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Accessing the amide functionality by the mild and low-cost oxidation of imine

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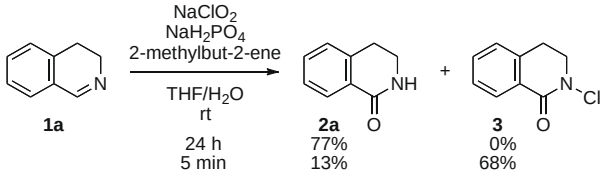
ABSTRACT

Oxidation of imines using sodium chlorite under buffered conditions gave the corresponding amides in good to high yield. The reaction was generally fast and was completed within 5–40 min. As has been established in the corresponding oxidation of aldehyde, so-called Pinnick oxidation, the good functional group tolerance and the use of inexpensive reagents are the advantages of this protocol.

The amide moiety is one of the most abundant functional groups found in the chemical structures of polymers, natural products, and pharmaceuticals.[1] Thus, the development of a new mild and versatile method for amide formation is important and valuable. The most common way to form an amide bond is condensation of amines with activated carboxylic acid derivatives, such as acyl chloride.[2] For the cases where highly reactive carboxylic acid derivatives should be avoided, however, alternative methods for the preparation of an amide moiety have been developed.[3] Oxidation of secondary amines[4] or imines[5] has also been utilized for the formation of amides. The oxidation of secondary amines to amides has been achieved by using hypervalent iodines[4a,c–e] or permanganate.[4b] The oxidation of imines proceeds under milder conditions, such as transition metal catalysis,[5a,b,e,g] nickel peroxide,[5d] *m*-CPBA,[5f] TBHP,[5h] and oxone.[5i] Because imines are readily prepared from aldehydes and amines, this strategy seems versatile and attractive. Recently, an efficient amide synthesis by catalytic oxidative linkage of alcohols and amines has been reported.[6]

Oxidation of aldehyde to carboxylic acid by sodium chlorite under buffered conditions was first reported by Lindgren and Nilsson in 1973.[7] This oxidation is now referred to as Pinnick oxidation because the generality of this oxidation was shown by Pinnick and co-workers in 1981.[8] During our investigation of an alkaloid synthesis, we encountered difficulty in the oxidation of amine to amide. After several attempts, we found that the oxidation under the Pinnick conditions is applicable to imines to provide corresponding amides in good to high yield. The required reagents were inexpensive and less toxic and the reaction has a reasonable functional group tolerance. Herein, we report this new protocol for oxidation of imine.

First, oxidation of 3,4-dihydroisoquinoline (**1a**) was tested (Scheme 1). The isoquinoline **1a** was prepared from 1,2,3,4-tetrahydroisoquinoline by treatment with NCS followed by the addition of DBU.[9] Sodium dihydrogenphosphate (0.92 mmol) and sodium



Scheme 1. Oxidation of isoquinoline **1a** to isoquinolinone **2a** and/or *N*-chloroisoquinolinone **3**.

chlorite (0.92 mmol) were successively added to a solution of **1a** (0.18 mmol) in a mixture of 2-methylbut-2-ene, THF, and water (1.8 mL each) at 0 °C. The solution was stirred at room temperature for 24 h. After work-up, desired lactam **2a** was obtained in 77% yield. Silica gel TLC monitoring indicated that **1a** was first converted into a less polar intermediate within 5 min and then the intermediate gradually transformed into more polar **2a** for 24 h. The intermediate, *N*-chloroamide **3** was obtained in 68% yield along with 13% yield of **2a** when the reaction was quenched after 5 min. It was found that **3** was convertible to **2a** by the treatment with 10% aqueous sodium thiosulfate; thus, the oxidation of **1** for 5 min, followed by dilution with ethyl acetate and a wash with aqueous sodium thiosulfate, gave **2a** in 98% yield (Table 1, entry 1).

This method was applicable to linear imines as well as to the cyclic imine (Table 1).[10] *N*-PMP imines (PMP = 4-methoxyphenyl) were good substrates to give the products in good yields (entries 2–4). In the reaction of *N*-PMP cinnamaldehyde imine, *N*-PMP cinnamamide was obtained in 67% yield, along with the corresponding α,β-epoxy amide in 11% yield. Using increased amount of 2-methylbut-2-ene (50 equiv), the yield of the cinnamide was improved to 73%, while almost the same amount of the epoxide was produced (entry 4). An enolizable imine is also applicable to this reaction to give the product in 85% yield (entry 5). Imine derived from alkylamine gave the corresponding amide in 65% yield along with the slight formation of dibenzoylimide (1%) (entry 6). Electron-deficient *N*-tosyl imine gave the product in high yield

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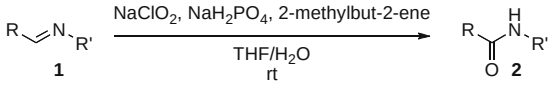
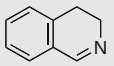
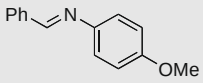
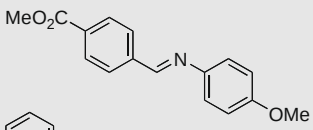
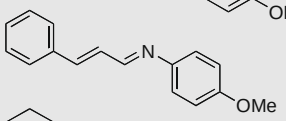
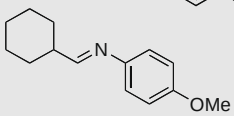
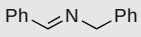
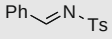
Table 1
Oxidation of imines **1** to amides **2**



Entry	1	Method[a]	Time (min)	2/yield (%)
1[b]		A	5	98
2		B	40	86
3		B	10	90
4[c]		B	15	73[d]
5		A	5	85
6		B	30	65[e]
7		B	480	85

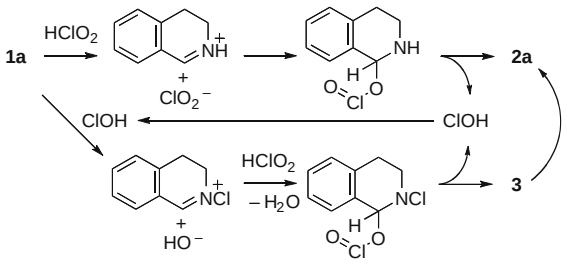
[a] See Ref. 10.
[b] Without 2-methylbut-2-ene.
[c] 50 equiv of 2-methylbut-2-ene was used.
[d] The corresponding α,β-epoxy amide was obtained in 9% yield.
[e] Dibenzoylimide was obtained in 1% yield.

but required prolonged reaction time (entry 7). It is worthy to note that the functionalities, such as an electron-rich aromatic ring (entries 2–5), ester (entry 3), and benzylic methylene (entry 6) were compatible with the conditions of this oxidation. These results clearly show the generality and the functional group tolerance of this oxidation protocol.

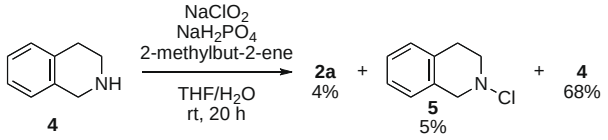
The reaction can also be conducted in other solvents, such as *tert*-butanol and 1,4-dioxane, which allowed the oxidation of **1a** to give **2a** in 98% and 95% yields after 15 and 10 min, respectively.

The formation of *N*-chloroamide **3** as an initial product (Scheme 1) implies that two pathways from imine to amide should be operative. One is the oxidation of protonated imine to give directly amide **2a** (Scheme 2). This pathway produces hypochlorous acid, which would initiate the other oxidation pathway by chlorinating **1a**. The oxidation of the produced *N*-chloroiminium gives *N*-chloroamide **3**, which is then converted to **2a**. The chlorination step should be rate-determining because the reactions of more electron-rich *N*-PMP and *N*-alkyl imines are much faster than that of more electron-deficient *N*-tosyl imine (Table 1). Dibenzoylimide (Table 1, entry 6) is probably produced by the oxidation of *N*-benzylidenebenzamide generated through dehydrochlorination of the *N*-chloroamide intermediate that results from the second pathway.

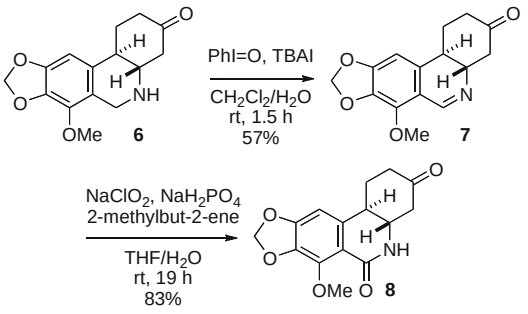
The mechanism proposed in Scheme 2 indicates that a hypochlorous acid scavenger, 2-methylbut-2-ene, should be unnecessary. Indeed, almost the same results were obtained in the oxidation of isoquinoline **1a** with and without 2-methylbut-2-



Scheme 2. Two plausible competing pathways for the oxidation of imines to amides.



Scheme 3. Attempted direct oxidation of amine **4**.



Scheme 4. Two-step oxidation of **6** to give **8**.

ene. However, in the oxidation of the substrates having the electron-rich PMP moiety, addition of 2-methylbut-2-ene was required to avoid chlorination of the aromatic ring. The α,β-epoxidation, observed in entry 4, was probably due to conjugate addition of chlorite because its production was independent of the amount of 2-methylbut-2-ene, which seems to simply protect the PMP moiety from chlorination.

Direct oxidation of amine **4** to amide **2a** was attempted (Scheme 3). Unfortunately, the oxidation of amine to imine **1a** was sluggish and unclean, resulting in **2a** in only 4% yield along with 5% yield of *N*-chloroamine **5** and 68% recovery of **4** after 20 h.[11]

Finally, the developed method was applied in an *Amaryllidaceae* alkaloid synthesis (Scheme 4).[12] Although all the attempts to oxidize tricyclic tetrahydroisoquinoline **6** or its protected derivatives directly to lactam **8** failed,[4] partial oxidation of **6** was accomplished using iodosobenzene with tetrabutylammonium iodide[4d] to afford dihydroisoquinoline **7**. The following oxidation by the method gave desired lactam **8** in 83% yield, while the permanganate oxidation[5c] of **7** resulted in a complex mixture.

In summary, we have shown that the oxidation by sodium chlorite under buffered conditions, so-called Pinnick oxidation widely used for the oxidation of aldehyde to carboxylic acid, was applicable to the formation of amide from imine. Because imine can be prepared by condensation of aldehyde and amine or by oxidation of secondary amine, this protocol provides a versatile two-step synthesis of amide from amine. The functional group tolerance, the mild buffered conditions, and the inexpensiveness of the reagents make this protocol useful and valuable.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.174.

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10. *General procedures. Method A*: An aqueous solution of NaH_2PO_4 (1.0 M, 1.5 mL, 1.5 mmol) was added to a mixture of 2-methylbut-2-ene (1.1 mL, 10 mol) and $NaClO_2$ (452 mg, 5.0 mmol) in THF (3.9 mL). To the resulting pale yellow solution, was added a solution of imine **1** (1.0 mmol) in THF (1 mL + 0.25 mL washing × 2) dropwise over 5–10 min. The mixture was vigorously stirred until disappearance of the starting imine was confirmed by TLC monitoring. Then, the reaction mixture was diluted with EtOAc (30 mL) and washed with water, 10% $Na_2S_2O_3$, and brine (10 mL each). The organic layer was dried over Na_2SO_4 and concentrated. The resulting crude material was purified by column chromatography or recrystallization.
Method B: Imine **1** (1.0 mmol) was dissolved in THF (3.9 mL). 2-Methylbut-2-ene (1.1 mL, 10 mol) and $NaClO_2$ (452 mg, 5.0 mmol) were added to the solution. An aqueous solution of NaH_2PO_4 (3.3 M, 1.5 mL, 5.0 mmol) was added dropwise to the vigorously stirred mixture. The same work-up as Method A was followed.
11. 10% $Na_2S_2O_3$ washing was omitted in the work-up procedure.
12. The preparation of **6** is to be submitted elsewhere afterward.