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 synthesis[1] or in the preparation of N-methyl compounds.[2] Although numerous methodologies for N-formylation[3] 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 anhydide (**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

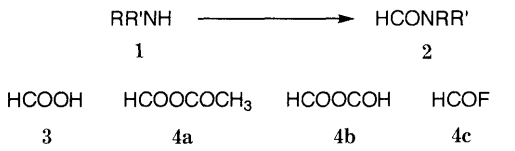
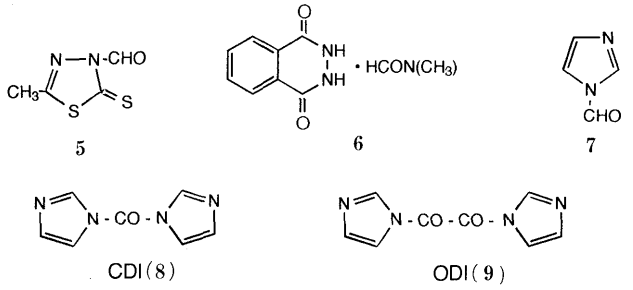


Chart 1



8 or 9 + HCOOH (3) ⟶ 7

Chart 2

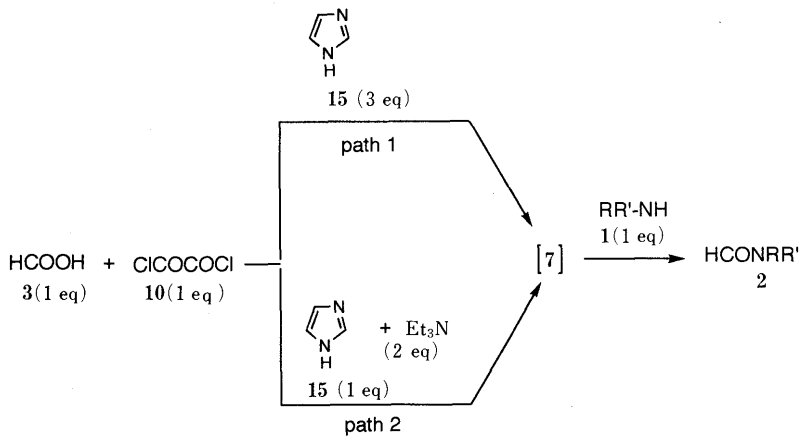


Chart 3

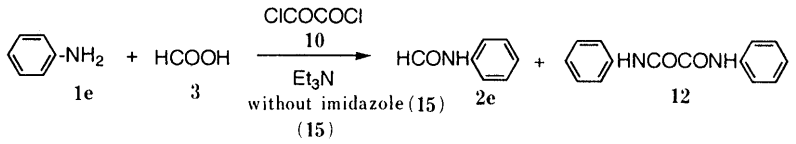


Chart 4

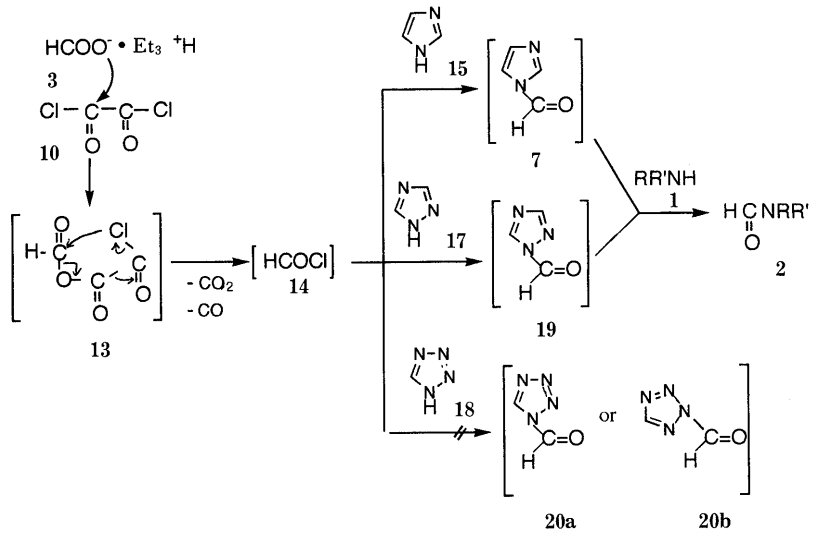
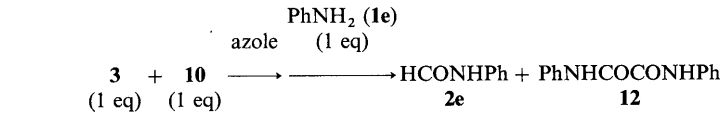


Chart 5

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

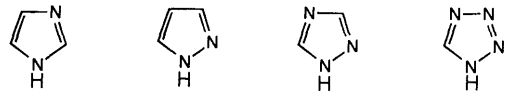


Entry	Azole	Ratio of isolated products (%)	
		HCONHPh (**2e**)[a]	PhNHCOCONHPh (**12**)[a]
1	Without imidazole (**15**)	41	37
2	Imidazole (**15**, 3 eq)	86	ND
3	Imidazole (**15**, 1 eq)+$(Et)_3N$ (2 eq)	95	ND
4	Pyrazole (**16**, 3 eq)	ND	61
5	1,2,4-Triazole (**17**, 3 eq)	82	ND
6	1,2,3,4-Tetrazole (**18**, 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 goup 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% yeild (entry 5). However, the combination of imidazole (**15**) and triethylamine gave a higher yeild (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**),



15 16 17 18

Chart 6

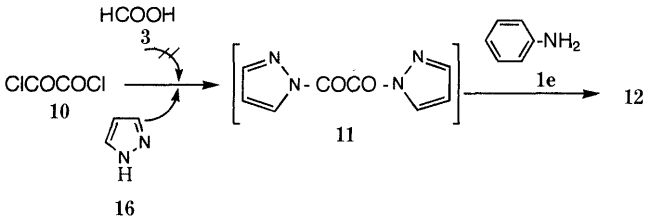
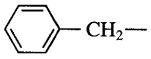
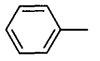
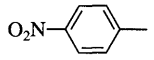
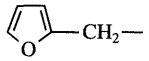
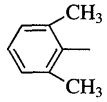
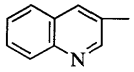


Chart 7

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

$$\underset{\mathbf{1}}{RR'NH} \longrightarrow \underset{\mathbf{2}}{HCONRR'}$$

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*-oxalyldipyrazole (**11**), which would react with aniline (**1e**) to give **12** as depicted in Chart 7. When aniline (**1e**) was not added, *N,N′*-oxalyldipyrazole (**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 (**1l**), with a primary amino group, and phthalimide (**1m**), with an imino group, failed to afford the desired formamides (**2l** and **2m**), propably 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 Seelinger.[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 $C_8H_6N_4O_2$: 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'*-dipehnyloxamide (**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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