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Archives of Organic and Inorganic Chemical Sciences

DOI: 10.32474/AOICS.2018.01.000113

ISSN: 2637-4609

Research Article

Camphor Sulfonic Acid Catalyzed Facile and Atom Economical Access to Highly Substituted Piperidines via One Pot Multi Component Reactions

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Received: January 25, 2018; **Published:** February 09, 2018

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Abstract

A simple and efficient protocol has been developed for the synthesis of highly substituted Piperidines derivatives. This strategy demonstrated five component reactions of two equivalents of aldehydes, two equivalents of anilines and β-keto esters in ethanol using 10 mol% of camphor sulfonic acid at reflux. The significant features of the present protocol include excellent yield, shorter reaction time, and easy work up procedure, broad substrate scope, high atom economy and formation of C-C and C-N bond in a single step operation.

Keywords: Piperidines; Camphor sulfonic acid; Multi component reactions; High atom economy

Introduction

The Piperidines and its analogues represent one of the most prominent compound classes which are widely distributed in biologically active compounds, pharmaceuticals and natural products [1]. Several compounds possessing Piperidines scaffold have been reported to exhibit a wide range of valuable bioactive properties including antihypertensive, neuro-protective, anti-inflammatory, antibacterial, anti malarial and anticonvulsant activities [2]. Also, some of Piperidines analogues possess enzyme inhibitory activity against farnesyl transferees and dihydroorotate dehydrogenase [3]. Especially, highly substituted Piperidines have been recognized as an important class of therapeutic agents in the treatment of cancer metastasis, influenza, Parkinson's disease, viral infections including AIDS and diabetes [4]. Recently, interest in the field of organ catalysis has enormously increased as a result of both the novelty of the concept and more importantly, the fact that the efficiency and selectivity of many organ catalytic reactions meet the standards of established organic reactions [5]. Examples of organ catalysis to accelerate organic reactions had been periodically reported in the literature for decades. These organic catalysts are inexpensive, readily available, low cost, non-toxic, biodegradable, and inert towards moisture and oxygen. Absences of transition metals make these protocols attractive for the synthesis of pharmaceutical products [6]. Search of an efficient organ catalyst for organic transformations remain a challenging task.

Recently, our group synthesized 1,5-benzodiazepine, α-hydroxy and α-amino phosphonates using camphor sulfonic acid as organ catalyst [7]. Also, camphor sulfonic acid (CSA) is achieving enormous significance in organic synthesis, as this catalyst is used in the synthesis of chromans, ligands, and pseudo glycosides, as an auxiliary and in some polymerization reactions [8]. So far, to the best of our knowledge, there is no report available on the use of camphor sulfonic acid as an organ catalyst for the synthesis of highly substituted Piperidines. The synthesis of such highly substituted Piperidines derivatives has gained considerable attention and are based on various reactions including- (a) cyclopropane ring opening/Conia-ene cyclization [9], (b) imino Diels–Alder reaction [10], (c) aza-Prins cyclizations [11], (d) intra molecular Michael reaction [12] and (e) intra molecular Mannich reaction onto iminium ions [13]. The pot atom step economic (PASE) synthesis of highly substituted Piperidines from relatively simple starting materials has been reported in the literature. Synthesis of highly substituted Piperidines involves three component reactions of two equivalents of aldehydes, two equivalents of anilines and one equivalent β-ketoesters. Boehm in 1943 reported the first

multi component reaction between an amine, aldehydes and 1,3-dicarbonyl to synthesize functionalized piperidines [14]. Recently, the synthesis of highly substituted Piperidines has been reported using $InCl_3$ [15], bromodimethylsulfonium bromide [16], tetrabutyl ammonium bromide [17], iodine [18], l-proline nitrate [19], thiourea dioxide [20] as catalysts.

One of the main challenges of synthetic chemists lies in the development and implementation of efficient methodologies for the synthesis of biologically significant scaffolds. However, methodologies reported for this reaction so far suffer from one or more shortcomings such as low yield, prolonged reaction time, use of toxic organic solvents, and requirement of excess of reagents or catalysts and harsh reaction conditions. Therefore, there is still a demand for the development of effective protocols for the expedient synthesis of highly substituted Piperidines under mild conditions using inexpensive catalysts. In view of the importance of all above discussed aspects and in continuation of our endeavor towards the development of synthetic methodologies for various organic transformations [21] it was thought to develop new and expeditious route for the synthesis of highly substituted piperidines using camphor sulfonic acid as an organ catalyst.

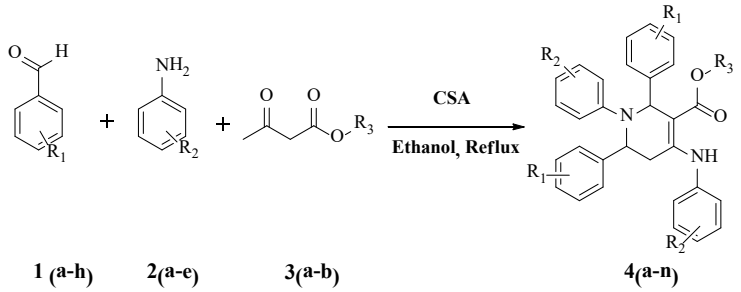
Material and Methods

General

All chemicals were purchased and used without any further purification. Progress of the reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light. Melting points were recorded in open capillary tubes and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 or 300MHz and Bruker DRX 75 or 100 MHz spectrometer respectively. Chemical shift values (δ) are expressed in (parts per million) ppm relative to TMS. The electro spray mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap mass spectrometer.

General experimental procedure for the synthesis of highly substituted Piperidines 4(a-n)

Table 1: Synthesis of highly substituted piperidines[a].



1 (a-h) **2(a-e)** **3(a-b)** **4(a-n)**

Product	R_1	R_2	R_3	Time (min)	Yieldb (%)	M.P.[c] (°C)
4a	H	H	Me	110	93	171-173
4b	2-Cl	H	Me	115	90	214-216
4c	2-OH	H	Me	130	87	212-214
4d	4-OMe	H	Me	125	85	185-187
4e	4-Me	H	Me	120	88	226-228
4f	4-NO_2	H	Me	135	83	235-237
4g	4-Me	4-Me	Me	125	88	206-208
4h	4-F	4-Me	Me	115	91	198-200
4i	4-F	4-OMe	Me	125	89	204-206
4j	4-F	H	Et	135	87	203-205
4k	3-Me	H	Et	130	82	150-152
4l	4-Me	4-F	Et	140	84	183-185
4m	4-F	4-Me	Et	125	89	200-202
4n	H	4-Cl	Et	130	85	201-203

aReaction condition: aldehydes (2 mmol), anilines (2 mmol), methyl/ethyl acetoacetate (1 mmol), CSA (10 mol%), ethanol (10 ml); [b]Isolated yields; [c]Melting points match with literature values.

A mixture of aromatic aldehydes (2mmol), aromatic anilines (2mmol), β-ketoesters (1mmol) and camphor sulfonic acid (10mol %) in ethanol (10ml) was refluxed for appropriate time as shown in Table 1. Progress of the reaction was monitored by TLC on silica with n-hexane: ethyl acetate (7:3) as mobile phase. After completion of the reaction, the products was poured on crushed ice and filtered to obtain crude product. Further, solid product was re crystallized from ethanol to afford pure compound.

Spectral data for representative compound

Methyl-2,6-bis(2-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4b): ^{1}H NMR (400 MHz, DMSO-d_6) : δ 9.96 (s, ^{1}H, -NH), 7.47-7.42 (m, 2H, Ar-H), 7.36-7.12 (m, 8H, Ar-H), 7.08-7.02 (m, 3H, Ar-H), 6.62-6.59 (t, J = 7.2 Hz, 1H, Ar-H), 6.47- 6.45 (d, J = 7.6 Hz, 2H, Ar-H), 6.35 (s, 1H), 6.30 (d, J = 8.0 Hz, 2H, Ar-H), 5.48 (t, J = 4.0Hz, 1H), 3.78 (s, 3H), 2.96-2.92 (m, 2H); 13C NMR (100 MHz, DMSO-d_6) : δ 167.6, 154.8, 146.3, 144.0, 142.8, 137.5, 128.9, 128.8, 128.7, 128.4, 128.3, 127.0, 126.4, 126.2, 126.1, 125.5, 124.8, 115.7, 112.3, 97.6, 56.6, 54.8, 51.1, 33.4; Mass (ES-MS) : m/z 529.2 [M + H]+

Results and Discussion

Initially, the reaction was performed with two equivalent of benzaldehyde (1a), two equivalents of aniline (2a) and one equivalent methyl acetoacetate (3a) in ethanol as the model substrates to find out the optimum reaction conditions (Scheme 1). When the reaction was carried out in the absence of catalyst, the product formed in very trace amount at room temperature and reflux (Table 2, entries 1-2). The yield of 4a was achieved with a maximum (93%) (Figure 1). When the reaction was carried out with the use of 10 mol% of camphor sulfonic acid in ethanol at reflux for 110 min (Table 2, entry 4). Subsequent screening of the various catalysts revealed that CSA exhibited superior results, while sulphuric acid, p-toluene sulfonic acid, glycine, polystyrene supported p-toluene sulfonic acid and β-cyclodextrin-SO_3H afforded the target molecule in <79% yield (Table 2, entries 6-10). The temperature had an obvious effect on the reaction: for example, by increasing the reaction temperature from room temperature to reflux, the yield was increased from 41 to 93% (Table 3, entries 1-4). Reflux temperature was proven to be advantageous and hence it was finalized for obtaining better results. Since solvents play crucial role to expedite the reaction rate, further efforts were diverted to screen the effect of solvents with the hope that reaction time may reduce and product yield may enhance. Subsequently, by changing the solvent to dichloromethane, tetrahydrofuran, dimethylformaamide and dimethylsulfoxide reduced the yields to 48, 53, 70 and 62%, respectively (Table 3, entries 5-8). When water or aq. ethanol (1:1) was used as the solvent, the desired product was obtained in moderate yield (Table 3, entries 9-10).

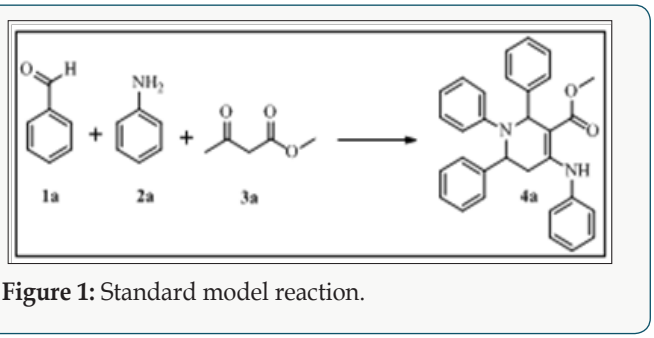


Figure 1: Standard model reaction.

Table 2: Screening and effect of concentration catalyst[a].

Entry	Catalyst	Concentration (mol %)	Temperature (°C)	Time (min)	Yieldb (%)
1	-	-	RT	600	trace
2	-	-	Reflux	600	trace
3	CSA	5	Reflux	150	80
4	CSA	10	Reflux	110	93
5	CSA	15	Reflux	110	93
6	Sulphamic acid	10	Reflux	110	67
7	p-TSA	10	Reflux	110	79
8	Glycine	10	Reflux	110	45
9	PS-PTSA	10 (mg)	Reflux	110	70
10	β-cyclodextrin-SO_3H	10	Reflux	110	76
[a]Reaction condition: 1a (2 mmol), 2a (2 mmol), 3a (1 mmol), ethanol (10 ml), [b]Isolated yields.					

Table 3: Effect of temperature and screening of solvents[a]

Entry	Solvent	Temperature (°C)	Yield[b] (%)
1	Ethanol	RT	41
2	Ethanol	40	59
3	Ethanol	60	78
4	Ethanol	Reflux	93
5	DCM	Reflux	48
6	THF	Reflux	53
7	DMF	Reflux	70

8	DMSO	Reflux	62
9	WATER	Reflux	84
10	Aq. Ethanol (1:1)	Reflux	80
aReaction condition: 1a (2 mmol), 2a (2 mmol), 3a (1 mmol), solvent (10 ml), CSA (10 mol%), 110 min; bIsolated yields.			

However, when ethanol was used as the solvent, the compound methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate 4a was isolated in 93% yield (Table 3, entry 4). Thus, the optimal reaction conditions were found to be 10 mol% camphor sulfonic acid catalysts with ethanol as the solvent at reflux for 110 min. The scope of this five component reaction under optimized reaction conditions were explored using a variety of aldehydes, anilines and β-keto ester, as summarized in Table 1. In general, aromatic aldehydes bearing electron-donating or electron withdrawing functional groups at different position reacted with methyl acetoacetate as well as ethyl acetoacetate smoothly in the presence of various anilines to generate the corresponding product in excellent yield. Also, several aromatic amines were examined. Various anilines with substituent such as -Me, -F, -Cl and -OMe were treated with varying aromatic aldehydes and β-keto esters under identical reaction conditions. All these reactions underwent smoothly to provide the corresponding Piperidines derivatives in excellent yields. Formation of the desired product was confirmed with the help of ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. The 1H NMR spectrum of compound 4b showed a singlet at δ 6.35 ppm for -CH, triplet at δ 5.48 ppm for -CH and multiple at δ 2.96-2.92 ppm for the methylene group.

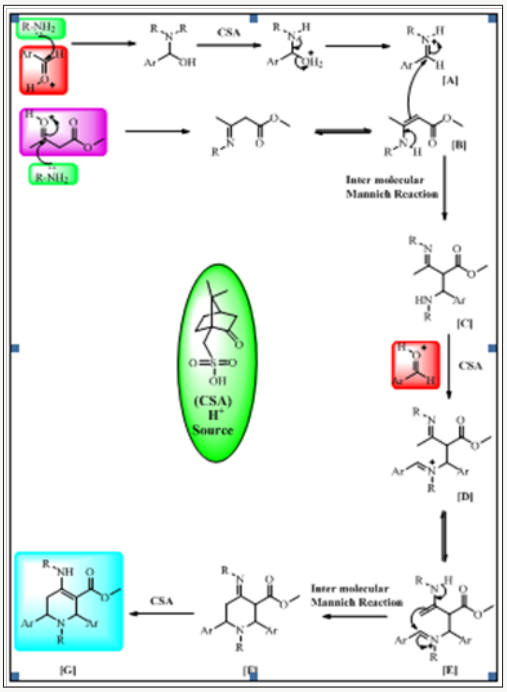


Figure 2: A Plausible mechanism for the synthesis of piperidines.

The presence of four characteristic carbon signals are observed at δ 97.6, 56.6, 51.1, 33.4 ppm in ^{13}C NMR spectrum of 4b owing to carbons of C=C, -CH, -CH, and -CH_2 groups of the piperidine ring, respectively authorizing the presence of a piperidine ring in 4b. The mass spectrum of 4b further support the structure as it display [M+H]+ ion peak at m/z 529.2 in consistent with its molecular formula $C_{31}H_{26}Cl_2N_2O_2$. A plausible reaction mechanism involved in the synthesis of highly substituted piperidines is proposed as shown in Figure 1. On the basis of the proposed mechanism in the literature, it is reasonable to presume that highly substituted piperidine [G] results from initial condensation of β-ketoester and aromatic aldehyde with aniline in the presence of CSA to give enamine [B] and imine [A]. Subsequently, enamine [B] reacts with imine [A] to produce intermediate [C] through intermolecular Mannich-type reaction. The reaction between intermediate [C] and aldehyde gives intermediate [D] by the elimination of H_2O. Then, tautomerization of [D] generates intermediate [E], which immediately undergoes intramolecular Mannich-type reaction to give intermediate [F]. Finally, this intermediate tautomerizes to generate the desired piperidine derivative [G] owing to conjugation with the ester group (Figure 2).

Conclusion

In conclusion, we have developed an efficient one pot multi component synthesis of highly substituted Piperidines derivatives using camphor sulfonic acid as the catalyst. A variety of aldehydes were efficiently converted in combination with different type of anilines into various substituted Piperidines in excellent yields. Additionally, different β-ketoesters gave substituted Piperidines in a straightforward manner. Furthermore, the simple experimental procedures, utilization of an inexpensive and readily available eco-friendly catalyst are the advantages of present methodology. This protocol proceeds with high atom-efficiency and shows a broad substrate scope and functional group tolerance, making it a highly practical approach for preparation of pharmaceutically interesting various Piperidines derivatives.

Acknowledgement

The Emeritus Scientist Scheme awarded to MSS by the Council of Scientific and Industrial Research, New Delhi is gratefully acknowledge. Thanks to Head, Department of Chemistry, Dr. B. A. M. University, Aurangabad, for providing the laboratory facilities. MAC is grateful to University authorities for financial assistance in the form of University fellowship.

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DOI: 10.32474/AOICS.2018.01.000113