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RESEARCH PAPER

# Formylation of Alcohol with Formic Acid under Solvent-Free and Neutral Conditions Catalyzed by Free $I_2$ or $I_2$ Generated in Situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI

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**Abstract:** Different alcohols were formylated by formic acid under solvent-free conditions in the presence of iodine as the catalyst with good-to-high yields at room temperature. $I_2$ generated in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI also catalyzed the formylation of the alcohols under solvent-free conditions. This gives a green and efficient reaction at room temperature, in which the use of toxic and corrosive molecular $I_2$ is avoided.

**Key words:** alcohol; formic acid; formylation; iodine; in situ iodine; solvent-free

Formylation is an important reaction in organic chemistry because it can affect selectivity by putting acetate or other ester protecting groups on a substrate [1]. Furthermore, if the alcoholic group is to be oxidized later in the synthetic scheme, the formylated alcoholic does not need to be de-protected, in which case direct oxidation under Oppenauer conditions can be used [2]. In addition, formate esters are useful synthetic reagents and intermediates [3–5]. Despite these potential uses, the formyl protecting group has been rather overlooked. This is partly due to the fact that efficient formylation procedures under mild conditions are not available because the unstable formyl halide or anhydride is unsuitable for use in formylation.

Several formylation procedures have been reported, but these were based on formylation with formic acid in the presence of a dehydrating agent [6–8], transesterification with ethyl/methyl formate [9–13], with active formates [14–16] or with *N*-formyl compounds [17,18], that is, most of these methods use uncommon, moisture sensitive, thermally unstable, and expensive reagents or catalysts. This work reports a procedure that does not have these disadvantages.

## 1 Experimental

### 1.1 General procedure for the formylation of alcohol or thiol by formic acid under solvent-free conditions catalyzed by $I_2$

To a stirred mixture of $I_2$ (0.1 mmol) and formic acid (20 mmol), alcohol or thiol (1 mmol) was added, and stirring was continued at room temperature for an appropriate time. After completion of the reaction (monitored by TLC), iodine and formic acid were destroyed by adding saturated sodium thiosulfate solution (5 ml) and 10% aqueous solution of NaOH (5 ml), respectively. Diethyl ether (10 ml × 2) was added and the phases were separated. The organic phase was washed with brine (5 ml × 2) and dried ($Na_2SO_4$). Evaporation of the solvent under reduced pressure to give the almost pure product. In some cases, flash column chromatography with silica gel (*n*-hexane/EtOAc 10:1) was used to provide the pure product. All the products were characterized by IR, $^1$H NMR, MS, and elemental analysis.

### 1.2 General procedure for formylation of alcohol by formic acid catalyzed with $I_2$ generated in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI

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Alcohol (1 mmol) was added to a mixture of $Fe(NO_3)_3·9H_2O$ (0.1 mmol), NaI (0.2 mmol), and HCOOH (20 mmol). The mixture was stirred vigorously at room temperature for a specific time. After completion of the reaction, the sample was treated as described in section 1.1.

### 1.3 Spectral data of some known formates

4-Chlorobenzyl formate (**1**). IR (Nujol, $cm^{-1}$): $\nu$ 3037, 2933, 1725, 1450. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 5.12 (s, 2H), 7.30 (m, 4H), 8.15 (s, 1H). Anal. Calcd. for $C_8H_7ClO_2$: C, 56.32; H, 4.14; Cl, 20.78; O, 18.76. Found: C, 56.57; H, 4.10. MS (*m*/*z*): 170 [$M^+$].

4-Nitrobenzyl formate (**3**). IR (KBr, $cm^{-1}$): $\nu$ 3082, 2854, 1726, 1607, 1521, 1459, 1347, 1152, 846, 738. $^1H$ NMR (90MHz, $CDCl_3$): $\delta$ 5.27 (s, 2H), 7.46–7.54 (m, 2H), 8.15–8.24 (m, 3H). Anal. Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73; O, 35.33. Found: C, 53.21; H, 3.50; N, 7.48. MS (*m*/*z*): 181 [$M^+$].

Cinnamyl formate (**4**). IR (Neat, $cm^{-1}$): $\nu$ 3027, 2934, 2975, 1724, 1449, 1494, 1165. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 4.82 (d, 2H), 6.23–6.68 (m, 2H), 7.25–7.40 (m, 5H), 8.12 (s, 1H). Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21; O, 19.73. Found: C, 73.96; H, 6.15. MS (*m*/*z*): 162 [$M^+$].

2-Phenylethyl formate (**5**). IR (Neat, $cm^{-1}$): $\nu$ 3023, 2980, 2975, 1760, 1155. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 2.9 (m, 2H), 4.40 (t, 2H), 7.3 (m, 5H), 8.01 (s, 1H). Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31. Found: C, 72.07; H, 6.50. MS (*m*/*z*): 150 [$M^+$].

Diphenylmethyl formate (**6**). IR (Neat, $cm^{-1}$): $\nu$ 3032, 2930, 2854, 1731, 1495, 1456, 1157. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 7.13 (s, 1H), 7.25–7.42 (m, 10H), 8.26 (s, 1H). Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70; O, 15.08. Found: C, 79.42; H, 5.80. MS (*m*/*z*): 212 [$M^+$].

1-Phenylethyl formate (**7**). IR (Neat, $cm^{-1}$): $\nu$ 3020, 2988, 2978, 1757, 1165. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 1.53 (d, 3H), 5.97 (q, 1H), 7.34 (m, 5H), 8.06 (s, 1H). Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31. Found: C, 71.75; H, 6.92. MS (*m*/*z*): 150 [$M^+$].

Cyclohexyl formate (**8**). IR (Nujol, $cm^{-1}$): $\nu$ 2980, 2970, 1725, 1475, 1150. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 0.95 (m, 4H), 1.22 (m, 4H), 1.67 (m, 2H), 4.82 (m, 1H), 8.02 (s, 1H). Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44; O, 24.97. Found: C, 65.35; H, 9.27. MS (*m*/*z*): 128 [$M^+$].

Cyclododecanyl formate (**9**). IR (Neat, $cm^{-1}$): $\nu$ 2940, 2864, 1725, 1471, 1183. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 1.32–1.53 (m, 22H), 5.11 (b, 1H), 8.01 (s, 1H). Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39; O, 15.07. Found: C, 73.75; H, 11.19. MS (*m*/*z*): 212 [$M^+$].

Methyl formate (**10**). IR (Neat, $cm^{-1}$): $\nu$ 3058, 2959, 2872, 1723, 1456, 1191. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 0.85–1.15 (m, 15H), 1.45–2.0 (m, 3H), 4.74 (m, 1H), 7.99 (s, 1H). Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94; O, 17.36. Found: C, 71.45; H, 10.72. MS (*m*/*z*): 180 [$M^+$].

2-Adamantanyl formate (**11**). IR (KBr, $cm^{-1}$): $\nu$ 2940, 2864, 1725, 1471, 1183. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 0.82–1.45 (complex, 14H), 4.93 (m, 1H), 7.97(s, 1H). Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; O, 17.756. Found: C, 73.12; H, 9.0. MS (*m*/*z*): 180 [$M^+$].

2-Heptanyl formate (**12**). IR (Neat, $cm^{-1}$): $\nu$ 2959, 2872, 1731, 1456, 1378. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 0.80–1.12 (m, 14H), 4.91 (m, 1H), 7.95 (s, 1H). Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18; O, 22.19. Found: C, 66.80; H, 11.28. MS (*m*/*z*): 144 [$M^+$].

1-Adamantanyl formate (**14**). IR (KBr, $cm^{-1}$): $\nu$ 2940, 2985, 1750, 1485, 1135. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 1.61–2.05 (complex, 15H), 7.99 (s, 1H). Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; O, 17.756. Found: C, 73.62; H, 8.69. MS (*m*/*z*): 180 [$M^+$].

1,4-Cyclohexanediyl diformate (**16**). IR (Nujol, $cm^{-1}$): $\nu$ 2983, 2969, 1727, 1473, 1150. $^1H$ NMR (90 MHz, $CDCl_3$): $\delta$ 1.52 (m, 4H), 1.80 (m, 4H), 4.85 (m, 2H), 8.04 (s, 2H). Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02; O, 37.17. Found: C, 55.85; H, 7.20. MS (*m*/*z*): 172 [$M^+$].

## 2 Results and discussion

In recent years, molecular iodine has received considerable attention as an inexpensive and readily available catalyst for various organic transformations under very mild and convenient conditions because it gives the corresponding products in excellent yields with high selectivity. This is due to the oxidizing ability and Lewis acidity of iodine [19]. As part of our work on the catalytic application of reagents in the transformation of organic functional groups [20–24], we report here the formylation of a wide range of alcohols using formic acid at room temperature under solvent-free conditions in the presence of a catalytic amount of molecular iodine.

We first optimized the reaction conditions by evaluating the influence of different amounts of formic acid and catalyst on the time and product yield in the formylation of benzhydrole, which was used as a model. The results are shown in Table 1. The optimum amount was 20 mmol of HCOOH in the presence of 0.1 mmol of $I_2$, which gave the complete conversion of benzhydrole to the corresponding formate ester.

**Table 1** Optimization of amount of formic acid and iodine for the formylation of benzhydrole (1 mmol) at room temperature

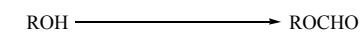
| HCOOH (mmol) | $I_2$ (mmol) | Time (min) | Conversion[a] (%) |
|---|---|---|---|
| 1 | 0.1 | 30 | 25 |
| 5 | 0.1 | 30 | 45 |
| 10 | 0.1 | 30 | 60 |
| 20 | 0.1 | 3 | 100 |
| 20 | 0.02 | 30 | 90 |
| 20 | 0.05 | 30 | 100 |

[a]Determined by $^1H$ NMR.

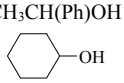
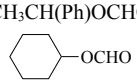
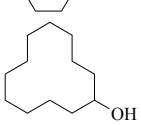
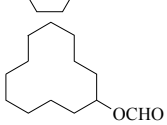
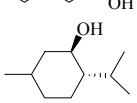
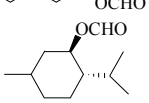
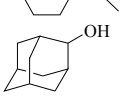
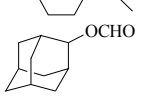
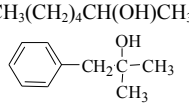
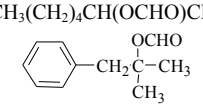
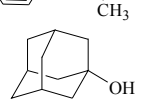
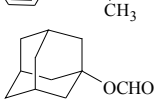
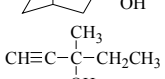
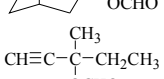
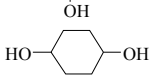
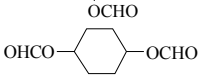
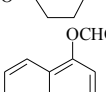
In order to determine the scope of the reaction, a series of structurally diverse alcohols including primary (benzylic, allylic, and acyclic), secondary (benzylic, cyclic, and acyclic), and tertiary (sterically hindered and acid-sensitive) alcohols were used. The formylation results under the optimized reaction conditions are shown in Table 2. The different alcohols were successfully converted to the corresponding formate esters in short reaction time in almost quantitative yields. This method was also useful for the formylation of diol (Table 2, entry 16). Thiols were converted to the corresponding formate thioester in low yields (Table 2, entries 19 and 20). We observed that 1-naphtol, as a model for phenols, was not converted in this reaction even after prolonged reaction time (Table 2, entry 18). Due to the nearly neutral nature of the reaction medium, no elimination byproduct was observed.

Although molecular iodine is a versatile reagent in organic synthesis, it is corrosive, which makes its use unattractive. Very recently, we reported a convenient system to generate $I_2$ in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI, and measured the amount of $I_2$ generated in situ by UV/Vis spectrophotometry [22,23]. Subsequently, we discovered that $I_2$ generated in situ from $Fe(NO_3)_3{\cdot}9H_2O$/NaI was an effective reagent for the formylation of a wide range of alcohols by HCOOH, giving good yields under solvent-free conditions at room temperature (Table 3). Compounds that were formylated in this way were primary and secondary (hindered and unhindered) alcohols and

**Table 2** Formylation of different alcohols by formic acid (20 mmol) in the presence of a catalytic amount of $I_2$ (0.1 mmol) under solvent-free conditions at room temperature

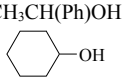
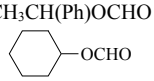
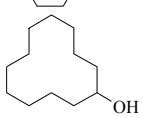
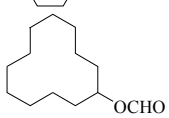
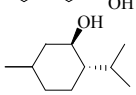
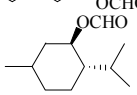
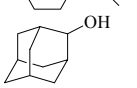
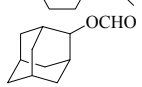
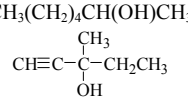
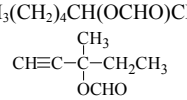
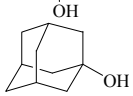
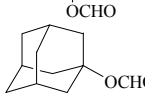
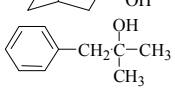
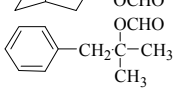
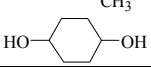
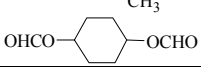



R = Benzylic, Linear, Cyclic

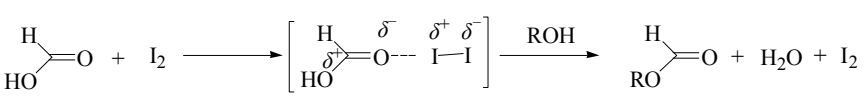
| Entry | Substrate | Product[a] | Time (min) | Isolated yield (%) |
|---|---|---|---|---|
| 1 | 4-Cl-$C_6H_4CH_2OH$ | 4-Cl-$C_6H_4CH_2OCHO$ | 35 | 96 |
| 2 | 4-OMe-$C_6H_4CH_2OH$ | 4-OMe-$C_6H_4CH_2OCHO$ | 7 | 94 |
| 3 | 4-$NO_2$-$C_6H_4CH_2OH$ | 4-$NO_2$-$C_6H_4CH_2OCHO$ | 60 | 88 |
| 4 | $C_6H_4CH_2$=$CH_2CH_2OH$ | $C_6H_4CH_2$=$CH_2CH_2OCHO$ | 45 | 70 |
| 5 | $PhCH_2CH_2OH$ | $PhCH_2CH_2OCHO$ | 10 | 93 |
| 6 | PhCH(OH)Ph | PhCH(OCHO)Ph | 3 | 94 |
| 7 | $CH_3CH(Ph)OH$ | $CH_3CH(Ph)OCHO$ | 40 | 93 |
| 8 |  |  | 40 | 90 |
| 9 |  |  | 60 | 96 |
| 10 |  |  | 60 | 91 |
| 11 |  |  | 30 | 97 |
| 12 | $CH_3(CH_2)_4CH(OH)CH_3$ | $CH_3(CH_2)_4CH(OCHO)CH_3$ | 40 | 91 |
| 13 |  |  | 90 | 76 |
| 14 |  |  | 120 | 77 |
| 15 |  |  | 140 | 80 |
| 16 |  |  | 35 | 89 |
| 17 |  |  | 120 | — |
| 18 | PhSH | PhSCHO | 120 | 60 |
| 19 | $PhCH_2SH$ | $PHCH_2SCHO$ | 240 | 45 |

[a]Products were characterized by comparison of their spectral data (IR, $^1$H NMR, MS, and elemental analysis) with those of standard samples [9–14].

**Table 3** Formylation of different alcohols (1 mmol) in the presence of $Fe(NO_3)_3·9H_2O$ (0.1 mmol)/NaI (0.2 mmol) and formic acid (20 mmol) under solvent-free conditions at room temperature

| Entry | Substrate | Product[a] | Time (min) | Isolated yield (%) |
|---|---|---|---|---|
| 1 | 4-Cl-$C_6H_4CH_2OH$ | 4-Cl-$C_6H_4CH_2OCHO$ | 45 | 95 |
| 2 | 4-OMe-$C_6H_4CH_2OH$ | 4-OMe-$C_6H_4CH_2OCHO$ | 13 | 94 |
| 3 | 4-$NO_2$-$C_6H_4CH_2OH$ | 4-$NO_2$-$C_6H_4CH_2OCHO$ | 120 | 69 |
| 4 | $C_6H_4CH_2$=$CH_2CH_2OH$ | $C_6H_4CH_2$=$CH_2CH_2OCHO$ | 90 | 76 |
| 5 | $PhCH_2CH_2OH$ | $PhCH_2CH_2OCHO$ | 60 | 97 |
| 6 | PhCH(OH)Ph | PhCH(OCHO)Ph | 35 | 90 |
| 7 | $CH_3CH(Ph)OH$ | $CH_3CH(Ph)OCHO$ | 45 | 87 |
| 8 |  |  | 60 | 90 |
| 9 |  |  | 240 | 90 |
| 10 |  |  | 150 | 82 |
| 11 |  |  | 90 | 92 |
| 12 | $CH_3(CH_2)_4CH(OH)CH_3$ | $CH_3(CH_2)_4CH(OCHO)CH_3$ | 150 | 94 |
| 13 |  |  | 120 | 50 |
| 14 |  |  | 140 | 45 |
| 15 |  |  | 240 | — |
| 16 |  |  | 50 | 92 |

[a]Products were characterized by comparison of their spectral data (IR, $^1$H NMR, MS, and CHN) with those of authentic samples [9–14].



**Scheme 1.** Proposed iodine-promoted formylation.

diols. Tertiary alcohols were converted to the corresponding formate esters in low yields (Table 3, entries 14–16). We observed that phenols and thiols were not converted in this reaction even after prolonged reaction time.

On the basis of the accepted mechanism for iodine as the catalyst in various organic transformations [19], it is proposed that in this reaction the carbonyl of formic acid is activated by iodine, which makes the carbonyl group susceptible to nucleophilic attack. The mechanism proposed for the reaction is shown in Scheme 1.

## 3 Conclusions

Iodine shows good catalytic activity for the formylation of a variety of alcohols by formic acid, and gives good to excellent yields under solvent-free conditions at room temperature. $I_2$ generated in situ from $Fe(NO_3)_3·9H_2O$/NaI was also shown to be an effective catalyst for the formylation of alcohol, which would be a green procedure.

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