



# A convenient method for the *N*-formylation of secondary amines and anilines using ammonium formate

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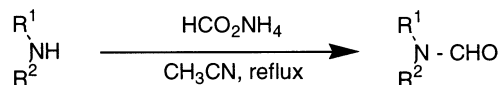
## Abstract

The *N*-formylation of secondary amines and anilines using ammonium formate as a formylating agent is described. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* ammonium formate; *N*-formylation; secondary amines and anilines.

Formamides are a class of important intermediates in organic synthesis. They have been widely used in the synthesis of pharmaceutically important compounds such as fluoroquinolones,<sup>1</sup> substituted aryl imidazoles,<sup>2</sup> 1,2-dihydroquinolines,<sup>3</sup> nitrogen bridged heterocycles,<sup>4</sup> etc. Formamides are Lewis bases, which are known to catalyze reactions such as allylation<sup>5</sup> and hydrosilylation<sup>6</sup> of carbonyl compounds. More recently, asymmetric allylation of aldehydes has been achieved with chiral formamides.<sup>7</sup> Furthermore, formamides are very useful reagents in Vilsmeier formylation reactions.<sup>8</sup> In addition, they have been used in the synthesis of formamidines<sup>9</sup> and isocyanides.

Numerous methods are available for the *N*-formylation of amines,<sup>10–13</sup> however, many of these methods involve reagents which are either toxic or expensive. In this communication, we report ammonium formate as relatively less expensive and efficient *N*-formylating agent for secondary amines and anilines.<sup>14</sup>



$\text{R}^1, \text{R}^2 = \text{alkyl or aryl}$

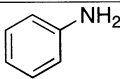
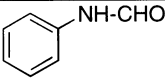
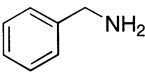
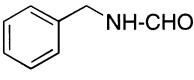
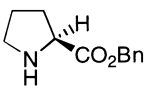
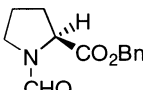
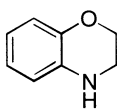
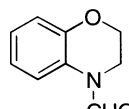
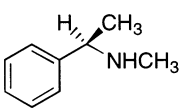
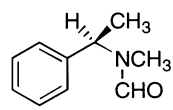
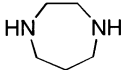
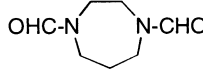
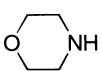
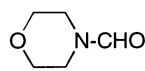
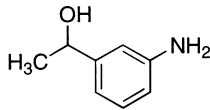
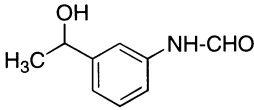
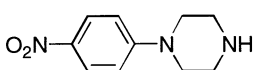
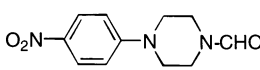
Ammonium formate mediated *N*-formylation of secondary amines and anilines takes place readily in acetonitrile at reflux temperature and the yields are usually very good. However, under

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similar reaction conditions, primary amines give alkyl ammonium formate salts, except benzylamine, which gave the desired *N*-formyl derivative in high yield.

The generality of this methodology has been studied with different secondary amines and anilines. The reaction time and yields are summarized in Table 1.<sup>15</sup> The benzyl ester of L-proline (entry 3) was converted to the corresponding *N*-formyl compound without racemization

Table 1  
*N*-Formylation of secondary amines and anilines with ammonium formate

Entry	Substrate	Eq. Of HCO <sub>2</sub> NH <sub>4</sub>	Time (hours)	Product	Yield %
1		1.5	11		96
2		1.5	6		88
3		2.0	8		75
4		2.0	12		93
5		1.5	9		96
6		3.0	8.5		97
7		1.5	10		95
8		2.0	15		71
9		1.5	7.5		95

{ $[\alpha]_D = -42.9$  ( $c$  3, MeOH)}. 4-(Piperazinyl) nitrobenzene (entry 9) gave the corresponding *N*-formyl derivative in excellent yield, which is a useful precursor in the synthesis of oxazolidinone<sup>16</sup> antibacterial agents. It is interesting to note that an aniline with a hydroxy group in the side chain (entry 8) undergoes chemoselective *N*-formylation in good yield.

*Typical experimental procedure:* To a solution of aniline (465 mg, 5 mmol) in dry acetonitrile (7.5 mL) was added anhydrous ammonium formate (473 mg, 7.5 mmol) and the resulting mixture was heated at 95°C (bath temperature) for 11 h. Acetonitrile was removed under reduced pressure. The residue was diluted with ethyl acetate (20 mL) and washed with water (2×10 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and then concentrated under reduced pressure to yield pure formanilide (580 mg, 96%) as a low melting solid, mp 48–50°C.

In conclusion, we have developed a convenient and mild method for *N*-formylation of secondary amines and anilines in excellent yields using the less expensive ammonium formate. We believe this novel methodology will find wide application in organic synthesis.

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