



A continuous-flow synthesis of primary amides from hydrolysis of nitriles using hydrogen peroxide as oxidant

Wei Zhan, Ling Ji, Ze-mei Ge, Xin Wang^{**}, Run-tao Li^{*}

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, Peking University, China

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ABSTRACT

A continuous-flow synthesis of primary amides from hydrolysis of nitriles using hydrogen peroxide as oxidant has been developed. Using this procedure, a variety of nitriles could be smoothly transformed into the desired primary amides in good to excellent yields. The mild reaction conditions and the flowing reaction system greatly improved the safety and make the reaction easy to scale up.

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1. Introduction

Amide, a very common class of organic compounds, has widely applied in organic chemistry, pharmaceuticals, material science and so on. Primary amide is an important kind of amides, among which, many are biological active compounds and even drugs (Scheme 1).¹ Thus, the development of efficient procedures for the formation of primary amide has received considerable attentions and many methods have been reported^{2–7}.

As shown in Scheme 2, the synthesis of primary amides can be mainly divided into four kinds: 1) hydrolysis of the corresponding nitriles²; 2) amidation of acids or acid chlorides with ammonia³; 3) oxidative amidation of corresponding aldehydes or aldoximes⁴; 4) oxidation of primary amines or alcohols.⁵ Among them, hydrolysis of nitriles has become one of the most widely used methods in both academia and industry.⁶ Yet, the conventional methods usually require strong acid or base as catalyst^{2a–c} which may cause over-hydrolysis⁸ of primary amides and are not suitable for sensitive substrates along with a large amount of salts after neutralization of the catalysts. In order to overcome these shortcomings, different kinds of metal catalysts, i.e. Ru, Pd, Ni, Au, have been used.^{2d–j} However, the cost of expensive metal-complex, the separation of

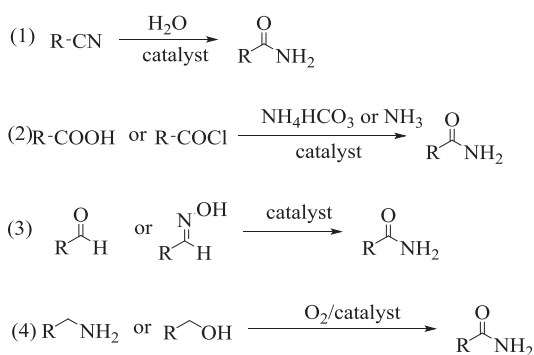
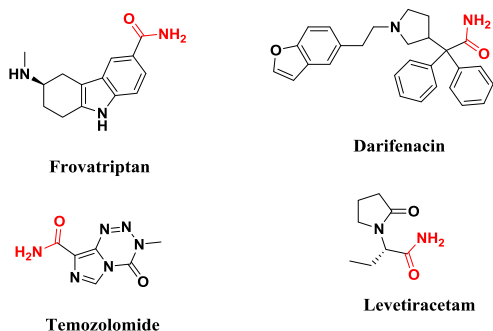
products and drastic condition are needed to be addressed. Therefore, oxidative hydrolysis of nitriles using hydrogen peroxide to produce primary amides was expanded.⁷ To improve its effectiveness, some efforts have been made such as adding surfactant or using sodium peroxide, sodium perborate or urea peroxide instead of hydrogen peroxide.⁹ Although oxidative hydrolysis of nitriles using hydrogen peroxide is well reported in the literature, its application, especially on a larger scale, is still limited due to the exothermic and explosive problem in high concentration and weak reactivity in low concentration.

In the past decade, micro-reactor technology has emerged as a powerful tool for solving synthetic problems in the field of pharmaceutical and fine chemical researches due to its environmental friendliness, efficiency and safety.^{10a–g} The latest issue of Bioorganic & Medicinal Chemistry has a special issue reported the organic synthesis in flow for medicinal chemistry.^{10h} The hydrogen peroxide as oxidant has been successfully applied in several reactions in continuous flow mode.¹¹ For example, Gavriilidis et al. used hydrogen peroxide as an oxidant to facilitate epoxidation of 1-pentene in a microchannel coated with titanium silicalite-1 zeolite^{12a}; Wiles and Watts et al. investigated the oxidation of 1-methylcyclohexene catalyzed by *Candida antarctica* lipase B (Novozymes 435) with H₂O₂ in a continuous flow packed-bed reactor in full conversion at 70 °C with a residence time of 2.6 min.^{12b} By using a packed-bed microreactor loaded with a new catalyst [PO₄{WO(O₂)₂}₄] @PIILP, Doherty and Hardacre et al. successfully obtained high yield of sulfoxide (92%) in methanol

* Corresponding author.

** Corresponding author.

E-mail address: lirt@bjmu.edu.cn (R.-t. Li).



Scheme 2. Methods for preparing primary amides.

within 4 min of residence time and sulfone (96%) in acetonitrile in a 15 min residence time.^{12c} Therefore, we envisioned to synthesize primary amide from hydrolysis of nitriles using hydrogen peroxide as oxidant in flow mode in order to improve the safety and make it easy to scale-up.

2. Results/Discussion

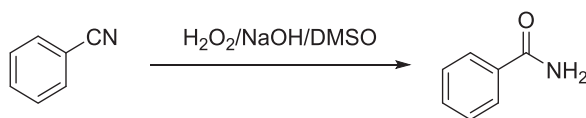
Firstly, benzonitrile was chosen as a model reaction substance. Considering the clogging of materials is the key issue to concern in a flow reaction, we first screened different volume alcohols as solvents in batch mode to make sure that there weren't any insoluble ingredients throughout the whole reaction process. As shown in Table 1, when using 15 mL EtOH as solvent (Table 1, entry

4) the reaction showed higher conversion and no solid precipitation. Later, a simple flow-platform was established as below, benzonitrile and DMSO were taken up in EtOH and pumped in inlet A, NaOH (aq) was taken up in EtOH and pumped in inlet B, and 30% H₂O₂(aq) was pumped in inlet C. The reaction stream was pressurized by a 10 bar back pressure regulator (BPR) and the outflow collected in saturated aqueous NaHSO₃ and EtOH. After being filtered, the outflow was analyzed by HPLC to determine conversion (Scheme 3).

In micro-reactors, temperature and residence time are parameters need to be optimized (Table 2). It can be seen that when the temperature rose from 0 °C to 35 °C in a residence time of 50s (Table 2, entry 1, entries 4–6), the conversion of benzonitrile would be increased from 84% to 98% and there was no obvious conversion difference between 25 °C and 35 °C. If the t_{R1} lengthened from 50s to 150s, the conversion would be raised from 84% to 100% (Table 2, entries 1–3). Reducing the amount of DMSO 1.0 eq to 0.5 eq would lead to a sharp drop in conversion (Table 2, entry 8) whereas reducing H₂O₂ to 1.8 eq or 1.2 eq would get a satisfied conversion with a prolonged residence time (Table 2, entry 9, 10, 11). Therefore, the reaction temperature of 25 °C, t_{R1} = 150s and a ratio of A:B:C = 1:0.0375:1.2 would be the preferable conditions (Table 2, entry 11).

With the optimized reaction conditions in hand, we then turned our attention to the substrate scope of this approach. As shown in Table 3, all tested substrates, including aromatic nitriles, hetero-aromatic nitriles and aliphatic nitriles produced the expected primary amides in good to excellent yields. For substituted benzonitriles, different functional groups, whether halogen, methyl, methoxyl, amino, nitro and ester group (Table 3, entries 2–9), or at different position (Table 3, entries 8–13), were all tolerated, achieving the yields of 80–99%. For the low reactive benzonitriles bearing strong electron withdrawing group (Table 3, entries 9–11), satisfied yields were obtained by extending the retention time. More importantly, the heteroaromatic nitriles containing pyridine, piperazine and thiophene were also high-yielding (Table 3, entries 14–16, 92–97%). Furthermore, this approach was also expanded to the aliphatic nitriles, such as phenylacetonitrile, 3-phenyl acrylonitrile and 3-acetoxy butyronitrile. Even high steric hindrance diphenyl-acetonitrile and pivalonitrile afforded the desired product in 75% and 62% yield respectively under 480s retention time (Table 3, entries 20, entries 21). It is worth noting that we have successfully applied this approach in the synthesis of 4-(4-methyl-piperazin-1-yl-methyl)-benzamide, a key intermediate for the synthesis of Imatinib, which is one of

Table 1
Reaction under batch mode.



Entry	Solvent	Volume (mL)	Conversion (%)	Additive	Result
1	ambient	–	100	DMSO	Much solid precipitation
2	EtOH	5	100	DMSO	Much solid precipitation
3	EtOH	10	92	DMSO	Few solid precipitation
4	EtOH	15	68	DMSO	No solid precipitation
5	EtOH	20	37	DMSO	No solid precipitation
6	MeOH	12	56	DMSO	No solid precipitation
7	EtOH	15	0	None	No solid precipitation

Reaction conditions: 10 mmol benzonitrile and 10 mmol DMSO was added into solvent under ice bath. After temperature went down to 0 °C, 0.5 mL 1 M NaOH and 1.2 mL 30% H₂O₂ was added, the mixture was reacted for 5 min and quenched by saturated aqueous NaHSO₃.

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