Selective formylation of alcohols in the presence of phenols with chloral

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Abstract—Primary and secondary alcohols were formylated selectively in the presence of phenols by stirring with chloral in acetone over anhydrous K$_2$CO$_3$ at ambient temperatures in high yields.

O-Formylation could be the method of choice for protecting an alcoholic group in a complex synthetic sequence because deformylation can be effected selectively in the presence of acetate or other ester protecting groups. Further, if the alcoholic group is planned to be oxidised later in the synthetic scheme, the formylated alcoholic group need not be deprotected and direct oxidation under Oppenauer conditions can be realised. In some steroidal transformations, formylation has been found to be superior in detail to acetylation. Formate esters also serve as useful synthetic reagents and intermediates. Despite these uses and considerable potential, 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. The acid halide or anhydride procedure is unsuitable for formylation because formyl halides and anhydride are unstable. The classical methods of formylation with formic acid with or without an acid catalyst (HClO$_4$, BF$_3$) employ rather drastic conditions. Therefore, several formylation procedures have been reported over the years. These are based on formylation with formic acid in the presence of a dehydrating agent (Ac$_2$O, DCC, 1,1'-oxalylldiimidazole), transesterification with methyl/ethyl formate (catalysed by silica-gel supported metal sulphates, Ce(OTf)$_3$, Cu(NO$_3$)$_2$H$_2$O, PPh$_3$/CBr$_4$, K$_5$CoW$_{12}$O$_{40}$3H$_2$O) or with active formates (enol formates, cyanomethyl formate, 3-(3-oxopropyl formate under imidazole or DBN catalysis) and formyl transfer from DMF (in conjunction with benzyol chloride, SOCl$_2$/LiI, polymer-supported phosphine-halogen complex, secondary bromide/Cs$_2$CO$_3$, ) or from other active A^formyl compounds such as A^formylacetamide, A^formylformamide (generated in situ by ozonolysis of oxazole as well as A^formyl heterocycles (A^formylbenzotriazole, A^formylimidazole, A^formyl-4-pyridone, A^formyl-2-pyridone, 4-formyl-2-methyl-1,3,4-thiadiazolin-5-thione). Most of these methods, however, use uncommon and in some cases moisture sensitive or thermally unstable reagents which need to be prepared before use, in some cases, by multistep procedures employing expensive catalysts. Many of these methods also suffer from some of the following limitations: elevated temperatures, long reaction times, inert atmosphere, separation of the spent or deformylated reagent, acidic reaction conditions or work up, side reactions, and moderate yields.

Chloral reacts with alcohols easily to form stable hemiacetals. It is also known to formylate the primary hydroxy group of methyl mannochranoside when heated in 1,2-dichloroethane at reflux in the presence of DCC. However, the reaction was not found to be selective and other hydroxy groups reacted differently as shown in Scheme 1.

Keywords: formylation; chloral; primary and secondary alcohols; selective formylation; phenolic alcohols.

Scheme 1.
Our interest in the synthesis of chlorofurans using chloral hemiacetals led us to observe that chloral cinnamyl hemiacetals was cleaved easily to give cinnamyl formate in high yield, apparently by elimination of CHCl₃, on stirring in acetone over anhydrous K₂CO₃ at ambient temperatures. Considering the potential of this reaction as a simple and mild formylation procedure, the reaction was investigated in acetone over anhydrous K₂CO₃ at ambient temperatures (~25°C) (Scheme 2). Taking cinnamyl alcohol as the test case, the reaction was examined in various other solvents. Et₃N was also used as the base in the place of K₂CO₃ (Table 1). The most effective solvent-base combinations were found to be acetone-K₂CO₃ and acetonitrile-K₂CO₃. Acetonitrile-Et₃N combination also gave the formate in comparable yields but required longer reaction time.

Next, a variety of primary and secondary alcohols was converted to their formates at ambient temperatures in high yields (Table 2) except benzylc alcohols where the yields of the products were curiously found to be lower (entries 3 and 10, Table 2). Cyclohexanol was also formylated but the formate could be isolated only in poor yields (17%) probably due to its volatility. The reaction seems to be unsuitable for tertiary alcohols, as the formylation of 2-phenyl-2-propanol was found not to be clean and gave a complex mixture of products along with the unreacted alcohol. Under these conditions, phenolic compounds, e.g., p-cresol and methyl p-hydroxybenzoate remained unreacted and were recovered unchanged, indicating that the reaction could be selective for the formylation of primary and secondary alcohols in the presence of phenols. The selectivity was demonstrated by competition experiments in which equimolar mixtures of an alcohol and a phenol could be selective for the formylation of primary and secondary alcohols in the presence of phenols. Most of the existing reports on formylation of alcohols do not describe this type of selectivity (entries 19-21, Table 2).

Thus, it was observed that the hemiacetal of chloral need not be prepared separately and the whole transformation could be done in a single step by mixing the alcohol, chloral and anhydrous K₂CO₃ together in acetone and stirring at ambient temperatures (~25°C) (Scheme 2). Taking cinnamyl alcohol as the test case, the reaction was examined in various other solvents. Et₃N was also used as the base in the place of K₂CO₃ (Table 1). The most effective solvent-base combinations were found to be acetone-K₂CO₃ and acetonitrile-K₂CO₃. Acetonitrile-Et₃N combination also gave the formate in comparable yields but required longer reaction time.

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Chloral is a stable inexpensive and commercially available reagent. The formylation procedure is very simple and the reaction conditions are mild enough not to seriously interfere, with many common functional and protecting groups.

1. Experimental

Melting points are unconnected and recorded in a glass capillary with electrical heating. The IR spectra have been recorded on a Nicolet 5DX FTIR Spectrometer on samples taken as neat or as KBr discs. The $^1$H and $^13$C NMR spectra were recorded on Bruker Spectrospin DPX 300 MHz NMR Spectrometer in CDC$_3$ with TMS as the internal standard. The mass spectra were recorded on Jeol SX-102 Spectrometer at RSIC, CDRI, Lucknow. The microanalysis was carried out using Perkin-Elmer 240 rapid elemental analyser.

2-Phenylethanol, 2-[(naphthyl)ethyl]ethanol and 4-hydroxyphenylethanol were prepared by reduction of the corresponding bromo phenylethanol were prepared by reduction of the corresponding carbonyl compounds with NaBH$_4$. The formylation procedure is very simple and the compounds have been characterised by IR and NMR spectroscopy.\[200]\] The formates 3, 10 and 11 have been characterised by spectral analysis. The formates 6, 9, 14, 19 and 21 of the formates 1, 2, 4, 5, 7, 8 and 12 for which the spectral data are not reported are given below:

1.2.1. Nonanyl formate (I).\[200]\] Colourless liquid. IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2926, 2856, 1731, 1467, 1378, 1170. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 0.88 (t, 3H, $J$=6.5 Hz), 1.28 (bs, 12H), 1.66 (quintet, 2H, $J$=6.9 Hz), 4.16 (t, 2H, $J$=6.7 Hz), 8.06 (s, 1H). $^13$C NMR (CDCl$_3$): $\delta$ (ppm) 13.91, 22.53, 25.71, 28.42, 29.09, 29.35, 31.74, 63.94, 161.03.

1.2.2. 1-Dodecanyl formate (2).\[200]\] Colourless liquid. IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2925, 2854, 1731, 1467, 1377, 1179. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 0.88 (t, 3H, $J$=6.6 Hz), 1.26 (bs, 18H), 1.66 (quintet, 2H, $J$=6.6 Hz), 4.16 (t, 2H, $J$=6.7 Hz), 8.06 (s, 1H). $^13$C NMR (CDCl$_3$): $\delta$ (ppm) 13.88, 22.55, 25.71, 28.41, 29.09, 29.24, 29.54, 31.80, 63.84, 160.89.

1.2.3. 2-Phenylethyl formate (4). Colourless liquid. IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 3030, 2936, 1724, 1498, 1455, 1170. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 2.97 (t, 2H, $J$=7.0 Hz), 4.38 (t, 2H, $J$=7.0 Hz), 6.71-7.33 (m, 5H), 8.02 (s, 1H). $^13$C NMR (CDCl$_3$): $\delta$ (ppm) 34.57, 63.93, 126.37, 128.23, 128.55, 137.14, 160.55.

1.2.4. Cinnamyl formate (5). Colourless liquid. IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 3027, 2934, 1724, 1449, 1494, 1165. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 4.82 (d, 2H, $J$=6.4 Hz), 6.23-6.33 (dt, 1H, $J$=6.4, 15.9 Hz), 6.68 (d, 1H, $J$=15.9 Hz), 7.25-7.40 (m, 5H), 8.12 (s, 1H). $^13$C NMR (CDCl$_3$): $\delta$ (ppm) 63.54, 122.08, 126.09, 127.52, 128.02, 135.50, 137.14, 160.11.

1.2.5. 2-(1-Naphthyl)ethyl formate (6). Colourless liquid. IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 3047, 2951, 1717, 1597, 1510, 1464, 1377, 1349, 1283, 1171, 1179, 1143, 1132, 1074, 1006, 996, 974, 956, 936, 916, 883, 835, 806, 760, 740, 704, 694, 664, 644, 634, 624, 614, 594, 574, 554, 534, 514, 494, 474, 454, 434, 414, 394, 374, 354, 334, 314, 294, 274, 254, 234, 214, 194, 174, 154, 134, 114, 94, 74, 54, 34, 14. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 3.16, 63.48, 123.04, 125.12, 125.35, 125.92, 126.08, 127.25, 128.53, 131.60, 132.86, 133.53, 160.64. Analysis: Found C, 77.48; H, 8.51%. $^1$H NMR requires C, 77.78; H, 8.04%. MS (m/z): 200 (M$^+$, 18%), 154 (M$^+$-HCOOH, 100%), 141 (83%).

1.2.6. 2-Phenylpropyl formate (7). Colourless liquid. IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) 2967, 1724, 1495, 1454, 1172. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 1.31 (d, 3H, $J$=7.0 Hz), 3.12 (sextet, 1H, $J$=6.9 Hz), 4.19-4.31 (m, 2H), 7.25-7.38 (m, 5H), 8.05 (s, 2H).
1H. 13C NMR (CD2Cl2): 8 (ppm) 17.96, 38.75, 68.67, 126.77, 127.17, 128.50, 142.68, 160.91.

1.2.7. 2-Benzoxoyethyl formate (8). 32 Colourless liquid. IR (neat): v_{max} (cm^{-1}) 2952, 1724, 1452, 1277, 1175, 1110. 1H NMR (CD2Cl2): 8 (ppm) 4.44 (d, 4H, /=4.8 Hz), 7.33-7.38 (m, 2H), 7.46-7.50 (m, 1H), 7.94-8.02 (m, 3H). 13C NMR (CD2Cl2): 8 (ppm) 61.52, 62.32, 128.35, 129.62, 133.15, 160.57, 166.19.

1.2.8. 3-(Methoxycarbonyl)benzyl formate (9). Colourless crystals (pentane), mp 49-50°C. IR (KBr): 4150, 3400, 1734, 1613, 1515, 1225, 1179, 1080. 1H NMR (CD2Cl2): 8 (ppm) 2.90 (t, 2H, /=6.9 Hz), 7.30 (t, 2H, /=7.4 Hz), 7.42 (t, 2H, /=7.4 Hz), 7.55 (d, 2H, /=7.4 Hz), 7.63 (d, 2H, /=7.5 Hz), 8.39 (s, 1H). 13C NMR (CD2Cl2): 8 (ppm) 4.14 (t, 2H, /=6.9 Hz). 4.78 (s, 1H, D_{2}O-exchangeable), 6.75-6.82 (m, 4H), 8.12 (s, 1H). 13C NMR (CD2Cl2): 8 (ppm) 62.47, 66.42, 115.92, 116.11, 150.14, 152.19, 161.25. Analysis: Found C, 59.62; H, 5.69%. C_{6}H_{10}O_{4} requires C, 59.34; H, 5.53%. MS (mlz): 182 (M^+, 12%), 110 (p-HOC_{6}H_{5}OH^+, 25%), 73 (CH_{3}CH_{2}OCH_{2}^+, 100%).

1.2.14. 2-(3-Hydroxyphenoxy)ethyl formate (21). Colourless crystals (pentane+ether), mp 67-68°C. IR (KBr): 4150, 3400, 1734, 1613, 1515, 1225, 1179, 1080. 1H NMR (CD2Cl2): 8 (ppm) 4.17 (t, 2H, /=4.6 Hz), 4.51 (t, 2H, /=4.6 Hz), 5.32 (s, 1H, D_{2}O-exchangeable), 6.42-6.50 (m, 3H), 7.13 (t, 1H, /=8.1 Hz), 8.12 (s, 1H). 13C NMR (CD2Cl2): 8 (ppm) 62.33, 65.44, 102.22, 106.68, 108.52, 130.18, 156.83, 159.39, 161.42. Analysis: Found C, 59.24; H, 5.67%. C_{6}H_{10}O_{4} requires C, 59.34; H, 5.53%. MS (mlz): 182 (M^+, 16%), 110 (m-HOC_{6}H_{5}OH^+, 16%), 73 (CH_{3}CH_{2}OCH_{2}^+, 100%).

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References