# Facile and Highly Efficient N-Formylation of Amines Using a Catalytic Amount of Iodine under Solvent-Free Conditions

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**Abstract:** We developed a simple, practical, and catalytic method for the N-formylation of a wide variety of amines in the presence of molecular iodine as a catalyst under solvent-free conditions. This reaction is applicable to the chemoselective N-formylation of amino groups and α-amino acid esters without epimerization.

**Key words:** amine, N-formylation, formic acid, iodine catalysis, solvent-free

Formamides have been widely used as amino acid protecting groups in peptide synthesis, as these amino acids are valuable starting materials in pharmaceutical syntheses.[1–3] Formamides have also been involved in Vilsmeier formylation[4] and in the allylation[5] and hydrosilylation[6] of carbonyl compounds. As such, a number of formylating methods have been reported. General formylation methodologies typically employ the use of mixed anhydrides including acetic formic anhydride,[7] formic acid/EDAC,[8] formic acid/DCC,[9] and formyl pivaloyl anhydride.[10] Formylation with formates such as 2,2,2-trifluoroethyl formate,[11] pentafluorophenyl formate,[12] cyanomethyl formate,[13] and ammonium formate[14] have been reported, although the reactivities of these reactions are low. In addition, chloral,[15] formic acid/Lewis acids,[16] PEG-400,[17] KF-alumina,[18] and solid-supported reagents[19] have also been used in formylation reactions. Regardless of the method, many of these formylation agents have drawbacks, including thermal instability, sensitivity to moisture, toxicity, high cost, prolonged reaction time, and formation of undesirable byproducts. Thus, a simple and efficient method for catalytic formylation of amines is highly desirable.

Molecular iodine has emerged as a versatile catalyst for various organic transformations, affording corresponding products in high levels of chemical yield and selectivity.[20] In addition, molecular iodine provides several advantages such as low cost, nontoxicity, and easy workup with environmentally benign reaction conditions. As part of our effort to develop new catalytic reactions,[21] we report herein a simple and convenient approach for N-formylation of amines using molecular iodine as a catalyst under solvent-free conditions. An initial study was performed in which aniline was treated with formic acid (3 equiv) at 70 °C in the presence of stoichiometric levels of iodine under solvent-free conditions. The reaction proceeded smoothly and was completed in two hours, affording formanilide in a 93% yield (Table 1, entry 1). To develop a catalytic variant, the reaction was carried out in the presence of catalytic amounts of iodine (0.1 equiv). The reaction proceeded efficiently, affording formanilide in the same yield as that of the stoichiometric version (entry 2).

Further studies to establish the optimal reaction conditions determined that 5 mol% iodine and 2 equivalents of formic acid were sufficient to efficiently perform the reaction (entry 5). A decrease in the amount of formic acid gave a lower yield of the desired product (entry 6). Higher reaction temperatures decreased the yield (entry 7), and the reaction did not reach completion after 72 hours at room temperature (entry 8). The reaction performed in MeCN was less effective than those performed under solvent-free conditions (entry 9).

**Table 1** The Optimization of Reaction Conditions for N-Formylation of Aniline in the Presence of Iodine

$$\text{Ph—NH}_2 \xrightarrow[\text{HCOOH}]{\text{I}_2} \text{Ph—NHCHO}$$

| Entry | HCOOH (equiv) | $I_2$ (equiv) | Time (h) | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 3 | 1 | 2 | 70 | 93 |
| 2 | 3 | 0.1 | 2 | 70 | 93 |
| 3 | 3 | 0.1 | 2 | 70 | 93 |
| 4 | 2 | 0.1 | 2 | 70 | 94 |
| 5 | 2 | 0.05 | 2 | 70 | 94 |
| 6 | 1 | 0.05 | 4 | 70 | 35 |
| 7 | 2 | 0.05 | 2 | 100 | 86 |
| 8 | 2 | 0.05 | 72 | r.t. | 42 |
| 9[a] | 2 | 0.05 | 4 | 70 | 71 |

[a] The reaction was performed in MeCN.

To demonstrate the versatility of the iodine method, we next investigated the scope of this reaction under the optimized conditions. A wide range of aromatic and aliphatic amines were subjected to the novel reaction conditions,

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and the results are summarized in Table 2. All of the amines examined reacted efficiently, affording the corresponding *N*-formyl products in good to excellent yields. Anilines containing either electron-donating or electron-withdrawing groups underwent the conversion smoothly (entries 1–4), although anilines with a strong electron-withdrawing group required longer reaction times (entry 4). Previously, the N-formylation of anilines with electron-withdrawing groups was found to be difficult.[22] Secondary aryl amines were also good substrates for the reaction, affording high yields of the corresponding formamides (entries 5–7). The reactions with aliphatic primary and secondary amines resulted in high product yields (entries 8–14).

**Table 2** Iodine-Catalyzed N-Formylation of Amines under Solvent-Free Conditions

$$\underset{\text{(1 equiv)}}{\text{R—NH}_2} + \underset{\text{(2 equiv)}}{\text{HCOOH}} \xrightarrow[70\ °\text{C}]{\text{I}_2\ (5\ \text{mol\%})} \text{R—NHCHO}$$

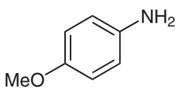
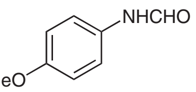
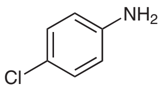
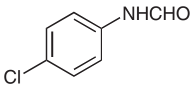
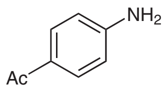
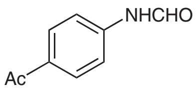
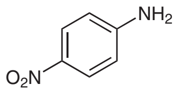
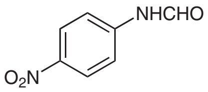
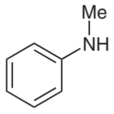
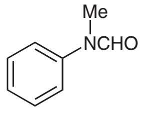
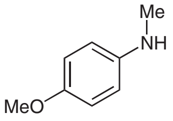
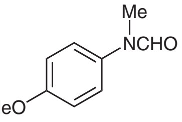
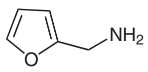
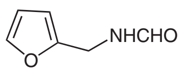
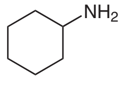
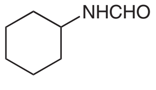
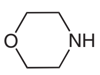
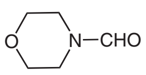
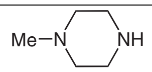
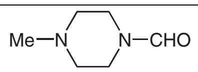
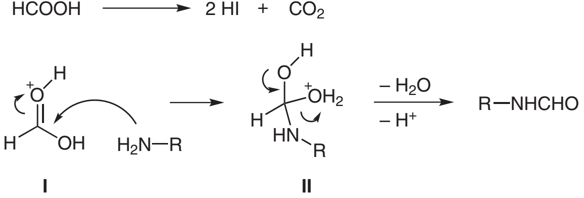
| Entry | Amine | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  |  | 2 | 96 |
| 2 |  |  | 2 | 96 |
| 3 |  |  | 4 | 82 |
| 4 |  |  | 8 | 86 |
| 5 |  |  | 3 | 82 |
| 6 |  |  | 3 | 84 |
| 7 | $Ph_2NH$ | $Ph_2NCHO$ | 3 | 85 |
| 8 | $BnNH_2$ | BnNHCHO | 2 | 91 |
| 9 | $n$-$BuNH_2$ | $n$-BuNHCHO | 4 | 79 |
| 10 |  |  | 2 | 89 |
| 11 |  |  | 3 | 82 |
| 12 | $(i$-$Pr)_2NH$ | $(i$-$Pr)_2NCHO$ | 4 | 69 |
| 13 |  |  | 4 | 71 |
| 14 |  |  | 3 | 74 |

**Table 2** Iodine-Catalyzed N-Formylation of Amines under Solvent-Free Conditions

Chemoselectivity of the iodine reaction was also investigated by performing formylation of amines in bifunctional compounds (Table 3). Excellent chemoselectivity was observed for substrates with hydroxy functionalities, providing *N*-formyl derivatives as the sole product without side reactions (entries 1–4). The iodine-catalyzed N-formylation strategy was also applied to the formylation of optically pure chiral α-amino acid esters (entries 5–7). When the α-amino acid esters were treated with formic acid in the presence of iodine, *N*-formyl amino acid esters were obtained in high yield without epimerization at the stereogenic centers, as determined by comparing the optical rotations of the products with those of the authentic samples.

It is known that iodine reacts with formic acid to afford HI.[23] Thus, we assumed that in situ generated HI is the real active species. Protonation of the carbonyl group of formic acid (**I**) is followed by an attack of the amine to give intermediate **II**, which is transformed into the desired formylated product, water, and proton, which further catalyzes the reaction (Scheme 1).



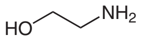
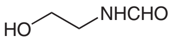
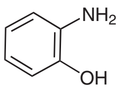
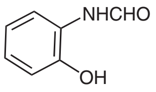
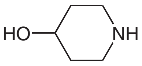
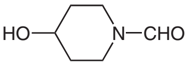
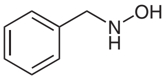
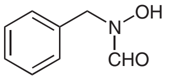
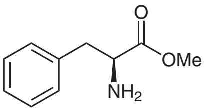
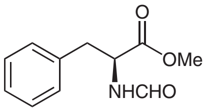
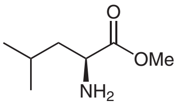
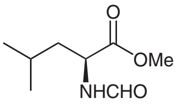
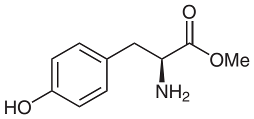
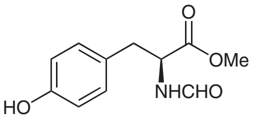
**Scheme 1**

In summary, we developed a simple, practical, and catalytic method for amine N-formylation in the presence of molecular iodine as a catalyst under solvent-free conditions. A wide variety of amines are good substrates for the reaction. This reaction is applicable to the chemoselective N-formylation of amino groups and α-amino acid esters without epimerization.

## Typical Experimental Procedure

A mixture of amine (2 mmol), formic acid (99% purity, 151 mL, 4 mmol), and iodine (12.7 mg, 5 mmol%) was stirred at 70 °C. After completion of the reaction as determined by TLC, the mixture was diluted with $CH_2Cl_2$ (20 mL), washed with sat. $Na_2S_2O_3$ (10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL), and then dried over anhyd $MgSO_4$. After filtration and evaporation of the solvent, the residue

**Table 3** N-Formylation of Amino Alcohols and α-Amino Acid Esters in the Presence of Iodine under Solvent-Free Conditions[a]

| Entry | Substrate | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  |  | 2 | 85 |
| 2 |  |  | 2 | 90 |
| 3 |  |  | 4 | 72 |
| 4 |  |  | 4 | 84 |
| 5 |  |  | 2 | 82 |
| 6 |  |  | 2 | 80 |
| 7 |  |  | 3 | 77 |

[a] Reaction conditions: a mixture of amine (2 mmol), formic acid (4 mmol), and iodine (5 mmol%) was stirred at 70 °C.

was purified by column chromatography on silica gel to give the formylated product.

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## References

(1) (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley Interscience: New York, **2007**. (b) Martinez, J.; Laur, J. *Synthesis* **1982**, 979.

(2) (a) Chen, B.-C.; Bendarz, M. S.; Zhao, R.; Sundeen, J. E.; Chen, P.; Shen, Z.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, *41*, 5453. (b) Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, 575. (c) Jackson, A.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1319.

(3) (a) Floresheimer, A.; Kula, M. R. *Monatsh. Chem.* **1988**, *119*, 1323. (b) Geiger, R.; Siedel, W. *Chem. Ber.* **1969**, *102*, 2487. (c) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offerman, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472.

(4) Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015.

(5) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *56*, 6620.

(6) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.

(7) (a) Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081. (b) Sheehan, J. C.; Yang, D. D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1154.

(8) Chen, F. M. F.; Benoiton, N. L. *Synthesis* **1979**, 709.

(9) Waki, J.; Meinhofer, J. *J. Org. Chem.* **1977**, *42*, 2019.

(10) Vlietstra, E. J.; Zwikker, J. W.; Nolte, R. J. M.; Drenth, W. *J. R. Neth. Chem. Soc.* **1982**, *101*, 460.

(11) Hill, D. R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 111.

(12) Kisfaludy, L.; Ötvös, L. Jr. *Synthesis* **1987**, 510.

(13) Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H.-J. *Synthesis* **1996**, 37.

(14) Reddy, P. G.; Kumar, G. D. K.; Baskaran, S. *Tetrahedron Lett.* **2000**, *41*, 9149.

(15) Blicke, F. F.; Lu, C. J. *J. Am. Chem. Soc.* **1952**, *74*, 3933.

(16) (a) Shekhar, A. C.; Kumar, A. R.; Sathaiah, G.; Paul, L.; Sridhar, M.; Rao, P. S. *Tetrahedron Lett.* **2009**, *50*, 7099. (b) Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652.

(17) Das, B.; Krishnaiah, K.; Balasubramanyam, P.; Veeranjaneyulu, B.; Kumar, D. N. *Tetrahedron Lett.* **2008**, *49*, 2225.

(18) Mihara, M.; Ishino, Y.; Minakara, S.; Komatsu, M. *Synthesis* **2003**, 2317.

(19) Desai, B.; Danks, T. N.; Wagner, G. *Tetrahedron Lett.* **2005**, 955.

(20) For recent examples, see: (a) Boëns, B.; Faugeras, P.-A.; Vergnaud, J.; Lucas, R.; Teste, K.; Zerrouki, R. *Tetrahedron* **2010**, *66*, 1994. (b) Lin, X.; Dai, X.; Mao, Z.; Wang, Y. *Tetrahedron* **2009**, *65*, 9233. (c) Jaratjaroonphong, J.; Sathalalai, S.; Techasauvapak, P.; Reutrakul, V. *Tetrahedron Lett.* **2009**, *50*, 6012. (d) Stępień, M.; Sessler, J. L. *Org. Lett.* **2007**, *9*, 4785. (e) Kidwai, M.; Bansal, V.; Mothsra, P.; Saxena, S.; Somvanshi, R. K.; Dey, S.; Singh, T. P. *J. Mol. Catal. A: Chem.* **2007**, *268*, 76. (f) Das, B.; Ravinder Reddy, K.; Ramu, R.; Thirupathi, P.; Ravikanth, B. *Synlett* **2006**, 1756. (g) Wu, J.; Xia, H.-G.; Gao, K. *Org. Biomol. Chem.* **2006**, *4*, 126. (h) Togo, H.; Iida, S. *Synlett* **2006**, 2159. (i) Wang, S.-Y. *Synlett* **2004**, 2642. (j) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213.

(21) (a) Kim, J.-G.; Jang, D. O. *Synlett* **2010**, 1231. (b) Kim, J.-G.; Jang, D. O. *Tetrahedron Lett.* **2009**, *50*, 2688. (c) Kim, J.-G.; Jang, D. O. *Synlett* **2007**, 2501. (d) Jang, D. O.; Moon, K. S.; Cho, D. H.; Kim, J.-G. *Tetrahedron Lett.* **2006**, *47*, 6063.

(22) Zaleska, B.; Karelu, M.; Flasiński, M.; Serda, P. *ARKIVOC* **2007**, *(vi)*, 64.

(23) (a) Perez-Benito, J. F.; Arias, C.; Brillas, E. *J. Chem. Res., Synop.* **1990**, *12*, 380. (b) Hammick, D. L.; Zvegintzov, M. *J. Chem. Soc.* **1926**, 1105.