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Mild and Highly Selective Formyl Protection of Primary Hydroxyl Groups

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Efficient conversion of primary alcohols to the corresponding formate esters can be carried out at room temperature in methylene chloride, using 2,4,6-trichloro-1,3,5-triazine and *N*,*N*-dimethylformamide in the presence of lithium fluoride. This procedure appears as a valid method for selectively protecting primary hydroxyl groups.

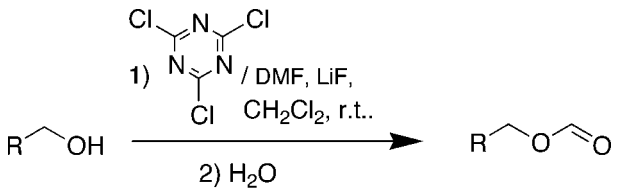
Introduction

During the multistep synthesis of natural products, the efficiency of the synthetic protocol employed often depends largely on protection and deprotection of the functional groups involved. To this end, protecting groups have played a crucial role during the synthesis of complex natural products. Among the various protecting groups used for hydroxyl function, O-formylation of alcohols is one of the most useful and versatile reactions in protective organic chemistry.[1] As a rule, formate protection is removed using $KHCO_3$ in aqueous methanol, thereby enabling selective deprotection even in the presence of other ester groups.

Various formylating reagents have been previously reported as mixed anhydride methodologies (formic acid/DCC,[2] acetic formic/anhydride,[3] formic acid/EDAC,[4] etc.). However, there are serious limitations for the preparation of formate esters due to the harsh experimental conditions, the use sometimes of uncommon reagents, formation of undesirable or toxic byproducts,[5] use of expensive procedures for preparation of formylating agents,[6] together with hygroscopicity and thermal instability of the reagents.

As the majority of formylating reagents are very reactive, selectivity in formylation between primary and secondary alcohol is generally lost and both groups are formylated under the reaction condition. Surprisingly, an accurate search of literature procedures revealed that to date no efficient formylating method exists able to protect the alcoholic groups in a selective manner. As part of an ongoing program directed to the development of efficient reagents to use in mild condition and following our late interest in the use of 1, 3, 5-triazine derivatives in organic synthesis,[7] we report a very mild and selective procedure for the quantitative conversion of alcohols into the corresponding formate.

SCHEME 1



Results and Discussion

The procedure is based on the reaction of a complex formed by 2,4,6-trichloro-1,3,5-triazine (TCT), a very inexpensive reagent, and DMF,[8] with a CH_2Cl_2 solution of 1 molar equiv of the alcohol, in the presence of 4 molar equiv of LiF (Scheme 1).

The complex is easily prepared by dissolving the TCT in the least volume of commercial DMF, followed by the addition of CH_2Cl_2 and LiF, after disappearance of free TCT (TLC monitoring). The mixture is kept overnight under stirring, and then 1 molar equiv of the alcohol is added at room temperature to give the corresponding formate ester, which can be recovered chemically pure in quantitative yields and high conversions (Table 1). The triazine byproducts are easily removed by a simple aqueous workup. The reaction is generally fast and requires from 15 to 30 min for completion in most of the cases. Moreover, this method can be also successfully applied on a large scale.

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TABLE 1. Conversion of Alcohols into Formate Esters

entry	alcohol	product	reaction time	conv. (%)
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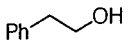
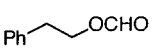
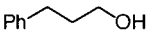
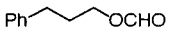
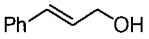
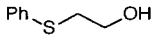
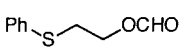
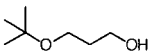
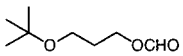
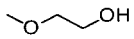
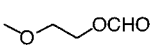
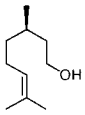
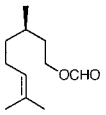
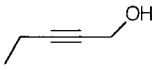
2			15 min	100
3			15 min	100
4		none	4 h	-----
5		none	4 h	-----
6			15 min	80
7			15 min	85
8			15 min	91
9			15 min	92
10		none	4 h	-----
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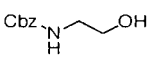
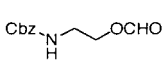
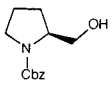
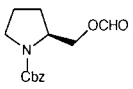
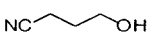
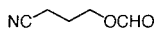
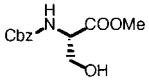
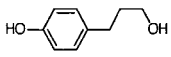
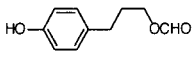
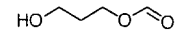
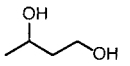
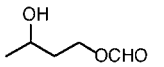
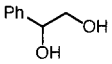
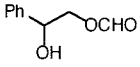
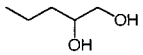
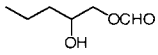
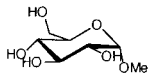
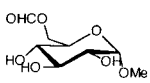
13			30 min	83
14			30 min	93
15			15 min	76
16			15 min	98
17		none	4 h	-----
18	Ph-OH	none	4 h	-----

The reaction is highly selective, as secondary and tertiary carbinols do not react even after long reaction times. Surprisingly, benzylic, allylic, and propargylic alcohols and phenols do not react even after long time and can be recovered quantitatively unreacted from the reaction mixtures.

TABLE 2. Conversion of Alcohols or Polyols into Formate Esters

entry	alcohol	product	reaction time	conv. (%)
19			15 min	94
20			15 min	90[a]
21			15 min	85
22			15 min	67
23			15 min	88
24			30 min	98
25			30 min	92
26			3 h	90[b]

[a] One equivalent of TCT was used. [b] TBAF was added.

Moreover, the reaction is applicable for the synthesis of N-protected β-amino formate esters, with the exception of *N*-Cbz serine methyl ester (Table 1, run 17).[9] Under the usual conditions, N-protected β-amino alcohols are in fact converted to the corresponding *O*-formates, with a slightly reduced rate (Table 1). However, the reaction is complete within 30 min. The same method can be successfully applied for the preparation the *O*-hydroxyformyloximes (e.g., Table 1, run 16).

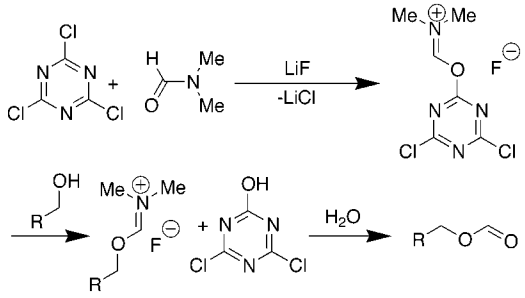
These experimental data suggested a possible use of this reaction as a very selective method for formylation of primary alcohols in the presence of secondary ones.

Thus, the procedure was applied to a series of polyols: the results reported are listed in Table 2. As is seen, monoformylation occurs in any case. The reaction conducted with 1,3-propanediol and 1 equiv of TCT (Table 2, run 20) gave formic acid 3-hydroxypropyl ester as the only product recovered, without any contamination of the diformyl derivative. Most interestingly, the treatment of polyols containing both primary and secondary hydroxyl groups with TCT /DMF complex, in the presence of LiF, furnished quantitatively alcohols with the sole primary hydroxyl group formylated. The same results were obtained using even a 4-fold excess of the reagent.

The data collected confirmed the high selectivity of the method, as only formylation of primary hydroxyl groups occurred leaving the secondary alcohols unchanged. Another example of the extreme selectivity was observed in the formylation of a methyl glucoside (Table 2, run

(9) Steric strains may not allow the formation of the intermediate reagent.

SCHEME 2



24): only the primary function was protected, leaving the other hydroxyl groups unchanged.

Another characteristic feature of the present formylation reagent is the possibility to quantitatively convert *O*-*tert*-butyldimethylsilylated alcohols in one step to their corresponding formates.[10] Thus, the removal of silicon protective groups can occur under extremely mild and highly selective conditions using fluoride ions that are compatible with most functional groups. Such an exchange of alcohol protecting groups without any intermediate deprotection is of great importance in multistep synthesis.

On the basis of our previous considerations on the mechanism of this kind of reactions, it is possible to suppose that even in this case a Vilsmeier−Haack-type complex should be formed, containing the triazine moiety.[11] The addition of LiF should prevent the formation of the alkyl chloride[7h,12] and allow the attack of the hydroxyl group of the alcohol to form an imminium intermediate salt. Subsequent hydrolysis should form the formate ester (Scheme 2). However, this simplified mechanism is not able to explain how the types of hydroxyl groups can play a different role so determining the high selectivity of the reaction.

In conclusion, the procedure reported here is operationally simple and allow a rapid, high-yielding, and selective formylation of primary alcohols under very mild conditions using inexpensive and readily available starting materials. Moreover, it seems to provide a convenient method for the conversion of *O*-TBDMS alcohols to their formate esters in one step.[13]

Experimental Section

The N-protected amino acids were prepared according standard methods, and their purities were established before utilization by melting point and optical rotation. The N-protected β-amino alcohols were prepared according to literature.[14] Cyanuric chloride was purchased from Aldrich.

All solvents and reagents were used as obtained from commercial sources. Standard ^{1}H NMR and ^{13}C NMR were recorded at 300 and 75.4 MHz, from $CDCl_3$ solutions. When possible, compounds were identified by comparison with authentic samples. All runs were conducted at least in duplicate.

Preparation of Formic Acid Phenethyl Ester (Table 1, Run 2).[15] This procedure is representative for formylation of alcohols. 2,4,6-Trichloro-1,3,5-triazine (1.0 g, 5.0 mmol) was added to DMF (2 mL), maintained at 25 °C. After the formation of a white solid, the reaction was monitored (TLC) until complete disappearance of TCT, then CH_2Cl_2 (25 mL) was added, followed by LiF (0.52 g, 20.0 mmol). After the mixture was stirred overnight at room temperature, the alcohol (0.68 g, 5.0 mmol) was added, and the mixture was monitored (TLC) until completion (15−30 min). Water was added, and then the organic phase was washed three times with 3 N HCl, followed by a saturated solution of Na_2CO_3 and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo to yield formic acid phenethyl ester that was isolated without other purifications (0.75 g, 99%): ^{1}H NMR δ 8.02 (1H, s), 7.32−7.21 (5H, m), 4.38 (2H, t, J = 6 Hz), 2.97 (2H, t, J = 6 Hz); ^{13}C NMR δ 160.9, 137.5, 128.8, 128.5, 64.3, 34.8.

Formic acid 3-phenylpropyl ester[16] **(Table 1, run 3):** 15 min, 99%; ^{1}H NMR δ 8.08 (1H, s), 7.30−7.17 (5H, m), 4.18 (2H, t, J = 6 Hz), 2.71 (2H, t, J = 6 Hz), 2.30−1.97 (2H, m). ^{13}C NMR δ 161.0, 138.9, 128.8, 128.3, 128.0, 68.3, 32.0, 31.6.

Formic acid 2-phenylsulfanylethyl ester (Table 1, run 6): 15 min, 80%; ^{1}H NMR δ 8.08 (1H, s), 7.39−7.19 (5H, m), 4.30 (2H, t, J = 6 Hz), 3.59 (2H, t, J = 6 Hz); ^{13}C NMR δ 160.7, 134.2, 130.4, 129.2, 127.0, 72.2, 36.0. Anal. Calcd for $C_9H_{10}O_2S$ (182.24): C, 59.32; H, 5.53; S, 17.59. Found: C, 59.32; H, 5.58, S, 17.57.

Formic acid 3-*tert*-butoxypropyl ester[17] **(Table 1, run 7):** 15 min, 85%; ^{1}H NMR δ 8.09 (1H, s), 5.08 (2H, m), 3.42−3.39 (2H, m), 1.30−1.27 (2H, m), 1.18 (3H, s); ^{13}C NMR δ 160.9, 72.9, 66.1, 61.2, 31.2, 27.5.

Formic acid 2-methoxyethyl ester (Table 1, run 8): 15 min, 91%; ^{1}H NMR δ 8.10 (1H, s), 4.33 (2H, t, J = 6 Hz), 3.63 (2H, t, J = 6 Hz), 3.41 (3H, s); ^{13}C NMR δ 160.8, 72.4, 69.9, 58.8. Anal. Calcd for $C_4H_8O_3$ (104.10): C, 46.15; H, 7.75. Found: C, 46.11; H, 7.78.

Formic acid 3,7-dimethyloct-6-enyl ester[18] **(Table 1, run 9):** 15 min, 92%; ^{1}H NMR δ 8.04 (1H, s), 5.07 (1H, t, J = 6 Hz), 4.16 (2H, t, J = 3 Hz), 2.10−1.94 (2H, m), 1.71 (3H, s), 1.67 (3H, s), 1.45−1.05 (5H, m), 0.11 (3H, d, J = 6 Hz); ^{13}C NMR δ 161.1, 131.4, 124.3, 62.3, 36.8, 35.2, 29.2, 25.6, 25.2, 19.2, 17.5.

Formic acid (6,6-dimethylbiciclo[3.1.1]hept-2-yl)methyl ester (Table 1, run 11): 15 min, 97%; ^{1}H NMR δ 8.02 (1H, s), 4.09 (2H, d, J = 9 Hz), 2.40−2.29 (2H, m), 1.95−1.82 (6H, m), 1.50−1.17 (1H, m), 1.15 (3H, s), 0.96 (3H, s); ^{13}C NMR δ 161.2, 68.2, 42.8, 41.1, 40.0, 38.4, 32.7, 27.7, 25.7, 23.1, 18.5. Anal. Calcd for $C_{11}H_{18}O_2$ (182.26): C, 72.49; H, 9.95. Found: C, 72.51; H, 9.99.

Formic acid 2-benzyloxycarbonylaminoethyl ester (Table 1, run 13): 30 min, 83%; ^{1}H NMR δ 8.08 (1H, s), 7.37 (5H, s), 5.12 (2H, s), 4.26 (2H, t, J = 6 Hz), 3.70−3.25 (3H, m); ^{13}C NMR δ 160.7, 156.4, 141.4, 132.5, 128.4, 127.9, 72.2, 66.8, 43.4. Anal. Calcd for $C_{11}H_{13}NO_4$ (223.23): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.21; H, 5.89; N, 6.25.

2-Formyloxymethylpyrrolidine-1-carboxylic acid benzyl ester (Table 1, run 14): 30 min, 93%; ^{1}H NMR δ 8.08 (1H, s), 7.38 (6H, bs), 5.15 (2H, s), 4.27 (1H, bs), 4.16 (2H, bs), 3.44 (2H, bs), 1.97−1.88 (4H, m); ^{13}C NMR δ 162.6, 160.8, 137.4, 128.7, 128.5, 128.0, 72.2, 67.24, 47.3, 46.2, 28.5, 21.8. Anal. Calcd for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.88; H, 6.52; N, 5.34.

(10) The reaction requires the addition of tetrabutylammonium fluoride (TBAF) together with LiF.

(11) In fact, TCT disappears (TLC) within a few minutes when dissolved in DMF.

(12) Similar results are obtained using TBAF or tetrabutylammonium bromide; however, in these cases the reaction rate is reduced and small amounts of alkyl chlorides are formed. On these bases, one can venture the hypothesis that precipitation of the chloride ion is responsible for the change of the course of the reaction.

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Formic acid 3-cyanopropyl ester (Table 1, run 15): 30 min, 76%; ^{1}H NMR δ 8.10 (1H, s), 4.39 (2H, t, J = 6 Hz), 3.87 (1H, t), 2.88 (1H, t, J = 3 Hz), 2.79 (2H, t, J = 3 Hz), 2.60 (1H, t, J = 3 Hz); ^{13}C NMR δ 160.2, 116.7, 72.3, 21.7, 17.8. Anal. Calcd for $C_5H_7NO_2$ (113.12): C, 53.09; H, 6.24; N, 12.38. Found: C, 53.11; H, 6.22; N, 11.40.

Cyclohexanone *O*-formyloxime (Table 1, run 16): 15 min, 98%; ^{1}HNMR δ 9.40 (1H, s), 3.79 (2H, m), 2.69 (2H, m), 1.74−1.50 (6H, m); ^{13}CNMR δ 178.0, 162.0, 43.7, 40.0, 38.1, 29.3, 29.2. Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.58; H, 7.88; N, 9.95.

Formic acid 3-(4-hydroxyphenyl)propyl ester (Table 2, run 19): 15 min, 94%; ^{1}H NMR δ 8.09 (1H, s), 7.07 (2H, m), 6.78 (2H, m), 4.81 (1H, bs), 4.15 (2H, t, J = 6 Hz), 2.72−2.61 (2H, m), 2.01−1.92 (2H, m); ^{13}C NMR δ 161.3, 153.9, 129.6, 129.4, 115.3, 63.3, 31.7, 30.2. Anal. Calcd for $C_{10}H_{12}O_3$ (180.20): C, 66.65; H, 6.71. Found: C, 66.63; H, 6.72.

Formic acid 3-hydroxypropyl ester[19] (Table 2, run 20): 15 min, 90%; ^{1}H NMR δ 8.07 (1H, s), 4.34 (2H, t, J = 6 Hz), 3.73−3.52 (2H, m), 3.50 (1H, bs), 2.22−2.09 (2H, m); ^{13}C NMR δ 160.8, 60.89, 59.2, 31.3. Anal. Calcd for $C_4H_8O_3$ (104.11): C, 6.15; H, 7.74. Found: C, 46.15; H, 7.79.

Formic acid 3-hydroxybutyl ester[20] (Table 2, run 21): 15 min, 85%; ^{1}H NMR δ 8.03 (1H, s), 5.16 (1H, bs), 4.19 (2H, m), 3.55 (1H, m), 2.15−1.91 (2H, m), 1.29 (3H, d, J = 6 Hz); ^{13}C NMR δ 160.7, 67.9, 67.2, 59.8, 40.16, 19.6. Anal. Calcd for $C_5H_{10}O_3$ (118.13): C, 50.84; H, 8.53. Found: C, 50.82; H, 8.50.

Formic acid 2-hydroxy-2-phenylethyl ester[21] (Table 2, run 22): 15 min, 67%; ^{1}H NMR δ 8.02 (1H, s), 7.36 (5H, m), 4.97 (1H, td, J_1 = 6 Hz, J_2 = 2 Hz), 4.84 (2H, dd, J_1 = 6 Hz, J_2 = 2 Hz), 2.21 (1H, bs); ^{13}C NMR δ 161.0, 140.5, 128.8, 127.4, 126.7, 74.6, 72.0.[22] Anal. Calcd for $C_9H_{10}O_3$ (166.18): C, 65.06; H, 6.07. Found: C, 65.08; H, 6.09.

Formic acid 3-hydroxypentyl ester (Table 2, run 23): 15 min, 88%; ^{1}H NMR δ 8.10 (1H, m), 5.22 (1H, bs), 4.33−4.06 (2H, m), 3.34 (1H, m), 1.65−1.35 (4H, m), 0.95 (3H, m); ^{13}C NMR δ 160.5, 76.5, 70.7, 32.5, 18.5, 13.8.[23] Anal. Calcd for $C_6H_{12}O_3$ (13216): C, 54.53; H, 9.15. Found: C, 54.50; H, 9.16.

Formic acid 3,4,5-trihydroxy-6-methoxytetrahydropyran-2-ylmethyl ester (Table 2, run 24): 15 min, 92%; ^{1}H NMR δ 8.10 (1H, s), 4.99 (m, 1H), 4.29 (2H, m), 4.19 (1H, m), 3.75 (1H, m), 3.6 (2H, m), 3.43 (3H, s), 2.3 (3H, m); ^{13}C NMR δ 160.9, 96.5, 72.4, 68.8, 67.2, 66.7, 62.2, 55.5. Anal. Calcd for $C_8H_{14}O_7$ (222.19): C, 43.24; H, 6.35. Found: C, 43.22; H, 6.37.

Formic acid 3-benzyloxycarbonylamino-2-hydroxypropyl ester (Table 2, run 25): 30 min, 92%; ^{1}HNMR δ 8.07 (1H, s), 7.35 (5H, m), 5.11 (2H, s), 5.01 (1H, bs), 4.44−4.39 (3H, m), 4.0 (1H, bs), 3.55−3.44 (2H, m); ^{13}CNMR δ 160.8, 156.4, 141.3, 128.5, 128.1, 126.0, 69.9, 68.8, 65.0, 40.9. Anal. Calcd for $C_{12}H_{15}NO_5$ (253.25): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.89; H, 5.96; N, 5.54.

Formylation of Di-*tert*-butylmethylphenethyloxysilane (Table 2, Run 26). 2,4,6-Trichloro-1,3,5-triazine (0.5 g, 2.7 mmol) was added to DMF (1 mL), maintained at 25 °C. After formation of a white solid, the reaction was monitored (TLC) until complete disappearance of TCT, and CH_2Cl_2 was added, followed by LiF (0.26 g, 10.0 mmol). To the mixture, stirred overnight at room temperature, was added a solution of the silyl protected alcohol (0,59 g, 2.5 mmol) and tetrabutylammonium fluoride (0.80 g, 2.5 mmol). The reaction, monitored by TLC, was continued to complete disappearance of starting materials (3 h). Water was added, and then the organic phase was washed with 3 N HCl and subsequently with a saturated solution of Na_2CO_3 and brine. The organic layer was dried over Na_2SO_4 and the solvent concentrated in vacuo to yield formic acid phenethyl ester,[13] which was isolated without other purifications (0.30 g, 80%).

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(22) The isomeric formic acid 2-hydroxy-1-phenylethyl ester has ^{1}H NMR δ 7.92 (1H, s), 7.30 (5H, m), 5.35 (s, 1H), 4.80 (1H, m), 4.25 (1H, t), 3.65 (1H, t) (Santaniello, E.; Farachi, C.; Manzocchi, A. *Synthesis* **1979**, 912).

(23) The isomeric formic acid 1-hydroxymethylbutyl ester has ^{1}H NMR δ 8.18 (1H, m), 4.68 (1H, bs), 4.40−4.38 (1H, m), 3.91−3.69 (2H, m), 1.80−1.66 (2H, m), 1.51 (2H, m), 1.04 (3H, t); ^{13}C NMR δ 160.6, 77.9, 65.1, 32.1, 18.7, 13.5.