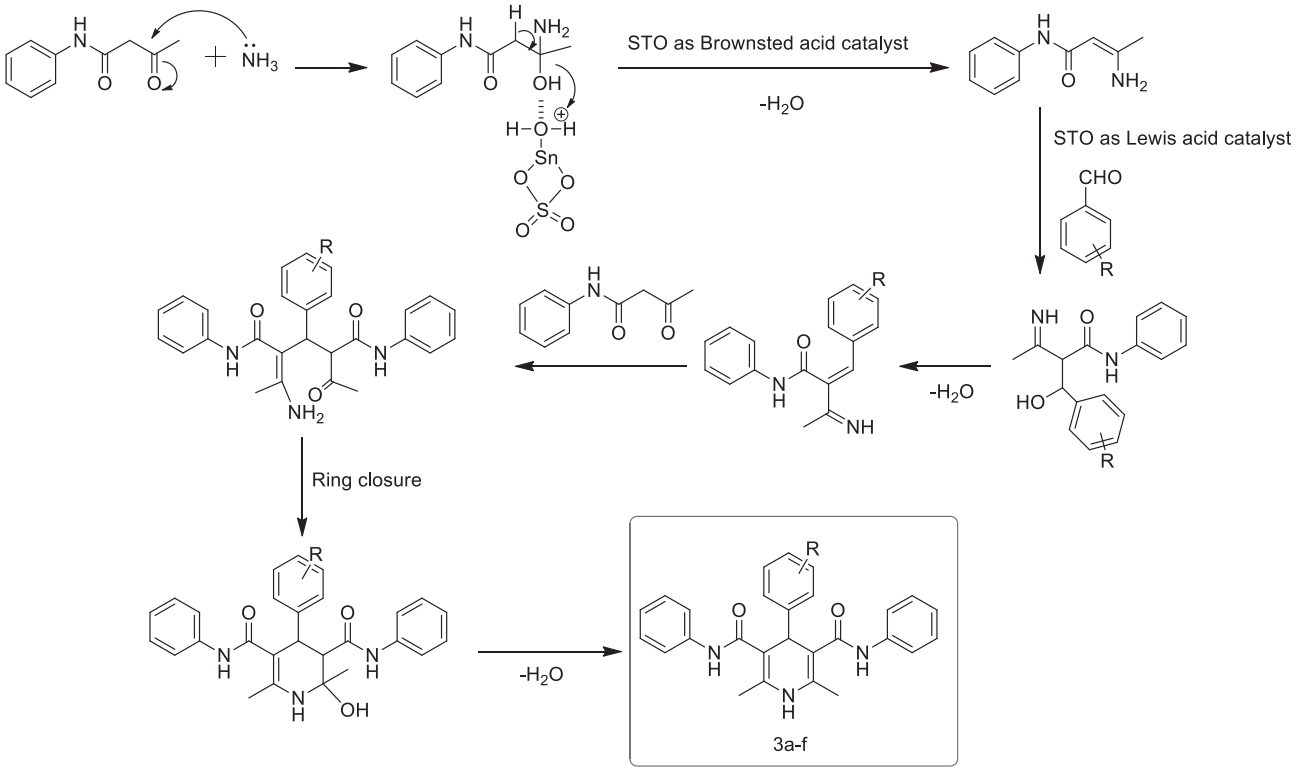
Mechanism: Plausible reaction mechanism for the construction of dihydropyridines.

3 | EXPERIMENTAL

3.1 | STO promoted synthesis of dihydropyridine derivative under silent conditions (3a)

One mole of benzaldehyde, 3 ml of acetonitrile, 2 ml of acetoacetanilide, 1.5 ml of ammonium hydroxide, and 30 mg of STO were taken in the same sequence in a round-bottom flask, condensed, heated up to 80°C, and magnetically stirred for an appropriate time as shown in Table 3.

The reaction progress was observed with Thin Layer Chromatography (TLC) (4:6 ratio of ethyl acetate/n-hexane), and after TLC was completed, the mixture was allowed to reach room temperature and was extracted into ethyl acetate. After filtering the STO solid, the ethyl acetate layer was



washed with H_2O and dried over anhydrous magnesium sulfate, and the solvent was removed to obtain the target compound as a precipitate. The resulting precipitate was recrystallized from ethanol to give the pure target product. The recovered STO catalyst was washed with methylene chloride, and the methylene chloride was completely removed under reduced pressure and used in the next sequence.

3.1.1 | Compound 3a

Light yellow solid (94%): mp. 299–301°C; IR (KBr, cm^{-1}): 1644 (C═O), 3,271, 3,414; HRMS of [$C_{27}H_{25}N_3O_2$ + Na] (m/z): 446.1837 (100%); Calc. Mass: 446.1843; 13C NMR δ (ppm): 17.35, 42.02, 105.77, 119.44, 122.68, 125.98, 127.18, 128.14, 128.42, 137.85, 139.49, 146.86, 167.45; 1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.10 (s, 6H, CH3), 5.09 (s, 1H, quaternary-H), 6.96–7.56 (m, 15H, Ar-H), 8.05 (s, 1H, NH), 9.29 (s, 2H, NH).

3.1.2 | Compound 3b

Light yellow solid (92%): mp. 284–287°C; IR (KBr, cm^{-1}): 1655 (C═O), 3,229, 3,282; HRMS of [$C_{29}H_{30}N_4O_2$ + Na] (m/z): 489.2271 (100%); Calc. Mass: 489.2265; 13C NMR δ (ppm): 17.37, 40.19, 40.86, 106.08, 112.47, 119.33, 122.60, 127.68, 128.44, 134.97, 137.76, 139.58, 149.01, 167.52; 1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.10 (s, 6H, CH3), 2.79 (s, 6H, CH3), 4.97 (s, 1H, quaternary-H), 6.58–7.57 (m, 14H, Ar-H), 8.01 (s, 1H, NH), 9.17 (s, 2H, NH).

3.1.3 | Compound 3c

Off-white solid (89%): mp. 275–276°C; IR (KBr, cm^{-1}): 1630 (C═O), 3,237, 3,277; HRMS of [$C_{27}H_{24}N_3O_2Br$ + Na] (m/z): 524.0938 (100%); Calc. Mass: 524.0949; 13C NMR δ (ppm): 17.35, 41.57, 105.52, 119.04, 119.49, 122.77, 128.44, 129.45, 130.66, 137.82, 139.42, 146.26, 167.32; 1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.07 (s, 6H, CH3), 5.08 (s, 1H, quaternary-H), 6.97–7.57 (m, 14H, Ar-H), 8.09 (s, 1H, NH), 9.35 (s, 2H, NH).

3.1.4 | Compound 3d

Yellowish orange solid (86%): mp. 261–263°C; IR (KBr, cm^{-1}): 1649 (C═O), 3,277, 3,384; HRMS of [$C_{27}H_{24}N_4O_4$ + Na] (m/z): 491.1694 (100%); Calc. Mass: 491.1694; 13C NMR δ (ppm): 17.44, 36.56, 105.34, 119.37, 122.78, 123.34, 127.37, 128.41, 131.28, 133.50, 139.18, 139.29, 141.39, 147.11, 166.60; 1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.14 (s, 6H, CH3), 5.63 (s, 1H, quaternary-H), 6.97–7.68 (m, 14H, Ar-H), 8.34 (s, 1H, NH), 9.34 (s, 2H, NH).

3.1.5 | Compound 3e

Light yellow solid (89%): mp. 220–222°C; IR (KBr, cm^{-1}): 1650 (C=O), 3,304, 3,374; HRMS of [$C_{27}H_{25}N_3O_3$ + Na] (m/z): 462.1802 (100%); Calc. Mass: 462.1795; 13C NMR δ (ppm): 17.35, 41.12, 106.12, 114.95, 119.38, 122.64, 128.16, 128.44, 137.46, 137.56, 139.52, 155.65, 167.55; 1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.06 (s, 6H, CH3), 4.99 (s, 1H, quaternary-H), 6.57–7.53 (m, 14H, Ar-H), 7.98 (s, 1H, NH), 8.98 (s, 1H, OH), 9.22 (s, 2H, NH).

3.1.6 | Compound 3f

Off-white solid (91%): mp. 245–247°C; IR (KBr, cm^{-1}): 1658 (C=O), 3,226, 3,277; HRMS of [$C_{28}H_{27}N_3O_3$ + Na] (m/z): 476.1945 (100%); Calc. Mass: 476.1951; 13C NMR δ (ppm): 17.37, 41.13, 54.86, 106.01, 113.55, 119.40, 122.68, 128.20, 128.42, 137.66, 139.13, 139.51, 157.57, 167.48; 1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.09 (s, 6H, CH3), 3.64 (s, 3H, OCH3), 5.03 (s, 1H, quaternary-H), 6.75–7.57 (m, 14H, Ar-H), 8.04 (s, 1H, NH), 9.24 (s, 2H, NH).

4 | CONCLUSIONS

An uncomplicated and straightforward scheme was demonstrated for the synthesis of Hantzsch 1, 4-dihydropyridines. This green protocol offers extra benefits such as mild and eco-friendly experimental conditions, less reaction time, good yield of target products, nontoxic reagents, economically viable catalysts, and simple isolation of products.

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SUPPORTING INFORMATION

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