Amberlite IR-120: A Reusable Catalyst for N-Formylation of Amines with Formic Acid Using Microwaves

Madhusudana Reddy MVTHUKUR BHOJEGOWD, Aatika NIZAM, Mohamed Afzal PASHA*

Department of Studies in Chemistry, Central College Campus, Bangalore University, Bengaluru 560 001, India

Abstract: A rapid and practical green route for the N-formylation of amines with formic acid using Amberlite IR-120 as a catalyst is described. This method provides an efficient and much improved modification over the reported methods in terms of yield, reaction time, and work-up procedure. A wide variety of substituents is tolerated, which is not the case for existing procedures.

Key words: N-formylation; Amberlite IR-120; formic acid; amine; microwave

Since the first report by Fieser et al. [1] on the N-formylation of amines, a number of strategies have been developed for their synthesis because of their importance as intermediates in the preparation of several fine chemicals [1] and pharmaceutically important compounds such as substituted aryl imidazoles [2], 1,2-dihydroquinolines [3], nitrogen-bridged heterocycles [5], etc. Formamides act as catalysts in the allylation [6] and hydroxylation [7] reaction of carbonyl compounds. The asymmetric allylation of aldehydes using chiral formamides has also been reported recently [8]. Formamides serve as very useful reagents in Vilsmeier formylation [9] and in the synthesis of formamidines and isocyanides [10]. In addition, a formyl group is used for the protection of the amino group during peptide synthesis [11,12].

Generally, the N-formylation of amines can be carried out using the esters of formic acid such as pentafluorophenyl formate and phenyl formate for direct N-formylation in the absence of a catalyst [13,14]. Apart from this, aryl formates and ethyl formate are useful for N-formylation in the presence of catalysts like TiCl3(OTf) [15] and silica-bonded N-propylsulfamic acid [16]. Chandra Shekhar et al. [17] have recently reported the N-formylation of amines using ZnCl2 as a catalyst, where the reaction requires a longer time for completion.

In addition to the above-mentioned reports, a number of other methods have been documented on the N-formylation of amines [18–20]. Many of the N-formylation methods have disadvantages such as the use of expensive reagents, the formation of side products, thermal instability, and difficulty to access reagents. Therefore, the pursuit of more convenient and practical synthetic methods for these compounds still remains an active research area.

On the other hand, a “green” reaction should ideally be conducted under solvent-free conditions with minimal or no side products and with the utmost atom economy [21]. One way to achieve this is by microwave heating. It is also well known that microwave heating dramatically accelerates the rate of many organic reactions and improves yields, and the reactions are highly selective [22–27]. Because of these advantages there is great interest in the use of environmentally benign reagents and procedures [28].

Recently, the use of solid acidic catalysts has gained importance in organic synthesis because of several advantages such as operational simplicity, non-toxicity, reusability, low cost, and ease of separation after completion of the reaction [29–32]. Amberlite IR-120[H+] resin has emerged as an efficient heterogeneous catalyst for various organic reactions [33]. Because of the numerous advantages associated with this inexpensive and non-hazardous recyclable catalyst we herein report a protocol for a solvent-free reaction using microwave activation for the synthesis of N-formamides using Amberlite IR-120 as a catalyst. To the best of our knowledge this is the first report on the N-formylation of amines with formic acid where the reaction is catalyzed by a reusable resin. The method is very simple as the resin can be filtered from the reaction mixture and simple evaporation of the solvent (used for washing the product) gives the desired product.

The chemicals used are commercially available. All the reactions were carried out in an LG domestic unmodified microwave oven Model MS-1947C/01, 230V/320W/2450 MHz. Melting points were determined using a Büchi apparatus. Nuclear magnetic resonance spectra were recorded on
a 400 MHz Bruker AMX spectrometer in CDCl₃ using tetramethylsilane as internal standard. GC-mass spectra were obtained using a Shimadzu GC-MS QP 5050A instrument equipped with a 30 m length and 0.32 mm diameter BP-5 column and the column temperature was 80–15–250 °C. Infrared (IR) spectra were recorded using a Shimadzu FT-IR-8400s spectrophotometer with KBr pellets for solids and thin films between NaCl plates for liquids.

Amine (2 mmol) and Amberlite IR-120 (100 mg) were placed in a 10 ml Pyrex glass tube and formic acid (0.22 ml, 6 mmol) was then added with constant mixing for 1 min. The reaction was subjected to microwave irradiation for an appropriate time at 320 W with 20 s intervals. The progress of the reaction was monitored with thin layer chromatography using 80%hexane-20%ethyl acetate as the mobile phase and the reaction was allowed to continue until the amine was fully consumed. When the reaction was complete, the mixture was cooled to room temperature and 5 ml ethyl acetate, and dried at 150 °C for 3 h before further use. The filtrate was washed with a saturated solution of NaHCO₃ (5 ml) and then with water (5 ml) and was dried over anhydrous MgSO₄. The filtrate was then concentrated under vacuum. The crude product was purified by column chromatography (silica gel 100–200 mesh, ethyl acetate:hexane:1:10) to obtain the corresponding N-formyl derivatives in pure form.

N-(4-Acetylphenyl)formamide (3a): ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 8.22 (brs, 1H), 7.94 (d, 2H, J = 1.82, Ar-H), 7.75 (d, 2H, J = 2.47, Ar-H), 2.53 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 16.0, 112.1, 117.1, 130.4, 130.7, 132.9, 141.5, 159.8, 162.3, 197.5; m/z 151 (M⁺).

4-Formylnitrobenzene (3b): ¹H NMR (400 MHz, CDCl₃) δ 12.73 (brs, 1H), 10.66 (s, 1H), 8.32 (s, 1H), 7.84 (d, 2H, J = 6.95, Ar-H), 7.65 (d, 2H, J = 8.67, Ar-H); ¹³C NMR (100 MHz, CDCl₃) δ 116.8, 118.96, 126.01, 130.96, 142.57, 160.53, 167.29; m/z 165.1 (M⁺).

N,N-Diphenylformamide (3c): ¹H NMR (400 MHz, CDCl₃) δ 8.55 (s, 1H), 7.03–7.36 (m, 10H); ¹³C NMR (100 MHz, CDCl₃) δ 124.0–129.5, 140.9, 162.3; m/z 197.2 (M⁺).

To further investigate the synthesis of biologically important compounds using simple, efficient, non-toxic, and readily available catalysts [34,35], we report on a simple and efficient procedure for the N-formylation of amines with formic acid using non-toxic, environmentally friendly, and reusable Amberlite IR-120 as a catalyst under solvent-free microwave irradiation conditions.

To optimize the reaction conditions and the catalytic activity of Amberlite IR-120, the reaction of 4-chloroaniline was selected as a model reaction. In our study, no reaction was observed when a mixture of 4-chloroaniline and formic acid was heated at 480 W in a microwave oven, even after 180 sec. However, the addition of a catalytic amount of Amberlite IR-120 (100 mg) to this mixture rapidly induced the N-formylation and formanilide was produced in 95% yield at 320 W in.

Based on these results and to investigate the scope and limitations of the reaction, various amines were subjected to this novel formylation reaction. The results are presented in Table 1. From this table it is clear that the reactions proceeded well irrespective of the substituents and the conversions were complete within 60–120 s. It is also clear that anilines containing electron donating substituents such as –CH₃, –OCH₃, –OH, and –N,N(CH₃)₂ (entries 2–4, 13, 14, and 19) and electron withdrawing groups such as –NO₂ and halides (entries 6–11) afforded the corresponding N-formamides in excellent yields. It is noteworthy that anilines having the keto and carboxyl substituents (entries 15 and 16) and secondary amines (entry 17) were also good substrates for the reaction. This protocol was successfully applied to aliphatic amines such as n-butylamine (entry 18). The structures of all the synthesized compounds were confirmed spectroscopically and found to be comparable in all respects with pure samples.

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<table>
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<th>Entry</th>
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Reaction conditions: amine 2 mmol, formic acid 6 mmol, Amberlite IR-120 100 mg. ¹Isolated yield. All the compounds are known and their physical properties are the same as the reported values. ¹¹H NMR, IR, and mass spectral data of all the products match the reported data.
Finally, we checked the reusability of the Amberlite IR-120 catalyst in the reaction of 4-chloroaniline with formic acid under the optimized conditions. After the completion of the reaction, ethylacetate was added and the insoluble catalyst was separated from the reaction mixture by filtration. The catalyst was washed with ethylacetate and dried for further use. The results of five runs showed that the recovered catalyst retains its activity in terms of yields of 95%, 92%, 93%, 89%, and 90%, respectively.

In conclusion, we developed a mild and selective method for the $N$-formylation of a variety of amines. This method has a number of advantages including low cost, reagent availability, easy handling, reusability of the catalyst, and ease of operation and workup. This novel $N$-formylation process can potentially be applied widely for the $N$-formylation of amines in organic synthesis.

References