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Catalytic Performance of Immobilized Sulfuric Acid on Silica Gel for N-Formylation of Amines with Triethyl Orthoformate

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Abstract: In the search for convenient, green, and practical catalytic methods for the current interest in organic synthesis, a simple, green, and highly efficient protocol for N-formylation of various amines was carried out in the presence of immobilized sulfuric acid on silica gel (H$_2$SO$_4$–SiO$_2$). All reactions were performed in refluxing triethyl orthoformate (65 °C). The product formamides were obtained with high-to-excellent yields within 4 min to 2 h. The current approach is advantageous, due to its short reaction time and high yields. The catalyst is recyclable with no significant loss in catalytic efficiency.

Keywords: N-formylation; amines; immobilized sulfuric acid; silica gel; triethyl orthoformate

1. Introduction

A fascinating trend in the synthesis of widely used organic molecules is the focus on green chemistry, including efficient reactions and the use of ecologically friendly reagents [1]. The use of silica gel as an effective catalyst in chemical processes has attracted much attention in recent years. The formylation of amines is a crucial process in organic chemistry, owing to the widespread application of N-formyl amine derivatives in industry and in biologically active compounds, such as fluoroquinolones, substituted imidazoles, 1,2-dihydroquinolines, and nitrogen-bridged heterocycles, among others [2]. N-formyl amine derivatives have also been used as reagents in Vilsmeier formylation reactions as amino acid-protecting groups [3] and in the synthesis of several other important derivatives, such as formamidines [4], isocyanates [5], and nitriles [6] (Figure 1).

Despite the fact that there are a variety of reagents for N-formylation of amines, the synthesis of formamides utilizing triethyl orthoformate as a formylating agent is still popular [1]. The reaction of ethyl orthoformate with aniline to afford N,N$'$-diphenylformamidine was initially reported in 1869 by Wichelhaus [7]. Subsequently, Claisen synthesized ethyl N-phenylformimidate in low yields from the same reactants, but under slightly different experimental conditions [8]. Swaringen and colleagues went on to show that the reaction of N-alkylanilines with orthoformates in the absence of a catalyst or with hydrochloric/acetic acid produced orthoamides in low yields [8]. These few examples demonstrate one of the major drawbacks of this system, namely, the low yield. Meanwhile, when p-toluensulfonic acid was employed as a catalyst, high yields of N-alkylanilines and N,N-dialkylanilines were generated, but the reactions still often required high temperatures and prolonged reaction times. For example, Swaringen and co-workers demonstrated the synthesis of N-ethyl formamides from the reaction of amines with triethyl orthoformate in the presence of H$_2$SO$_4$, but under severe conditions (temperature above 140 °C) [9].
Various other formylating agents have been reported, including chloral [10], acetic formic anhydride [11], formic acid [12], ammonium formate [13], formate esters [14], polymer-supported formate [15], ethyl formate [16], triethyl orthoformate [1,2], aldehydes and methanol [17], carbon monoxide [18], and carbon dioxide [19]. However, these also tend to suffer from similar problems of long reaction times (hours to days), variable or low yields, and harsh conditions (or expensive catalyst systems).

Several catalysts have been employed for the formylation of amines, including silica-supported sulfuric acid [20], H$_2$SO$_4$/NaHSO$_4$-activated charcoal [21], K-F alumina [22], Amberlite IR 120 [23], ZnO [24], nano-CeO$_2$ [25], nano-MgO [26], natrolite zeolite [27], indium metal [28], sulfated titania [29], and sulfated tungstate [30], among others (Table 1).

Table 1. Catalysts in combination with formylating agents employed for the formylation of various amines.

| Entry | Catalyst | Formylating Agent | Reaction Condition | Time   | Yield % | Reference |
|-------|----------|-------------------|--------------------|--------|---------|-----------|
| 1     | Sodium formate | Formic acid | Solvent free | >8 h   | 90–97   | [31]      |
| 2     | Amberlite IR-120 | Formic acid | Microwave irradiation | 2 min  | 60–99   | [23]      |
| 3     | Molecular iodine (I$_2$) | Formic acid | Solvent free | 2 h    | 88–96   | [32]      |
| 4     | Thiamine hydrochloride | Formic acid | Solvent free | 85–95  |         | [33]      |
| 5     | Fe$_2$O$_3$-Hap-SO$_3$H | Formic acid | Solvent free | 15–60 min | 95–99  | [34]      |
| 6     | Sulfated tungstate | Formic acid | Solvent free | 10–45 min  | 85–95  | [35]      |
| 7     | CDMT II | Formic acid | Microwave irradiation | 3–6 min | 64–94   | [36]      |
| 8     | Amidine and Guanidine | Methyl formate | Solvent free | 1–96 h | 65–98   | [37]      |
| 9     | TBD-based ionic liquids | Formic acid | Solvent free | 10–35 min | 75–98   | [38]      |
| 10    | Indium | Formic acid | Solvent free | 1.5–24 h | 70–98   | [28]      |

Figure 1. Schematic representation depicting N-formamide as versatile synthetic reagent.
In the absence of a catalyst or promoter, N-formylation of amines is a sluggish reaction that usually requires unique reaction conditions or long time frames for completion [25]. However, some of these methods have quite a number of limitations, including harsh reaction conditions, the need for expensive metal catalysts or organocatalysts, and long reaction time frames. Thus, for organic transformations, the development of a safe, benign, environmentally friendly, high-yield, quick-reaction, and recyclable catalyst for N-formylation of amines remains extremely desirable [3].

In the last few years, H$_2$SO$_4$–SiO$_2$ (Table 2) has demonstrated significant promise as a cost-effective and easily retrievable solid catalyst for driving a variety of essential organic reactions in solvent-free environments. H$_2$SO$_4$–SiO$_2$ is appealing for industrial usage because of its high catalytic activity, operational simplicity, and recyclability. There are two types of functional groups on the silica surface: siloxane (Si–O–Si) and silanol (Si–OH). Thus, silica gel modification can occur through the reaction of a specific molecule with either the siloxane (nucleophilic substitution at the Si) or silanol (direct reaction with the hydroxyl group) functions, though it is widely accepted that the reaction with the silanol function is the most common modification pathway (Figure 2) [47,48]. The notion of employing H$_2$SO$_4$–SiO$_2$ as a transamidation catalyst was inspired by Rasheed et al. [20]. We became interested in employing the same catalyst to build a generic formylation with triethyl orthoformate. To the best of our knowledge, no reports of H$_2$SO$_4$–SiO$_2$-catalyzed formylation with triethyl orthoformate have been published, and so for the first time, we present findings in this regard.

### Table 1. Cont.

| Entry | Catalyst | Formylating Agent | Reaction Condition | Time    | Yield % | Reference |
|-------|----------|-------------------|--------------------|---------|---------|-----------|
| 11    | ZnO      | Formic acid       | Solvent free       | 10–720 min | 65–99  | [24]      |
| 12    | ZnCl$_2$ | Formic acid       | Solvent free       | 10–900 min | 60–98  | [39]      |
| 13    | TiO$_2$-P25 or TiO$_2$-SO$_4^{2-}$ | Formic acid | Solvent free       | 30–45 min | 40–99  | [29]      |
| 14    | FSG-HF(N(SO$_2$C$_8$F$_{11}$)$_2$)$_4$ | Formic acid | Solvent free       | 1–4 h    | 60–88  | [40]      |
| 15    | Iridium  | Paraformaldehyde  | Reflux in H$_2$O   | 5–10 h   | 41–91  | [41]      |
| 16    | Silver and gold surfaces | Formaldehyde | Solvent free       | 6 h      | 75–97  | [42]      |
| 17    | Gold nanoparticles (Au/Al$_2$O$_3$ or Au/NiO) | Methanol | Reflux in H$_2$O   | 4 h      | 72–97  | [43]      |
| 18    | Ruthenium N-heterocyclic catalyst (Ru-NHC) | Methanol | Reflux in toluene (125 °C) | 12–24 h | 27–99  | [44]      |
| 19    | Copper salt (CuCl$_2$.H$_2$O) | Methanol | Solvent free       | 45–90 min | 63–80  | [45]      |
| 20    | Ionic liquid catalyzed formylation | CO | Reflux in methanol (140 °C) | 4 h | 42–99  | [18]      |
| 21    | Inorganic ligand-supported chromium (III) catalyst (NH$_4$)$_3$[CrMo$_6$O$_{18}$(OH)$_6$] | Methanol | Reflux in H$_2$O (80 °C) | 12 h | 60–99  | [46]      |
| 22    | Lipase   | Ethyl formate     | Reflux in THF at room temperature | 1–8 h | 29–99  | [14]      |
| 23    | No catalyst | Triethyl orthoformate in water | Ultrasound irradiation | 3 h | 35–88  | [1]       |
| 24    | Catalyst free | Ammonium formate | Solvent free       | 5 min–24 h | 43–98  | [13]      |

n/a: not applicable.

### Table 2. Silica-supported Brønsted acids as catalyst for the formylation of various amines.

| Entry | Catalyst | Formylation Agent | Reaction Condition | Time   | Yield % | Reference |
|-------|----------|-------------------|--------------------|--------|---------|-----------|
| 1     | HClO$_4$–SiO$_2$ | Formic acid   | Solvent free       | 15–90 min | 70–96  | [25]      |
| 2     | Fe$_3$O$_4$@SiO$_2$–APTES-TFA | 1,3-dicarbonyl compound | Solvent free | n/a | 68–98  | [34]      |
| 3     | H$_2$SO$_4$–SiO$_2$ | Formic acid | Solvent free       | 4–46 min | 65–99  | [20]      |
| 4     | H$_2$SO$_4$–SiO$_2$ | N,N-dimethyl amide | Solvent free       | 6–12 h  | 75–95  | [25]      |
2. Results and Discussion

Initially, the reaction of aniline with triethyl orthoformate was chosen as the model reaction (Figure 3). During the optimization of reaction parameters, it was observed that aniline reacted smoothly with triethyl orthoformate, providing the desired product with a good yield (96%) within a short period of time (Table 3).

![Figure 2. Immobilized sulfuric acid on silica gel.](image)

**Table 3.** Optimization of reaction parameters for N-formylation of amines with triethyl orthoformate (TEOF).

| Entry | Reaction Condition | Time | Yield |
|-------|--------------------|------|-------|
| 1     | Aniline (1 mmol)/TEOF (1 mmol), SIS (0.2 g) | 10 min | 44% |
| 2     | Aniline (1 mmol)/TEOF (2 mmol), SIS (0.2 g) | 6 min | 66% |
| 3     | Aniline (1 mmol)/TEOF (3 mmol), SIS (0.2 g) | 4 min | 96% |
| 4     | Aniline (1 mmol)/TEOF (4 mmol), SIS (0.2 g) | 4 min | 90% |

In order to generalize the protocol for the formylation of stericly hindered amines, the reaction was optimized with respect to temperature and molar ratio. The temperature was raised to 65 °C and was observed to be quite sufficient to carry out the reaction with an optimum yield of the desired product (Table 3). It was observed that the need for an excess of triethyl orthoformate was no longer required, as a 1:3 molar ratio of amine to triethyl orthoformate was sufficient to yield the desired product (Table 3, entry 3).

We next explored the impact of immobilized sulfuric acid on silica gel stoichiometry on the outcome of the reaction (Table 4). We observed that excess H$_2$SO$_4$–SiO$_2$ was not beneficial for faster conversion. Conversely, a lower amount of H$_2$SO$_4$–SiO$_2$ led to substantially slower conversion. The background reaction (used as a model) was also measured in the absence of H$_2$SO$_4$–SiO$_2$, confirming its vital role.

**Table 4.** N-formylation of aniline under different catalytic conditions.

| Entry | Catalytic Condition | Time | Yield |
|-------|--------------------|------|-------|
| 1     | Aniline (1 mmol)/TEOF (3 mmol) without catalyst at 65 °C | 3 h | traces |
| 2     | Aniline (1 mmol)/TEOF (3 mmol), SIS (0.1 g), 65 °C | 5 min | 78% |
| 3     | Aniline (1 mmol)/TEOF (3 mmol), SIS (0.2 g), 65 °C | 4 min | 96% |
| 4     | Aniline (1 mmol)/TEOF (3 mmol), SIS (0.3 g), 65 °C | 4 min | 88% |
| 5     | Aniline (1 mmol)/TEOF (3 mmol), SIS (0.4 g), 65 °C | 6 min | 71% |
| 6     | Aniline (1 mmol)/TEOF (3 mmol), SIS (0.5 g), 65 °C | 6 min | 64% |
In general, the reaction proceeded efficiently, with various amines reacting with triethyl orthoformate to produce the corresponding N-formylated product with good-to-excellent yield within a very short time. Aliphatic and aromatic primary amines underwent smooth N-formylation and gave the product in 70–96% yields (Table 5).

**Table 5.** N-formylation of amines using triethyl orthoformate in the presence of immobilized sulfuric acid on silica gel.

| Entry | Amines | Time (Min) | Product | Yield (%) |
|-------|--------|------------|---------|-----------|
| 1     | NH₂    | 4          | O       | 96        |
| 2     | H₂N    | 4          | O       | 81        |
| 3     | H₂N    | 4          | O       | 78        |
| 4     | NH₂    | 9          | O       | 95        |
| 5     | NH₂    | 4          | O       | 90        |
| 6     | NH₂    | 4          | O       | 97        |
| 7     | NH₂    | 10         | O       | 83        |
| 8     | NH₂    | 10         | O       | 97        |
| 9     | NH₂    | 10         | O       | 90        |
Table 5. Cont.

| Entry | Amines          | Time (Min) | Product         | Yield (%) |
|-------|-----------------|------------|-----------------|-----------|
| 10    | \( \text{NH}_2\text{NO}_2 \) | 10         | \( \text{O NH}_2\text{NO}_2 \) | 96        |
| 11    | \( \text{OH NH}_2 \) | 15         | \( \text{OH N}_2\text{O} \) | 90        |
| 12    | \( \text{NH}_2 \) | 13         | \( \text{NH}_2 \) | 75        |
| 13    | \( \text{OH NH}_2 \) | 13         | \( \text{OH N}_2\text{O} \) | 81        |
| 14    | \( \text{O OH} \) | 5          | \( \text{O OH} \) | 86        |
| 15    | \( \text{COOH \text{NH}_2} \) | 5          | \( \text{COOH \text{NH}_2} \) | 94        |
| 16    | \( \text{H}_2\text{N OH} \) | 20         | \( \text{O N OH} \) | 75        |
| 17    | \( \text{Cl OH} \) | 12         | \( \text{Cl OH} \) | 73        |
Table 5. Cont.

| Entry | Amines          | Time (Min) | Product          | Yield (%) |
|-------|-----------------|------------|------------------|-----------|
| 18    | O\(\text{HCO}\text{C}_6\text{H}_4\text{NH}_2\) | 20         | O\(\text{HCO}\text{C}_6\text{H}_4\text{N}=\text{O}\) | 85        |
| 19    | F\(\text{C}_6\text{H}_4\text{NH}_2\)        | 6          | F\(\text{C}_6\text{H}_4\text{N}=\text{O}\)       | 97        |
| 20    | Br\(\text{C}_6\text{H}_4\text{NH}_2\)       | 6          | Br\(\text{C}_6\text{H}_4\text{N}=\text{O}\)       | 78        |
| 21    | I\(\text{C}_6\text{H}_4\text{NH}_2\)        | 5          | I\(\text{C}_6\text{H}_4\text{N}=\text{O}\)        | 94        |
| 22    | Cl\(\text{C}_6\text{H}_4\text{NH}_2\)       | 6          | Cl\(\text{C}_6\text{H}_4\text{N}=\text{O}\)       | 78        |
| 23    | Br\(\text{C}_6\text{H}_4\text{Br}\)         | 6          | Br\(\text{C}_6\text{H}_4\text{Br}\)              | 84        |
| 24    | Br\(\text{C}_6\text{H}_4\text{NH}_2\)       | 5          | Br\(\text{C}_6\text{H}_4\text{NH}_2\)            | 81        |
| 25    | F\(\text{C}_6\text{H}_4\text{NH}_2\)        | 10         | F\(\text{C}_6\text{H}_4\text{N}=\text{O}\)       | 56        |
| 26    | Cl\(\text{C}_6\text{H}_4\text{Cl}\)         | 10         | Cl\(\text{C}_6\text{H}_4\text{Cl}\)              | 81        |
Table 5. Cont.

| Entry | Amines  | Time (Min) | Product | Yield (%) |
|-------|---------|------------|---------|-----------|
| 27    | H₂N Cl  | 12         | O-H₂N Cl| 82        |
| 28    | H₂N O|m  | O-H₂N O|m | 85        |
| 29    | H₂N | 15         | O-H₂N | 96        |
| 30    | NH₂ O  | 8          | O-NH₂ O| 93        |
| 31    | NH₂ CN | 6          | O-NH₂ CN| 94        |
| 32    | H₂N H₂N| 20         | O-H₂N H₂N| 96        |
| 33    | H₂N | 18         | O-NH₂ | 95        |
| 34    | H₂N | 5          | O-NH₂ | 86        |
Table 5. Cont.

| Entry | Amines | Time (Min) | Product | Yield (%) |
|-------|--------|------------|---------|-----------|
| 35    | ![Amine](image1) | 12         | ![Product](image2) | 93        |
| 36    | ![Amine](image3) | 12         | ![Product](image4) | 98        |
| 37    | ![Amine](image5) | 15         | ![Product](image6) | 80        |
| 38    | ![Amine](image7) | 20         | ![Product](image8) | 91        |
| 39    | ![Amine](image9) | 24         | ![Product](image10) | 93        |
| 40    | ![Amine](image11) | 15         | ![Product](image12) | 95        |
| 41    | ![Amine](image13) | 13         | ![Product](image14) | 92        |
| 42    | ![Amine](image15) | 25         | ![Product](image16) | 77        |
| 43    | ![Amine](image17) | 30         | ![Product](image18) | 67        |
| 44    | ![Amine](image19) | 54         | ![Product](image20) | 76        |
| Entry | Amines | Time (Min) | Product | Yield (%) |
|-------|--------|------------|---------|-----------|
| 45    | ![Image](image1.png) | 45         | ![Image](image2.png) | 79        |
| 46    | ![Image](image3.png) | 45         | ![Image](image4.png) | 71        |
| 47    | ![Image](image5.png) | 60         | ![Image](image6.png) | 94        |
| 48    | ![Image](image7.png) | 50         | ![Image](image8.png) | 94        |
| 49    | ![Image](image9.png) | 40         | ![Image](image10.png) | 87        |
| 50    | ![Image](image11.png) | 40         | ![Image](image12.png) | 78        |
| 51    | ![Image](image13.png) | 50         | ![Image](image14.png) | 73        |
| 52    | ![Image](image15.png) | 40         | ![Image](image16.png) | 85        |
| 53    | ![Image](image17.png) | 40         | ![Image](image18.png) | 75        |
| 54    | ![Image](image19.png) | 60         | ![Image](image20.png) | 85        |
Aniline with electron-donating groups provided an excellent yield of 65–96% with triethyl orthoformate. The halogen (F, Cl, Br, I)-containing anilines provided good yields, ranging from 73% to 96%, of corresponding products. Similarly, electron-withdrawing groups were found to react smoothly under the optimized reaction conditions and demonstrate good yields of desired products (85–96%). Generally, under these optimized reaction conditions, various functional groups were tolerated. However, finding a general method for generating amide bonds will surely benefit the drug discovery process. In general, the formylation of aryl/heteroaryl amines (electron-neutral, -rich, -deficient), aliphatic, and cyclic secondary amines afforded the formylation products in excellent yields (70–96%). Interestingly, sterically hindered aryl amines, such as products 6, 7, 10, 11, 16, 17, and 33–38, were found to react smoothly under the optimized reaction conditions, demonstrating good yields of desired products. Less reactive hetero aromatics, such as 42–51 and 56, produced the product with a surprisingly high yield (77–90%) and a longer reaction time (35–60 min). When secondary amines 52–54 were employed, the reaction was somehow slow, providing a good yield of products in 1 h (Table 5). NMR spectral data of all synthesized compounds are available in the Supplementary Materials (S1–S56).

Table 5. Cont.

| Entry | Amines | Time (Min) | Product | Yield (%) |
|-------|--------|------------|---------|-----------|
| 55    | H₂N →SH | 35         | O →N →SH | 93        |
| 56    | H₂N →N →O | 60         | HN →N →O | 93        |

3. Reusability of Catalyst

The reusability of the catalytic system was explored. The catalyst was separated by simple filtration and washed with ethyl acetate after the reaction was completed, and it was reused for two consecutive cycles within the same time frame (4 min), with a slight decrease in catalytic activity (9–13%) (Table 6).

Table 6. Efficiency of the recycled SIS in the N-formylation of aniline.

| Entry | Turn | Yield % |
|-------|------|---------|
| 1     | 1    | 96      |
| 2     | 2    | 89      |
| 3     | 3    | 83      |

In order to demonstrate the efficiency and versatility of the H₂SO₄–SiO₂ system, we compared the result of N-formylation of aniline with other protocols that have been published based on reaction times and yields (Table 7). The results showed that the other approaches required longer reaction times for efficient conversion than for the present protocol. Therefore, on this basis, the present protocol is more efficient or comparable with other methodologies.

Even though we have yet to prove the mechanism of our reaction in an experimental manner, Figure 4 suggests a possible explanation. The first step is the activation of the electrophilic carbon of triethyl orthoformate by the sulfonic group of H₂SO₄–SiO₂, which led to the formation of a cationic intermediate. The cationic intermediate reacted with amine nucleophiles, which, on further elimination of ethanol, furnished the desired formylated product.
Table 7. Comparison of efficiency of various conditions in the N-formylation of aniline.

| Entry | Conditions | Time | Yield | References |
|-------|------------|------|-------|------------|
| 1     | Triethyl orthoformate in H₂O under ultrasound irradiation. | 3 h | 88% | [1] |
| 2     | Solid-supported formate, DMSO, 70–80 ºC | 4 h | 60% | [15] |
| 3     | SSA, HCOOH, 50–60 ºC, solvent-free | 7 min | 99% | [49] |
| 4     | SA on activated charcoal, ethylformate, 54 ºC | 4 min | 95% | [21] |
| 5     | Triethyl orthoformate in H₂O under neutral condition. Microwave irradiation, 90 ºC | 2 h | 87% | [2] |
| 6     | SIS, triethyl orthoformate, 60–65 ºC, solvent-free | 3 min | 96% | Present protocol |

Figure 4. Proposed mechanism for N-formylation of amines with triethyl orthoformate.

While 1,8-diformamido-napthalein (38) and 3-formamido-1,2,4-triazole-5-thiol (53) are new derivatives and were characterized by one- and two-dimensional NMR analysis and high-resolution mass spectroscopy, all other products are known compounds and were identified by melting point, IR, ¹H NMR, and ¹³C NMR spectroscopy. The synthesis of formamides was confirmed by IR spectra, which revealed two distinct absorption bands between 3300 and 3400 cm⁻¹ (secondary NH) and 1640 and 1680 cm⁻¹ (N-formyl, C=O).

Furthermore, formamide molecules have both a conformational stereogenic axis and a configurational stereogenic centre. These molecules take on two distinct conformational diastereomers as a result of restricted rotation around the Ar–N bond [50]. The ¹H and ¹³C NMR spectra of most of the synthesized formamides at 25 ºC were consistent with the presence of two rotamers. Only one rotamer was observed for the compounds 8, 14, 27, 45 and 46.

During the purification of compounds 12 and 35, two products appeared as partially separated spots on thin-layer chromatography (TLC) plates. Using normal silica gel chromatography, these compounds were identified as A and B rotamer pairs. After purifying compounds 12 and 35, pure rotamers 12A and 35A were isolated (Figure 5). 12A and 35A were the only pure isomers that could be isolated, while 12B and 35B were always contaminated to some degree by 12A and 35A, respectively. The fact that we were able to isolate rotamers A and B at room temperature and characterize them using basic spectroscopic techniques astounded us. This occurrence may be viewed as a specific form of atropisomerism, because atropisomers are stereoisomers with restricted rotation around a single bond where the rotational barrier is high enough to allow isolation of the isomeric species [51].
4. Materials and Methods

A PerkinElmer Spectrum 100 FT-IR Spectrometer (Valencia, CA, USA) was used for the FT-IR analysis. The IR spectra were obtained by the attenuated total reflection (ATR) method. For each experiment, 16 scans were performed in the frequency range from 650 to 4000 cm⁻¹. Melting points of all the compounds were determined using a Kofler hot-stage apparatus and were uncorrected. NMR spectra were recorded on a Bruker Advance III 400 spectrometer (Rheinstetten, Germany) using CDCl₃ or DMSO-d₆ as a solvent with tetramethylsilane used as internal standard. LC-MS/MS data were recorded on a Bruker Compact quadrupole time of flight (QToF) mass spectrometer (Bremen, Germany). Raw mass spectrometry data were processed using MZmine software (version 2.38) (San Diego, CA, USA). Solvents and chemicals used were of analytical grade, purchased from Sigma Aldrich (St. Louis, MO, USA) and used without further purification. The purity determination of the starting materials and reaction monitoring were performed by thin-layer chromatography (TLC) on Merck silica gel G F254 plates (Duren, Germany).

4.1. Preparation of Sulfuric Acid Adsorbed on Silica Gel (H₂SO₄–SiO₂)

The preparation of H₂SO₄–SiO₂ was carried out by following the reported procedure [32]. To a suspension of silica gel (29.5 g, 230–400 mesh size) in EtOAc (60 mL), H₂SO₄ (1.5 g, 15.5 mmol, 0.8 mL of a 98% aq. solution of H₂SO₄) was added and the mixture was stirred magnetically for 30 min at room temperature. EtOAc was removed under reduced pressure (rotary evaporator) and the residue was heated at 100 °C for 72 h under vacuum to afford H₂SO₄–SiO₂ as a free-flowing powder.

4.2. A General Procedure for N-Formylation of Amines with Triethyl Orthoformate Promoted by Immobilized H₂SO₄ on Silica Gel

To a mixture of aniline (0.548 mL, 6 mmol) and triethyl orthoformate (24 mmol), the immobilized H₂SO₄ on silica gel (1.2 g) was then added and the reaction mixture was stirred under reflux conditions (65 °C). Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with EtOAc (20 mL), filtered, water (30 mL) was added, the solution was extracted with EtOAc, and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The residue was subjected to column chromatography and eluted with (EtOAc–Pet Ether (3:1)) to afford the product in high yields.

5. Conclusions

We have developed a simple, green, and highly efficient protocol for N-formylation of various amines in the presence of immobilized sulfuric acid on silica gel, with excellent yields and remarkably simple and environmentally benign processes. The approach is compatible with a wide range of aromatic, heteroaromatic, aliphatic, and cyclic/acyclic primary or secondary amines. The H₂SO₄–SiO₂ catalytic system described here is a good
complement to previously reported protocols, due to its ease of manipulation, low cost, and benign nature. We are optimistic that, with this approach, we will be able to develop the biologically relevant heterocyclic ring system more efficiently. This protocol is generic, and it will undoubtedly offer value to the growing area of organic synthesis.

**Supplementary Materials**: The following supporting information can be downloaded at: [https://www.mdpi.com/article/10.3390/molecules27134213/s1](https://www.mdpi.com/article/10.3390/molecules27134213/s1). Figure S1–S56: NMR spectral data of synthesized compounds. References [53–58] are cited in the Supplementary Materials.

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**References**

1. Habibi, D.; Sahebekhtiari, H.; Nasrollahzadeh, M.; Taghipour, A. A Very Simple, Highly Efficient and Catalyst-free Procedure for the N-Formylation of Amines Using Triethyl orthoformate in Water Under Ultrasound-irradiation. *Lett. Org. Chem.* 2013, 10, 209–212. [CrossRef]

2. Kaboudin, B.; Khodamorady, M. Organic reactions in water: A practical and convenient method for the N-formylation of amines in water. *Synlett* 2010, 19, 2905–2907. [CrossRef]

3. Khatri, C.K.; Chaturbhuj, G.U. Sulfated polyborate-catalyzed N-formylation of amines: A rapid, green and efficient protocol. *J. Iran. Chem. Soc.* 2017, 14, 2513–2519. [CrossRef]

4. Han, Y.; Cai, L. An efficient and convenient synthesis of formamidines. *Tetrahedron Lett.* 1997, 38, 5423–5426. [CrossRef]

5. Gould-Fogerite, S.; Mannino, R.J. Protein or peptide-cochleate vaccines and methods of immunizing using the same. U.S. Patent 5,643,517, 1 July 1997.

6. Pravin, P.; Maryam, A.M.; Alexander, D. Isocyanide 2.0. *Green Chem.* 2020, 22, 6902–6911. [CrossRef]

7. Roberts, R.M.; Vogt, P.J. Ortho esters, imidic esters and amidines: N-alkylformanilides from alkyl orthoformates and primary aromatic amines; Rearrangement of alkyl N-arylformimidates. *J. Am. Chem. Soc.* 1956, 78, 4778–4782. [CrossRef]

8. de la Mare, P.B.D. Kinetics of thermal addition of halogens to olefinic compounds. *Q. Rev. Chem. Soc.* 1949, 3, 126–145. [CrossRef]

9. Swaringen, R.A.; Eaddy, J.F.; Henderson, T.R. Reaction of Ortho Esters with Secondary Amines. *J. Org. Chem.* 1980, 45, 3986–3989. [CrossRef]

10. Blicke, F.F.; Lu, C.-J. Formylation of Amines with Chloral and Reduction of the N-Formyl Derivatives with Lithium Aluminum Hydride. *J. Am. Chem. Soc.* 1952, 74, 3933–3934. [CrossRef]

11. Kño, T.; Yoshida, I.; Katsuragawa, M.; Sakushima, M.; Usui, S.; Ukai, S. Polysaccharides in Fungi. XXXIV. A Polysaccharide from the Fruiting Bodies of Amanita muscaria and the Antitumor Activity of Its Carboxymethylated Product. *Biol. Pharm. Bull.* 1994, 17, 1460–1462. [CrossRef]

12. Jung, S.H.; Ahn, J.H.; Park, S.K.; Choi, J.K. A practical and convenient procedure for the N-formylation of amines using formic acid. *Bull. Korean Chem. Soc.* 2002, 23, 149–150. [CrossRef]

13. Ganapati Reddy, P.; Kishore Kumar, G.D.; Baskaran, S. A convenient method for the N-formylation of secondary amines and anilines using ammonium formate. *Tetrahedron Lett.* 2000, 41, 9149–9151. [CrossRef]

14. Rupesh Patre, E.; Sanjib Mal, A.; Pankaj, R.; Nilkanth, R.; Sujit Ghorai, K.; Nandan Kumar, D. A remarkably simple N-formylation of anilines using polyethylene glycol. *Tetrahedron Lett.* 2008, 49, 2225–2227. [CrossRef]

15. Noh, H.W.; An, Y.; Lee, S.; Jung, J.; Son, S.U.; Jang, H.Y. Metal-free Carbon Monoxide (CO) Capture and Utilization: Formylation of Amines. *Adv. Synth. Catal.* 2019, 361, 3068–3073. [CrossRef]

16. Zhang, L.; Han, Z.; Zhao, X.; Wang, Z.; Ding, K. Highly efficient ruthenium-catalyzed N-formylation of amines with H$_2$ and CO$_2$. *Angew. Chem. Int. Ed.* 2015, 54, 186–6189. [CrossRef]
20. Rasheed, S.; Rao, D.N.; Reddy, A.S.; Shankar, R.; Das, P. Sulphuric acid immobilized on silica gel (H2SO4-SiO2) as an eco-friendly catalyst for transamination. RSC Adv. 2015, 5, 10567–10574. [CrossRef]

21. Zeynizadeh, B.; Abdollahi, M. The immobilized NaHSO4·H2O on activated charcoal: A highly efficient promoter system for N-formylation of amines with ethyl formate. Curr. Chem. Lett. 2016, 5, 51–58. [CrossRef]

22. Das, V.K.; Devi, R.R.; Raul, P.K.; Thakur, A.J. Nano rod-shaped and reusable basic Al2O3 catalyst for N-formylation of amines under solvent-free conditions: A novel, practical and convenient NOSE’ approach. Green Chem. 2012, 14, 847–854. [CrossRef]

23. Madhukur Bhojegowd, M.R.; Nizam, A.; Pasha, M.A. Amberlite IR-120: A reusable catalyst for N-formylation of amines with formic acid using microwaves. Cuihua Xuebao/Chin. J. Catal. 2010, 31, 518–520. [CrossRef]

24. Hosseini-sarvari, M.; Sharghi, H. ZnO as a New Catalyst for N-Formylation of Amines under Solvent-Free Conditions. Tetrahedron 2006, 8, 6652–6654.

25. Zeynizadeh, B. Catalytic Performance. J. Chem. Soc. Pak. 2017, 39, 1–11.

26. Nasrollahzadeh, M.; Motahharifar, N.; Sajjadi, M.; Aghbolagh, A.M.; Shokouhimehr, M.; Varma, R.S. Recent advances in N-formylation of amines and nitroarenes using efficient (nano)catalysts in eco-friendly media. Green Chem. 2019, 21, 5144–5167. [CrossRef]

27. Bahari, S.; Sajadi, S.M. Natrolite zeolite: A natural and reusable catalyst for one-pot synthesis of α-aminophosphonates under solvent-free conditions. Arab. J. Chem. 2012, 10, 700–704. [CrossRef]

28. Kim, J.G.; Jang, D.O. Indium-catalyzed N-formylation of amines under solvent-free conditions. Synlett 2010, 8, 1231–1234. [CrossRef]

29. Krishnakumar, B.; Swaminathan, M. A convenient method for the N-formylation of amines at room temperature using TiO2-P25 or sulfated titania. J. Mol. Catal. A Chem. 2011, 334, 98–102. [CrossRef]

30. Veer, S.D.; Pathare, S.P.; Akamanchi, K.G. Sulfated tungstate catalyzed hydration of alkynes. J. Fluor. Chem. 2010, 5804–5806. [CrossRef]

31. Thirunarayanan, G.; Muthuvel, I.; Sathiyendiran, V. Spectral LFER studies in some N-(substituted phenyl) formamides. Curr. Chem. Lett. 2017, 5, 31. [CrossRef]

32. Kim, J.G.; Jang, D.O. Facile and highly efficient N-formylation of amines using a catalytic amount of iodine under solvent-free conditions. Tetrahedron Lett. 2014, 54, 2093–2096. [CrossRef]

33. Lei, M.; Ma, L.; Hu, L. A convenient one-pot synthesis of formamide derivatives using thiamine hydrochloride as a novel catalyst. Tetrahedron Lett. 2010, 51, 4186–4188. [CrossRef]

34. Jafarzadeh, M.; Soleimani, E.; Norouzi, P.; Adnan, R.; Sepahvand, H. Preparation of trifluoroacetic acid-immobilized Fe3O4@SiO2-APTES nanocatalyst for synthesis of quinolines. J. Fluor. Chem. 2015, 178, 219–224. [CrossRef]

35. Pathare, S.P.; Sawant, R.V.; Akamanchi, K.G. Sulfated tungstate catalyzed highly accelerated N-formylation. Tetrahedron Lett. 2012, 53, 3259–3263. [CrossRef]

36. De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. A new, simple procedure for the synthesis of formyl amides. Synlett 2004, 14, 2570–2572. [CrossRef]

37. Deutsch, J.; Eckelt, R.; Köckritz, A.; Martin, A. Catalytic reaction of methyl formate with amines to formamides. Tetrahedron 2009, 65, 10365–10369. [CrossRef]

38. Baghbanian, S.M.; Farhang, M. Protic [TBD][TFA] ionic liquid as a reusable and highly efficient catalyst for N-formylation of amines using formic acid under solvent-free condition. J. Mol. Liq. 2013, 183, 45–49. [CrossRef]

39. Chandra Shekhar, A.; Ravi Kumar, A.; Sathaiah, G.; Luke Paul, V.; Sridhar, M.; Shanthan Rao, P. Facile N-formylation of amines using Lewis acids as novel catalysts. Tetrahedron Lett. 2009, 50, 7099–7101. [CrossRef]

40. Hong, M.; Xiao, G. Hafnium(IV) bis(perfluorooctanesulfonyl)imide complex supported on fluorous silica gel catalyzed N-formylation of amines using aqueous formic acid. J. Fluor. Chem. 2013, 146, 11–14. [CrossRef]

41. Ourida, S.; Mark, J.B.; John, B.; James, L.; Stephen, P.M.; Pawel, P.; Robert, J.W.; Williams, J.M. J. Iridium-catalyzed formylation of amines with paraformaldehyde. Tetrahedron Lett. 2010, 51, 5804–5806. [CrossRef]

42. Lundberg, H. Group (IV) Metal-Catalyzed Direct Amidation: Synthesis and Mechanistic Considerations. Ph.D. Thesis, University of Stockholm, Stockholm, Sweden, 2015.

43. Ishida, T.; Haruta, M. N-formylation of amines via the aerobic oxidation of methanol over supported gold nanoparticles. ChemSusChem 2009, 2, 538–541. [CrossRef] [PubMed]

44. Ortega, N.; Richter, C.; Glorius, F. N-Formylation of amines by methyl activation. Org. Lett. 2013, 15, 1776–1779. [CrossRef] [PubMed]

45. Tumma, H.; Nagaraju, N.; Reddy, K.V. A facile method for the N-formylation of primary and secondary amines by liquid phase oxidation of methanol in the presence of hydrogen peroxide over basic copper hydroxyl salts. J. Mol. Catal. A Chem. 2009, 310, 121–129. [CrossRef]

46. Han, Y.; Zhikang, W.; Zheyu, W.; Yongyan, Z.; Shi, R.; Qixin, Z.; Jingjing, W.; Sheng, H.; Yongge, W. N-formylation of amines using methanol as a potential formyl carrier by a reusable chromium catalyst. Commun. Chem. 2019, 2, 1–7. [CrossRef]

47. Kaur, M.; Sharma, S.; Bedi, P.S. Silica supported Brønsted acids as catalyst in organic transformations: A comprehensive review. Cuihua Xuebao/Chinese J. Catal. 2015, 36, 520–549. [CrossRef]

48. Pramanik, A.; Bhar, S. Silica-sulfuric acid and alumina-sulfuric acid: Versatile supported炳rdenedBronsted acids catalyst. New J. Chem. 2021, 45, 16355–16388. [CrossRef]
49. Habibi, D.; Rahmani, P.; Akbaripanah, Z. N-formylation of anilines with silica sulfuric acid under solvent free conditions. J. Org. Chem. 2013, 2013, 268654. [CrossRef]
50. Hu, D.X.; Grice, P.; Ley, S.V. Rotamers or diastereomers? An overlooked NMR solution. J. Org. Chem. 2012, 77, 5198–5202. [CrossRef]
51. Lanyon-Hogg, T.; Ritzefeld, M.; Masumoto, N.; Magee, A.I.; Rzepa, H.S.; Tate, E.W. Modulation of Amide Bond Rotamers in 5-Acyl-6,7-dihydrothieno [3,2-c]pyridines. J. Org. Chem. 2015, 80, 4370–4377. [CrossRef]
52. Habibi, D.; Nasrollahzadeh, M.; Sahebekhtiari, H. Green synthesis of formamides using the Natrolite zeolite as a natural, efficient and recyclable catalyst. J. Mol. Catal. A Chem. 2013, 378, 148–155. [CrossRef]
53. Ma’mani, L.; Sheykhan, M.; Heydari, A.; Faraji, M.; Yamini, Y. Sulfonic acid supported on hydroxyapatite-encapsulated-$\gamma$-Fe$_2$O$_3$ nanocrystallites as a magnetically Brønsted acid for N-formylation of amines. Appl. Catal. A Gen. 2010, 377, 64–69. [CrossRef]
54. Bose, A.K.; Ganguly, S.N.; Manhas, M.S.; Guha, A.; Pombo-Villars, A. Microwave promoted energy-efficient N-formylation with aqueous formic acid. Tetrahedron Lett. 2006, 47, 4605–4607. [CrossRef]
55. Lygin, A.V.; De Meijere, A. ortho-Lithiophenyl isocyanide: A versatile precursor for 3H-quinazolin-4-ones and 3H-quinazolin-4-thiones. Org. Lett. 2009, 11, 389–392. [CrossRef]
56. Landquist, J.K. Synthetic antimalarials. Part XLVI. Some 4-[(dialkylaminoalkyl)amino] quinoline derivatives. J. Chem. Soc. 1951, 10, 1038–1048. [CrossRef]
57. Kim, J.J.; Park, Y.D.; Cho, S.D.; Kim, H.K.; Chung, H.A.; Lee, S.G.; Falck, J.R.; Yoon, Y.J. Efficient N-arylation of pyridazin-3(2H)-ones. Tetrahedron Lett. 2004, 45, 8781–8784. [CrossRef]
58. Trost, B.M. The Atom Economy—A Search for Synthetic Efficiency. Science 1991, 254, 1471–1477. [CrossRef] [PubMed]