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Silica supported tungstic acid (STA): an efficient catalyst for the synthesis of bis-spiro piperidine derivatives under milder condition

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ABSTRACT

A mild, efficient, and expeditious method has been developed for the synthesis of 3,5-dispirosubstituted piperidines via a three component, one-pot cyclocondensation reaction of aromatic amines, formaldehyde, and dimedone using Silica supported tungstic acid as heterogeneous catalyst for the first time. The reaction involving formation of six new covalent bonds was conveniently promoted by Silica supported tungstic acid and the catalyst could be recovered easily after the reaction and reused without any loss of its catalytic activity. The advantageous features of this methodology are high atom-economy, operational simplicity, shorter reaction time, convergence, and facile automation.

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The condensation reaction of carbonyl compounds with active methylene compounds in the presence of amines, known as the Knoevenagel condensation,¹ represents one of the most significant bond-forming reactions in organic chemistry.² Especially, due to the fact that the resulting α,β -unsaturated dicarbonyl or related compounds are useful intermediates, combination of this reaction with other reactions in a domino fashion³ has been increasingly employed, thereby making the formation of multiple bonds possible.⁴ For example, Knoevenagel condensation has been successfully combined with hetero Diels–Alder reactions, Michael addition reactions, ene reactions, and/or sigmatropic rearrangements for the synthesis of highly functionalized molecules.⁵ The combined achievement of making multiple bonds in a one-pot synthesis is well known as multicomponent coupling reaction promotes a sustainable synthetic approach to new molecule discovery.

Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three different substrates join through covalent bonds, have steadily gained importance in synthetic organic chemistry. MCRs allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, facile automation, and reduction in the number of work-up, extraction, and purification processes, and hence minimize waste generation, rendering the transformations green.^{6–8}

One of the important reactions in the field of multicomponent synthesis is a three-component condensation of anilines with dimedone and formaldehyde in the presence of catalyst leading to the formation of 3,5-dispirosubstituted piperidines. The synthesis of highly functionalized piperidines is an important synthetic transformation⁹ as these compounds find extensive applications in the synthesis of a number of organic fine and bioactive compounds.¹⁰ Also the piperidine ring is present in many natural products¹¹ such as alkaloids, which are responsible for a number of unique activities including anti-hypertensive,¹² anticonvulsant, and anti-inflammatory activities. Spiropiperidinyl compounds have attracted an increasing interest as the synthetic targets due to their important activity as pharmacophores in several biologically active compounds, mainly alkaloids.¹³ The synthetic compounds with a 4-spiropiperidine motif (types A–D) possess interesting activities as well¹⁴ (Fig. 1). In addition, spirofused piperidines have attracted particular attention due to their miscelaneous interesting physiological activities.¹⁵

Figure 1. Compounds with 4-spiro piperidine skeleton as pharmaceuticals.





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Scheme 1.

Recently, only two reports¹⁶ on the synthesis of various 3,5-dispirosubstituted piperidines have used FeCl₃ and In(OTf)₃ for spirohexahydropyrimidine, but unfortunately, both reports use homogenous catalysts. The use of homogenous catalysts has received little attention as alternatives in alleviating some of the limitations. Thus, the search for an inexpensive, readily available, and convenient catalyst is desirable. The usage of heterogeneous metal Lewis catalyst instead of traditional homogeneous metal Lewis and Brønsted acid catalysts, could possess a more environmentally friendly alternative. The development of environmentally friendly solid catalysts for the synthesis of fine chemicals and pharmaceuticals is becoming an area of growing interest because the use of heterogeneous catalytic processes allows easier separation, recovery, and recycling of the catalysts from the reaction mixtures.¹⁷ Solid catalysts provide numerous opportunities for recovering and recycling catalysts from reaction environments. Among the various heterogeneous catalysts, particularly, silica gel-supported tungstic acid (STA) has advantages of low cost, ease of preparation, environment friendly, highly efficient, and catalyst recycling. Karami et al. reported that silica tungstic acid is an efficient catalyst for the synthesis of benzimidazoles¹⁸ and benzopyrazines.¹⁹

In continuation of our ongoing effort to development of new environmentally benign methodology for the synthesis of an useful precursor in the field of biology, industry, and key intermediate for the multistep synthesis,²⁰ we decided to investigate the efficiency of supported silica tungstic acid catalyst for the synthesis of 3,5dispirosubstituted piperidines. So herein we wish to report the multicomponent reaction for the synthesis of 3,5-dispirosubstituted piperidines from Dimedone, formaldehyde, and various aromatic amines using silica tungstic acid as a reusable catalyst at room temperature in quantitative yield (Scheme 1). The reaction is easy to perform and allows synthesizing various multi functionalized derivatives. These reaction work-up procedures were simple and we can isolate products with high purity and yields.

Initially, in search of best catalytic system for this one-pot synthesis, optimization of various reaction parameters like different metal Lewis acid catalysts, temperature, and solvent was carried out (Table 1) with the standard reaction of aniline, dimedone, and formaldehyde. In order to establish the real effectiveness of the catalyst for the synthesis of 3,5-dispirosubstituted piperidines, a test reaction was performed without catalyst using aniline, formaldehyde, and dimedone at room temperature. It was found that only a trace amount of product was obtained in the absence of catalyst even after 10 h (Table 1, entry 1).

Even though we increased the temperature up to 100 °C for this catalyst free reaction, there was no appreciable improvement in yield (Table 1, entry 2). In search of effective, eco-friendly, and efficient reusable catalytic system for this reaction, same test reaction was performed with different supported metal Lewis acid catalysts such as Cu–Sn (200 mesh, 100 mg), Cu(OTf)₂·SiO₂, Zn(OTf)₂·SiO₂, TiO₂·SiO₂, BF₃·SiO₂, and ZnCl₂·SiO₂ (Table 1). To study the role of SiO₂, the reaction was tested with SiO₂ (100 mg) only, and we

Table 1 Screening of various types of catalysts and solvents for the synthesis of compound $4a^a$

		→ → → → → → → → → → → → → → → → → → →	tic acid , rt.		
	1 2	3	/ O 4a	N N	
Entry	Catalyst (10 mol %)	Solvent	Condition	Time (h)	Yield ^b (%)
1	_	DCM	rt	10	Trace
2	_	Neat	100 °C	5	≼10
3	SiO ₂	DCM	rt	10	58
4	CuSn (200 mesh, 100 mg)	DCM	Reflux	10	52
5	$ZnCl_2 \cdot SiO_2$	DCM	rt	6	58
6	$BF_3 \cdot SiO_2$	DCM	rt	6	40
7	$Cu(OTf)_2 \cdot SiO_2$	DCM	rt	4	78
8	TiO ₂ ·SiO ₂	DCM	rt	6	50
9	$Zn (OTf)_2 \cdot SiO_2$	DCM	rt	4	80
10	STA	DCM	rt	4	93
11	STA	Ethanol	rt	5.5	85
12	FeCl ₃ ·SiO ₂	DCM	rt	8	85
13	FeCl ₃ ·SiO ₂	Ethanol	rt	8	82
14	STA	Water	rt	6	74
15	STA	THF	rt	6	52
16	STA	Toluene	rt	8	65
17	STA	ACN	rt	8	72
18	STA	DCE	rt	6	88
19	STA	DCM	Reflux	2	85
20	STA	DCM	100 °C	4	93
21	STA (05 mol %)	DCM	rt	4	82
22	STA (20 mol %)	DCM	rt	4	90

^a Reactions and conditions: aniline (1 mmol), Dimedone (2 mmol), formaldehyde (3 mmol).

^b Isolated yields.

Table 2 (continued)

Yields^b (%)

82

92

84

70

nr

85

82

84

nr

Table 2

Entry

4a

4b

4c

4d

4e

4f

4g

4h

4i

Anilines

ŅH₂



Time (h)

Products

Entry Anilines Products Time (h) Yields^b (%) NH2 4k 6 93 NH₂ 41 4 88 NH_2 MeO .OMe ОМе 0 C 4m 6 MeO 90 NH₂ 4n 6 88 $\dot{N}H_2$ 10 40 91 Ó NH₂ OFt 4p 4 όEt 92 Ó OPh NH₂ 4q 5 85 о́Рн O ٥_ö NH₂ Ph 87 4r 4.5 °0// ÇOOH NH₂ 85 6 4s соон °ő

^a Reactions and conditions: aniline (1 mmol), Dimedone (2 mmol), formaldehyde (3 mmol). ^b Isolated yields, nr = no reaction.

observed comparable good yield as compared to catalyst free reaction (Table 1, entry 3). Among all screened catalysts STA gave the



5

86



NH₂



Scheme 2. Probable mechanism of 3,5-dispirosubstituted piperidine ring formation.

best result in view of yield and reaction time (Table 1, entry 10). In contrast $TiO_2 \cdot SiO_2$, $BF_3 \cdot SiO_2$, and $ZnCl_2 \cdot SiO_2$ did not afford the desired product in good yields (Table 1, entries 5, 6, and 8). The supported Lewis acid catalyst $FeCl_3 \cdot SiO_2$ shows effective, but required time for the completion of the reaction which is more as compared with STA catalyst with slight lower yield (Table 1, entry 10, 12, 13). Careful analysis of screened supported Lewis acid catalyst, shows that silica supported metal triflates such as $Cu(OTf)_2 \cdot SiO_2$, $Zn(OTf)_2 \cdot SiO_2$ were effective, but promising results were obtained with silica supported tugstic acid catalyst in lesser time with better yield (Table 1, entry 7,9,10).

Once we found STA as best catalyst for this reaction, temperature and solvent optimization was done. We screened various solvents, such as toluene, EtOH, acetonitrile, DCM, DCE, Water, and THF at room temperature. Among tested different organic solvents, EtOH, DCM, and DCE found to give good yields. It is worthy of note, that when we performed the reaction in dichloromethane, reaction was completed with good yield as compared to dichloroethane and ethanol in shorter time (Table 1, entries 10, 11, and 18). Once found best catalyst and solvent condition, we studied the effect of varying amounts of STA catalyst for this one-pot multicomponent system. In order to evaluate the appropriate catalyst loading, a model reaction was carried out using 5 and 20 mol % of STA at room temperature (Table 1, entries 21 and 22). It was found that 10 mol % of catalyst shows maximum yield in minimum time. A larger loading amount of the catalyst (20 mol %) neither increases the yield nor shortens the conversion time. So, 10 mol % of catalyst was found to be the optimal quantity and sufficient to push the reaction forward.

After optimizing the conditions, the generality of this method²¹ was examined by the reaction of several substituted aryl/heteroaryl/aliphatic amines, dimedone, and formaldehyde using STA in dichloromethane at room temperature, the results are shown in Table 2. In all cases, aromatic amines substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in good yields. Unfortunately, anilines bearing strong electron-withdrawing groups, for example, COOH at para position did not give any spiro-products (Table 2, entry 4s). It could also be concluded that the amines bearing electron-donating groups required shorter time than electronwithdrawing groups and gave higher yields (Table 2, entries 4b and 4c). On the basis of the above results, this process was then extended to heterocyclic and aliphatic amines. The 2-amino pyridine afforded the corresponding product in 70% yield (Table 2, entry 4n), but unfortunately the chemistry not worked well with cyclohexylamine (Table 2, entry 40). Compared with aromatic amines, heterocyclic amine afforded relatively lower yields of the corresponding 3,5-dispirosubstituted piperidine.

A possible mechanism of this one pot reaction is expected on the basis of reported literature. A possible mechanism for the

Table 3	
The reusability of STA in	the synthesis of compound 4a

Entry	Reaction cycle	Yield ^a
1	I st (Fresh run)	93
2	II nd cycle	90
3	III rd cycle	88
4	IV th cycle	88
5	V th cycle	86
6	VI th cycle	86

^a Isolated yield.

3,5-dispirosubstituted piperidine ring formation is outlined in Scheme 2. The spirocyclization looks to proceed as a domino sequence of Knoevenagel, Michael, and double Mannich reactions. The well known reaction of dimedone with formaldehyde leads to the formation of the standard dimedone–formaldehyde adducts. In cycle, this undergoes two consecutive Mannich reactions with aniline to produce the spiro-piperidine.

The reusability of the STA catalyst was also examined. The catalyst was reused six times and the results show that silica supported tungstic acid (STA) can be reused as such without a significant loss in yield (Table 3). The reusability of the catalyst reduces the cost of the production. Accordingly, after the first fresh run with 93% yield, the catalyst was removed by filtration. The recovered catalyst was dried under vacuum at 120 °C for 12 h and tested up to five more reaction cycles. Recycling and reuse of the catalyst showed minimal decreases in yields. The product 4a was obtained in 93%, 90%, 88%, 88%, 86%, and 86% yields after successive cycles. (Table 3, entries 1–6), thus proving the catalyst's reusability. Careful analysis of Table 3 shows that there no significant loss of catalytic activity of this supported catalyst.

The reported as well as synthesized novel compounds were further characterized by their spectral properties (¹H, ¹³C NMR, and HRMS).

In summary, a mild, efficient, and expeditious method has been developed for the synthesis of 3,5-dispirosubstituted piperidines via a three component; one-pot cyclocondensation reaction of aromatic amines, formaldehyde, and dimedone using Silica supported tungstic acid as heterogeneous catalyst. The main advantage of this present methodology is the simple work-up, easy recovery of catalyst, no need for anhydrous condition, no base or any additional activator required, and the residue was crystallized from ethanol to give the pure product without further purification.

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- 21. General Procedure for the synthesis of 3,5-dispirosubstituted piperidines. A mixture of aniline (1 mmol), dimedone (2 mmol), formaldehyde (3 mmol, 37–41% aqueous solution), and a catalytic amount of STA (10 mol%) in dichloromethane (5 mL) was stirred at room temperature for the stipulated time mentioned in Table 2. The progress of the reaction was monitored by TLC. After the completion of the reaction STA was removed from the reaction mixture by filtration. The solvent was removed under reduced pressure. The crude product was then purified directly by crystallization from ethanol. The spectral and analytical data of one of the representative compounds is given here: 3,3,11,11-Tetramethyl-15-(phenyl)-15 azadispiro [5.1.5.3]hexadecane=1,5,9,13-tetrone (4a) (Table 2, entry 1) mp: 190–192 °C ¹H NMR (400 MHz, CDCl₃): δ 1.00 (s, 6H), 1.01 (s, 6H), 2.50 (s, 2H), 2.68-2.64 (d, *J* = 16 Hz, 4H), 2.86–2.82 (d, *J* = 16 Hz, 4H), 3.45 (s, 4H), 6.96–6.92 (t, *J* = 16 Hz, 1H), 7.12 7.10 (d, *J* = 8 Hz, 2H), 7.29–7.25(m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 28.35, 28.65, 30.78, 32.24, 51.23, 65.70, 118.89,121.66,129.11,151.64,205.95. HRMS (ESI, *m*/ z): Calcd for C₂₅H₃₁NO₄ (*m*/z) 409.2253. Found: 409.2251.