



# Iron-catalyzed benzamide formation. Application to the synthesis of moclobemide



Xavier Bantreil\*, Nasreddine Kanfar, Nicolas Gehin, Ethan Golliard, Pauline Ohlmann, Jean Martinez, Frédéric Lamaty\*

Institut des Biomolécules Max Mousseron, UMR 5247 CNRS–UM I–UM II–ENSCM, Université Montpellier II, Place E. Bataillon, 34095 Montpellier Cedex 5, France

## ARTICLE INFO

### Article history:

Received 30 April 2014

Received in revised form 30 May 2014

Accepted 1 June 2014

Available online 9 June 2014

### Keywords:

Iron

Homogeneous catalysis

Amides

Oxidation

Green chemistry

## ABSTRACT

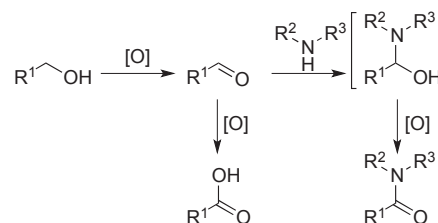
A convenient and user-friendly method to yield benzamides from primary and secondary amines and various benzylic alcohols in the presence of a cheap iron salt ( $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ ) and *tert*-butylhydroperoxide (70% in water) as a stoichiometric oxidant is described. Control experiments indicated that this reaction might involve radical species. This method proved to be general, generating a family of 30 benzamides and was applied to the preparative synthesis of anti-anxiety drug moclobemide.

© 2014 Elsevier Ltd. All rights reserved.

## 1. Introduction

Amides are highly important functional groups due to their preponderance in many natural products such as peptides and proteins, pharmaceutical agents or man-made polymers, such as Nylon 6,6.<sup>1</sup> In most cases, common techniques to generate an amide bond involve the use of toxic coupling agents and toxic solvents. On industrial scale, these drawbacks directly impact environment and economics. To circumvent such issues, organometallic methodologies to form amides directly from alcohols and amines have recently emerged.<sup>2</sup> The general mechanism for this type of reaction involves the oxidation of an alcohol to the corresponding aldehyde, which will react with the amine to form a hemiaminal intermediate that is converted to the amide upon oxidation. It is important to note that in a competitive pathway, the aldehyde could be oxidized to the carboxylic acid, an undesired side-product (Scheme 1).

Efficient approaches have been reported using transition metals such as ruthenium<sup>3</sup> and rhodium,<sup>4</sup> and heterogeneous catalysts,<sup>5</sup> such as Au/TiO<sub>2</sub> systems,<sup>6</sup> Au/DNA nanohybrids,<sup>7</sup> and alumina-supported silver clusters.<sup>8</sup> Such approaches are highly attractive

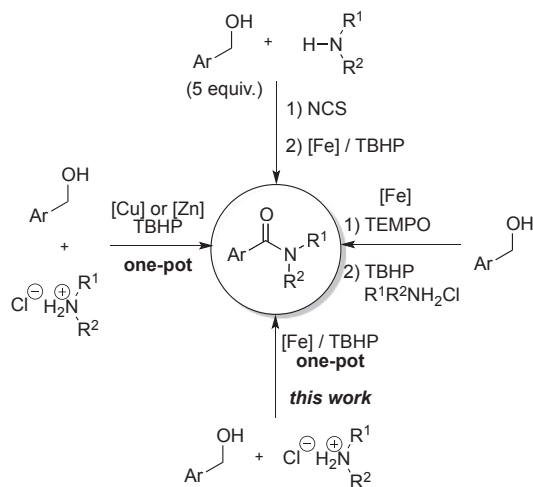


Scheme 1. General mechanism for amide formation.

as catalysis, step and atom economy are part of the 12 principles of green chemistry developed by Anastas and Warner.<sup>9</sup>

To compete with those techniques involving expensive metals, studies on copper- or iron-catalyzed formation of amides from aldehydes have been reported.<sup>10</sup> As a part of our general interest in amide bonds,<sup>11</sup> we recently reported the copper-catalyzed amidation directly from benzylic alcohols and amines, which allowed to go one-step further and realize a one-pot double oxidation.<sup>12</sup> Similar approach using zinc was developed (Scheme 2, left).<sup>13</sup> In 2013, Porcheddu et al. reported the iron-catalyzed amidation of *N*-chloramines, generated from toxic and non atom-economic *N*-chlorosuccinimide, which required the use of 5 equiv of alcohols to obtain good yields (Scheme 2, top).<sup>14</sup> More recently, Ghosh et al. reported a stepwise iron-catalyzed synthesis of benzamides, requiring a first step of oxidation of alcohol into aldehyde prior to

\* Corresponding authors. Tel.: +33 (0) 467143967; fax: +33 (0) 467144866; e-mail addresses: [xavier.bantreil@univ-montp2.fr](mailto:xavier.bantreil@univ-montp2.fr) (X. Bantreil), [frederic.lamaty@univ-mont2.fr](mailto:frederic.lamaty@univ-mont2.fr) (F. Lamaty).



Scheme 2. Benzamide formation from alcohols in the literature.

addition of the amine and TBHP (*tert*-butylhydroperoxide) as final oxidant (Scheme 2, right).<sup>15</sup> In here, we want to report a one-pot two-steps convenient and practical method using a cheap iron salt as catalyst and readily available hydrochloric salt of amines (TON < 8.9, TOF < 2.2 h<sup>-1</sup>).

## 2. Results/discussion

Optimization of the reaction conditions was started using benzylic alcohol and cyclohexamine hydrochloric salt (1.5 equiv) in the presence of TBHP (70% in H<sub>2</sub>O) as oxidant and an iron salt in refluxing acetonitrile. It is worth noting that initial attempts to perform the amidation directly from free amines failed, proving that masking of the nitrogen as its ammonium salt was compulsory to the reaction. As already stated for copper catalysis,<sup>12</sup> calcium carbonate gave the best results. Its weak basicity and poor solubility induce a slow and controlled release of free amine within the reaction media. In the meantime, the alcohol would be oxidized to aldehyde that could react with free amine to yield corresponding amide after a second oxidation. This choice of base proved to be the key point for the feasibility of a one-pot two-steps reaction.

Screening of iron salts was realized. Apart from K<sub>4</sub>Fe(CN)<sub>6</sub>·3H<sub>2</sub>O that gave only 53% conversion, all sources of iron tested gave around 80–85% conversion independently of the oxidation state of the metal (Table 1, entries 1–6). The best results were obtained using FeCl<sub>2</sub>·4H<sub>2</sub>O and FeCl<sub>3</sub>, giving 87% conversion of amide **3aa**. As FeCl<sub>2</sub>·4H<sub>2</sub>O is less corrosive than FeCl<sub>3</sub>, the optimization was continued with this salt. Replacement of TBHP (70% in H<sub>2</sub>O) by TBHP (5.5 M in nonane) or hydrogen peroxide induced a decrease to, respectively, 45% and 5% conversion (entries 7–8).

As explained above (Scheme 1), the main side-product formed during the amidation is carboxylic acid. During our previous study on copper-catalyzed amidation, we realized that alcohols featuring electron-donating groups were prone to convert quickly to corresponding benzoic acids. Thus, in view to develop the most general conditions and increase the isolated yield of this reaction, a reverse of the amine/alcohol stoichiometry was envisioned (Table 2). While the use of 1.3 equiv of alcohols in the presence of 5 equiv of TBHP and 5 mol % of FeCl<sub>2</sub>·4H<sub>2</sub>O gave a 72% yield (entry 1), increasing the quantity of iron salt to 10 mol % induced a satisfactory 89% yield (entry 2). Decreasing the excess of TBHP to 4 equiv did not affect the isolated yield (89%, entry 3). As commercially available iron salts are often contaminated with other metals, the reaction was performed using extra pure iron source and base. Resulting amide was isolated in 82% (entry 4), indicating that traces of metals were not

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

Entry	[Fe] (mol%)	[Ox] (equiv.)	Conversion (%) <sup>b</sup>
1	FeSO <sub>4</sub> ·7H <sub>2</sub> O (5)	TBHP (4)	84
2	FeCl <sub>2</sub> ·4H <sub>2</sub> O (5)	TBHP (4)	87
3	K <sub>4</sub> Fe(CN) <sub>6</sub> ·3H <sub>2</sub> O (5)	TBHP (4)	53
4	Fe(acac) <sub>3</sub> (5)	TBHP (4)	78
5	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O (5)	TBHP (4)	84
6	FeCl <sub>3</sub> (5)	TBHP (4)	87
7	FeCl <sub>2</sub> ·4H <sub>2</sub> O (5)	TBHP (4) <sup>c</sup>	45
8	FeCl <sub>2</sub> ·4H <sub>2</sub> O (5)	H <sub>2</sub> O <sub>2</sub> (4)	<5

<sup>a</sup> Reaction conditions: benzylic alcohol (0.5 mmol), cyclohexamine hydrochloride (0.75 mmol), CaCO<sub>3</sub> (0.75 mmol), TBHP (70% in H<sub>2</sub>O, 270 μL, 4 equiv.), CH<sub>3</sub>CN (1 mL), 80 °C, 4h.

<sup>b</sup> Conversion was determined by HPLC, based on **1a**.

<sup>c</sup> *tert*-butylhydroperoxide, 5.5M in nonane.

Table 2  
Optimization of the reaction conditions with a reverse stoichiometry<sup>a</sup>

Entry	[Fe] (mol %)	[Ox] (equiv)	Ratio <b>2a/1a</b>	Yield (%) <sup>b</sup>
1	FeCl <sub>2</sub> ·4H <sub>2</sub> O (5)	TBHP (5)	1:1.3	72
2	FeCl <sub>2</sub> ·4H <sub>2</sub> O (10)	TBHP (5)	1:1.3	89
3	FeCl <sub>2</sub> ·4H <sub>2</sub> O (10)	TBHP (4)	1:1.3	89
4	FeCl <sub>2</sub> ·4H <sub>2</sub> O (10) <sup>c</sup>	TBHP (4)	1:1.3	82
5	—	TBHP (4)	1:1.3	27

<sup>a</sup> Reaction conditions: Benzylic alcohol (0.65 mmol), cyclohexamine hydrochloride (0.5 mmol), CaCO<sub>3</sub> (0.5 mmol), TBHP (70% in H<sub>2</sub>O, 270 μL, 4 equiv.), CH<sub>3</sub>CN (1 mL), 80 °C, 4 h.

<sup>b</sup> Isolated yield, based on **2a**.

<sup>c</sup> FeCl<sub>2</sub>·4H<sub>2</sub>O 99.99% and CaCO<sub>3</sub> 99.995% pure were used.

responsible for the amidation reaction. Finally, a control experiment in the absence of iron salt indicated that the transition metal was necessary to the reaction (27% without FeCl<sub>2</sub>·4H<sub>2</sub>O, entry 5).

The scope of the reaction was then examined. First, variation of the amine was investigated (Table 3). For convenience, even if not specified, the amine hydrochloride salts were used throughout this study. Methyl and butyl amine reacted efficiently yielding **3ab** and **3ac** in 70% and 76%, respectively. Increasing the bulkiness with *iso*-propyl and cyclohexamine did not affect the amidation reaction (**3ad**, 72%; **3aa**, 89%). Even bulkier *tert*-butyl amine gave **3ae** in 59% yield. Benzyl amine, which was shown to yield easily benzamide in the presence of iron and TBHP,<sup>16</sup> was found to produce amide **3af** in 63% yield. Substituted benzylamines **2g–i** furnished corresponding amides in yields spanning from 52% to 86%. Phenethyl and *p*-methoxyphenethyl amines **2j** and **2k** gave corresponding amides in moderate yields (≈ 60%). Phenylalanine *tert*-butyl ester gave 77% of corresponding benzoylated amino acid **3al**. To our delight, the use of unprotected phenylalanine hydrochloric salt allowed the coupling in 70% yield (**3am**), indicating the tolerance of the conditions toward the carboxylic acid functionality. To the best of our knowledge, such reaction with substrate featuring a free acid had never been accomplished in previous reports. The iron-catalyzed amidation was also performed in the presence of more nucleophilic but also more hindered secondary amines. Although bearing two benzylic oxidable positions, dibenzylamine gave a good 81% yield of **3an**. Cyclic amines reacted correctly, HCl-Pro-<sup>t</sup>Bu (**2o**), piperidine (**2p**) and morpholine (**2q**) yielding the corresponding amides in, respectively, 55% (**3ao**), 65% (**3ap**) and 64% (**3aq**).

The diversification was continued using various benzylic alcohols in the presence of ( $\alpha$ )-methylbenzyl amine **2g** (Table 4).

Download English Version:

<https://daneshyari.com/en/article/5215955>

Download Persian Version:

<https://daneshyari.com/article/5215955>

[Daneshyari.com](https://daneshyari.com)