Rapid and Selective Formylation With Pentafluorophenyl Formate

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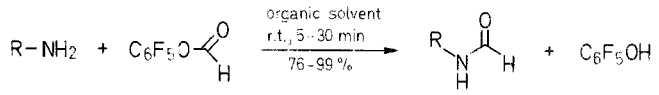
Pentafluorophenyl formate reacts smoothly with *N*-nucleophiles under mild conditions to give the *N*-formyl derivatives, whereas *O*- and *S*-nucleophiles remain unaffected even in the presence of a tertiary base.

The most widely used formylating agent, acetic formic anhydride[1] may cause undesirable side reactions, especially in the presence of acid-sensitive groups.[2] In recent years, more efficient formylation procedures have been proposed to enhance the selectivitly of the reaction.[3–7] We now report a rapid and selective formylation procedure using pentafluorophenyl formate (**2**). The reagent can easily be prepared, it is relatively stable, and it reacts with *N*-nucleophiles within minutes at room temperature to give the *N*-formyl derivatives **3**. No reaction takes place with alcohols, mercaptans, and sterically hindered amines.



1 2 3

Pentafluorophenyl Formate (2):
To a stirred solution of pentafluorophenol (1.84 g, 10 mmol) in chloroform (15 ml) at 0 °C, 98% formic acid (0.444 ml, 12 mmol) and dicyclohexylcarbodiimide (2.47 g, 12 mmol) are added and stirring at 0 °C is continued for 90 min. The precipitated dicyclohexylurea is then filtered off, the filtrate is evaporated to dryness, and the residue is dissolved in ether (50 ml). This solution is washed with 5% sodium hydrogen carbonate solution (15 ml) and with water (15 ml), dried with magnesium sulfate, and evaporated to constant weight to give reagent **2** as a colorless oil; yield: 1.59 g (75%); d^{20}: 1.67 g/ml; n_D^{25}: 1.4240; IR (KBr): ν_{CO} = 1760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ = 8.23 ppm; UV: λ_{max} = 258, ε 1150 (ethanol); purity: 95–99% (as determined by perchloric acid titration after reaction with morpholine in acetonitrile at room temperature for 1 h); stability: slow decomposition is observed (10%/week at +4 °C and 25%/week at r.t.) but this does not affect the applicability of the reagent.

***N*-Formylation of Primary Amines with Reagent 2; General Procedure:**
Pentafluorophenyl formate (**2**; 10 mmol) is added to a stirred solution of the amine (**1**; 5 mmol) in an organic solvent (see Table) at room temperature. The formylation can be monitored by TLC. Generally, the reaction is completed within 5–30 min. The excess of the reagent can be removed either (a) by trituration of the residue obtained after evaporation of the solution with ether (20 ml), or (b) by adding *N,N*-dimethyl-1,2-ethanediamine (dimethylaminoethylamine[8]) (10 mmol) to the solution followed by extraction with 1 normal hydrochloric acid (25 ml), 5% sodium hydrogen carbonate solution (10 ml), and water (10 ml). The solution is dried with sodium sulfate and evaporated. Purification of the remaining *N*-formyl derivative **3** can be carried out by recrystallization from ether/hexane or by trituration with hexane.

One-Pot *N*-Formylation Procedure including Preparation of Reagent 2:
N-(CHO)-Lys(Z)-ε Ahx-OCH$_3$: To a stirred solution of pentafluorophenol (1.84 g, 10 mmol) in ether (20 ml) at 0 °C, 98% formic acid (0.444 ml, 12 mmol) and dicyclohexylcarbodiimide (2.06 g, 10 mmol) are added, followed after 10 min by the addition of a solution of H-Lys(Z)-ε Ahx-OCH$_3$ · HCl (2.22 g, 5 mmol) and triethylamine (0.7 ml, 5 mmol) in chloroform (20 ml). Stirring is continued for 2 h at room temperature, and the mixture then diluted with chloroform (40 ml). *N,N*-Dimethyl-1,2-ethanediamine (88 g, 10 mmol) is added and the mixture extracted with 1 normal hydrochloric acid (40 ml), 5% sodium hydrogen carbonate solution (40 ml), and water (40 ml). The solution is dried with sodium sulfate and evaporated, and the remaining *N*-formyl derivative recrystallized from chloroform/hexane; yield: 2.1 g (97%); m.p. 107–109 °C.

$C_{22}H_{33}N_3O_6$ (439.7) calc. C 61.04 H 7.56 N 9.57
found 60.92 7.65 9.56

IR (KBr): ν = 3300 (NH); 1735 (CO); 1690 (CO); 1665 (CO); 1180 (C–O–C); 740, 703 cm^{-1} (Ar).

^{1}H-NMR ($CDCl_3$/TMS_{int}): 1–2 (m, 12 H, CH_2); 2.3 (t, 2 H, CH_2); 3.2 (m, 4 H, CH_2); 3.71 (s, 3 H, CH_3); 4.55 (m, 1 H, CH); 5.1 (s, 2 H, CH_2); 5.45 (t, 1 H, NH); 7.2 (m, 2 H, NH); 7.4 (s, 5 H, Ar); 8.18 ppm (s, 1 H, HCO).

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Table. *N*-Formylamines **3** Prepared from Primary Amines **1** and (Isolated) Pentafluorophenyl Formate **2**

Amine **1**	Solvent	Yield[a] (%)	m.p. (°C) (solvent)		R_f
			found	reported	
hexadecanamine	$CHCl_3$	86	43–44	–	0.7[c], 0.3[b]
aniline	$CHCl_3$	90	48 (ether/hexane)	50[9]	0.6[b], 0.6[c]
4-methylaniline	$CHCl_3$	96	55–57	53[10]	0.6[c], 0.5[e]
2-aminobiphenyl	$CHCl_3$	99	67–70	75[11]	0.6[c], 0.7[b]
2-aminonaphthalene	$CHCl_3$	94	120–130	128[12]	0.6[b], 0.6[c]
benzylamine	$CHCl_3$	90	62–63	60–61[13]	0.35[c], 0.55[e]
(–)-ephedrine	$CHCl_3$	85[d]	oil	–	0.6[c], 0.3[b]
H-Thr-OBzl	$CHCl_3$	92	89–90	84–85[14]	0.7[c], 0.7[e]
H-Val-OC_4H_9-*t*	$CHCl_3$	93	68–71	63–64[14]	0.7[b], 0.7[c]
H-Lys(Z)-εAhx-OCH_3	$CHCl_3$	99	106–107 ($CHCl_3$/hexane)		0.15[b], 0.4[c]
H-Met-Leu-Phe-OCH_3	$CHCl_3$	93	135–136	151–155[15]	0.4[b], 0.5[c]

[a] Yield of isolated chromatographically homogeneous products.
[b] Ethyl acetate.
[c] Chloroform/methanol, 9 : 1.
[d] Purified by preparative TLC.
[e] Benzene/methanol/acetic acid, 7 : 2 : 1.
[f] Chloroform/methanol, 3 : 1.
[g] Ethyl acetate: (pyridine/acetic acid/water, 20 : 6 : 11) = 4 : 1.