SILICA SULFURIC ACID: AN EFFICIENT, REUSABLE, HETEROGENEOUS CATALYST FOR THE ONE-POT, FIVE-COMPONENT SYNTHESIS OF HIGHLY FUNCTIONALIZED PIPERIDINE DERIVATIVES

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GRAPHICAL ABSTRACT

Abstract A series of highly functionalized piperidine derivatives was synthesized through one-pot, five-component reaction of aldehydes, amines, and β-ketoesters. Silica sulfuric acid efficiently catalyzes the reaction to afford the corresponding piperidine derivatives in good yields. As a representative example, heating of 4-methylaniline, 4-fluorobezaldehyde, and methyl-acetoacetate in methanol in the presence of silica sulfuric acid furnished the corresponding ethyl 2,6-bis(4-fluorophenyl)-1-p-tolyl-4-(p-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate in excellent yield (85%). Most of the synthesized compounds were screened in vitro for their antibacterial and antifungal activities. Most of compounds showed significant antibacterial activity.

Keywords Antimicrobial activity; heterogeneous catalysis; piperidine derivatives; silica sulfuric acid

INTRODUCTION

Piperidines and their analogs are important core structures in many biologically active natural products.[1] Piperidine derivatives have a wide variety...
of biologically activities such as antibacterial,[2] antimalarial,[3] anti-influenza,[4] antihypertensive,[5] anticonvulsant,[6] and anticancer[7] activites.

The first report on the synthesis of piperidine derivatives from aromatic aldehydes, aromatic amines, and a β-ketoester was done by Bohm, et al. in 1943.[8] They predicted a slightly different structure for their products. The true structure of these compounds was rightly described by Haller and his group in 1974.[9] As a consequence, the development of general methods for the synthesis of piperidine derivatives involving a variety of cyclization techniques such as imino Diels–Alder reactions,[10,11] aza-Prins–cyclizations,[12–14] tandem cyclopropane ring-opening/Conia-ene cyclization,[15] intramolecular Michael reactions,[16] and intramolecular Mannich reaction onto iminium ions.[17]

In view of the recent trend in catalytic processes toward clean and green chemical processes, investigation of new, less hazardous chemical catalysts has become a priority in organic synthesis. In recent times, very few methods have been reported describing the one-pot multicomponent synthesis of functionalized piperidines with high diastereoselectivity, based on catalysts such as L-proline/trifluoroacetic acid (TFA),[3] oxalic acid dehydrate,[18] bromodimethylsulfonium bromide (BDMS),[19] tetrabutylammonium tribromide (TBATB),[20] iodine,[21] InCl3,[22,23] bismuth nitrate,[24] cerium ammonium nitrate (CAN),[25] ZrOCl2·8H2O,[26] picric acid,[27] and silica-supported boron trifluoride (BF3-SiO2)[28] and Bi(OII)3.[29] Owing to the importance of piperidines from pharmaceutical and biological points of view, there is still the need to develop an efficient, mild, and environmentally benign protocol for the synthesis of highly substituted piperidines. Recently, a silica sulfuric acid (SSA)–catalyzed multicomponent reaction has been applied. The use of silica sulfuric acid reagents has received considerable attention in organic synthesis because of their ease of handling, greater selectivity, enhanced reaction rate, and recoverability of catalyst. Therefore, special emphasis is given to catalysts in general as important and rapidly growing areas among the chemical sciences.[30]

Moreover, the search for new and effective antimicrobial agents, resistant to the mechanisms of defense of bacteria and fungi, is of paramount importance.[31,32] In view of these facts and as a continuation of our previous efforts[30] carried out in our laboratories to develop new synthetic methodologies, we reported a new, efficient, and convenient method for the one-pot synthesis of piperidine derivatives catalyzed by silica sulfuric acid.

RESULTS AND DISCUSSION

To optimize the reaction conditions, 4-toluidine, 4-fluorobenzaldehyde, and methyl acetoacetate were taken as model reactants (Scheme 1). In the initial study, when 4-toluidine left to react with 4-fluorobenzaldehyde and methyl acetoacetate in absolute ethanol without catalyst (Table 1, entry 1); it was found that no piperidine was obtained even at prolonged reaction time.

Different catalysts and solvents were investigated with regard to the yield of the piperidine derivatives. The reaction was carried out using various catalysts (namely ZnCl2, FeCl3, SiCl4, Me3SiCl, PPA/SiO2, HClO4SiO2, and SSA) alone to set up standard reaction conditions and obtain the best catalyst, as shown in Table 1. From the obtained results, it was found that, the best catalyst in terms of yield and time
was silica sulfuric acid (Table 1, entry 8). Our attention was then focused toward the effect of solvents on the yield of the one-pot assembly of the model. Replacing ethanol with CH$_3$CN or CH$_2$Cl$_2$ (Table 1, entries 9 and 10, respectively) produced the model 1 in an appreciable yield lower than that of the one produced by ethanol (Table 1, entry 8). Replacing ethanol by methanol (Table 1, entry 11) produced the model in a greater yield (Table 1, entry 8). Moreover, we studied the efficacy of the ratio of the catalyst (2, 3, 4 mmol), and our study revealed that 2 mol of the catalyst was the optimum ratio (Table 1, entry 11). From the obtained results, it was found that the best catalyst was silica sulfuric acid (2 mmol). Optimized condition was established in MeOH as a solvent, which gave the best result with 85% yield of the required ethyl 2,6-bis(4-fluorophenyl)-1-p-toly1-4-(p-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (1) (Table 1, entry 11). This remarkable activation in reaction rate prompted us to explore the potential of this protocol for the synthesis of other pipridine derivatives.

Reusability of the catalyst is an important factor from economical and environmental points of view and has attracted much attention in recent years. Therefore, the reusability of silica sulfuric acid was examined under optimized reaction conditions. The catalyst silica sulfuric acid is a super solid acid. Hence it is convenient and cost-effective catalyst. It exists in the solid state and easily separated

![Scheme 1](image)

**Scheme 1.** Optimization of reaction conditions for the synthesis piperidine derivative 1.

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**Table 1.** Results of piperidine derivative 1 with different catalyst and solvent

| Entry | Catalyst (mmol) | Solvent/condition | Time (h) | Yield (%) |
|-------|-----------------|-------------------|---------|-----------|
| 1     | None            | EtOH/reflux       | 30      | 0         |
| 2     | ZnCl$_2$ (2)    | EtOH/reflux       | 15      | 60        |
| 3     | FeCl$_3$ (2)    | EtOH/reflux       | 16      | 45        |
| 4     | SiCl$_4$ (2)    | CH$_2$Cl$_2$/rt   | 15      | 58        |
| 5     | Me$_3$SiCl (2)  | EtOH/reflux       | 14      | 55        |
| 6     | PPA/SiO$_2$ (2)| EtOH/reflux       | 13      | 61        |
| 7     | HClO$_2$/SiO$_2$ (2) | EtOH/reflux | 13 | 53 |
| 8     | SSA (2)         | EtOH/reflux       | 10      | 75        |
| 9     | SSA (2)         | CH$_3$CN/reflux   | 11      | 70        |
| 10    | SSA (2)         | CH$_2$Cl$_2$/rt   | 12      | 68        |
| 11    | SSA (2)         | MeOH/reflux       | 8       | 85        |
| 12    | SSA (3)         | MeOH/reflux       | 9       | 82        |
| 13    | SSA (4)         | MeOH/reflux       | 8       | 80        |
from reaction mixture simply by filtration. The catalyst was washed with ethyl acetate and diethyl ether and a fresh reaction was then performed under the same condition; SSA could be used for at least four times without significant loss in product yield (Table 2).

The scope and limitations of this five-component reaction under optimized conditions were explored using a variety of aromatic aldehydes containing electron-donating or electron-withdrawing substituents in the aromatic ring, various aromatic amines, and various \( \beta \)-ketoesters. Thus, the unsubstituted benzaldehyde and substituted anilines having electron-donating as well as electron-withdrawing groups were reacted with various \( \beta \)-ketoesters in the presence of SSA. The reactions were finished at a specified time and afforded the corresponding piperidine derivatives 2a–e in good yields (60–90\%) as shown in Scheme 2 and Table 3. Regarding the effect of changed the alkyl group (R) in \( \beta \)-ketoesters (methyl \( \rightarrow \) ethyl), the presence of an ethyl group (Table 3, entry 2) resulted in greater yield of the product (2b; 83\%) with compared to the methyl group (2a, 82\%, Table 3, entry 1). From the obtained results it was found that aromatic amine bearing electron-donating group (2e, entry 5) resulted in a greater yield of the product (90\%) while reducing the time of reaction (6h) compared to amines with electron-withdrawing groups (2c and 2d, 60\% and 73\%, Table 3, entries 3 and 4). Also, the reaction was found to be faster with unsubstituted aniline (1a and 1b, Table 3, entry 1 and 2), whereas the reaction was found to be slow with aniline, which contains an electron-withdrawing group (Table 3, entries 3 and 4).

To generalize this reaction, benzaldehyde was replaced by 4-fluorobenzaldehyde in the model of the one-pot reaction. When 4-fluorobenzaldehyde was left to react with various amines and \( \beta \)-ketoesters in the presence of SSA, the reaction was finished at specified time and afforded the corresponding piperidine derivatives 3a–f in good yields (63–85\%). From the obtained results it was found that aromatic amines bearing electron-donating groups (3f, Table 3, entry 11) resulted in a greater yield of the product (85\%) while reducing the time of reaction compared to amines

Table 2. Effect of reusability of SSA catalyst on the piperidine yield

| Number of uses | Time (h) | Yield (%) | Recovery of SSA (%) |
|---------------|----------|-----------|---------------------|
| 1             | 8        | 85        | 96                  |
| 2             | 9        | 84        | 94                  |
| 3             | 10       | 83        | 92                  |
| 4             | 11       | 83        | 91                  |

Scheme 2. One-pot synthesis of functionalized piperidine compounds 2–5.
with electron-withdrawing groups (3c–e, Table 3, entries 8–10). The reaction of 4-fluorobenzaldehyde with unsubstituted anilines (3a and 3b, 80 and 79%, Table 3, entries 6 and 7) was found to be better than the aniline, which contains an electron-withdrawing group (3c–e, Table 3, entries 8–10).

Also, benzaldehyde was replaced by 4-methoxybenzaldehyde in the model of the one-pot reaction. When 4-methoxybenzaldehyde was left to react with various amines and β-ketoester in the presence of SSA, the reaction was finished at specified time and afforded the corresponding piperidine derivatives 4a–c in good yields (66–88%). The reaction was found to be faster with unsubstituted aniline (4a, 82%, Table 3, entry 12) or anilines having electron-donating groups (4c, 88%, Table 3, entry 14), whereas the reaction was found to be slow with aniline which contains an electron-withdrawing group (4b, 66%, Table 3, entry 13).

Moreover, our investigation was extended to include the behavior of heterocyclic aldehyde toward this reaction. Thus, the reaction of 2-thiophene aldehyde (as heterocyclic aldehyde) with various amines and β-ketoester in the presence of SSA, the reaction was finished at specified time and afforded the corresponding pipridine derivatives 5a–f in good yield, as shown in Scheme 2. The heterocyclic aldehyde had the same behavior of aromatic amines toward this reaction. The representative results are summarized in Table 3.

The structure of new compounds was deduced on the basis of IR, 1H NMR spectroscopy, mass spectrometry, and elemental analyses. The known compounds were identified by comparing their physical and spectral properties with those of authentic samples. The IR spectrum of 2c exhibited the absorption bands at 1650–1585 cm⁻¹, indicating that the carbonyl group of carbethoxy substituents and olefinic bonds are in conjugation, and 3145 cm⁻¹, indicating the

### Table 3. Reaction times and yields of piperidine derivatives 2–5

| Entry | Compound | Ar | Ar′ | R | Time (h) | Yield (%) | Mp (°C) | Lit. mp (°C) |
|-------|----------|----|-----|---|----------|-----------|--------|-------------|
| 1     | 2a       | Ph | Ph  | Me| 9        | 82        | 183–185| 185–186[21]| |
| 2     | 2b       | Ph | Ph  | Et| 10       | 83        | 173–175| 174–175[19]| |
| 3     | 2c       | Ph | 4-FC₆H₄| Et| 16       | 60        | 185–187|             | |
| 4     | 2d       | Ph | 4-ClC₆H₄| Et| 14       | 73        | 199–201| 200–202[3] | |
| 5     | 2e       | Ph | 4-MeC₆H₄| Et| 6        | 90        | 200–202|             | |
| 6     | 3a       | 4-FC₆H₄| Ph  | Me| 11       | 80        | 191–193| 193–195[21]| |
| 7     | 3b       | 4-FC₆H₄| Ph  | Et| 11       | 79        | 206–208| 205–207[24]| |
| 8     | 3c       | 4-FC₆H₄| 4-ClC₆H₄| Et| 14       | 71        | 202–204|             | |
| 9     | 3d       | 4-FC₆H₄| 4-BrC₆H₄| Me| 17       | 65        | 203–205|             | |
| 10    | 3e       | 4-FC₆H₄| 4-BrC₆H₄| Et| 17       | 63        | 198–200|             | |
| 11    | 3f       | 4-FC₆H₄| 4-MeC₆H₄| Et| 8        | 86        | 202–204|             | |
| 12    | 4a       | 4-OMeC₆H₄| Ph  | Et| 10       | 82        | 201–203|             | |
| 13    | 4b       | 4-OMeC₆H₄| 4-BrC₆H₄| Et| 16       | 66        | 190–192|             | |
| 14    | 4c       | 4-OMeC₆H₄| 4-MeC₆H₄| Et| 7        | 88        | 179–181|             | |
| 15    | 5a       | 2-Thiophenyl| Ph  | Me| 13       | 75        | 209–211|             | |
| 16    | 5b       | 2-Thiophenyl| Ph  | Et| 13       | 73        | 207–209|             | |
| 17    | 5c       | 2-Thiophenyl| 4-ClC₆H₄| Et| 15       | 70        | 213–215|             | |
| 18    | 5d       | 2-Thiophenyl| 4-BrC₆H₄| Me| 18       | 60        | 238–240|             | |
| 19    | 5e       | 2-Thiophenyl| 4-BrC₆H₄| Et| 18       | 61        | 222–224|             | |
| 20    | 5f       | 2-Thiophenyl| 4-MeC₆H₄| Me| 9        | 85        | 223–225|             | |
NH group. The IR spectrum of 5e exhibited the absorption bands at around 1649–1606 cm⁻¹, indicating that the carbonyl group of carbethoxy substituents and olefinic bonds are in conjugation, and 3238 cm⁻¹, indicating the NH group. The ¹H NMR spectrum of 2c exhibited a triplet at δ = 1.34 ppm for methyl protons of the carbethoxy group and two doublets of doublets were shown at δ = 2.64 and 2.85 ppm for methylene protons of the piperidine ring (H-5a, H-5b). The methylene protons of the carbethoxy group, being distereotopic protons, were observed as multiplets at δ = 4.24, 4.35 ppm. One of the methine protons of the piperidine ring (H-6) was observed as a singlet at δ = 5.30 ppm, and another methine proton (H-2) appeared as a singlet at δ = 6.21 ppm. The aromatic protons were observed as mixture of multiplets at δ = 6.32–7.29 ppm. A singlet for the NH group at δ = 10.08 ppm indicated intramolecular hydrogen bond formation with the vicinal carbonyl group. The ¹H NMR spectrum of 5e exhibited a triplet at δ = 1.44 ppm (J = 6.87 Hz) for methyl protons of the carbethoxy group and two doublets of doublets were shown at δ = 2.83 and 3.08 ppm for methylene protons of the piperidine ring (H-5a, H-5b). The methylene protons of the carbethoxy group, being distereotopic protons, were observed as multiplets at δ = 4.29, 4.42 ppm. One of the methine protons of the piperidine ring (H-6) was observed as a singlet at δ = 5.35 ppm, and the aromatic protons and another methine proton (H-2) were observed as mixture of multiplets at δ = 6.34–7.78 ppm. A singlet for the NH group at δ = 10.40 ppm indicated intramolecular hydrogen bond formation with the vicinal carbonyl group. The mass spectrum of 2c displayed the molecular ion peak (M⁺) at m/z = 510, which is consistent with the proposed structure. The mass spectrum of 5e displayed the molecular ion peak (M⁺) at m/z = 644.75, which is consistent with the proposed structure.

We turned our attention to a study of the mechanistic aspect of this one-pot, five-component reaction. A plausible mechanism for the present reaction proceeds. A plausible reaction mechanism (Scheme 3) was suggested in which SSA can serve as a Lewis acidic catalyst for the reaction of amine with the β-ketoester and aldehyde to give the β-enaminone I and imine II respectively. The intermolecular Mannich addition of I to the imine II affords the butanoate intermediate III. Subsequently,
the reaction of activated aldehyde with the intermediate III proceeded to afford the intermediate IV with elimination of H$_2$O. Next, tautomerization of IV generates intermediate V, which immediately undergoes intramolecular Mannich-type reaction to give intermediate VI. Eventually, the intermediate VI tautomerizes to generate the desired piperidine derivatives due to conjugation with the ester group.

**Antibacterial and Antifungal Activity**

Most of the synthesized compounds were tested in vitro for antibacterial and antifungal activities against the following strains: Gram-positive bacteria (*Bacillus subtilis* NCIB 3610, *Staphylococcus aureus* NCTC 7447), Gram-negative bacteria (*Escherichia coli* NCTC 10416, *Pseudomonas aeruginosa* NCIB 9016), and fungi (*Candida albicans* and *Aspergillus fumigatus*). Antimicrobial tests were carried out by the agar well diffusion method. Ciprofloxacin was used as standard reference. The results of antibacterial activity values are furnished in Table 4.

From Table 4, it is clear that compounds 2c, 3b, and 3e were the most active compounds against the tested bacterial strains. It was noticed that the presence of 4-fluorophenyl at N-1 position in compound 2c with substitution 4-fluoroaniline in C-4 with the presence of phenyl rings at C-2 and C-6 displayed strong effect on the antimicrobial activity and resulted in the greatest antimicrobial activity among all the compounds investigated in this study. The introduction of a 4-fluorophenyl moiety at C-2 and C-6 in the tetrahydropyridine ring of compounds 3b and 3e with the presence of phenyl or bromophenyl substitution at the N-1 position with substituted C-4 by aniline (3b) or 4-bromoaniline (3e), respectively, exhibited high antibacterial activity. The compounds 3d, 3f, 4c, and 5d showed moderate activity against tested organisms. The remaining compounds exhibited weak antibacterial activity against all bacterial strains. In general, all the synthesized compounds exerted a moderate antifungal activity against all the tested organisms, except for compounds 1, 5b, 5e, and 5f, which showed weak antifungal activities.

**Table 4.** Antimicrobial activity of the synthesized compounds

| Compound | Gram positive | Gram negative | Fungi |
|----------|---------------|---------------|-------|
|          | *B. subtilis* | *S. aureus*   | *E. coli* | *P. aeruginosa* | *C. albicans* | *A. fumigatus* |
| 1        | 12            | 10            | 15      | 11               | 12            | 11               |
| 2c       | 22            | 20            | 20      | 20               | 19            | 19               |
| 3b       | 23            | 21            | 21      | 22               | 18            | 19               |
| 3c       | 11            | 11            | 11      | 11               | 16            | 15               |
| 3d       | 16            | 19            | 17      | 17               | 16            | 18               |
| 3e       | 22            | 21            | 20      | 21               | 19            | 19               |
| 3f       | 17            | 17            | 19      | 17               | 19            | 17               |
| 4b       | 13            | 12            | 15      | 11               | 16            | 17               |
| 4c       | 17            | 19            | 19      | 18               | 18            | 18               |
| 5b       | 14            | 13            | 15      | 12               | 15            | 13               |
| 5d       | 17            | 18            | 18      | 18               | 17            | 19               |
| 5e       | 16            | 15            | 14      | 12               | 13            | 12               |
| 5f       | 11            | 11            | 11      | 11               | 09            | 09               |
| Standard | 27            | 25            | 27      | 26               | 26            | 25               |
CONCLUSION

We have developed a simple and efficient method for the synthesis of highly substituted piperidines by a one-pot multicomponent reaction under mild conditions using silica sulfuric acid (SSA) as the catalyst in methanol. This reaction can be regarded as an efficient approach for the preparation of synthetically and pharmaceutically important piperidine systems. This one-pot reaction has some important advantages such as easy workup procedure, simple and readily available precursors, nontoxic and inexpensive catalyst, and good to excellent yields.

EXPERIMENTAL

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed with silica gel GF254 plates, and the products were visualized by ultraviolet (UV) detection. The infrared (IR) spectra were measured on a Mattson 5000 FTIR spectrometer in potassium bromide discs. The NMR spectra were recorded in CDCl₃ on a Bruker WP spectrometer (500 MHz) and the chemical shifts are δ downfield from tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a Finnegan MAT 212 instrument, with the ionizing voltage of 70 eV, at the Faculty of Science, Cairo University. Elemental analyses were carried out by the Micro-analytical Laboratory, National Research Centre, Cairo, Egypt.

General Procedure for the Preparation of Piperidine Derivatives[3,18,19,21,24,26]

A mixture of β-ketoester (1.0 mmol), aldehyde (2.0 mmol), amine (2 mmol), and SSA (2 mmol) in 5 mL of MeOH was heated at 85 °C for an appropriate time (Tables 1 and 3) After completion of the reaction as monitored by TLC, 20 mL of ethyl acetate was added, and catalyst was removed by filtration. The mixture was stirred for a few minutes, and then the reaction was quenched with cold water. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL), washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by silica-gel chromatographic methods to obtain the pure product.

Methyl 2,6-Bis(4-fluorophenyl)-1-p-tolyl-4-(p-tolylamino)-1,2,5,6-tetra-hydropyridine-3-carboxylate (1)

White solid; yield 86%; mp 200–202 °C; Rf = 0.55 (17% ethyl acetate in petroleum ether); IR, ν/cm⁻¹: 3252 (NH), 1658 (C=O), 1599 (C=C); ¹H NMR, δ/ppm: 2.15 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 2.70 (dd, 1H, J = 15.30 and 2.20 Hz, H-5a), 2.78 (dd, 1H, J = 15.30 and 5.60 Hz, H-5b), 3.91 (s, 2H, OCH₃), 5.06 (s, 1H, H-6), 6.24–7.91 (m, 17H, ArH and H-2), 10.17 (br, 1H, NH); MS (m/z, %): 524.1 (M⁺, 21.29). Anal. Calcd. for C₃₃H₃₀F₂N₂O₂: C, 75.55; H, 5.76; N, 5.34. Found: C, 75.50; H, 5.70; N, 5.29%.
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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

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