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Das Reagenz · The Reagent

Formyloxy-acetonitrile – A Reagent for Convenient *N*- and *O*-Formylations

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Formyl compounds have been widely used for the protection of amino and hydroxy groups [1]. Furthermore, formyl compounds are useful for synthetic purposes. Thus, the most common method for the synthesis of isocyanides involves the dehydration of the corresponding formamide [2a]. Several methods for the conversion of formamides into carbamoyl chlorides have also been reported, using various chlorinating mixtures [2b]. In some cases, formamides are applied in aminations and ring transformations of benzofurazan derivatives [3, 4].

N-Formylamino acid esters are useful derivatives for preparing selected *N*-formylamino acids (cf. [5] and lit. cited therein), for incorporating polyfunctional amino acids into peptides [6], for the enzymatic synthesis of peptides in aqueous media [7]. *N*-Formylation of amino acid *tert*-butyl esters are important because the products are readily converted into isocyano acid *tert*-butyl esters, which are used as starting materials in Ugi four-component condensations [8, 9].

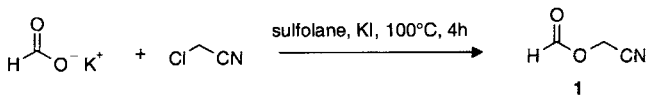
Excellent reviews describe numerous formylating methods and formylating agents available [10, 11]. Typical *N*- and *O*-formylating agents are formic acid, formic acid in conjunction with dehydrating reagents such as dicyclohexylcarbodiimide, some formic acid esters, formic anhydride and mixed anhydrides of formic acid, and formylfluoride [10].

N-Formyl derivatives have been extensively used for the formylation of amines, amides, imines and alcohols [10, 11]. For example, *N*-formylbenzotriazole is an *N*- and *O*-formylating agent [12] (for *N*-formylazoles cf. [24]). Moreover, the chemoselective formylation of primary amines in the presence of alcohols or secondary amines succeeds with *N*-(diethylcarbamoyl)-*N*-methoxyformamide [13]. *N*-Formyl-pyridones enable the selective formylation of alcohols [14–16].

N-Formyl amino acid esters can be obtained from amino acid esters by reaction with formic acid and acetic anhydride [17], formic acid and dicyclohexylcarbodiimide [18], *in situ* formed formic anhydride [19], pentafluorophenyl formate [20], chloro- and nitro-substituted aryl formate [21], chloral followed by elimination [22], enol formates [23], trialkyl orthoformates [8], or *N*-(diethylcarbamoyl)-N-methoxyformamide [13].

Despite the usefulness of the reagents mentioned above there are several factors in some cases limiting their application. For example, formylations using formylfluoride or anhydrides are difficult to carry out due to the instability of these reagents [10, 11]. Commercially available *N*-formylimidazole is an effective formylating agent, but it is extremely hygroscopic [24]. *N*-Formyl-pyridones are unstable above 40 °C [14–16]. Other reagents require the use of expensive catalysts [23].

Recently, we described the previously unreported use of stable, non-hygroscopic and easily accessible formyloxy-acetonitrile (cyanomethyl formate) **1** as a convenient, chemoselective *N*- and *O*- formylating agent [25–27]. Formyloxy-acetonitrile **1** is a readily available starting material and the synthesis is very simple by treatment of chloroacetonitrile with potassium formate (previously prepared by Henry and Dewael [28]; cf. also ref. [26]).



1

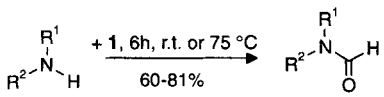
Cyanomethyl formate (Formyloxy-acetonitrile) **1** [26]

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 4h, 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 [28]: 172–173 °C).*

N-Formylation of Aliphatic and Aromatic Amines

Aliphatic and aromatic amines (with exception of nitroanilines) give an exothermic reaction. Yields of purified formamides **2** are in the range from 60 to 81%. 4- and 3-Nitroanilines are formylated in the presence of imidazole at 75 °C furnishing the appropriated formylated compounds **2** in 60 to 69% yield.

The formylation of imides such as phthalimide cannot be realized under these reaction conditions.



2

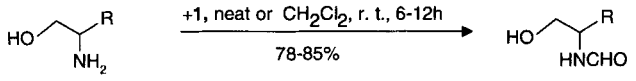
R^1: H R^2: *n*-Oct, $PhCH_2$, *c*-Hex, Ph, 2-MeC_6H_4, 4-$MeOC_6H_4$, 3-Cl,4-FC_6H_3, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$
R^1: 4-$MeOC_6H_4$ R^2: Me; R^1: *n*-Hex, R^2: *n*-Hex

Cyclohexylformamide (**2**: R^1=c-Hex, R^2=H); Typical Procedure [25, 26]:

Cyclohexylamine (14.9 g, 0.15 mol) is added dropwise under vigorous stirring and cooling with ice to **1** *(12.8 g, 0.15 mol). The reaction temperature is kept at 15–20 °C. After standing at room temperature for 6h the product obtained is distilled in vacuo. Yield: 14.3 g (75%); b.p.: 148–151°C/17 torr.*

N-Formylation of Aminoalcohol Derivatives

Aminoalcohols such as ethanolamine are chemospecifically *N*-formylated to give *N*-formyl-ethanolamine (**3**: R=H) in 78% yield. The benzyl ester of serine (used as hydrochloride, cf. Typical Procedure for **5**) gave only the *N*-formylated serine benzyl ester (**3**: R=$COOCH_2Ph$); yield: 85%).

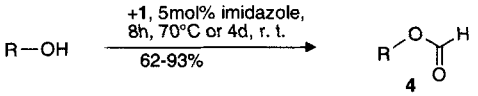


3

R = $COOCH_2Ph$, H

O-Formylation of Primary and Secondary Alcohols

The *O*-formylation of primary and secondary alcohols succeeds only in the presence of a catalytic amount of imidazole. Alkylformates **4** are formed in up to 93% yield. The formylation of primary and secondary alcohols is 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%.



4

R: Et, *i*-Pr, *n*-Bu, -CH(Me)Pr, *c*-Pent

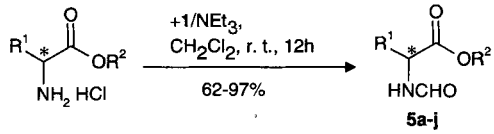
*n-Butyl formate (***4***: R = n-Bu)* Typical Procedure [25, 26]

A mixture of **1** *(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 2h. The reaction mixture is allowed to stand at ambient temperature for 22h and fractionated. Yield: 13.5 g (88%); b.p. 104–106 °C.*

N-Formylation of Amino Acid Esters

The preparation of *N*-formyl amino acid esters **5** succeeds using formyloxy-acetonitrile **1**, which accomodates chirality and functionality.

The procedure can be used directly on hydrochlorides of amino acid methyl, ethyl, benzyl and *tert*-butyl esters. The reaction is carried out at room temperature within 12h furnishing the compounds **5a–j** in good to excellent yields and in high optical purity (ee ≥ 99%). The *tert*-butyl esters of leucine, valine and phenylalanine are formylated without special care to give the corresponding *N*-formyl compounds **5h–j** in 78–88% yield. In all cases, the formylations proceed without any catalysts.



5a-j

	a	b	c	d	e
R^1	Me	*i*-Bu	$PhCH_2$	$PhCH_2$	$EtO_2C(CH_2)_2$
R^2	Me	Me	Me	Et	Et
	f	**g**	**h**	**i**	**j**
R^1	*i*-Pr	*i*-Pr	*i*-Bu	*i*-Pr	$PhCH_2$
R^2	Et	$PhCH_2$	*t*-Bu	*t*-Bu	*t*-Bu

N-Formyl-D-phenylalanine methyl ester ***5c****;* Typical Procedure [27]

The D-phenylalanine methyl ester hydrochloride (4 mmol) and **1** *(0.34 g, 4 mmol) were dissolved in dichloromethane (6 mL) and cooled in an ice-bath. Then, a solution of NEt_3 (0.55 ml, 4 mmol) in CH_2Cl_2 (1 mL) was added. After 12h at room temperature, 43ml of CH_2Cl_2 were added. Finally, the mixture obtained was washed three times with brine (15mL each), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by distillation: b.p. 175–180 °C. Yield: 97%, $[\alpha]_D = 84.18°$ (c = 1, CH_2Cl_2).*

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