A Practical and Convenient Procedure for the *N*-Formylation of Amines Using Formic Acid

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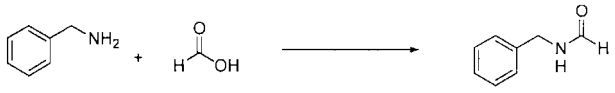
N-Formyl compounds have been widely used in organic synthesis as protecting group of amines,[1] precursor for isocyanide preparation,[2,3] an intermediate for mono methylated amines from primary amines,[4] and catalyst for allylation or reduction.[5] Thus a number of formylating methods have been reported. Acetic formic anhydride[1,6] continues to be the most widely used formylating reagent, but it is sensitive to atmospheric moisture and cannot be stored due to decomposition to acetic acid and carbon monoxide. Many other useful formylation reagents have been reported such as chloral,[7] activated formic acid using DCC[8] or EDCI,[9] activated formic esters[10-13] and ammonium formate.[14] Despite the usefulness of these reagents, such as high yields and mild conditions, they are less practical: they are either toxic or expensive and the preparation and use of these reagents require strictly anhydrous conditions.

We now report a practical formylation procedure using aqueous 85% formic acid. The reaction of amine with formic acid first appeared in 1955.[15] Fieser reported that *N*-methylaniline reacted with formic acid to give *N*-methylformanilide. We have extended this method to a general procedure which accommodates practicality, chirality and functionality. We reexamined *N*-formylation of amines using 85% formic acid as shown in Table 1, with benzylamine as a model compound. The use of excess formic acid under reflux provided only a trace amount of desired product (entry 1). When the amount of formic acid was reduced and toluene was used as a solvent with Dean-Stark trap, yields were dramatically increased (entries 2, 3).

The effect of changing the solvent was studied with 1.2 equivalents of formic acid. When the reaction was carried out in benzene, the formamide was obtained in only 40% yield (entry 5). The yield was improved to 98% when the reaction was run in either toluene or xylene (entries 4, 6). The best result was obtained with 1.2-2.0 equiv. of formic acid in refluxing toluene using Dean-Stark trap (entries 3, 4). Use of molecular sieve also gave satisfactory result with less convenience (entry 7). Based on these preliminary results, the application of this procedure (with 1.0-1.2 equiv. of formic acid in toluene with Dean-Stark trap) to various amines were investigated. The results are summarized in Table 2. Aromatic amines such as aniline and *N*-methylaniline proceeded smoothly to give the corresponding *N*-formyl compound in quantitative yields (entries 1, 2).

Table 1. Reaction of Benzylamine with Formic Acid under Several Conditions



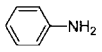
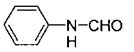
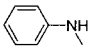
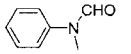
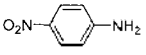
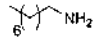
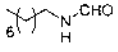
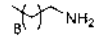
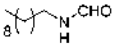
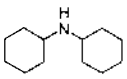
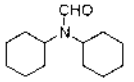
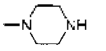
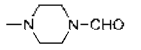
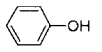
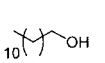
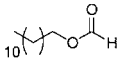
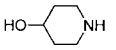
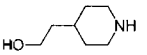
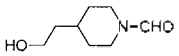
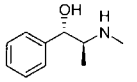
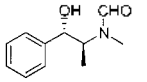
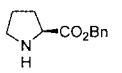
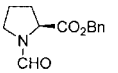
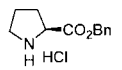
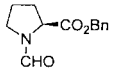
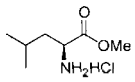
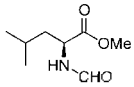
Entry	Benzyl amine (equiv)	Formic acid (equiv)[b]	Solvent	Time (h)	Yield[a,c] (%)
1	1	excess	none	15	trace
2	1	5.0	toluene Dean-Stark	3	74
3	1	2.0	toluene Dean-Stark	3	99
4	1	1.2	toluene Dean-Stark	9	98(95[d])
5	1	1.2	benzene Dean-Stark	24	40
6	1	1.2	xylene Dean-Stark	3	98
7	1	1.2	toluene MS 3A	3	98

[a]Benzyl amine (1g scale, 9.3 mmol) was reacted with formic acid under various conditions. [b]85% formic acid. [c]Yield was determined after evaporation. [d]Yield was determined after chromatographic purification

whereas, *p*-nitroaniline was inert under the condition (entry 3). Primary amines were easily formylated to provide alkyl formamide in excellent yields (entries 4, 5). Also, secondary amines readily reacted to afford the corresponding formamide in 98 and 94% yields, respectively (entries 6, 7).

O-formylation of alcohol or phenol derivatives under these reaction conditions was not successful. No reaction was observed with phenol (entry 8). With alkyl alcohol the reaction proceeded to only 25% conversion after 24 hours (entry 9). It was found that this reaction is chemoselective, then only *N*-formylated product was formed with molecules containing both the hydroxyl and the amino group (entries 10-12). *N*-Formyl amino acid esters could be obtained in good to excellent yields without racemization using the procedure outlined in this report. L-Proline benzyl ester was converted to the corresponding *N*-formyl compound without racemization in 99% yield {$[\alpha]_D = -47.3°$ (c 3, MeOH), lit[14] $-42.9°$ (c 3, MeOH)}, and the hydrochloride of L-Proline benzyl ester could be directly formylated without cumbersome conversion to free amine by adding 1.0 equiv. of tri-

Table 2. Reaction of various Amines and Alcohols with Formic Acid in toluene with Dean-Stark to give Formylation Product[a]

Entry	Amine	Formic acid (equiv)	Time	Product	Yield
1		1.2	9		99%
2		1.2	6		99%
3		1.2	3	No Reaction	
4		1.2	6		98%
5		1.2	6		98%
6		1.2	5		98%
7		1.2	5		94%
8		1.2	9	No Reaction	
9		3	24		25%[d]
10		1.0	4		96%
11		1.0	4		96%
12		1.0	5		94%
13		1.2	5		99%
14		1.2	5		92%[e]
15		1.2	5		88%[e]

[a]Amines (1g scale) were reacted with formic acid (1.0-1.2 equiv.) in toluene with Dean-Stark. [b]Isolated yields. [d]75% of starting material was recovered. [e]1.0 Equiv. triethylamine was added.

ethylamine with equally satisfactory yields (92%. $[\alpha]_D$= –47.3° (c 3. MeOH)) (entries13 and 14).

Leucine methyl ester was also formylated to give *N*-formyl-L-leucine methyl ester {$[\alpha]_D$ = –44.7° (c 1. MeOH). lit[13] –43.5° (c 1. MeOH)}(entry 15).

In conclusion. we have developed a practical and convenient procedure for *N*-formylation using aqueous 85% formic acid; This procedure has several advantages: 1) no need of anhydrous condition, 2) no racemization. 3) excellent yields, 4) no purification. 5) selective *N*-formylation in the presence of hydroxyl group.

Experimental Procedure

A mixture of 1 g of amine, 1.0-1.2 equiv. of aqueous 85% formic acid in toluene was heated under reflux using a Dean-Stark trap for 4-9 h. The progress of reaction was monitored by TLC. and after starting material was disappeared, the reaction mixture was evaporated to give the crude *N*-formyl compound, essentially as a sole product. The purity of the product was usually satisfactory for further use. If necessary, the evaporation residue was purified by short column chromatography. The yields practically represented the purity of the amines.

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