Improved Procedure for N-Formylation of Amines to Formamides Using Formic Acid, Oxalyl Chloride and Imidazole

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The reaction of imidazole (15) with formyl chloride (14), generated *in situ* by the action of oxalyl chloride (10) on formic acid (3), afforded *N*-formylimidazole (7), which is a convenient formylating reagent. This procedure was used to prepare *N*-formyl derivatives (2) of aliphatic, aromatic and heteroaromatic amines (1) under mild conditions.

Keywords formylation; *N*-formylimidazole; imidazole; formamide; *N,N'*-carbonyldiimidazole; oxalyl chloride

N-Formylation of amines is often required in peptide synthesis¹⁾ or in the preparation of N-methyl compounds.²⁾ Although numerous methodologies for N-formylation³⁾ are available, a convenient and high-yield procedure under mild conditions would be valuable.

For the N-formylation of amines (1) to formamides (2), formic acid (3) is frequently used in conjunction with reagents such as acetic anhydride, dicyclohexylcarbodiimide and cyanuric fluoride to prepare acetic formic anhydride (4a),⁴⁾ formic anhydride (4b)⁵⁾ and formyl fluoride (4c),⁶⁾ respectively. The handling of these formic acid derivatives (4a—c), however, requires careful exclusion of moisture. For this reason, much interest has been focused on reactive N-formyl heterocyclic compounds such as 4-formyl-2-methyl-1,3,4-thiadiazolin-5-thione (5),⁷⁾ 2,3-dihydro-1,4-phthalazinedione/dimethylformamide (6)⁸⁾ and *N*-formylimidazole (7).⁹⁾ The synthetic versatility of *N*-formylimidazole (7) has been demonstrated by Staab and Polenski,⁹⁾ who prepared this formylating reagent through the reaction of formic acid (3) with *N,N*-carbonyldiimidazole (CDI, 8). We have shown that the same reagent (7) can be obtained by the

action of formic acid (3) on *N,N'*-oxalyldiimidazole (ODI, 9).¹⁰⁾

We now report a convenient preparation of *N*-formylimidazole (7) directly from the reaction of imidazole (15) with formyl chloride (14) generated *in situ* by the action of oxalyl chloride (10) on formic acid (3), and we describe the application of this procedure for the transformation of various amines (1) to formamides (2) under nearly neutral conditions.

Firstly, we examined path 1 in Chart 3. Namely, formic acid (3) was allowed to react with oxalyl chloride (10) in the presence of 3 eq of imidazole (15) in methylene chloride at room temperature for 15 min, then aniline (1e) was added and the mixture was held at the same temperature

Chart 4

Chart 5

TABLE I. Effect of Azole Addition on the N-Formylation Reaction

<div>PhNH₂ (1e) azole (1 eq)</div> <div>3 + 10 $\longrightarrow$ HCONHPh + PhNHCOCONHPh (1 eq) (1 eq) 2e 12</div>			
Entry	Azole	Ratio of isolated products (%)	
		HCONHPh (2e) ^{a)}	PhNHCOCONHPh (12) ^{a)}
1	Without imidazole (15)	41	37
2	Imidazole (15 , 3 eq)	86	ND
3	Imidazole (15 , 1 eq) + (Et) ₃ N (2 eq)	95	ND
4	Pyrazole (16 , 3 eq)	ND	61
5	1,2,4-Triazole (17 , 3 eq)	82	ND
6	1,2,3,4-Tetrazole (18 , 3 eq)	ND	ND

a) Isolated yield based on the amount of aniline (1e). ND = not detected.

for 1 h to afford formanilide (2e) in 86% yield. The yield was increased from 86% to 95% when two-thirds of the imidazole was replaced with 2 eq of triethylamine (path 2 in Chart 3) as a scavenger of hydrogen chloride. On the other hand, treatment of aniline (1e) with formic acid (3)/oxalyl chloride (10) in the presence of triethylamine, but in the absence of imidazole (15), gave a 41% yield of formanilide (2e) and a 37% yield of *N,N'*-diphenyloxamide (12), as shown in Chart 4. These results suggest that imidazole (15) is essential for the high-yield formation of formanilide (2e) in our procedure. The mechanism involved is considered to be as follows: nucleophilic attack of formic acid anion on the carbonyl carbon of oxalyl chloride (10), followed by the intramolecular rearrangement of an anhydride-type intermediate (13) yields unstable formyl chloride (14), which immediately reacts

with imidazole (15) to form *N*-formylimidazole (7) (Chart 5). Subsequently, transfer of the formyl group from 7 to amine nitrogen occurs smoothly to afford the corresponding formamide (2).

We next examined the importance of the imidazole structure in *N*-formylimidazole (7). Namely, we investigated the *N*-formylation of aniline (1e) with pyrazole (16), 1,2,4-triazole (17) and 1,2,3,4-tetrazole (18) in place of imidazole (15). The results are shown in Table I. *N*-formylation of aniline (1e) using 1,2,4-triazole (17) led to the formation of formanilide (2e) in 82% yield (entry 5). However, the combination of imidazole (15) and triethylamine gave a higher yield (95%) (entry 3). As shown in Chart 5, 1,2,3,4-tetrazole (18) failed to give 2e under a variety of reaction conditions, presumably because it was resistant to *N*-formylation with formyl chloride (14),

Chart 6

Chart 7

TABLE II. N-Formylation of Amines (**1**) to Formamides (**2**) Using Formic Acid (**3**)/Oxalyl Chloride (**10**) in the Presence of Imidazole (**15**)

		$RR'NH \longrightarrow HCONRR'$				
		1	2			
Compd. No. 1, 2	R	R'	Product yield ^a (%)	IR (neat or [KBr]) cm^{-1} C=O of product	Lit.	
a	$CH_3(CH_2)_3-$	H	93	1670	12	
b	$(EtOOC)_2CH-$	H	80	[1650]	11	
c		H	92	1670	13	
d			83	1680	14	
e		H	95	[1690]	15	
f		H	77	[1670]	9	
g		CH_3	87	1680	9	
h		H	61	[1690]	9	
i		H	85	1670	16	
j		H	60	[1660]	17	
k		H	82	[1700]	18	

a) Yield of isolated product (**2**) based on **1** after flash column chromatography (silica gel, ethyl acetate/toluene = 3/7).

failing to generate 1- or 2-formyl(1,2,3,4-tetrazole) (**20a** or **20b**). On the other hand, pyrazole (**16**) afforded a 61% yield of *N,N'*-diphenyloxamide (**12**) (entry 4, Table I). Oxalyl chloride (**10**) may react with pyrazole (**16**) in preference to formic acid (**3**), affording *N,N'*-oxalyldipyrrole (**11**), which would react with aniline (**1e**) to give **12** as depicted in Chart 7. When aniline (**1e**) was not added, *N,N'*-oxalyldipyrrole (**11**) was isolated in 78% yield. Compound **11** reacted almost quantitatively with aniline (**1e**) in refluxing acetonitrile for 1 h to afford *N,N'*-

diphenyloxamide (**12**).

Based on the above results, we selected imidazole as the preferred reagent, and proceeded to examine the applicability of our methodology to amines (**1**) other than aniline (**2e**) (Table II). Diethyl 2-aminomalonate (**1b**) afforded diethyl 2-formylaminomalonate (**2b**), which is a useful synthon in peptide synthesis, in 80% yield. 2-Aminopyrimidine (**1i**), with a primary amino group, and phthalimide (**1m**), with an imino group, failed to afford the desired formamides (**2i** and **2m**), probably because of the weak nucleophilicity of the amino or imino group toward the carbonyl carbon of *N*-formylimidazole (**7**). On the other hand, a hindered amine, 2,6-dimethylaniline (**1j**), readily afforded *N*-(2,6-dimethylphenyl)formamide (**2j**) in 60% yield. These results and other examples chosen to demonstrate the effectiveness of our method are summarized in Table II.

In summary, the present procedure provides a simple and convenient synthetic route to *N*-formylimidazole (**7**), which reacts *in situ* with amines (**1**) to form the corresponding formamides (**2**). The advantages of our procedure over previous methods include short reaction times under essentially neutral conditions and greater ease of product isolation.

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.

Synthesis of Formanilide (2e) Procedure A Using Excess Imidazole (**15**) as a Scavenger of Hydrogen Chloride: A solution of oxalyl chloride (**10**) (2.5 g, 20 mmol) in methylene chloride (10 ml) was added dropwise to an ice-cold, stirred solution of imidazole (**15**) (4.1 g, 60 mmol) and formic acid (**3**) (0.9 g, 20 mmol) in methylene chloride (30 ml). The mixture was stirred at room temperature for 15 min, then a solution of aniline (**1e**) (1.9 g, 20 mmol) in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. On cooling to ice-bath temperature, imidazole hydrochloride precipitated, and was removed by filtration. The filtrate was concentrated *in vacuo*, and the resulting residue was subjected to flash chromatography on a column of silica-gel (40 g) with ethyl acetate/toluene (3/7) to give 2.1 g (86%) of formanilide (**2e**). After recrystallization from petroleum ether/ethyl acetate, the melting point was 47–48 °C (lit.¹⁶ mp 48 °C). The IR (KBr) spectrum showed NH 3270 and C=O 1690 cm^{-1} , and was identical with that of a sample obtained by another method.¹⁰

Procedure B Using Imidazole (**15**) with Triethylamine as a Scavenger of Hydrogen Chloride: A solution of oxalyl chloride (**10**) (2.5 g, 20 mmol) in methylene chloride (10 ml) was added dropwise to an ice-cold, stirred solution of imidazole (**15**) (1.4 g, 20 mmol), triethylamine (4.0 g 40 mmol) and formic acid (**3**) (0.9 g, 20 mmol) in methylene chloride (30 ml). The mixture was stirred at room temperature for 15 min, then a solution of aniline (**1e**) (1.9 g, 20 mmol) in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and then worked up in the manner described above to afford 2.3 g (95%) of formanilide (**2e**).

Procedure C Using 1,2,4-Triazole (**17**): A solution of oxalyl chloride (**10**) (2.5 g, 20 mmol) in methylene chloride (10 ml) was added dropwise to an ice-cold, stirred solution of 1,2,4-triazole (**17**) (4.1 g, 60 mmol) and formic acid (**3**) (0.9 g, 20 mmol) in methylene chloride (30 ml). The mixture was stirred at room temperature for 15 min, then a solution of aniline (**1e**) (1.9 g, 20 mmol) in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and then worked up according to procedure A to afford 2.0 g (82%) of formanilide (**2e**).

Reaction of Aniline (1e) with Formic Acid (3)/Oxalyl Chloride (10) in the Presence of Triethylamine Leading to Formanilide (2e) and *N,N'*-Diphenyloxamide (12) This procedure was undertaken without imidazole (**15**). A solution of oxalyl chloride (**10**) (2.5 g, 20 mmol) in

methylene chloride (10 ml) was added dropwise to an ice-cold, stirred solution of aniline (**1e**) (1.9 g, 20 mmol), formic acid (**3**) (0.9 g, 20 mmol) and triethylamine (4.0 g, 40 mmol) in methylene chloride (30 ml). The reaction mixture was stirred at room temperature for 1 h. On cooling to ice-bath temperature, a mixture of *N,N'*-diphenyloxalylamide (**12**) and triethylamine hydrochloride precipitated. It was collected by filtration, washed with a mixture of water-ethanol (1:1), and dried under reduced pressure at 40 °C to afford 0.9 g (37%) of **12**. An analytical sample, mp 250–253 °C (lit.¹⁹) mp 246–250 °C), was prepared by recrystallizing some of this material from ethanol. The IR spectrum showed NH 3310 and C=O 1670 cm⁻¹, and it was identical with that of an authentic sample obtained by the procedure of Meyer and Seeliger.²⁰ The filtrate was concentrated *in vacuo*, and the resulting residue was chromatographed on a silica gel column using ethyl acetate/toluene (3/7) as the eluent to afford 1.0 g (41%) of formanilide (**2e**).

Reaction of Aniline (1e) with Formic Acid (3)/Oxalyl Chloride (10) in the Presence of Pyrazole (16) Leading to *N,N'*-Diphenyloxamide (12)
A solution of oxalyl chloride (**10**) (1.3 g, 10 mmol) in methylene chloride (10 ml) was added dropwise to an ice-cold, stirred solution of pyrazole (**16**) (2.0 g, 30 mmol) and formic acid (**3**) (0.5 g, 10 mmol) in methylene chloride (20 ml). The mixture was stirred at room temperature for 15 min, then a solution of aniline (**1e**) (1.9 g, 20 mmol) in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. On cooling to ice-bath temperature, the product (**12**) precipitated. It was collected by filtration, washed with a mixture of water-ethanol (1:1), and finally air-dried at room temperature to yield 1.5 g (61%) of **12**.

Synthesis of *N,N'*-Oxalyldipyrazole (11) A solution of oxalyl chloride (**10**) (2.5 g, 20 mmol) in acetonitrile (10 ml) was added dropwise to an ice-cold, stirred solution of pyrazole (**16**) (2.7 g, 40 mmol) and triethylamine (4.0 g, 40 mmol) in acetonitrile (40 ml). The mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, and the resulting residue was chromatographed on a silica gel column (60 g) using ethyl acetate/toluene (3/7) as the eluent to give 3.0 g (78%) of the product (**11**). An analytical sample, mp 251–252 °C, was prepared by recrystallizing some of this product from toluene. *Anal.* Calcd for C₈H₆N₄O₂: C, 50.58; H, 3.18; N, 29.47. Found: C, 50.71; H, 3.10; N, 29.29. The IR spectrum showed C=O 1730 cm⁻¹. The aminolysis of *N,N'*-oxalyldipyrazole (**11**) (1.9 g, 10 mmol) with aniline (**1e**, 1.7 g, 20 mmol) in refluxing acetonitrile (40 ml) for 1 h afforded 2.3 g (95%) of *N,N'*-diphenyloxamide (**12**).

Syntheses of Formamides (2) The standard procedure for *N*-formylation of amines (**1**) is based on procedure B described above for the preparation of formanilide (**2e**). A solution of oxalyl chloride (**10**) (2.5 g, 20 mmol) in methylene chloride (10 ml) was added dropwise to an ice-cold, stirred solution of imidazole (**15**) (1.4 g, 20 mmol), triethylamine (4.0 g, 40 mmol) and formic acid (**3**) (0.9 g, 20 mmol) in methylene chloride (20 ml). The mixture was stirred at room temperature for 15 min, then

a solution of an amine (**1**) (20 mmol) in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and then worked up in the same manner as described under procedure B for the synthesis of **2e**. All of the formamides (**2a–k**) obtained are known compounds, and physical data of the samples prepared were identical with reported values.¹⁰ Yields and IR data for **2a–k** are shown in Table II.

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