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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_2SO_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

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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*-toluenesulfonic acid was employed as a catalyst, high yields of *N*-alkylformanilides 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_2SO_4, but under severe conditions (temperature above 140 °C) [9].

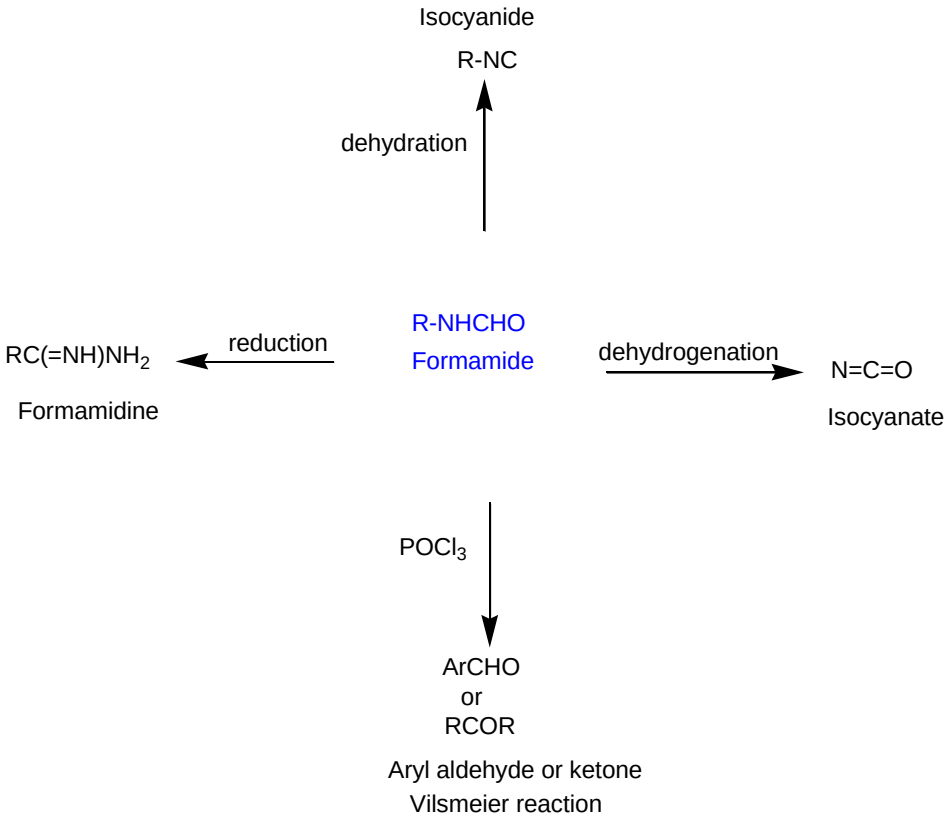


Figure 1. Schematic representation depicting *N*-formamide as versatile synthetic reagent.

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_2SO_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		[31]
2	Amberlite IR-120	Formic acid	Microwave irradiation	2 min	90–97	[23]
3	Molecular iodine (I_2)	Formic acid	Solvent free	2 h	60–99	[32]
4	Thiamine hydrochloride	Formic acid	Solvent free		88–96	[33]
5	Fe_2O_3-Hap-SO_3H	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]

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$(N(SO_2C_8F_{11})_2)_4$	Formic acid	Solvent free	1–4 h	60–88	[40]
15	Iridium	Paraformaldehyde	Reflux in H_2O	5–10 h	41–91	[41]
16	Silver and gold surfaces	Formaldehyde	Solvent free	6 h	75–97	[42]
17	Gold nanoparticles (Au/Al_2O_3 or Au/NiO)	Methanol	Reflux in H_2O	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 ($CuCl_2.H_2O$)	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 $(NH_4)_3[CrMo6O18(OH)_6]$	Methanol	Reflux in H_2O_2 (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]

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_2SO_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_2SO_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_2SO_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_2SO_4–SiO_2-catalyzed formylation with triethyl orthoformate have been published, and so for the first time, we present findings in this regard.

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_3O_4@SiO_2–APTES-TFA	1,3-dicarbonyl compound	Solvent free	n/a	68–98	[34]
3	H_2SO_4–SiO_2	Formic acid	Solvent free	4–46 min	65–99	[20]
4	H_2SO_4–SiO_2	*N*,*N*-dimethyl amide	Solvent free	6–12 h	75–95	[25]

n/a: not applicable.

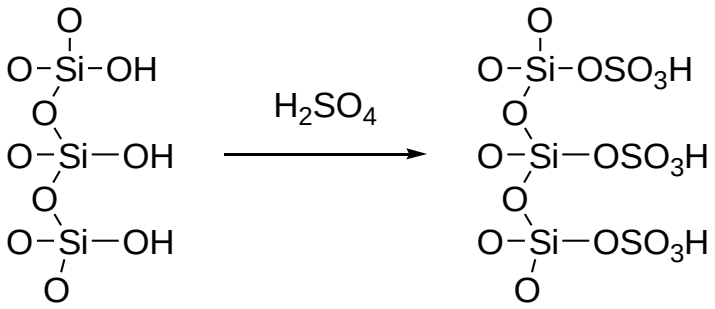


Figure 2. Immobilized sulfuric acid on silica gel.

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).

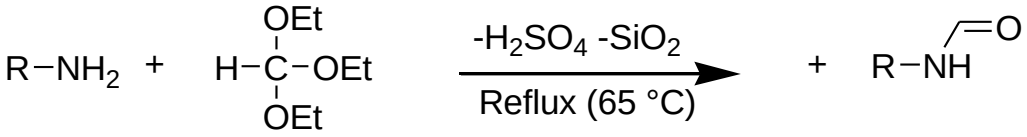


Figure 3. *N*-formylation of amines with triethyl orthoformate.

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 sterically 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_2SO_4–SiO_2 was not beneficial for faster conversion. Conversely, a lower amount of H_2SO_4–SiO_2 led to substantially slower conversion. The background reaction (used as a model) was also measured in the absence of H_2SO_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.

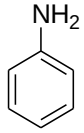
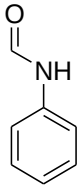
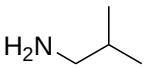
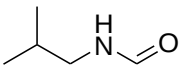
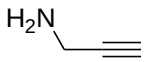
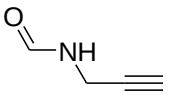
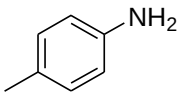
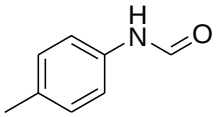
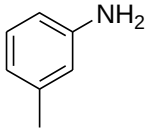
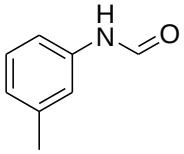
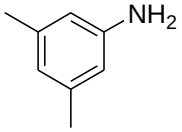
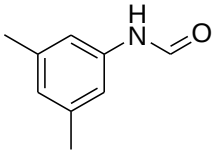
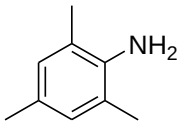
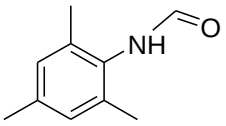
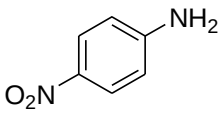
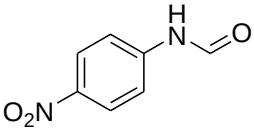
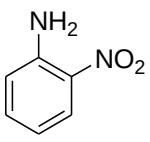
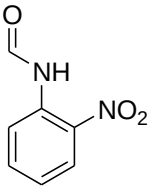
Entry	Amines	Time (Min)	Product	Yield (%)
1		4		96
2		4		81
3		4		78
4		9		95
5		4		90
6		4		97
7		10		83
8		10		97
9		10		90

Table 5. *Cont.*

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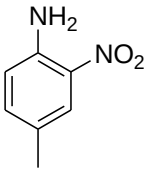
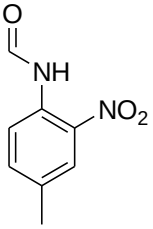
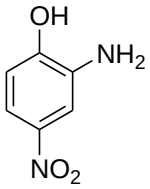
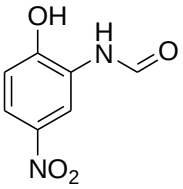
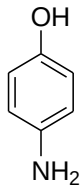
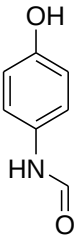
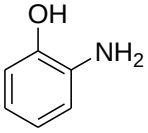
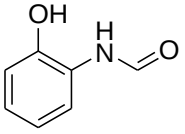
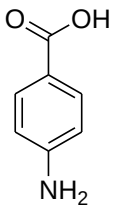
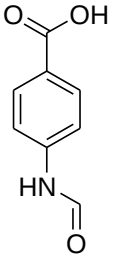
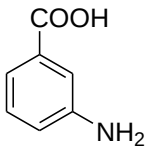
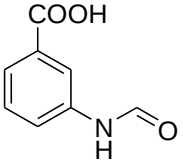
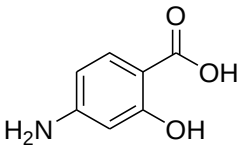
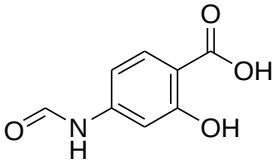
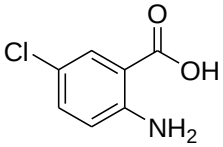
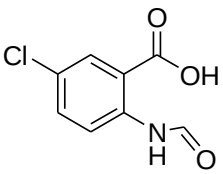
10		10		96
11		15		90
12		13		75
13		13		81
14		5		86
15		5		94
16		20		75
17		12		73

Table 5. *Cont.*

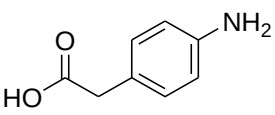
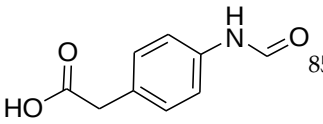
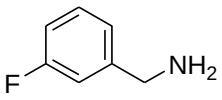
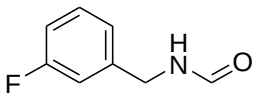
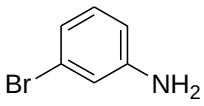
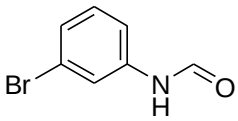
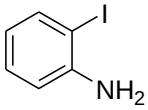
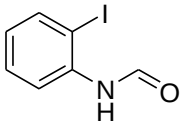
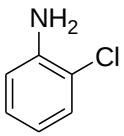
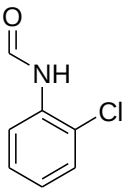
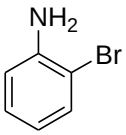
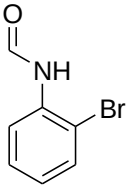
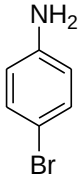
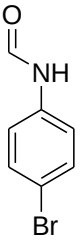
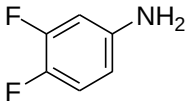
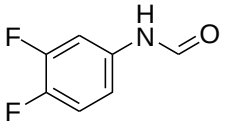
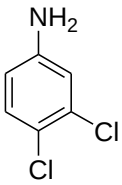
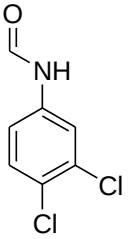
Entry	Amines	Time (Min)	Product	Yield (%)
18		20		85
19		6		97
20		6		78
21		5		94
22		6		78
23		6		84
24		5		81
25		10		56
26		10		81

Table 5. *Cont.*

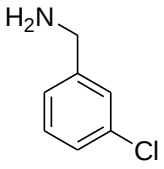
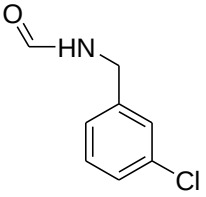
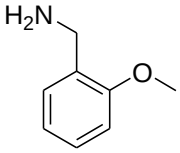
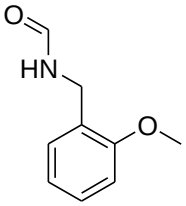
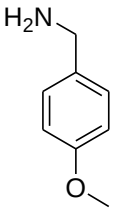
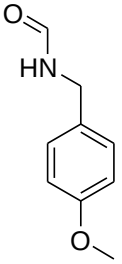
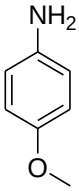
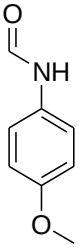
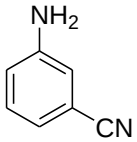
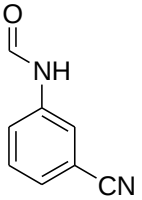
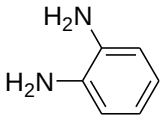
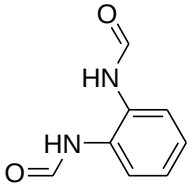
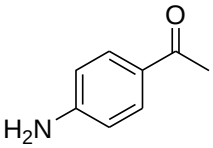
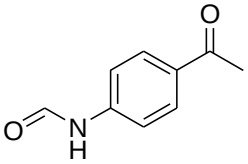
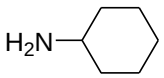
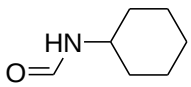
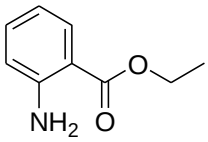
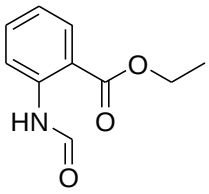
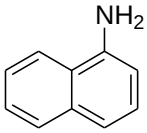
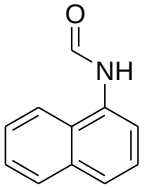
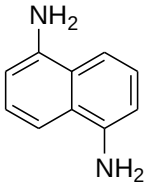
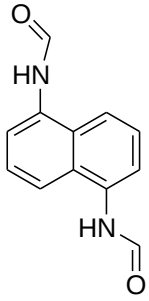
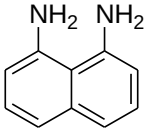
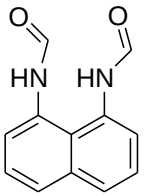
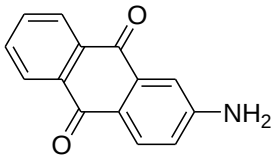
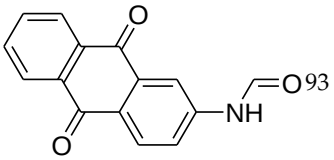
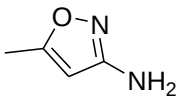
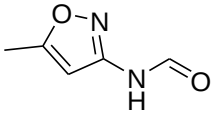
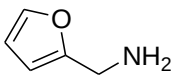
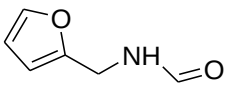
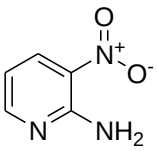
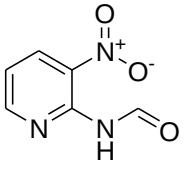
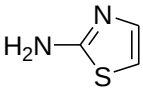
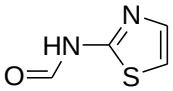
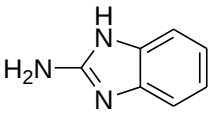
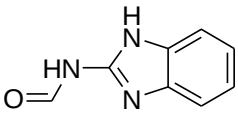
Entry	Amines	Time (Min)	Product	Yield (%)
27		12		82
28		15		85
29		15		96
30		8		93
31		6		94
32		20		96
33		18		95
34		5		86

Table 5. *Cont.*

Entry	Amines	Time (Min)	Product	Yield (%)
35		12		93
36		12		98
37		15		80
38		20		91
39		24		93
40		15		95
41		13		92
42		25		77
43		30		67
44		54		76

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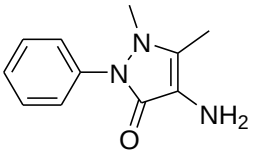
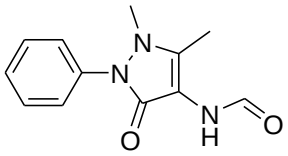
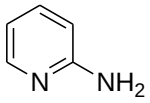
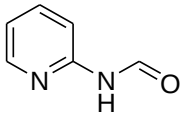
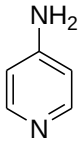
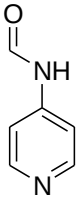
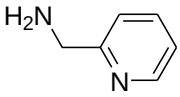
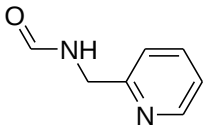
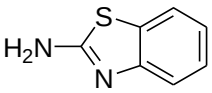
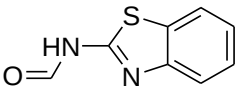
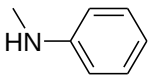
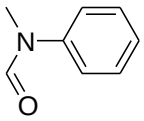
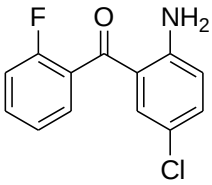
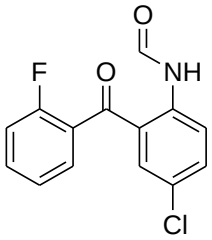
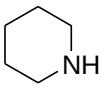
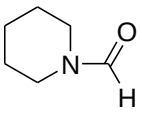
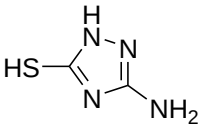
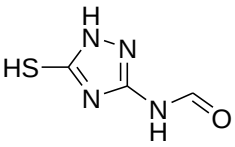
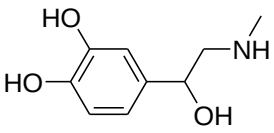
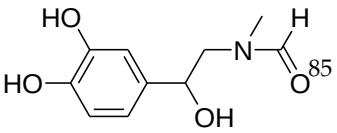
45		45		79
46		45		71
47		60		94
48		50		94
49		40		87
50		40		78
51		50		73
52		40		85
53		40		75
54		60		85

Table 5. *Cont.*

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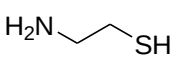
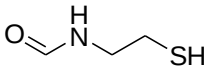
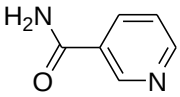
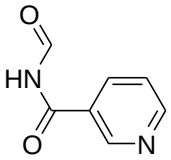
55		35		93
56		60		93

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).

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 H_2SO_4–SiO_2 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 H_2SO_4–SiO_2, 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 H_2O under ultrasound irradiation.	3 h	88%	[1]
2	Solid-supported formate, DMSO, 70–80 °C	4 h	60%	[15]
3	SSA, HCOOH, 50–60 °C, solvent-free	7 min	99%	[49]
4	SA on activated charcoal, ethylformate, 54 °C	4 min	95%	[21]
5	Triethyl orthoformate in H_2O under neutral condition. Microwave irradiation, 90 °C	2 h	87%	[2]
6	SIS, triethyl orthoformate, 60–65 °C, solvent-free	3 min	96%	Present protocol

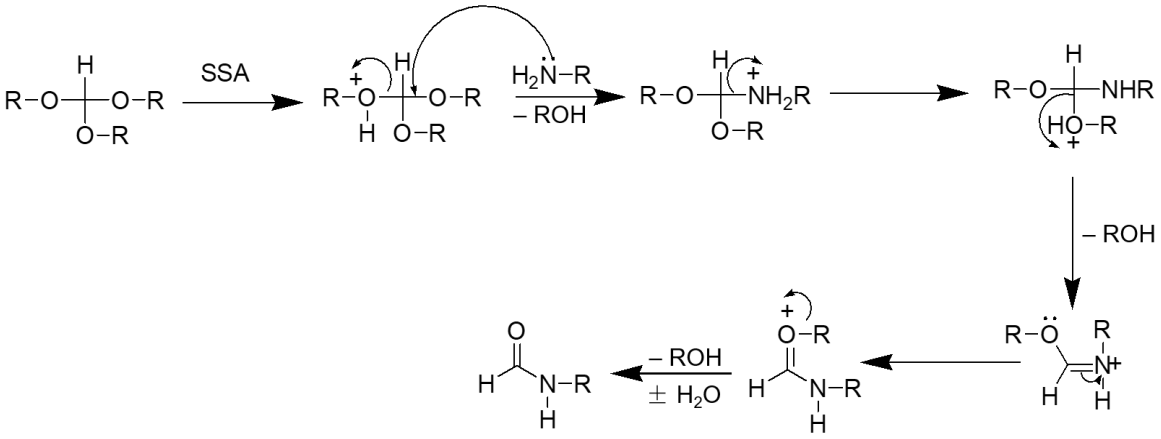
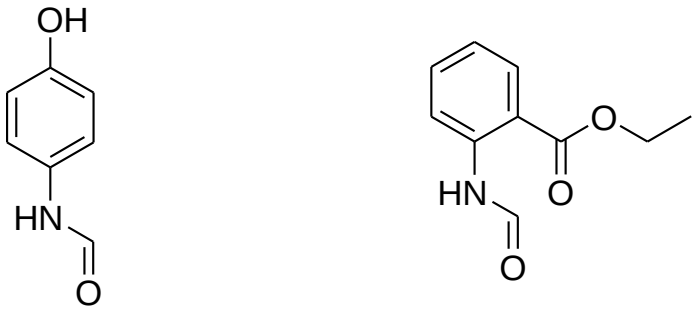


Figure 4. Proposed mechanism for *N*-formylation of amines with triethyl orthoformate.

While 1,8-difformamido-naphthalein (**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, ^{1}H NMR, and ^{13}C 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 *syn* and *anti*-conformational diastereomers as a result of restricted rotation around the Ar–N bond [50]. The ^{1}H and ^{13}C NMR spectra of most of the synthesized formamides at 25 °C 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].



12A
37%

35A
62%

Figure 5. Yield of isolated conformers **12A** and **35A**.

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 Koffler hot-stage apparatus and were uncorrected. NMR spectra were recorded on a Bruker Advance III 400 spectrometer (Rheinstetten, Germany) using $CDCl_3$ or DMSO-d_6 as a solvent with tetramethyl silane 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 F254plates (Duren, Germany).

4.1. Preparation of Sulfuric Acid Adsorbed on Silica Gel (H_2SO_4–SiO_2)

The preparation of H_2SO_4–SiO_2 was carried out by following the reported procedure [52]. To a suspension of silica gel (29.5 g, 230–400 mesh size) in EtOAc (60 mL), H_2SO_4 (1.5 g, 15.5 mmol, 0.8 mL of a 98% aq. solution of H_2SO_4) 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 H_2SO_4–SiO_2 as a free-flowing powder.

4.2. A General Procedure for N-Formylation of Amines with Triethyl Orthoformate Promoted by Immobilized H_2SO_4 on Silica Gel

To a mixture of aniline (0.548 mL, 6 mmol) and triethyl orthoformate (24 mmol), the immobilized H_2SO_4 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 Na_2SO_4 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 H_2SO_4–SiO_2 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: Figure S1–S56: NMR spectral data of synthesized compounds. References [53–58] are cited in the Supplementary Materials.

Author Contributions: Conceptualization, R.W.M.K. and S.A.S.; methodology, S.A.S.; writing—original draft preparation, S.A.S.; writing—review and editing, X.S.-N.; supervision, R.W.M.K. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Original data from experiments are available from the authors.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

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