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# Silica supported perchloric acid catalysed rapid N-formylation under solvent free conditions

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**Abstract**

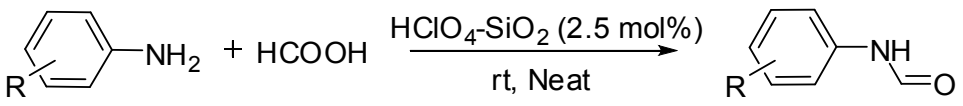
A rapid and chemoselective method for the N-formylation of structurally diverse amines using silica supported perchloric acid ($HClO_4$-$SiO_2$) at room temperature and under solvent free conditions has been developed. The catalyst was found to be compatible with different amines and the formylation proceeded smoothly with amines bearing electron withdrawing as well as electron donating functional groups

**Keywords:** Amines; N-Formylation; $HClO_4$-$SiO_2$; Room Temperature

## 1.Introduction

The development of non-toxic, low cost, eco-friendly, recyclable catalyst systems which give high productivity under mild reaction conditions has received much attention in organic synthesis.[1] In recent years, solid supported catalysts[2] have gained much prominence due to their inherent economic and environmental benefits, easy to handle, easy catalyst separation and regeneration, thermal stability and long catalytic life. Silica supported perchloric acid ($HClO_4$-$SiO_2$) is a versatile solid supported catalyst known to catalyse numerous organic reactions like acetylation,[3] condensation,[4] N-tert-butoxycarbonylation of amines,[5] synthesis of 2,3-unsaturated-O-glucosides and furan diol from 2,3-glycals,[6] 2,3-unsaturated glyco-pyranosides,[7] Micheal addition of thiols to electron deficient alkenes,[8] esterification of carboxylic acid with alcohols[9] etc.

Formamides, generally formed by formylation of amines are an extremely useful class of intermediates in the synthesis of medicinally important heterocyles such as substituted aryl imidazoles,[10] 1,2-dihydroquinolines,[11] oxazolidinones,[12] cancer chemotherapeutic compounds,[13] as reagent for Vilsmeir formylation, allylation,[15] hydrosilylation of carbonyl compounds[16] and for the synthesis of formamidines[17]and isocyanides.[18] In addition, formyl group also functions as an amino-protecting group in peptide synthesis.[19] Several methods for the amine formylation have been reported,[20] however, many of these methods suffer from drawbacks as being expensive and toxic, sensitivity to moisture, thermal instability, lack of generality, strict anhydrous conditions, long reaction times, high reaction temperature and use of solvents. In search of a convenient, eco-friendly procedure using inexpensive and reusable catalyst system, we report for the first time the use of silica supported perchloric acid ($HClO_4$-$SiO_2$) as a mild and a highly efficient, recyclable heterogenous N-formylation catalyst. To our delight, rapid and chemoselective N-formylation of amines occured using $HClO_4$-$SiO_2$ with formic acid under neat (solvent free) reaction conditions at room temperature giving formamides in excellent yields (Scheme 1).




**Scheme 1**

**Results and discussion**

The study was initiated by carrying out the reaction of aniline and formic acid without any catalyst or solvent at room temperature. No reaction was observed even after 24h of stirring,[21] however, addition of $HClO_4$-$SiO_2$ (1 mol%) to the reaction mixture completed the reaction in 90 minutes (TLC). Spectral analysis of the column chromatography purified product (yield,55%) revealed it to be N-formylated aniline. With the success of the reaction and to increase the yield, the same was repeated with 2.5 mol% of $HClO_4$-$SiO_2$ and surprisingly the reaction was complete in 15 minutes. Pure N-formylated aniline was isolated in 96% yield by column chromatography. Further increasing the catalyst loading to 5 or 7.5 mol% did not lead to any noticeable change in the reaction time and more so yields were also slightly decreased (Figure 1). From the above experiments, catalyst loading of 2.5 mol% gave the best results.

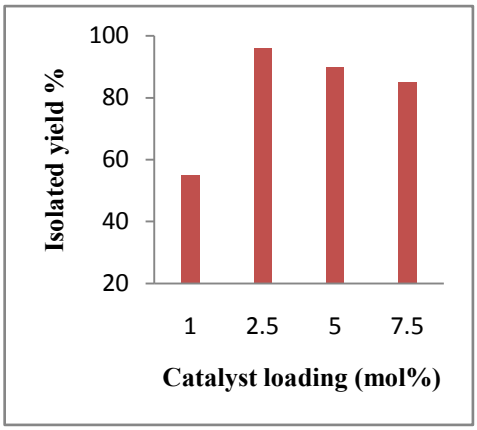



**Fig. 1**

Having accomplished the optimization of catalyst loading, more experiments were performed to delineate the best reaction conditions. To see the effect of solvent, reaction was carried out using DMSO, DMF, toluene, acetonitrile, methanol, dioxane, THF etc. It was observed that with the use of any solvent, reaction time was increased (30-45 min) and a decrease in yields was also noted. Toluene and THF were found to be comparable with solvent free (neat) conditions giving N-formylated product in yields of 61 and 65% in 30 min. From the above observations, best yields were obtained in (neat) solvent free reaction conditions at room temperature. (Table. 1)

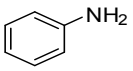
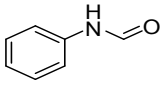
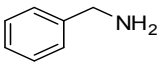
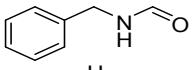
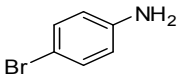
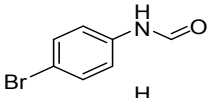
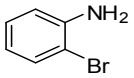
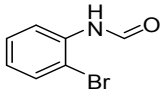
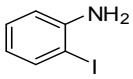
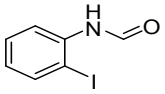
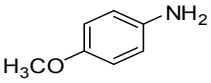
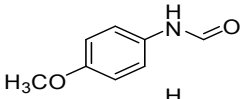
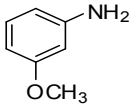
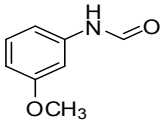
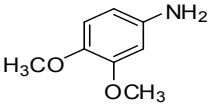
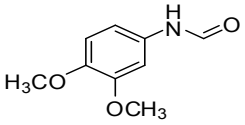
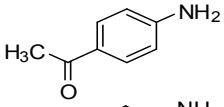
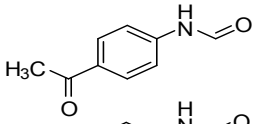
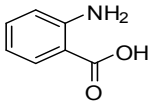
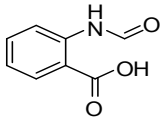
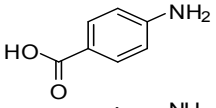
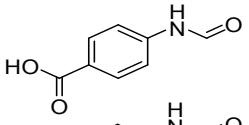
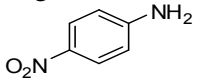
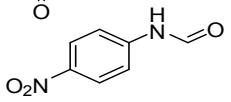
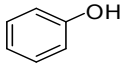
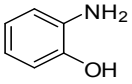
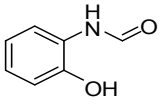
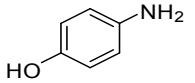
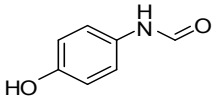
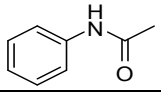
**Table.1** Optimization of reaction conditions

| Entry | Solvent | Time(min) | Yield(%) |
|---|---|---|---|
| 1 | Neat | 15 | 96 |
| 2 | THF | 30 | 65 |
| 3 | Toluene | 30 | 61 |
| 4 | Dioxane | 30 | 58 |
| 5 | $CH_3CN$ | 45 | 54 |
| 6 | DMF | 35 | 52 |
| 7 | $CH_3OH$ | 40 | 47 |
| 8 | DMSO | 40 | 45 |

Further, to check the effectiveness of the optimized method with different amines like, substituted primary amines, secondary amines, amino acids etc. (Table 2), it was observed that with primary amines substituted with a halogen or an electron donating group, the reaction was rapid and smoothly proceeded to completion within 15-25 min leading to the formation of the N-formylated product in 75-96% yields, whereas, presence of electron withdrawing groups like nitro or carboxyl prolonged the reaction time to an hour or more. The catalyst was found to be

compatible with different functional groups and the N-formylation proceeded chemoselectively. With aromatic amines containing both an amino and a phenolic or an acylated amino group, N-formylated product was selectively obtained. No reaction was observed either with phenol or N-acylated aniline (entry 13, 16, Table 2).

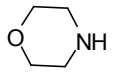
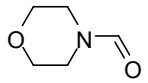
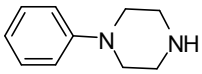
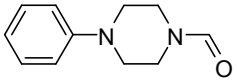
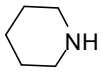
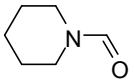
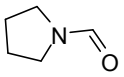
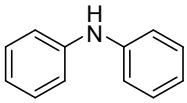
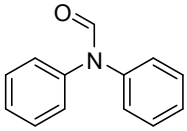
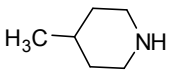
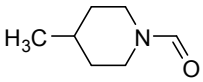
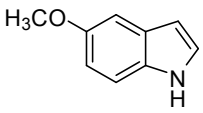
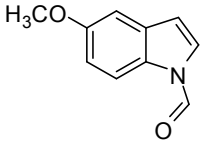
**Table 2** N-Formylation of primary amines

| Entry | Amine | N-Formamide | Time (min.) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | 15 | 96 |
| 2 |  |  | 40 | 92 |
| 3 |  |  | 20 | 90 |
| 4 |  |  | 25 | 94 |
| 5 |  |  | 25 | 90 |
| 6 |  |  | 25 | 93 |
| 7 |  |  | 30 | 75 |
| 8 |  |  | 35 | 80 |
| 9 |  |  | 30 | 85 |
| 10 |  |  | 50 | 86 |
| 11 |  |  | 60 | 78 |
| 12 |  |  | 90 | 88 |
| 13 |  | | NR | |
| 14 |  |  | 40 | 74 |
| 15 |  |  | 50 | 78 |
| 16 |  | | NR | |

[a]Isolated yield,

Encouraged by the results obtained from the primary amines, we extended the same reaction protocol to the secondary amines, here also formamides were obtained in good to excellent yields (55-94%, Table 3). In most of the cases, reactions were almost neat and the N-formylated products could be purified by simple filtration of the crude reaction mixture through a small silica gel column. However, amino acids could not be formylated, the reaction formed a complex mixture which showed the peak for the desired formamide in mass spectroscopy but the pure N-formylated product could not be isolated.

**Table 3** N-Formylation of secondary amines

| Entry | Amine | N-Formamide | Time (min.) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | 30 | 91 |
| 2 |  |  | 40 | 94 |
| 3 |  |  | 25 | 86 |
| 4 |  |  | 20 | 74 |
| 5 |  |  | 30 | 72 |
| 6 |  |  | 30 | 70 |
| 7 |  |  | 40 | 55 |

[a] Isolated yield

Further, the reaction was also studied using other protic acids immobilized on silica gel like, $H_2SO_4$-$SiO_2$, $HBF_4$-$SiO_2$ and TFA-$SiO_2$. Best yields of formamides were obtained with silica supported perchloric acid (Table 4). In addition, the advantage of using $HClO_4$-$SiO_2$ is its recyclability.The catalyst is easily recover- ed by simple filtration, washing with diethyl ether (2-3 times) and drying at 80°C under vaccum for 2h. The recovered catalyst was reused for N-formylation without any significant loss of activity (Table 5).

**Table 4** Comparison of N-formylation with other silica supported protic acids

| Entry | Catalyst | Time(min.) | Yield(%) |
|---|---|---|---|
| 1 | $HClO_4$-$SiO_2$ | 15 | 96 |
| 2 | $H_2SO_4$-$SiO_2$ | 35 | 55 |
| 3 | $HBF_4$-$SiO_2$ | 40 | 50 |
| 4 | TFA-$SiO_2$ | 20 | 48 |

**Table 5** The catalytic activity of $HClO_4$-$SiO_2$ in the model reaction with aniline

| Entry | No. of cycles | Yield (%) |
|---|---|---|
| 1 | 1 | 96 |
| 2 | 2 | 90 |
| 3 | 3 | 85 |
| 4 | 4 | 65 |

## Conclusions

In conclusion, we have developed a highly efficient and solvent free $HClO_4$-$SiO_2$ catalyzed method for N-formylation of primary and secondary amines at room temperature. Excellent chemoselectivity was observed with substrates having phenolic OH providing N-formamide as the sole product. This protocol can be used to generate a diverse range of primary and secondary formamides in excellent yields. The catalyst is completely recoverable and the efficiency of the catalyst remains unaltered even after three to four cycles.

## Experimental

**Preparation of $HClO_4$-$SiO_2$ Catalyst:** Perchloric acid (1.25 g, 12.5 mmol, 70% aq. solution) was added to a suspension of silica-gel (230–400 mesh, 23.7 g) in $Et_2O$ (70.0 mL) and the mixture was stirred for 30 min. The residue obtained after removal of ether was heated at 100°C for 72 hours under vacuum to furnish silica supported perchloric acid as a free flowing powder (1g silica gel contains 0.37 mmol of $HClO_4$).

**General procedure of N-formylation-** To a mixture of 2-bromoaniline (0.11 ml, 1 mmol) and formic acid (0.12 ml, 3 mmol) in a 10 ml round bottom flask was added $HClO_4$-$SiO_2$ (50 mg, 0.025 mmol). The solution was stirred at room temperature for 25 min. On completion, the mixture was diluted with diethyl ether and filtered to remove the solid catalyst. The filtrate was washed with sat. solution of $NaHCO_3$ (5ml×3), water and dried over anhy. $Na_2SO_4$. The solvent was evaporated and the crude residue was purified by column chromatography to give a colourless solid, yield 94%, mp: 89°C, IR (KBr): 3297, 1666 (C=O), 1536, 1435, 1401, 1293, 740 $cm^{-1}$ ESIMS, m/z: 199.97; $^1H$ NMR (300 MHz, DMSO) δ 9.71 (brs, s, 1H, NH), 8.35 (s, 1H, CHO), 8.01 (d, J=7.5, 1H), 7.65 (d, J=6.97, 1H), 7.37 (t, J=7.66, 1H), 7.09 (t, J=6.97, 1H), $^{13}C$, 50MHz (DMSO): 162.5, 160.3, 135.4, 133.1, 128.1, 126.1, 124.3, 124.0, 114.4.

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