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Hydrogen peroxide-promoted metal free oxidative amidation of 2-oxoaldehydes: a facile access to unsymmetrical oxamides

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ABSTRACT

A novel and green H_2O_2-promoted oxidative amidation of 2-oxoaldehydes with amines to synthesize unsymmetrical oxamides has been developed. The reactions proceeded smoothly at room temperature under metal-free conditions and generated the corresponding products in good yields. This methodology has a broad substrate scope and opens up an interesting and attractive avenue for the synthesis of unsymmetrical oxamide derivatives.

1. Introduction

Amides, as an important structural backbone of various natural products, pharmaceuticals and polymers, have attracted considerable interest because of their important biologically active properties.[1] A recent survey on drug discovery shown that more than 50% of known drugs contain an amide functional group.[2] As an important and unique member of amides, oxamides also represents a key framework of many bioactive compounds.[3] They have been developed as acetylcholine esterase inhibitors,[4] C5a inhibitors,[5] nitric oxide synthase inhibitors,[6] *anti*-HIV agents,[7] antiepileptic drugs[8] and HIV integrase inhibitors[9] (Fig. 1).

A number of synthetic methods for oxamides have been established in the past decades.[10] However, only a few examples of the synthetic methods for unsymmetrical oxamides have been reported. Traditionally, unsymmetrical oxamides are synthesized from the condensation of corresponding carboxylic acids with amines, which needs either activating agents or conversion into more reactive derivatives (Scheme 1a).[11] In recent years, several innovative approaches have been developed, which include the direct amidation of isocyanates,[12] α-keto benzotriazole[13] or trichloropyruvamides[14] with amines (Scheme 1b–d). Nevertheless, these methods have several drawbacks, such as harsh conditions, expensive reagents, poor atom-efficiency and limited substrate scope. Therefore, a more mild, convenient and efficient method for the synthesis of unsymmetrical oxamides is still in high demand.

As far as we know, there has been no report on the synthesis of unsymmetrical oxamides via oxidative amidation yet. Our work is focused on the green oxidative amidation of 2-oxoaldehydes utilizing clean and inexpensive oxidants. Hydrogen peroxide is a very attractive candidate because of its wide application in laboratory and industrial synthesis. In this study, we report a new method for synthesizing unsymmetrical oxamides from 2-oxoaldehydes and amines by using hydrogen peroxide as a reactant (Scheme 1).

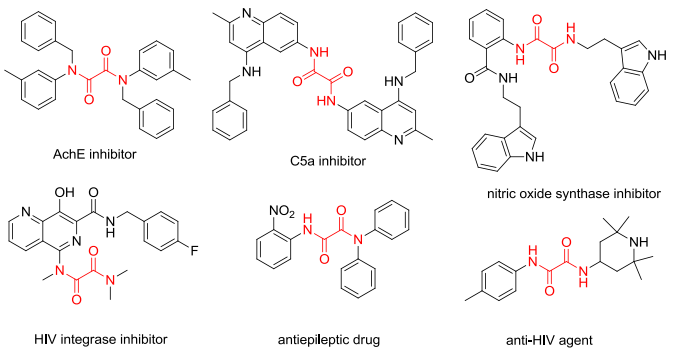

Fig. 1. Biologically active molecules containing an oxamide moiety.

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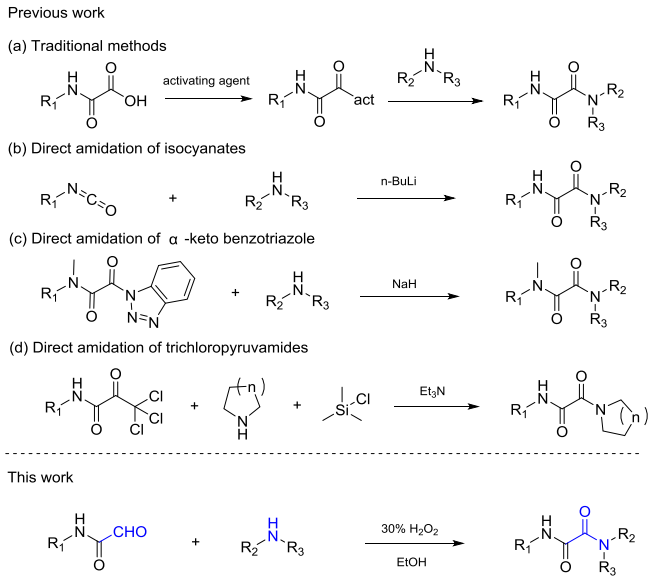
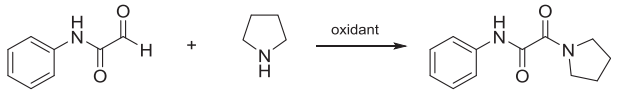


Scheme 1. Typical pathways for the synthesis of unsymmetrical oxamides.

2. Results and discussion

At the beginning of our investigation, the optimization of reaction conditions was focused on a variety of reaction parameters by using a model reaction of 2-oxo-*N*-phenylacetamide (**1a**) with pyrrolidine (**2a**). As shown in Table 1, all the peroxides could promote this reaction to give the corresponding products with moderate to high yields (Table 1, entries 1–3), while IBX, DMP, DIB, SeO_2, CrO_3 and OsO_4 had only 13–33% yields of **3aa** (Table 1, entries 4–9). Among various solvents examined, EtOH turned out to be the best choice, while others such as CH_2Cl_2, $CH_3COOC_2H_5$, CH_3CN, THF, DMSO, dioxane and PEG-400 were less effective (Table 1, entries 10–16). The yield decreased to 11% when EtOH was replaced with water (Table 1, entry 17). And addition of cosolvent such as Tween 80 or Bu4NI did not improve the yield (Table 1, entries 18–19). Further investigation indicates that temperature is important for this transformation. An excellent yield has been obtained when the reaction carries out at 25 °C (Table 1, entry 1). However, when the temperature increases to 40 °C, the yield of the desired product drops to 56% (Table 1, entry 20). And no product formation was observed when the reaction was conducted at 0 °C (Table 1, entry 21). For the optimization of the amount of H_2O_2 used in the model reaction, less than 3 equiv of H_2O_2 led to the incompletion of the reaction (Table 1, entries 22–23). Meanwhile, up to 4 equiv of H_2O_2 did not increase the yield if **3aa** significantly (Table 1, entry 24). With respect to the molar proportion of the reactants, a 3:1 M ratio of aldehyde and amine was found to be adequate, as neither bigger nor smaller proportion shows better yields (Table 1, entries 25–27). Finally, as observed in this study, the optimized reaction conditions tends to be: 2-oxoaldehyde (3.0 mmol), amine (1.0 mmol) and 30% H_2O_2 (3.0 mmol) in EtOH under standard atmosphere at 25 °C.

Table 1
Optimization studies for the synthesis of unsymmetrical oxamides[a]



1a 2a 3aa

Entry	1a:2a	Oxidant (equiv)	Solvent	Additive	T (°C)	Yield[b] (%)
1	1:1	H_2O_2 (3.0)	EtOH	/	25	81
2	1:1	TBHP (3.0)	EtOH	/	25	68
3	1:1	BPO (3.0)	EtOH	/	25	61
4	1:1	IBX (3.0)	EtOH	/	25	33
5	1:1	DMP (3.0)	EtOH	/	25	27
6	1:1	DIB (3.0)	EtOH	/	25	26
7	1:1	SeO_2 (3.0)	EtOH	/	25	19
8	1:1	CrO_3 (3.0)	EtOH	/	25	11
9	1:1	OsO_4 (3.0)	EtOH	/	25	13
10	1:1	H_2O_2 (3.0)	CH_2Cl_2	/	25	73
11	1:1	H_2O_2 (3.0)	$CH_3COOC_2H_5$	/	25	71
12	1:1	H_2O_2 (3.0)	CH_3CN	/	25	65
13	1:1	H_2O_2 (3.0)	THF	/	25	67
14	1:1	H_2O_2 (3.0)	DMSO	/	25	40
15	1:1	H_2O_2 (3.0)	dioxane	/	25	50
16	1:1	H_2O_2 (3.0)	PEG-400	/	25	37
17	1:1	H_2O_2 (3.0)	H_2O	/	25	11
18	1:1	H_2O_2 (3.0)	H_2O	Tween 80	25	12
19	1:1	H_2O_2 (3.0)	H_2O	Bu_4NI	25	14
20	1:1	H_2O_2 (3.0)	EtOH	/	40	56
21	1:1	H_2O_2 (3.0)	EtOH	/	0	0
22	1:1	H_2O_2 (1.0)	EtOH	/	25	54
23	1:1	H_2O_2 (2.0)	EtOH	/	25	65
24	1:1	H_2O_2 (4.0)	EtOH	/	25	82
25	2:1	H_2O_2 (3.0)	EtOH	/	25	84
26	3:1	H_2O_2 (3.0)	EtOH	/	25	91
27	5:1	H_2O_2 (3.0)	EtOH	/	25	90

[a] Reaction condition: **1a** (1 mmol), **2a** (1 mmol) and oxidant (3 mmol) in 2 mL solvent at corresponding temperature, air, 3 h.
[b] Isolated yield.

With optimized conditions in hand, a series of oxidative amidations of pyrrolidine **2a** with various 2-oxoaldehydes was thus carried out. The results are summarized in Fig. 2. A host of oxanilic acids bearing either the electron-donating groups such as methyl and methoxy, or electron-withdrawing groups such as chloro and bromo, were well tolerated during the course of the reaction providing the desired oxamides **3ba**–**ha** in moderate to good yields. Besides, synthetically useful naphthyl and benzyl are tolerated in this transformation, giving **3ja**–**ka** in good to moderate yields. Notably, in addition to the aromatic systems, an aliphatic oxamide **3la** could also be obtained in an excellent yield.

To further define the scope of this transformation, a wide range of 2-oxoaldehydes and amines were reacted under the optimized reaction conditions (Fig. 3). Good to excellent yields of tertiary oxamides were obtained in most cases (**3ab**–**ad**, **bc**–**eb** and **hc**–**jb**). However, primary amines remained difficult substrates, giving secondary amides in only moderate yields (**3bb**, **hb** and **lb**). Interestingly, chiral oxamide could be synthesized from the corresponding chiral amine in moderate yield without detectable racemization when compared with the HPLC chromatograms of the racemic compounds (**3ec**). Furthermore, a variety of functional groups such as ether, ester, and halogen are well tolerated for this reaction.

A serious of control experiments has also been performed to explore the mechanism of this transformation (Scheme 2). When 1,1-diphenylethylene (a radical scavenger) was added to the reaction mixture, the oxidative amidation process was suppressed dramatically, which suggested that the oxidative amidation step may involve a radical pathway (Scheme 2a). When the reaction was conducted in the darkness, only 29% yield of **3aa** was obtained, which implies that the sunlight is likely to play an important role in the reaction process (Scheme 2b).

In Scheme 3, a plausible mechanism for the oxidative amidation reaction has been proposed. Initially, hydrogen peroxide can be transformed into hydroxyl radical under the triggering effect of sunlight (Scheme 3a). Then, the hydroxyl radical traps the H of **1a** to produce the acyl radical **4a**. Meanwhile, the aminyl radical **5a** is generated efficiently from **2a** with the assistance of the hydroxyl radical. Finally, the acyl radical **4a** and aminyl radical **5a** combine to result in the desired amide **3aa**.

The products prepared by this procedure are valuable precursors for the synthesis of heterocycles. For example, **3ac** could