Research Article

***N*-Formylation of Anilines with Silica Sulfuric Acid under Solvent-Free Conditions**

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N-formylation of primary and secondary amines was carried out with formic acid in the presence of silica sulfuric acid under solvent-free conditions to give the corresponding formamides in excellent yield and short reaction times.

1. Introduction

Introduction of a formyl group into the compounds has a very long story and despite some published papers having mentioned that Fieser and Jones were two chemists that reported the *N*-formylation of amines in 1955 [1], apparently just was the first chemist who formylated phenylhydrazine with formamide in 1886 [2], and several chemists proposed different procedures later. Hirst and Cohen obtained *N*-methylformamide by heating methylaniline with formamide in glacial acetic acid solution [3]. Pettit and Thomas reported the facile formylation of aromatic amines with dimethylformamide in the presence of sodium methoxide [4]. Bose and coworkers reported the microwave-induced organic reaction enhancement chemistry technique for the *N*-formylation of aliphatic and aromatic amines and amino heterocycles with aqueous formic acid [5]. Shekhar and coworkers reported the *N*-formylation of amines using ZnCl_2 as novel Lewis acids catalysts [6]. Tumma and coworkers reported 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 [7]. Bhojagowd and coworkers applied Amberlite IR-120 as a reusable catalyst for *N*-formylation of amines with formic acid in microwave condition [8]. The semiconductor catalyzed *N*-formylation of a variety of amines using formic acid as formylating agent has been investigated by Krishnakumar and Swaminathan

and they found that primary and secondary amines react efficiently with formic acid in the presence of TiO_2 -P25 or sulfated Titania giving *N*-formyl derivatives in high yields at room temperature. Sulfated Titania is found to be more efficient and reusable than TiO_2 -P25 for *N*-formylation of amines [9].

Also, several other formylating reagents have been developed [10–24] for different purposes (protection of amino group, synthesis of pharmaceutical compounds, etc.) [25–34] but due to some difficulties such as formation of side products, thermal instability, long reaction times, and the application of expensive reagents, there are still high demands for new methods.

In continuation to our environmentally benign synthesis and synthesis of the nitrogen-containing compounds [35–42], we intend to report a mild, efficient, and convenient procedure for the *N*-formylation of anilines with formic acid as a formylating agent in the presence of silica sulfuric acid (SSA) as a heterogeneous catalyst under solvent-free conditions (Scheme 1).

2. Experimental

2.1. General Procedures. All reagents were purchased from the Merck and Aldrich chemical companies and used without further purification. Products were characterized by FT-IR, ^1H NMR, and melting points. The NMR spectra were

TABLE 1: *N*-Formylation of anilines using SSA.

Entry	Substrate	Product ^a	Time (min)	Yield (%)
1			7	99
2			27	90
3			7	90
4			5	90
5			26	90
6			4	98
7			45	70
8			46	65
9			10	95

TABLE 1: Continued.

Entry	Substrate	Product ^a	Time (min)	Yield (%)
10			10	90
11			20	75
12			10	90
13			5	99
14			10	90
15			5	85
16			45	70
17		—	No reaction	

^a All products were known [44, 45].

recorded on a Bruker Avance DRX 300 and 500 MHz instruments in DMSO and CDCl₃. The chemical shifts (δ) are reported in ppm relative to the TMS as internal standard and *J* values are given in Hz. FT-IR (KBr) spectra were recorded

on a Perkin-Elmer 781 spectrophotometer. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. TLC was performed on silica gel polygram SIL G/UV 254 plates.

TABLE 2: *N*-Formylation of 4-bromoaniline (4BA) under different reaction conditions.

Entry	Conditions	Solvent	Time (min)	Yield %
1	4BA (1.0 mM), HCOOH (1.0 mM), SSA(0.5 g), 50–60°C	CH ₂ Cl ₂	20	20
2	4BA (1.0 mM), HCOOH (1.0 mM), SSA (0.5 g), 50–60°C	CH ₃ CN	30	35
3	4BA (1.0 mM), CH ₃ COOH (1.0 mM), SSA (0.5 g), 50–60°C	None	50	35
4	4BA (1.0 mM), HCOOH (1.0 mM), 50–60°C	None	20	60
5	4BA (1.0 mM), HCOOH (1.0 mM), r.t.	None	16	40
6	4BA (1.0 mM), HCOOEt (1.0 mM), SSA (0.5 g), 50–60°C	None	50	40
7	4BA (1.0 mM), HCOOH (1.0 mM), SSA (0.5 g), 50–60°C	None	27	90

TABLE 3: Comparison of efficiency of various conditions in the *N*-formylation of aniline.

Entry	Conditions	Time (h)	Yield %	Literature reference
1	Solid-supported formate, DMSO, 70–80°C	4.0	60	[20]
2	Al ₂ O ₃ /HCOOH, DMSO, 70°C	3–4	70	[20]
3	Silphos[PCl _{3–n} (SiO ₂) _n], ethyl formate, r.t	1.25	92	[46]
4	HCO ₂ NH ₄ (1.5 eq.), CH ₃ CN, reflux	11	96	[17]
5	ZnO, HCOOH (3.0 mM), 70°C, solvent-free	10 min	99	[44]
6	SSA, HCOOH (1.0 mM), 50–60°C, solvent-free	7.0 min	99	[present work]

SCHEME 1: General *N*-formylation procedure.

2.2. General Experimental Procedure for the *N*-Formylation of Anilines. To a mixture of aniline (1.0 mM) and HCOOH (1.0 mM), SSA [35–42] (0.5 g) was added. The mixture was stirred at 50–60°C and the progress of the reaction was monitored by TLC. After completion, the mixture was diluted with CH₂Cl₂ (15 mL), filtered, water (15 mL) added, the solution extracted with EtOAc (3 × 10 mL), and the combined organic layer dried over anhydrous Na₂SO₄ and concentrated. The residue was subjected to column chromatography to obtain the pure *N*-formyl aniline.

3. Results and Discussion

We have observed that the *N*-formylation of aniline can efficiently be accomplished in the presence of SSA under solvent-free conditions by treatment with formic acid at 50–60°C. Thus a series of primary and secondary amines was converted into the corresponding *N*-formyl amines in high yields and relatively short reaction times (Table 1).

Anilines contain either electron-releasing or electron-withdrawing groups underwent the conversion (Table 1, entries 2–13). It is well known that the amino group in 4-nitroaniline is of very low basicity and hence not easily acylated, so Jung and coworkers were not able to do the *N*-formylation of 4-nitroaniline [43], while it was formylated in

65% isolated yield using the present protocol (Table 1, entry 8).

For a variety of amines, for example, hindered amines (entry 16), the reaction shows good results without the significant influence of its structure on the product yield.

The reaction of 4-bromoaniline as a model compound was examined with formic acid under various reaction conditions and the effect of solvents also studied (Table 2). It should be mentioned that the SSA catalyzed *N*-formylation reaction in solvent-free conditions is faster than other solvents such as CH₂Cl₂ and CH₃CN (Table 2, entries 1 and 2). On the basis of these preliminary results, the application of 0.5 g of SSA with 1.0 mM of formic acid in solvent-free conditions at 50–60°C is the best procedure and this condition was applied to various amines.

The reaction mechanism probably involves the attack of the amine to the activated formic acid so the activity of the amine decreases as it gets bulkier. The method is very simple and a filtration removes the SSA to give the product almost pure in high to excellent yields.

In order to show the merit of the present work in comparison with some reported protocols, we compared them with respect to the reaction times (Table 3, entry 6), where the other methods need longer reaction times than SSA. Also, the reaction will take place at lower temperature by SSA (Table 3, entries 1, 2, 4, and 5) as well as the lesser amount of formic acid (Table 3, entry 5).

3.1. Reusability of the Catalyst. Also, we investigated the reusability of the applied catalytic system. After completion of the reaction, the catalyst was separated by a simple filtration, washed with CH₂Cl₂, and reused for four successive reaction runs (Table 4) without the significant loss of activity. The results of the first reaction and subsequent reactions were almost consistent.

TABLE 4: Efficiency of the recycled SSA in the *N*-formylation of 4-bromoaniline.

Entry	Turn	Yield %
1	1	99
2	2	96
3	3	94
4	4	94

4. Conclusions

We have developed a novel method for the direct and efficient conversion of aniline to *N*-formanilides by SSA under solvent-free conditions. We are confident that this one-pot *N*-formylation method will allow us to construct the biologically important heterocyclic ring systems in a more efficient manner.

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