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A convenient procedure for N-formylation of amines

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ABSTRACT

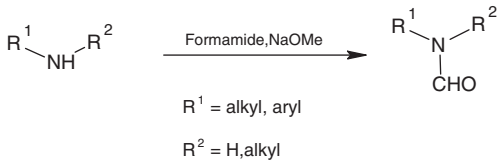
A simple and convenient method for the N-formylation of primary and secondary amines including amino acids has been developed utilizing formamide and sodium methoxide in moderate to excellent yield. This reagent is also utilized for one pot conversion of compounds having amino esters to *N*-formyl amides.

N-formylation of amines has utmost importance in organic synthesis and medicinal chemistry. A variety of medicinally active compounds have formamides as their intermediates.[1] *N*-Formyl protection gained popularity in peptide synthesis[2–4] since *N*-formyl deprotection can easily be achieved without affecting peptide bond and also it may serve as a precursor for isocyanide[5] and formamidine[6] synthesis.

Reported literature methods for N-formylation[1,3,7] use reagents such as chloral, formic acid–DCC, formic acid–EDCI, formic acid–$ZnCl_2$, formic acid–PEG 400, formic acid esters, CMT, DMF–NaOMe, formic acid–thiamine hydrochloride, and imidazole–DMF. Most of these methods suffer from disadvantages such as harsh condition, low yield, very high reaction temperature, expensive reagent etc.

In this Letter we report a simple and efficient method for N-formylation of amines using formamide and sodium methoxide. The amidation of carboxylic esters and *N*-Boc amino esters using formamide and sodium methoxide is a widely used method for the synthesis of carboxamide.[8–10] We explored the synthetic utility of this method for N-formylation of amino group. The reaction can be carried out using formamide as solvent or as reactant in THF.

N-formylation of various primary and secondary aliphatic, aromatic amines, and amino acids was studied using this method (Scheme 1). Primary and secondary amines undergo reaction at room temperature[11] in 2–6 h in very good yield except entry 4 (Table 1) which requires higher temperature of 60–70 °C. The results are summarized in Table 1. Both aliphatic and aromatic amines with ester functionality resulted in one pot conversion to N-formylated amide derivatives in good yield Table 1 (entries 5–7) (Scheme 2).



Scheme 1.

The reported methods of N-formylation of amino acid require inert atmosphere, expensive reagents, and harsh reaction conditions resulting in tedious purification and in certain cases protection and deprotection of carboxylic group.[1,3,4] We explored this method for the N-formylation of amino acids and studied the reaction with phenyl alanine, phenyl glycine, and proline.[12] The reaction was carried out in THF under reflux condition (8–12 h) and the corresponding *N*-formyl product was isolated in 61–92% yield (Table 1 entries 8–10) (Scheme 2).

In conclusion we have developed a simple, convenient, and commercially viable method for N-formylation of amines and amino ester to *N*-formyl amides using inexpensive formamide and sodium methoxide.

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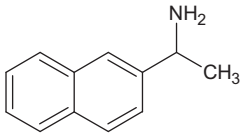
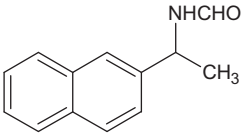
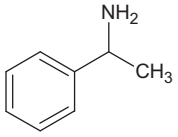
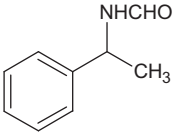
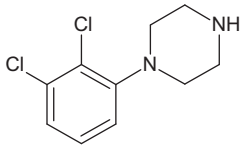
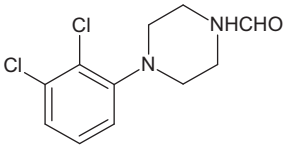
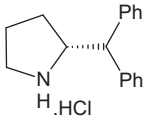
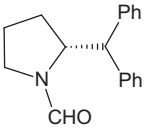
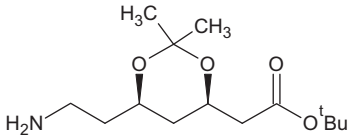
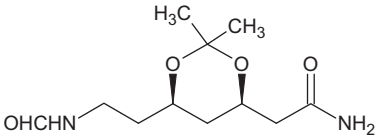
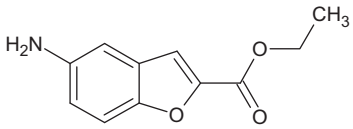
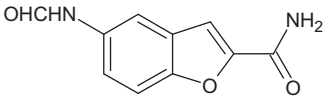
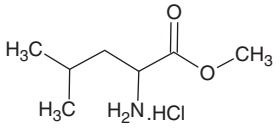
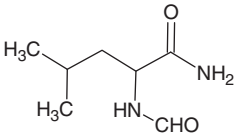
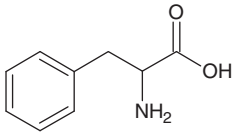
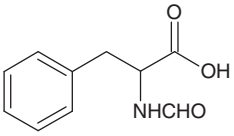
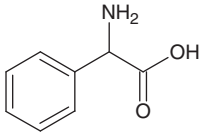
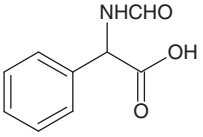
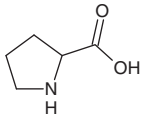
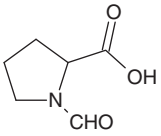
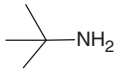
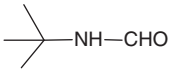
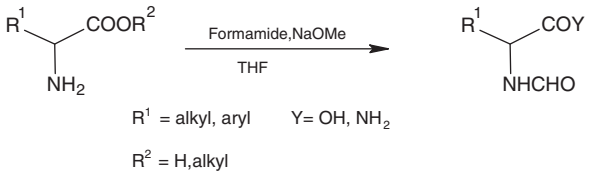
Table 1
N-formylation of amines

Entry	Starting material	Reaction temp (°C)	Product	Yield (%)
1		rt		88
2		rt		85
3		rt		92
4		60–70		76
5		rt		63
6		rt		86
7		60–70		68
8		60–70		92
9		60–70		87
10		60–70		61
11		rt		44



Scheme 2.

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11. General procedure for N-formylation of amines: To a stirred solution of 1-(2,3-dichlorophenyl) piperazine (entry 3) (5 g, 0.022 mol) in THF (25 mL) was added formamide (2.4 g, 0.054 mol).To the above mixture was added sodium methoxide (30% solution in methanol, 9.7 g, 0.054 mol) and stirred at room temperature for 6 h. The solvent was evaporated and the reaction mixture was diluted with water and extracted with dichloromethane (50 mL × 2). The dichloromethane layer was washed with 25 mL of dilute HCl and concentrated under reduced pressure to give the product (5.1 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.99–3.056 (m, 4H), 3.55–3.57 (t, 2H), 3.73 (t, 2H), 6.91–6.96 (d, 1H), 7.14–7.21 (m, 2H), 8.09 (s, 1H); MS: (*m*/*z*) 259.2.
12. General procedure for N-formylation of amino acids: To a stirred solution of phenyl alanine (entry 8) (5 g, 0.03 mol) in THF (25 mL) was added formamide (3.4 g, 0.075 mol). To the above mixture was added sodium methoxide (30% solution in methanol, 13.6 g, 0.09 mol) and stirred at 60–70 °C for 12 h. The solvent was evaporated and the reaction mixture was diluted with water (25 mL) and pH was adjusted to ~3 using aq HCl (~1 N). The precipitated product was filtered and washed with water and dried under vacuum to give the product (5.3 g, 92%). ^{1}H NMR (400 MHz, CD_3OD): δ 2.97–3.03 (dd, 1H), 3.20–3.25 (dd, 1H), 4.76–4.79 (dd, 1H), 7.20–7.33 (m, 5H), 8.02 (s, 1H); MS: (*m*/*z*) 194.2 (M+1).