



## In situ protection and deprotection of amines for iron catalyzed oxidative amidation of aldehydes



Thulasiram Bathini, Vikas S. Rawat, Sreedhar Bojja\*

*Inorganic and Physical Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500607, India*

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### ABSTRACT

An environmentally friendly synthetic route by the application of CO<sub>2</sub> to synthesize amides via in situ protection and deprotection of amines for iron catalyzed oxidative amidation of aldehydes was developed. Various secondary and tertiary amides have been synthesized in moderate to good yields under mild and neutral reaction conditions. The use of amine hydrochloride salts and hence base for neutralization step is totally avoided in this protocol.

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### Introduction

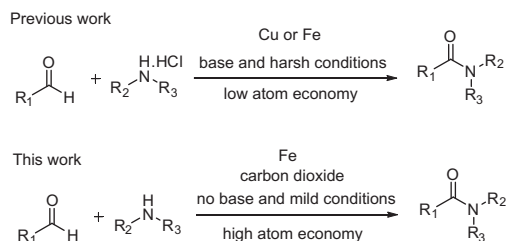
Nowadays, the catalytic formation of an amide bond is an active subject in modern organic synthesis and is one of the nature's incredibly significant chemical linkage of proteins. In addition, amides are found in many synthetic polymers, pharmaceutically active small molecules, and biologically active naturally occurring compounds. Amide bond construction is one of the most important reactions in organic chemistry and it is often hidden as an existing challenge, because of the prevalent occurrence of amides in nature.<sup>1</sup> As reported earlier by Sogani et al. most of the 3,4,5-trimethoxy-substituted benzamides were found to be CNS depressants and also to potentiate pentobarbital hypnosis in albino mice.<sup>2</sup> Here, we could easily synthesize various 3,4,5-trimethoxy-substituted benzamides and also different substituted benzamide derivatives that have various important biological activities like inhibition of tumor cells,<sup>3</sup> leishmanicidal,<sup>4</sup> antinociceptive activity,<sup>5</sup> fungicidal,<sup>6</sup> repellent,<sup>7</sup> antimalarial,<sup>8</sup> etc.

The most prevalent and straight forward approach to amide bond formation is the condensation of an amine with a carboxylic acid derivative or by using a coupling reagent.<sup>9</sup> On the other hand, due to instability of activated carboxylic acid derivatives, it confines their universal applications and creates significant challenges.<sup>10</sup> To overcome these challenges, alternative routes

include transition metal catalyzed hydrative amide synthesis with terminal alkynes,<sup>11</sup> carbonylation of alkynes,<sup>12</sup> alkenes and haloarenes,<sup>13</sup> modified Staudinger reaction<sup>14</sup> using azide as a source of nitrogen, thio acid/ester ligation methods,<sup>15</sup> direct amidation of aldehydes,<sup>16</sup> oxidative amidation of aldehydes with amine hydrochloride salts, etc. Among all the reported protocols, oxidative amidation of aldehydes with amine hydrochloride salts is the most attractive atom economic strategy by the direct reaction of an acyl C–H bond of aldehydes with amines in the presence of transition metals under oxidative conditions. Yoo and Li have developed this method by using CuI as catalyst and silver iodate as an additive.<sup>17</sup> Ghosh et al., have recently shown that copper and iron salts are effective catalysts for the oxidative amidation of aldehydes with amine hydrochloride salts.<sup>18</sup> In all the methods described so far, amine hydrochloride salts rather than free amines are used. As it is well known that, amines undergo *N*-oxidative decomposition or imine formation (for primary amines) in the presence of TBHP, hence the use of amine salts is vital for this oxidative amidation as it is less prone to oxidation by TBHP. However, numerous amines are present in free form, and are not suitable for this TBHP-mediated oxidative amidation, thus it necessitated us to expand the substrate scope by in situ preparation of amine salts from free amines. In this direction, Chen et al., successfully demonstrated the in situ formation of amine salts from free amines in the case of morpholine and benzyl amine and the corresponding amides were obtained in yields comparable to those using commercial amine salts.<sup>17</sup> Although these are effective methods, many of these are still suffering from one or more

\* Corresponding author. Tel.: +91 40 27191715; fax: +91 40 27160921.

E-mail address: [sreedharb@iict.res.in](mailto:sreedharb@iict.res.in) (S. Bojja).



**Figure 1.** Comparison of previous work with present work.

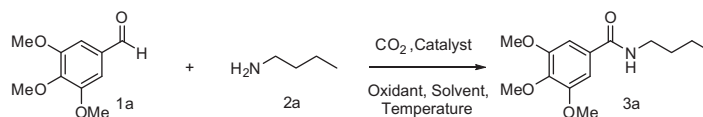
disadvantages, such as use of hazardous reagents, expensive catalysts, harsh reaction conditions, difficult operation, lower yields, poor functional group tolerance, and narrow substrate scope. To circumvent these problems we have recently developed an oxidative amidation of aldehydes with amine hydrochloride salts by using environmentally benign magnetic CuFe<sub>2</sub>O<sub>4</sub> nanoparticles.<sup>19</sup> In light of our recent success in oxidative amidation reaction we turned our attention to the much more challenging amidation reaction of simple aldehydes and amines. Herein, we present an

efficient iron-catalyzed oxidative amidation of aldehydes with amines instead of using amine hydrochloride salts by in situ synthesis of carbamate ammonium salts from free amines by reacting with carbon dioxide (see Fig. 1).

## Results and discussion

Delightfully, our initial reaction of 3,4,5-trimethoxybenzaldehyde (**1a**) (1.0 equiv) and *n*-butyl amine (**2a**) (1.2 equiv) as reactants, FeCl<sub>2</sub>·4H<sub>2</sub>O (10 mol %) as catalyst, and TBHP (1.1 equiv) as oxidant in CH<sub>3</sub>CN (2 ml) under N<sub>2</sub> atmosphere at 60 °C lead to the formation of *N*-butyl-3,4,5-trimethoxybenzamide (**3a**) in 61% yield (Table 1, entry 1). For CO<sub>2</sub> absorption, the *n*-butyl amine (**2a**) was stirred vigorously under CO<sub>2</sub> atmosphere for 15 min before the addition of other reagents and catalyst. This absorption reaction is exothermic and leads to the formation of white solid carbamate of *n*-butyl amine (**2a**). For further optimization study, we chose 3,4,5-trimethoxybenzaldehyde (**1a**) and *n*-butyl amine (**2a**) as our model substrates. We initially undertook the study of effect of temperature on reaction output, since the release of free amine from carbamate is govern by temperature of the reaction

**Table 1**  
Optimization of the reaction conditions<sup>a</sup>



| Entry | Catalyst                                  | Oxidant   | Solvent            | Additive | Temp (°C) | Yield <sup>b</sup> (%) |
|-------|---|---|--------------------|----------|-----------|------------------------|
| 1     | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 60        | 61                     |
| 2     | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 25        | 0                      |
| 3     | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 30        | 42                     |
| 4     | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 40        | 67                     |
| 5     | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 50        | 62                     |
| 6     | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 70        | 58                     |
| 7     | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 80        | 52                     |
| 8     | <i>np</i> -Fe <sub>3</sub> O <sub>4</sub> | Aq TBHP   | CH <sub>3</sub> CN | —        | 40        | <5                     |
| 9     | FeSO <sub>4</sub> ·7H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 40        | 60                     |
| 10    | Fe(acac) <sub>3</sub>                     | Aq TBHP   | CH <sub>3</sub> CN | —        | 40        | 57                     |
| 11    | FeCl <sub>3</sub> ·6H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | —        | 40        | 55                     |
| 12    | FeCl <sub>2</sub>                         | Aq TBHP   | CH <sub>3</sub> CN | —        | 40        | 62                     |
| 13    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | Dioxane            | —        | 40        | Trace                  |
| 14    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | Toluene            | —        | 40        | 25                     |
| 15    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | THF                | —        | 40        | 10                     |
| 16    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | MeOH               | —        | 40        | 13                     |
| 17    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | H <sub>2</sub> O   | —        | 40        | 0                      |
| 18    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | EtOAc              | —        | 40        | 20                     |
| 19    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | PEG-400            | —        | 40        | 0                      |
| 20    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | DMF                | —        | 40        | 0                      |
| 21    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | DMSO               | —        | 40        | 0                      |
| 22    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | (NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> | CH <sub>3</sub> CN | —        | 60        | 0                      |
| 23    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | PhI(OAc) <sub>2</sub>   | CH <sub>3</sub> CN | —        | 60        | 16                     |
| 24    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | NaOCl   | CH <sub>3</sub> CN | —        | 60        | 0                      |
| 25    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq H <sub>2</sub> O <sub>2</sub>                              | CH <sub>3</sub> CN | —        | 60        | 0                      |
| 26    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | O <sub>2</sub>  | CH <sub>3</sub> CN | —        | 60        | 1                      |
| 27    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | TBAF     | 40        | 67                     |
| 28    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | TBAC     | 40        | 77                     |
| 29    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | TBAB     | 40        | 83                     |
| 30    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | TBAI     | 40        | 75                     |
| 31    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | TBHP  | CH <sub>3</sub> CN | TBAB     | 40        | 83 <sup>c</sup>        |
| 32    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | —   | CH <sub>3</sub> CN | TBAB     | 40        | 0 <sup>d</sup>         |
| 33    | —   | Aq TBHP   | CH <sub>3</sub> CN | TBAB     | 40        | Trace <sup>e</sup>     |
| 34    | FeCl <sub>2</sub> ·4H <sub>2</sub> O      | Aq TBHP   | CH <sub>3</sub> CN | TBAB     | 40        | Trace <sup>f</sup>     |

<sup>a</sup> Reaction conditions: 3,4,5-trimethoxybenzaldehyde (1.0 mmol), *n*-butylamine (1.2 mmol), oxidant (1.1 mmol), catalyst, (10 mol %) and additive (10 mol %) in solvent (2 mL) for 10 h under an inert atmosphere.

<sup>b</sup> Isolated yield.

<sup>c</sup> TBHP in decane.

<sup>d</sup> Without oxidant.

<sup>e</sup> Without catalyst.

<sup>f</sup> Without CO<sub>2</sub> absorption.

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