Convenient One-Pot Method for Formylation of Amines and Alcohols Using Formic Acid and 1,1′-Oxalyldiimidazole

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1,1′-Oxalyldiimidazole (7) reacts with formic acid (8) in acetonitrile at room temperature to give *N*-formylimidazole (5), which promptly undergoes aminolysis and alcoholysis to yield formamides (2) or formates (4).

Keywords formylation; *N*-formylimidazole; 1,1′-oxalyldiimidazole; formamide; formate; aminolysis

Many methods have been described for the formylation of amines (**1**) and alcohols (**3**) to formamides (**2**) or formates (**4**). The formylating reagents which have been used include formic acid/acetic anhydride,[1] formic acid/1,3-dicyclohexylcarbodiimide,[2] trisformaminomethane,[3] *N*,*N*-diformylacetamide,[4] 4-formyl-2-methyl-1,3,4-thiadiazolin-5-thione,[5] active esters of formic acid,[6] *N*,*N*-dimethylformamide/hydrous zirconium oxide,[7] *N*,*N*-dimethylformamide/2,3-dihydro-1,4-phthalazinedione[8] and *N*-(diethylcarbamoyl)-*N*-methoxyformamide.[9] In addition, *N*-formylimidazole (**5**) reported by Staab and Polenski in 1962 can be prepared in 85% yield by the reaction of formic acid (**8**) with 1,1′-carbonyldiimidazole (CDI, **6**),[10a] and **5** is a suitable reagent for the conversion of amines (**1**) and alcohols (**3**) to formamides (**2**) or formates (**4**) under non-acidic conditions.[10b] The key compound, CDI (**6**), is commercially available, but is too costly for utilization on a large scale. Although phosgene can be used for the preparation of CDI (**6**), it is a toxic gas. We therefore examined the feasibility of using 1,1′-oxalyldiimidazole (ODI, **7**)[11] instead of CDI (**6**) to generate *N*-formylimidazole (**5**).

We report here the conversion of ODI (**7**) to *N*-formylimidazole (**5**), which can be applied for the formylation of aliphatic and aromatic amines (**1**) and alcohols (**3**) to the corresponding *N*- or *O*-formyl compounds, **2** or **4**, respectively. The formylation described herein was carried out basically as a two-step, one-pot procedure, as shown in Chart 2. In step 1, *N*-formylimidazole (**5**) is prepared by the reaction of formic acid (**8**) with ODI (**7**) at room temperature for 15 min, accompanied with liberation of carbon dioxide and carbon monoxide, and in step 2, *N*-formylimidazole (**5**), which is used without isolation, reacts with amines (**1**) and alcohols (**3**) as nucleophiles to afford formamides (**2**) or formates (**4**) conveniently and in good yield.

Syntheses of Formamides (2) Dropwise addition of an acetonitrile solution of aniline (**1f**) to a mixture of formic acid (**8**) and ODI (**7**) in acetonitrile resulted in the formation of formanilide (**2f**) in 90% yield. *N*-Hexylamine (**1a**) was also converted into *N*-hexylformamide (**2a**) in acceptable yield. The products (**2**) were separated from the reaction mixture by silica-gel column chromatography to increase the isolated yield, because formyl compounds (**2**) such as *N*-hexylformamide (**2a**) and *N*-(2-furfuryl)-formamide (**2h**) are soluble in water.

Formylations of other aromatic and heteroaromatic amines (**1**) to the corresponding formamides (**2**) were accomplished without difficulty as summarized in Table I. However, 2-aminopyrimidine (**1j**) and phthalimide (**1k**) were unreactive, probably due to weak nucleophilicity of the amino or imino group. Nevertheless, the highly hindered amine, 2,6-dimethylaniline (**1i**), reacted readily with *N*-formylimidazole (**5**), affording *N*-(2,6-dimethylphenyl)formamide (**2i**) in 93% yield.

Syntheses of Formates (4) Next, we examined the usefulness of **5** in the formylation of alcohols (**3**) to the corresponding formates (**4**). Benzyl alcohol (**3c**) was treated with *N*-formylimidazole (**5**) at 35 °C for 1 h to give benzyl formate (**4c**) in 91% yield. Furfuryl alcohol (**1e**) contains the acid-sensitive furyl group, but our procedure under neutral conditions afforded furfuryl formate (**2e**) in 80% yield, after purification by silica gel column chromatography to remove small amounts of the starting material (**1e**) and imidazole (**9**) derived from ODI (**7**) as shown in Chart 3.

The reaction probably proceeds *via* the formation of a mixed acid anhydride intermediate (**10**) from the reaction of formic acid (**8**) with ODI (**7**) at room temperature for 15 min, followed by concerted eliminations of carbon dioxide and carbon monoxide to afford *N*-formylimidazole (**5**), which reacts with amines (**1**) and alcohols (**3**) to yield the corresponding formamides (**2**) or formates (**4**), as

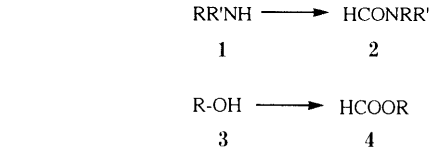

Chart 1

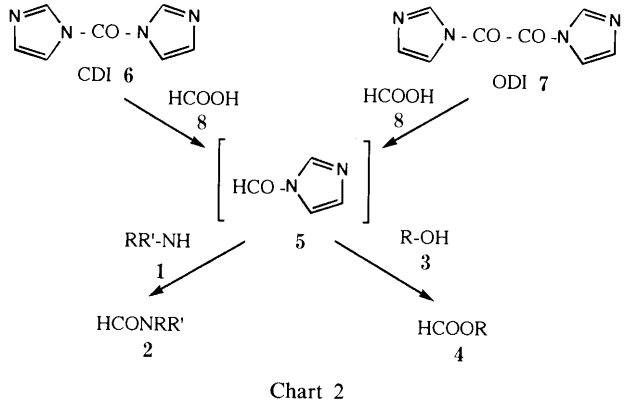

Chart 2

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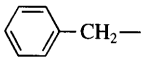
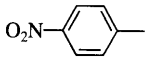
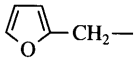
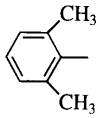
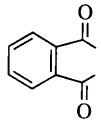
TABLE I. Formylation of Amines (**1**) to Formamides (**2**) with *N*-Formylimidazole (**5**)

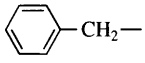
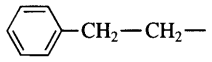
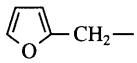
R R′ NH → HCONR R′
1 **2**

Compound No. **1, 2**	R	R′	Yield[a] (%)	IR (neat or KBr) cm^{-1} C=O	mp [°C] (bp/mmHg) Found	mp [°C] (bp/mmHg) Reported
a	$CH_3(CH_2)_3$–	H	84	1670	(95—97/2)	(122—123/16)[12]
b		H	92	1670	(97—99/2)	(135—140/15)[13]
c			98	1680	(78—80/2)	(108/14—15)[14]
d		H	80	[1670]	60—61[b]	62—63[10a]
e		H	67	[1690]	192—194[c]	194—195[10a]
f		H	90	[1690]	47—48[b]	48[6b]
g		CH_3–	92	1680	(91—95/2)	(125—126/14)[10a]
h		H	86	1670	(140—143/2)	(120/0.01)[15]
i		H	93	[1660]	174—176[d]	175—176[16]
j		H	—			
k			—			

a) Yields of the products (**2a**—**i**) after purification. *b*) Recrystallized from ethyl acetate. *c*) Recrystallized from toluene. *d*) Recrystallized from water.

TABLE II. Formylation of Alcohols (**3**) to Formates (**4**) with *N*-Formylimidazole (**5**)

R OH → HCOOR
3 **4**

Compound No. **3, 4**	R	Yield[a] (%)	IR (neat) cm^{-1} C=O	bp (°C/mmHg) Found	bp (°C/mmHg) Reported
a	$CH_3(CH_2)_5$–	72	1746	67—70/40	146[17]
b		78	1725	78—80/30	162—165[18]
c		91	1728	103—105/30	84—85/10[19]
d		85	1728	115—117/30	94/9[20]
e		80	1725	69—71/30	66.2—66.5/16[21]

a) Yields of the products (**4a**—**e**) after purification.

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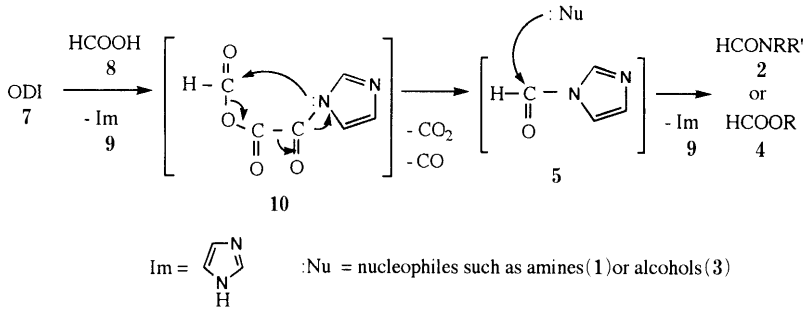

Chart 3

shown in Chart 3.

In summary, ODI (**7**) can be simply used for the preparation of *N*-formylimidazole (**5**), and the formyl group of **5** is transferred readily to amines (**1**) and alcohols (**3**), affording the corresponding formamides (**2**) or formates (**4**) conveniently and in acceptable yields under mild reaction conditions.

Experimental

Melting points were taken on a Yanagimoto melting point apparatus. All melting and boiling points are uncorrected. Infrared (IR) spectra were measured on a Hitachi model 270-30 IR spectrophotometer. ODI **7** was prepared by the known procedure.[11]

Syntheses of Formamides (2) General Procedure: A solution of formic acid (**8**) (0.9 g, 20 mmol) in acetonitrile (10 ml) was added dropwise to an ice-cold, stirred solution of ODI (**7**) (3.8 g, 20 mmol) in acetonitrile (20 ml). The mixture was stirred at room temperature for 15 min, then a solution of the amine (**1**, 20 mmol) in acetonitrile (5 ml) was added. The reaction mixture was stirred at room temperature for 1 h. After removal of the solvent *in vacuo*, the resulting residue was chromatographed on a silica gel column (40 g, 70—230 mesh) with ethyl acetate/toluene = 3/7 to give the crude product (**2**), which was purified by distillation or recrystallization.

Syntheses of Formates (4) General Procedure: A solution of formic acid (**8**) (0.9 g, 20 mmol) in acetonitrile (10 ml) was added dropwise to an ice-cold, stirred solution of ODI (**7**) (3.8 g, 20 mmol) in acetonitrile (20 ml). The mixture was stirred at room temperature for 15 min, then a solution of the alcohol (**3**) (20 mmol) in acetonitrile was added. The reaction mixture was stirred at 35 °C for 1 h. After removal of the solvent *in vacuo*, the resulting residue was chromatographed on a silica gel column (40 g, 70—230 mesh) with ethyl acetate/toluene = 1/9 to give the crude product (**4**), which was purified by distillation.

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