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A CONVENIENT PROCEDURE FOR THE FORMYLATION OF AMINES AND ALCOHOLS USING CYANOMETHYL FORMATE

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Abstract: A simple method for the direct formylation of amines using cyanomethyl formate is described. The formylation succeeds in moderate to high yields under mild and neutral conditions. Thus, formamides **2a-f, 2i-m** are obtained at room temperature. A chemoselective N-formylation is achieved in the case of ethanolamine. The formylation of nitroanilines and the O-formylation of alcohols only succeeds in the presence of a catalytic amount of imidazole leading to **2g,h** and **3a-e**, respectively.

One of the most useful and versatile functional groups to be introduced is the formyl group. A number of formylating methods and formylating agents have been reported (cf. ref.[1,2]).

Formyl compounds have been widely used for the protection of amino and hydroxy groups.[3] Formamides are useful as starting material in the preparation of isocyanides[4] or in aminations and ring transformations of benzofurazan derivati-

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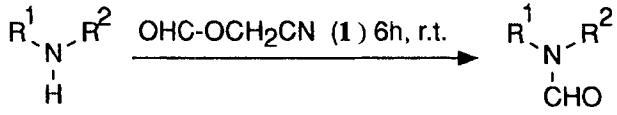
ves.[5,6] Furthermore, formamides have been used to prepare biologically active compounds.[4] Typical N- and O-formylating agents are formic acid, some formic acid esters, formic anhydride and mixed anhydrides of formic acid, formyl halides, and N-formyl derivatives.[1,2] Recently, a procedure for the N-formylation of secondary amines using chlorotrimethylsilane and imidazole was reported.[7] The chemoselective formylation of primary amines in the presence of alcohols or secondary amines succeeds with N-(diethylcarbamoyl)-N-methoxyformamide.[8] Moreover, enol formates are used as formylating reagents.[4]

Despite the usefulness of the agents mentioned above there are several factors limiting their application, for example thermal instability, formation of undesirable or toxic by-products, difficult accessibility or the application of expensive catalysts for the preparation of formylating reagents.[4]

We report here the use of cyanomethyl formate **1** for N- and O-formylations. Surprisingly, up to now the easily accessible and rather stable compound **1** has not been used as formylating agent.

Reagent **1** was prepared by treatment of chloroacetonitrile with potassium formate in sulfolane at 100°C for 4 h (modified according to ref.[9]). **1** can be used for the N-formylation of primary and secondary amines.



2a-f, 2i-m

Aliphatic and aromatic amines (with exception of nitroanilines) gave an exothermic reaction. Yields of purified formamides **2a-f, 2i-m** are in the range from

Table 1: N-Formylation of primary and secondary amines

2	R^1	R^2	Yld.[a] (%)	m.p. or b.p./torr (°C)	Lit. data (°C)
a	$n\text{-}C_8H_{17}$	H	78	149-151/4	289-291[11]
b	$C_6H_5CH_2$	H	66	58-60	60-61[10]
c	C_6H_5	H	69	133-137/2	166/14[12]
d	$2\text{-}CH_3C_6H_4$	H	60	57-59	60-61[13]
e	$4\text{-}CH_3OC_6H_4$	H	76	79-81	80-81[14]
f	$3\text{-Cl,4-F-}C_6H_3$	H	70	95-96	94-97[15]
g	$3\text{-}NO_2\text{-}C_6H_4$	H	69	133-135	134[16]
h	$4\text{-}NO_2\text{-}C_6H_4$	H	60	197-199	194-196[10]
i	$c\text{-}C_6H_{11}$	H	75	148-151/17	135-137/10[17]
k	$HO\text{-}CH_2CH_2$	H	78	130/0.5	145-148/0.5[18]
l	$4\text{-}CH_3OC_6H_4$	CH_3	69	108-120/0.6-0.8	117-118/1.2[19]
m	$n\text{-}C_6H_{13}$	$n\text{-}C_6H_{13}$	81	125-127/1	[b]

[a] **2a, 2i-m**, purity (% GC): 93-99%. [b] IR (film), νCO: 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ: 0.79-1.46 (m,22H), 3.09-3.50 (m, 4H), 7.97 (s, 1H); MS (m/e, rel. intensity): 213 (M^+, 4), 142 (100).

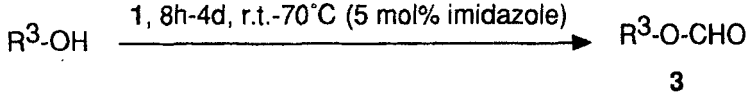
60 to 81%. Nitroanilines are formylated in the presence of imidazole (cf. ref.[10]) at 75°C furnishing **2g,h** in 60 to 69% yield. Ethanolamine gave only the N-formylated product **2k** (Table 1). The formylation of imides such as phthalimide cannot be realized under these reaction conditions.

The O-formylation of primary and secondary alcohols succeeds only in the presence of a catalytic amount of imidazole. Alkyl formates **3** are formed in up to 93% yield (Table 2). The formylation of primary and secondary alcohols is

Table 2: O-Formylation of primary and secondary alcohols

3	R^3	Time (d)	Yld. (%)	b.p. (°C)	Purity (%GC)	Lit. data (°C)
a	C_2H_5	1	93	54	94	54.5[20]
b	n-C_4H_9	1	88	104-106	95	106.5[21]
c	$CH(CH_3)_2$	1	65	65-68	89	67.5-68[21]
		4	62	66-69	94	
d	$CH(CH_3)CH_2$-CH_2CH_3	2	73	117-119	87	115.5[22]
		8h	65	117-120	90	
e	c-C_5H_9	2	79	138-139	91	138[23]
		8h	69	137-139	96	

carried out at ambient temperature within 1 to 4 days or at 70°C within a few hours. The rate of formylation of t-butanol at 75°C after 20h is only 50%.



Experimental

Amines and alcohols used as starting materials are commercially available. The microanalyses of formylated products **2b-h** were in good agreement with the calculated values: C ± 0.16, H ± 0.03, N ± 0.12 . The purity of compounds **2a**, **2i-m**, and **3a-e** was determined by GC. GC analyses were performed with capillary columns (compounds **2:** 0.1% Oxydwachs H 6000 Buna, 26m, 0.2 mm diame-

ter; compounds **3**: Stabilwax-DB, 30m, 0.25 mm diameter). Yields are referred to pure (recrystallyzed or distilled) substances. The compounds obtained were characterized by ^{1}H-NMR, ^{13}C-NMR, and IR spectra. All procedures were carried out under a dry atmosphere (drying tubes).

Cyanomethyl formate **1**

(modified according to ref.[9])

Potassium formate (16.8 g, 0.2 mol) is suspended in anhydrous sulfolane (30 ml) at 30°C. To this suspension chloroacetonitrile (15.1 g, 0.2 mol) and potassium iodide (1.0 g, 0.006 mol) are added. The stirred reaction mixture is then heated to 100°C for 4 h, cooled to room temperature, the potassium chloride formed is filtered off and washed thoroughly several times with dichloromethane. After removing of dichloromethane the combined filtrates are fractionally distilled in vacuo. B.p.: 60-66°C/12 torr. Furthermore, 85% of sulfolane may be recovered. For further purification, compound **1** is distilled using a Vigreux column. Yield: 12.9 g (76%); b.p.: 62-64°C/12 torr (Lit. data[9]:172-173°C). ^{13}C-NMR ($CDCl_3$), δ: 47.87, 114.47, 159.46 ppm.

Benzylformamide **2b**

(Typical procedure)

A solution of benzylamine (16.1 g, 0.15 mol) in anhydrous dichloromethane (25 ml) is added dropwise under vigorous stirring and cooling with ice to cyanomethyl formate (12.8 g, 0.15 mol). The reaction temperature is kept between 15 and 20°C. After standing for 6 h at ambient temperature, the solvent is evaporated and the resulting residue is allowed to stand at 0°C overnight. Then 25 ml of ice-

cold water is added, the solid is thoroughly crushed, isolated by suction, washed with a little water, and dried under vacuum. Yield: 13.4 g (66%); m.p.: 58-60°C (toluene).

Compounds **2d, 2e,** and **2f** were prepared in analogous manner.

3-Nitroformanilide **2g**

A mixture of cyanomethyl formate (12.8 g, 0.15 mol), 3-nitroaniline (20.7 g, 0.15 mol), and imidazole (0.9g, 0.013 mol) in anhydrous dichloroethane (50 ml) is heated under stirring to 75°C for 12 h. Then the solvent is evaporated, the remaining residue is thoroughly washed with water, isolated by suction, and dried under vacuum. The solid is recrystallized from methanol (45 ml). Further 3-nitroformanilide may be obtained by working up the mother liquor. Yield: 17.2 g (69%); m.p. 133-135°C.

Compound **2h** is prepared analogously with the exception: reaction time 18 h, imidazole 1.8 g (0.026 mol).

Cyclohexylformamide **2i**

(Typical procedure)

Cyclohexylamine (14.9 g, 0.15 mol) is added dropwise under vigorous stirring and cooling with ice to cyanomethyl formate (12.8 g, 0.15 mol). The reaction temperature is kept at 15-20°C. After standing at room temperature for 6 h the product obtained is distilled in vacuo. Yield: 14.3 g (75%); b.p.: 148-151°C/17 torr.

Compounds **2a, 2c,** and **2k-m** were prepared as described above; synthesis of **2k**: the reaction temperature is kept at 0°C while the amine is added.

n-Butyl formate **3b**

(Typical procedure)

A mixture of cyanomethyl formate (14.0 g, 0.165 mol), n-butanol (11.1 g, 0.15 mol), and imidazole (0.5 g, 0.0075 mol) is vigorously stirred at room temperature for 2 h. The reaction mixture is allowed to stand at ambient temperature for 22 h and fractionated. Yield: 13.5 g (88%); b.p. 104-106°C.

Compounds **3a** and **3c-e** were prepared as described above.

Acknowledgements

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