General Method for the Formylation of Alcohols with Dimethylformamide: An Extension of the Vilsmeier-Haack Reaction

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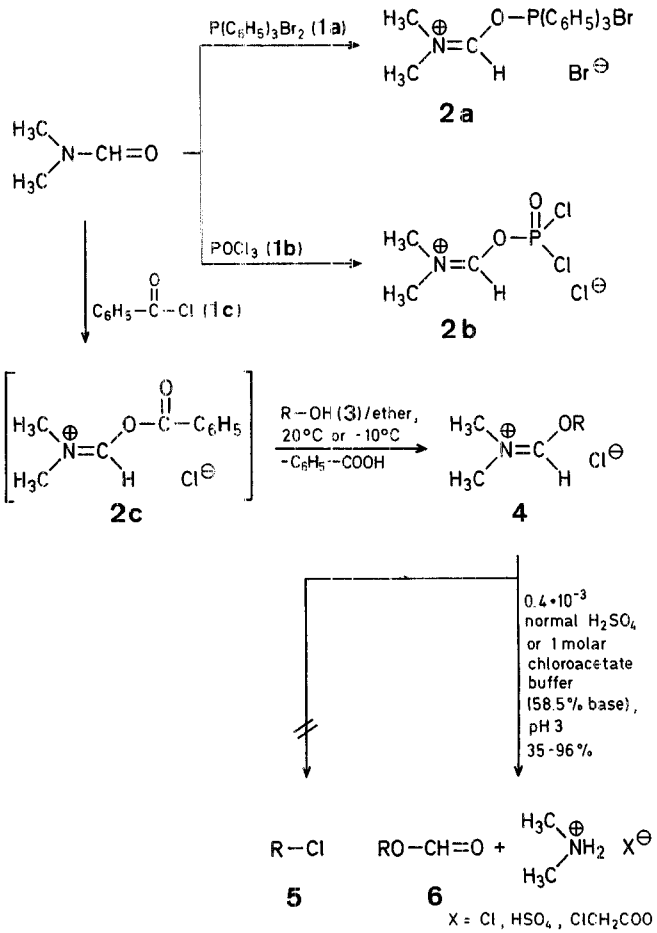
Vilsmeier-Haack reagents are widely used for the formylation of nucleophilic substrates such as amines or activated C=C double bonds[1]. However, these adducts react with alcohols to afford alkyl halides, except in a few and particular instances in which the expected formic acid esters are obtained[2,3,4]. The formyl group has found application as a protective group for alcohols, but suffers from the limitation that it can only be introduced under rather drastic conditions, i.e. heating the alcohol at 50–60°C in 80% formic acid or by reaction with the less common acetic-formic anhydride[5], or with *N,N*-diformylacetamide[6].

On these grounds we felt that it would be of interest to explore the reaction of different Vilsmeier-Haack adducts with alcohols in order to find a suitable and general method to synthesize formic acid esters under mild conditions.

Vilsmeier-Haack adducts **2** derived from dimethylformamide and triphenylphosphine dibromide (**1a**), phosphoryl chloride (**1b**), and benzoyl chloride (**1c**) were assayed in the formylation of alcohols. Adducts **2a** and **2b** were found to be ineffective. The adduct **2a** gives high yields of alkyl bromides except when reacted with sterically hindered alcohols such as **3a**, and **3b**. On other hand, the reaction of **2b** with phenols, which cannot give substitution reactions, has been reported to afford the corresponding aryl formates **6** in good yields[4]. On the other hand, we found that this process when applied to alcohols gives very poor results.

We have now discovered that the reaction of the adduct benzoyl chloride-dimethylformamide (**2c**), generated *in situ*, with the stoichiometric amount of a wide variety of alcohols in ether solution at room temperature, gives rise to the formation of the corresponding imidate ester chlorides **4** in good yields (Table 1).

By contrast with other imidate ester salts **4** derived from different acid halides, those obtained from benzoyl chloride were found to be stable and, in some cases, crystalline compounds that precipitate from the reaction medium. The low nucleophilic character of the chloride anion and the basicity of the benzoate anion avoid the decomposition of **4** to the alkyl chloride **5**. The formation of **4** when derived from allylic or benzylic alcohols must be done below room temperature (−10°C) due to the easy S_N1 substitution reaction to afford **5**. Yields in compounds **4** are greatly enhanced upon addition of sodium carbonate when tertiary alcohols are involved.



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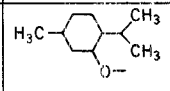
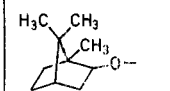
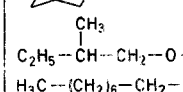
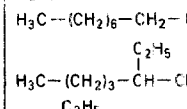
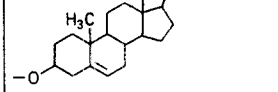
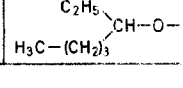
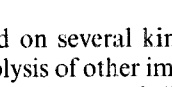
a		g	
b		h	
c		i	
d		j	
e		k	
f			

Based on several kinetic reports on the mechanism of the solvolysis of other imidate salts and related compounds[7], we selected the use of slightly acidic conditions to perform the hydrolysis of compounds **4** to obtain the corresponding formic acid esters **6**. Thus, imidate salts **4** were treated with 0.4×10^{-3} normal sulfuric acid or 1 molar chloroacetate buffer (58.5% base) at 0° to 5°C. In this way, formic acid esters **6** derived from primary, secondary, allylic, and benzylic alcohols were obtained in uniformly good yields (Table 2).

Table 1. Imidate Ester Salts **4a–h** Isolated

4	Yield[a] [%]	Molecular Formula[b]	^{13}C-N.M.R. (CCl_4/TMS)[c] δ [ppm]
a	71	$C_{13}H_{26}ClNO$ (247.8)	33.8 (q), 39.7 (q), 86.7 (d), 165.1 (d)
b	75	$C_{13}H_{24}ClNO$ (245.8)	33.7 (q), 39.5 (q), 93.02 (d), 166.1 (d)
c	65	$C_8H_{18}ClNO$ (179.7)	34.3 (q), 39.3 (q), 77.5 (t), 166.0 (d)
d	67	$C_{11}H_{24}ClNO$ (221.8)	34.3 (q), 39.5 (q), 76.8 (t), 166.2 (d)
e	69	$C_{11}H_{22}ClNO$ (219.8)	34.3 (q), 39.2 (q), 78.5 (t), 165.9 (d)[d]
f	69	$C_{10}H_{22}ClNO$ (207.7)	33.8 (q), 39.3 (q), 91.6 (d), 166.4 (d)
g	50	$C_9H_{18}ClNO$ (193.7)	34.1 (q), 39.4 (q), 86.2 (d), 165.5 (d)
h[e]	59	$C_9H_{18}ClNO_2$ (209.7)	34.6 (q), 39.8 (q), 86.3 and 91.2 (2d); 165.9 and 166.1 (2d)[f]

[a] Yields are given relative to starting alcohol.
[b] Microanalyses could not be carried out due to the instability of the imidate ester salts towards air.
[c] Only data for carbon and hydrogen atoms in position α-to the formyl group functionality and those of the N—CH_3 group are given.
[d] ^{1}H-N.M.R. (CCl_4/TMS): δ = 3.2 (s, 3H); 3.4 (s, 3H); 4.7 (d, 2H, J = 9 Hz); 9.8 ppm (s, 1H)[c].
[e] *cis*/*trans*-mixture, only one hydroxy group has reacted.
[f] ^{1}H-N.M.R. (CCl_4): δ = 3.2 (s, 3H); 3.5 (s, 3H); 4.3 and 5.2 (2m, 1H each); 8.8 (br. s, 2H); 9.5 ppm (br. s, 1H)[c].

Imidate salts **4** derived from tertiary alcohols, undergo cleavage of the C—O bond in the hydrolysis due to stereoelectronic factors[8] and, hence, lead to the recovery of the starting materials.

The generality, mildness of the reaction conditions and the availability of all reagents used, make of our method an advantageous one for the formylation of a wide variety of alcohols.

Preparation of the Imidate Ester Salt 4 g; General Procedure:
To a stirred solution of benzoyl chloride (5.62 g, 40 mmol) in dry ether (25 ml), a mixture of dry dimethylformamide (2.92 g, 40 mmol) and cyclohexanol (4.01 g, 40 mmol) is added at 20 °C under an argon atmosphere. After stirring for 14 h, the mixture is cooled to − 15 °C. The solid is filtered at low temperature, washed with dry ether, dried under reduced pressure and characterized (Table 1).

Formylation of Alcohols; Typical Procedures:

Preparation of 2-Ethylhexyl Formate **(6e)**:
Method A: To a stirred solution of benzoyl chloride (5.62 g, 40 mmol) in dry ether (25 ml), a mixture of dry dimethylformamide (2.92 g, 40 mmol) and 2-ethyl-1-hexanol (5.21 g, 40 mmol) is added, at 20 °C under argon. The solution is maintained with stirring overnight, poured into $0.4 \cdot 10^{-3}$ normal sulfuric acid (80 ml) with vigorous shaking and then treated with solid sodium carbonate (4.24 g, 40 mmol) to dissolve the benzoic acid precipitated. The mixture is extracted with ether (3 × 50 ml), and the organic layer is dried with anhydrous sodium sulfate. The solvent is removed under vacuum and the liquid residue is distilled under reduced pressure to afford **6e**; yield: 2.46 g (39%).

Method B: To a stirred solution of benzoyl chloride (5.62 g, 40 mmol) in dry ether (25 ml), a mixture of dry dimethylformamide (2.92 g, 40 mmol), 2-ethyl-1-hexanol (5.21 g, 40 mmol), and sodium

Table 2. Formate Esters **6a–k** prepared[a]

6	Method	Reaction time [h]/ Temp. [°C]	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. data	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm] CH—O/CH_2—O	CH=O	13C-N.M.R. (CCl_4/TMS) δ [ppm] CH—O/CH=O	CH_2—O
a	A	14/20°	96[c]	45–60°/0.01	$C_{11}H_{20}O_2$ (184.3)	4.6 (m, 1H)	7.9 (s)	74.3 (d)	161.1 (d)
b	A	14/20°	91[c]	50–70°/0.01	$C_{11}H_{18}O_2$ (182.3)	5.2 (t, J = 9 Hz, 1H)	8.2 (s)	77.3 (d)	160.6 (d)
c	A	14/20°	85[c]	40–50°/0.01	$C_6H_{12}O_2$ (140.2)	4.1 (d, J = 5 Hz, 2H)	8.1 (s)	62.5 (t)	161.2 (d)
d	A	14/20°	86[c]	198°/760	b.p. 198.8°/760[9]	4.1 (t, J = 6 Hz, 2H)	8.0 (s)	64.6 (t)	161.5 (d)
	B	14/20°	50[d]						
e	A	14/20°	57[c]	45–60°/0.01	$C_9H_{18}O_2$ (158.2)	4.2 (d, J = 5 Hz, 2H)	8.1 (s)	62.2 (t)	157.6 (d)
	B	14/20°	49[d]						
f	A	14/20°	56[c]	35–50°/0.01	$C_8H_{16}O_2$ (144.2)	4.8 (m, 1H)	8.0 (s)	75.7 (d)	161.3 (d)
	B	5/20°	41[d]						
g	B	5/20°	35[d]	160°/760	162.5°/760[10]	4.7 (m, 1H)	7.9 (s)	72.3 (d)	161.3 (d)
h[e]	A	14/40°	96[c]	47–60°/0.01	$C_7H_{12}O_3$ (144.2)	3.5, 3.9 (2m, 1H)	8.1 (br. s)	68.6, 71.3 (2d)	161.2 and
						4.7, 5.1 (2m, 1H)		74.5, 77.1 (2d)	161.3 (2d)
i	A	1/−10°	68[d]	85–100°/0.01	203°/760[11]	5.4 (s, 2H)[f]	8.4 (s)	–	–
j	A	1/−15°	61[d]	56–80°/0.01	$C_8H_{14}O_2$ (142.2)	4.7 (d, J = 6 Hz, 2H)[g]	8.3 (s)	–	
k	A[h]	6/20°	60[d]	m.p. 112°	$C_{28}H_{47}O_2$ (415.8)	5.3 (m, 1H)[i]	8.3 (s)	71.5 (d)[j]	160.9 (d)

[a] All compounds displayed a characteristic absorption at ~1760 cm^{-1} in the I.R.
[b] Satisfactory microanalyses obtained: C ± 0.22, H ± 0.20.
[c] Yields are reported relative to **4**.
[d] Yields are relative to starting alcohol.
[e] *cis*/*trans*-mixture, only one OH group has reacted.
[f] Additional peak at δ = 7.7 ppm (m, $5H_{arom}$).
[g] Additional peak at δ = 6.1 ppm (m, 2H, CH=CH).
[h] A 2:2:1 ratio of benzoyl chloride: dimethylformamide: cholesterol was used and the product purified by column chromatography on silica using toluene as eluent.
[i] Additional peaks for identification at δ = 2.8 (d, 2H, J = 6 Hz, =C—CH_2) and 5.9 ppm (m, 1H, =CH)
[j] Additional peaks for identification at δ = 32.4 (t), 43.3 (t), 121.3 (d) and 141.6 ppm (s).

carbonate (4.24 g, 40 mmol) is added, under argon at 20°C. When bubbling has ceased, the reaction mixture is poured into 1 molar chloroacetate buffer (58.5% base pH = 3; 80 ml) with vigorous shaking. The resulting mixture is extracted with ether (3 × 50 ml) and the organic layer dried with anhydrous sodium sulfate. The solvent is removed under vacuum and the residue distilled under reduced pressure to afford **6e**; yield: 3.02 (49%) (Table 2).

An alternative purification method useful for high boiling formates is the column chromatography of the residue on silica gel (eluent: toluene). Compound **6** is eluted first.

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