A New, Simple Procedure for the Synthesis of Formyl Amides

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Abstract: A simple and mild method for the N-formylation of amines and α-amino esters is described via reaction with 2-chloro-4,6-dimethoxy[1,3,5]triazine and formic acid. The reaction can be accelerated under microwave irradiation and yields the N-formyl species in high yields and without racemization in the case of optically active α-amino esters.

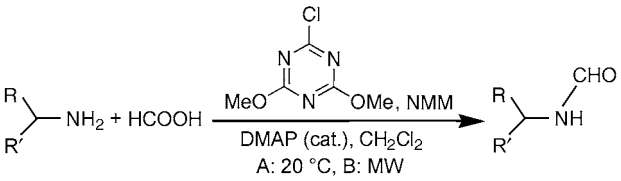
Key words: amines, formyl amides, cyanuric acid, formylamino esters, microwave

The formylation of amines and alcohols is an important reaction that is used in organic synthesis. Formamides are a class of important intermediates that have been widely used in synthesis of pharmaceutically important compounds such as fluoroquinolones,[1] substituted aryl imidazoles,[2] 1,2-dihydroquinolines,[3] and nitrogen bridged heterocycles.[4] Moreover, the formyl group is a useful amino-protecting group in peptide synthesis[5] and *N*-formylamino acid esters can, for example, serve as starting materials for peptide synthesis[6] and for conversion to isocyano acids that are requested for the four-component condensation methods[7] or especially in enzymatic synthesis in aqueous media.[6]

A number of formylating methods and formylating agents have been reported even in recent years. *N*-Formyl amines and in particular *N*-formyl amino acid esters can be obtained from the corresponding amino derivatives by reaction with formic acid and acetic anhydride,[8] in situ formed formic anhydride,[9] chloral followed by elimination,[10] ammonium formate[11] and other reagents.[12–15] Heating with ethyl or phenyl formate seems a good procedure, but the method requires very long times and high temperature for completion.[16] However, there are several factors in some cases limiting their applications, for example thermal instability, formation of by-products, difficult accessibility to the preparation of the formylating agents.

Recently, there was reported a synthesis of *N*-formyl amino acid esters under mild conditions.[17] The procedure, although simple, required the use of cyanomethyl formate that has to be prepared. Following our interest in the use of [1,3,5]triazine derivatives in organic synthesis,[18] we report here a new simple and high yielding synthesis of formyl amides from amines and amino acid esters that uses 2-chloro-4,6-dimethoxy[1,3,5]triazine (CDMT)[19] as the coupling agent. The reaction can be conducted at reflux of the solvent (CH_2Cl_2) or under microwave irradiation,[20] using a self-tunable microwave synthesizer.

The method allows the preparation of formyl amides in a single step reaction. Thus, dry formic acid (1.0 equiv) and the amine derivative (1.0 equiv) are treated with CDMT (1.1 equiv), and dimethylamino pyridine (DMAP) as catalyst (0.1 equiv), in CH_2Cl_2, followed by *N*-methylmorpholine (NMM, 1.1 equiv) in dichloromethane (method A). Stirring is continued at reflux of the solvent until complete conversion of the carboxylic acid (monitored by TLC). The reaction mixture is then diluted with CH_2Cl_2 and then washed with aqueous HCl, water, aqueous $NaHCO_3$, and brine. The desired product is recovered in pure form, simply by concentration of the organic extracts at reduced pressure. The triazine by-product is easily removed by this simple aqueous work-up. The reaction is not fast and requires from five to 20 hours for completion in most of the cases examined.



Scheme 1

With the goal of reducing the reaction times, we have therefore checked the possibility to carry out the reactions under microwave irradiation, using a self-tunable microwave synthesizer. The MW experiments were performed in a self-tuning single mode CEM Discover™ Focused Synthesizer apparatus. The instrument continuously adjusts the applied wattage to maintain the desired temperature.

Reactions were performed using a flask equipped with a reflux condenser mounted outside the apparatus. The formylation was successfully carried out in CH_2Cl_2 under microwave irradiation that gave high yields of the desired formyl amides after 3–6 minutes (Scheme 1).

The procedure could be used directly on hydrochlorides of amino acid methyl esters. In these cases, the hydrochloride has to be added with 1.1 equivalents of TEA, in order to free the amino acid ester. Both the reactions carried out according method A and that under microwave irradiation (method B) furnished the formyl compounds in practically quantitative yields and conversions depending on the structure of the starting amino compound (Table 1).

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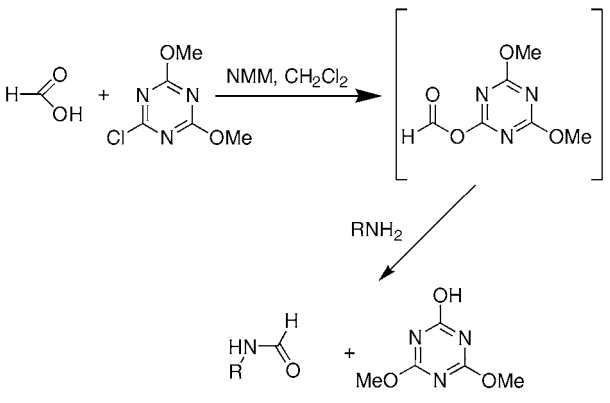
Table 1 N-Formylation of Amines and α-Amino Acid Esters (Scheme 1)

Run	Compound	Method	Conditions	Yield (%)
1	Pyrrolidine	A	35 °C, 4 h	88
		B	MW, 3 min	95
2	Heptylamine	A	35 °C, 8 h	98
		B	MW, 3 min	90
3	Cyclohexylamine	A	35 °C, 13 h	87
		B	MW, 6 min	85
4	Benzylamine	A	35 °C, 5 h	95
		B	MW, 6 min	99
5	4-Methoxyaniline	B	MW, 6 min	86
6	4-(Trifluoromethyl)aniline	B	MW, 3 min	92
7	4-Methoxybenzylamine	B	MW, 3 min	91
8	3-Phenylpropan-1-amine	A	35 °C, 5 h	90
		B	MW, 3 min	99
9	2-(3,4-Dimethoxyphenyl)ethanamine	A	35 °C, 5 h	95
		B	MW, 3 min	98
10	Furan-2-ylmethanamine	B	MW, 6 min	95
11	(*S*)-Alanine methyl ester	A	35 °C, 10 h	93
		B	MW, 6 min	99
12	(*S*)-Valine methyl ester	A	35 °C, 9 h	90
		B	MW, 6 min	95
13	(*S*)-Phenylalanine methyl ester	B	MW, 6 min	92
14	(*S*)-Leucine methyl ester	B	MW, 6 min	95

Optical rotations compared well with the literature data, indicating that the chiral center is not involved during the reaction. Thus, (*S*)-methyl 2-formamido-3-methylbutanoate, $[\alpha]_D^{25}$ –27.5 (*c* 1.7, EtOH)[13,14] was recovered, without significant racemization of the chiral center, from (*S*)-valine methyl ester.

The results obtained may be consistent with the mechanism depicted in Scheme 2. As other carboxylic acids, formic acid should form an active formate ester with CDMT[21] that reacts with the amine compound to form the formyl derivative.



Scheme 2

In conclusion, we think that the one-flask method described here is simple and convenient, particularly using the procedure under microwave irradiation, for the preparation of formyl amides even in large scale, as it uses friendly reaction conditions and cheap reagents.[22] The method can be used as a valid alternative to other ones, however, as it avoids any tedious subsequent purification of the final product.

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(22) **A. Conventional Procedure:** Formic acid (0.35 g, 7.62 mmol), benzylamine (0.71 g, 7.62 mmol), 2-chloro-4,6-dimethoxy[1,3,5] triazine (CDMT, 1.47 g, 8.30 mmol), 4-dimethylaminopyridine (DMAP, 0.03 g, 0.2 mmol) and *N*-methylmorpholine (NMM, 0.92 mL, 8.30 mmol) were placed in this order in a flask containing CH_2Cl_2 (20 mL) and maintained at r.t. The mixture was stirred at reflux (6 h), monitored by TLC in order to control the end of the conversion, then diluted with CH_2Cl_2, washed twice with aq HCl (15 mL), aq $NaHCO_3$ (15 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4). Removal of the solvent in vacuo gave 0.98 g of chemically pure *N*-benzylformamide, (95%), mp 57 °C.[12]
B. Microwave Procedure: TEA (1.2 mL, 8.38 mmol) and L-valine methyl ester hydrochloride (1.27 g, 7.62 mmol) were placed in a flask equipped with a reflux condenser, containing CH_2Cl_2 (20.0 mL). Then formic acid (0.35 g, 7.62 mmol), CDMT (1.47 g, 8.30 mmol), DMAP (0.03 g, 0.20 mmol) and *N*-methylmorpholine (NMM, 0.92 mL, 8.30 mmol) were added in this order. The open flask was irradiated at 35 °C (by modulation of the power) for 6 min in a self-tuning single mode CEM Discover™ Focused Synthesizer. The solution was cooled rapidly at r.t. by passing compressed air through the 25 microwave cavity for 1 min, then diluted with CH_2Cl_2 and worked up as above. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 6.23 (br s, 1 H), 4.67 (dd, 1 H, *J* = 9.0, 4.8 Hz), 3.76 (s, 3 H), 2.24–2.17 (m, 1 H), 0.97 (d, 3 H, *J* = 6.8 Hz), 0.92 (d, 3 H, *J* = 6.6 Hz). (*S*)-Methyl 2-formamido-3-methylbutanoate from method A had $[\alpha]_D^{25}$ –27.2 (*c* 2.0, EtOH). Similarly, (*S*)-methyl 2-formamidobutanoate, (*S*)-methyl 2-formamido-3-phenylpropanoate, and (*S*)-methyl 2-formamido-4-methylpentanoate were recovered and had $[\alpha]_D^{25}$ values of –36.1 (*c* 3.5, EtOH),[13] +85.3 (*c* 2.3, EtOH),[14] and –43.2 (*c* 1.2, EtOH), respectively.[13]