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Peroxidation of C−H Bonds Adjacent to an Amide Nitrogen Atom under Mild Conditions

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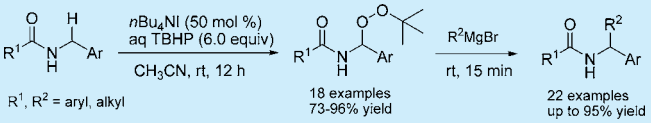
Supporting Information

ABSTRACT: Under mild conditions, the oxidative functionalization of C−H bonds adjacent to an amide nitrogen atom was achieved. *tert*-Butylperoxyamido acetal was obtained in high yields and could be further converted into α-substituted amides by treatment with Grignard reagents.

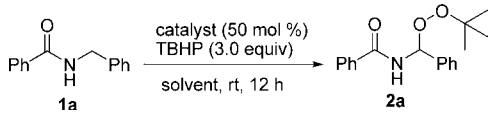


In recent decades, catalytic functionalization reactions of C−H bonds adjacent to a nitrogen atom have received considerable attention with noticeable progress having been made.[1] These reactions provide novel methods for the synthesis of nitrogen containing compounds in an economically favorable way by using environmentally benign processes. *N*-Aryl substituted amines are appropriate substrates for the investigation of such reactions, such as *N*,*N*-dialkylanilines,[2] *N*-aryl tetrahydroisoquinolines (THIQ),[3] glycine derivatives,[4] and aminoketones.[5] Most of these reactions are believed to proceed with the *in situ* generated iminium ion or imine as the intermediate, which is subsquently attacked by a nucleophile to form C−C, C−N, and C−P bonds. Although reasonable amounts of synthetically meaningful compounds have been prepared under mild conditions by such a strategy, one drawback still exists in that it is difficult to remove the aryl group from the obtained products, which has limited the application of this methodology in organic synthesis.

Compared with the aryl group, the acyl group is a more commonly used protective group for the synthesis of amine derivatives for the convenient preparation and cleavage of amides. Thus, functionalization of a C−H bond adjacent to the nitrogen atom of an amide is of great importance in organic synthesis and has attracted much interest in recent years. Various methods for the direct functionalization of a C−H bond adjacent to the nitrogen atom of an amide have been reported on including (a) Mannich-type reactions of *N*-acylglycine derivatives with aldimine or ketimine as intermediates,[4a,6] (b) Friedel−Crafts type arylation of amides in the presence of a metal catalyst such as Fe or Cu,[7] and (c) direct sp^3 C−H bond activation of amides using an Ir(I) complex as the catalyst.[8] A developed indirect strategy that differs from these direct functionalization processes is to convert amides to *tert*-butyloperoxyamido acetals, which could be isolated and reacted with nucleophiles to provide final products, while avoiding byproducts in a one-pot reaction.[9] *N*-Acyl tetrahydroisoquinoline (THIQ) derivatives are familiar models for these peroxidation processes, and corresponding *tert*-butylperoxyamido acetals have been prepared under different conditions. However, these methods commonly require air- and moisture-sensitive transition metal reagents, expensive oxidants, or a high temperature.[10] To the best of our knowledge, the preparation of *tert*-butyloperoxyamido acetals directly from secondary amides has not been reported on before. Herein, we describe our work on the C−H bond peroxidation of amides under mild conditions and its application in organic synthesis.

Initially, *N*-benzylbenzamide **1a** was chosen as the model substrate to optimize reaction conditions including the catalyst type, solvent, and temperature. As shown in Table 1, the reaction of **1a** with 3.0 equiv of TBHP (70% solution in water) was examined in CH_3CN with copper salts (50 mol %) as the catalyst at room temperature, and no reaction occurred (Table 1, entries 1−2). When I_2 or NIS was used as the catalyst, the

Table 1. Screening of Reaction Conditions



entry	catalyst (0.5 equiv)	solvent (2 mL)	yield (%)[a]
1	CuBr	CH_3CN	N.R.
2	CuI	CH_3CN	N.R.
3	I_2	CH_3CN	trace
4	NIS	CH_3CN	8
5	NaI	CH_3CN	32
6	KI	CH_3CN	25
7	CsI	CH_3CN	37
8	NH_4I	CH_3CN	11
9	nBu_4NI	CH_3CN	68 (85[b])
10	nBu_4NI	CH_3CN	43[c](60[d])
11	nBu_4NI	EtOAc	38
12	nBu_4NI	CH_2Cl_2	62

[a]Isolated yield. [b]6.0 equiv of TBHP were used. [c]Reaction carried out at 40 °C. [d]Reaction carried out at 0 °C.

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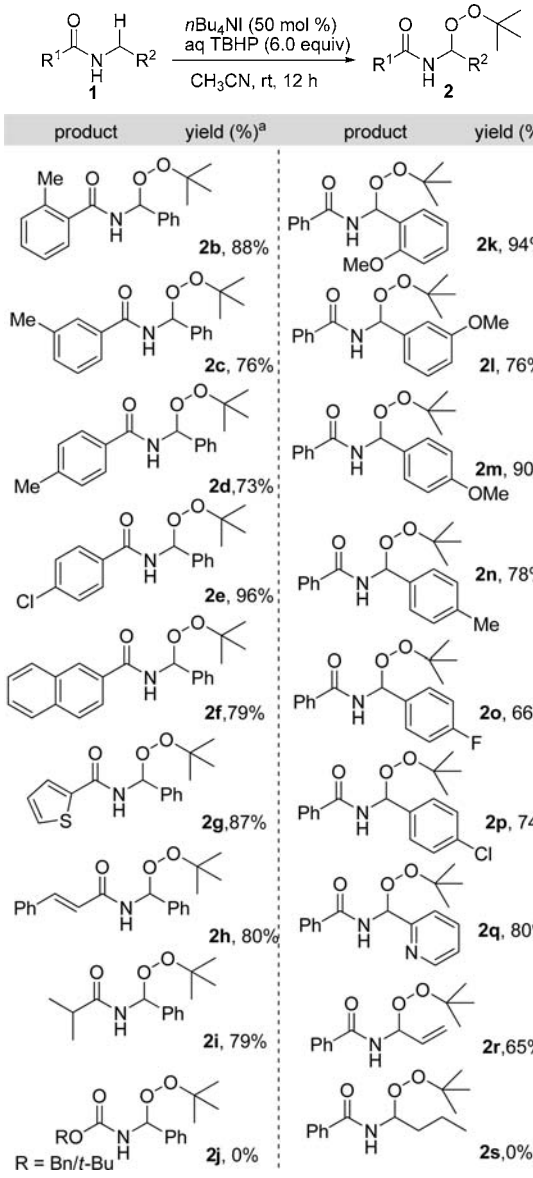
desired product *tert*-butyloperixyamido acetal **3a** was isolated in low yield (Table 1, entries 3−4). Other iodine sources including metal iodides and NH_4I resulted in the formation of **3a** in moderate yields (Table 1, entries 5−8). When *n*-Bu_4NI[11] was used as the catalyst, **3a** could be obtained in 68% yield together with 20% **1a** recovered. To promote the reaction, an additional portion of 3.0 equiv of TBHP was added to the reaction mixture after being stirred for 6 h. All the starting material was consumed, and the yield of **3a** was increased to 85% (Table 1, entry 9). Increasing the reaction temperature to 40 °C resulted in a low yield, and decreasing the reaction temperature to 0 °C led to long reaction times and the increased consumption of TBHP (9.0 equiv) (Table 1, entry 10). Changing the solvent to EtOAc or CH_2Cl_2 resulted in the formation of **2a** in lower yields (Table 1, entries 11−12). On the basis of these results, entry 9 represents the best conditions.

Once the optimized reaction conditions were established, the effect of the substrate was examined, with the results summarized in Table 2. *N*-Benzyl amides of substituted benzoic acid were investigated first, and the corresponding peroxides were obtained in good yields regardless of the electron-donating or -withdrawing groups on the benzene ring (Table 2, **2b−e**). *N*-Benzylnaphthoylamides also gave the desired product in 79% yield for the optimized reaction. Heterocyclic substrate *N*-benzylthiophene-2-carboxamide underwent a smooth reaction to give the product in excellent yields (Table 2, **2g**). Aliphatic substrates such as *N*-benzyl-cinnamamide and *N*-benzylisobutyramide could also be converted into the corresponding products in good yields (Table 2, **2h−i**). Carbamates including benzyl benzylcarbamate and *tert*-butyl benzylcarbamate were also tested using the optimized reaction, but no desired products were found (Table 2, **2j**).

For substrates with methyloxyl substituted at different positions on the benzyl group of *N*-benzylbenzamide, no significant steric hindrance was observed, and the substrate with the MeO group in the *ortho*-position afforded the desired product in 94% yield (Table 2, **2k−m**). When the substituted groups were located in the *para*-position, substrates with electron-donating groups gave higher yields than those with electron-withdrawing groups (Table 2, **2m−p**). The heterocyclic substrate *N*-(pyridin-2-ylmethyl)benzamide also gave a good yield (Table 2, **2q**). *N*-Allylbenzamide is also a suitable substrate for the reaction, and the corresponding product was obtained in 65% yield (Table 2, **2r**). *N*-Butylbenzamide was also tested, but no reaction occurred and all the starting materials remained untouched (Table 2, **2s**).

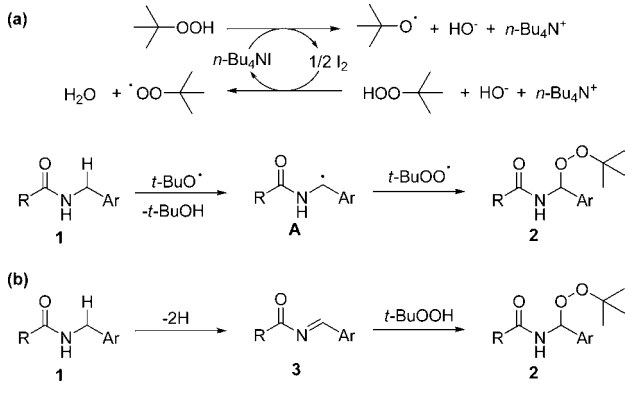
Although the detailed reaction mechanism still remains to be clarified, a radical reaction pathway is proposed as shown in Scheme 1a. The *tert*-butoxyl and *tert*-butylperoxy radicals were generated from the *n*-Bu_4NI−TBHP system. The H atom adjacent to the nitrogen atom of the amide was abstracted by the *tert*-butoxyl radical to form radical **A**, which was trapped by the *tert*-butylperoxy radical to give the product.[11b,j] A control experiment was carried out to elucidate the mechanism. When 1.0 equiv of TEMPO was added to the reaction, the yield of **2a** decreased significantly to 35%, which suggests the possibility of a radical pathway. An alternative plausible pathway is the nucleophilic addition of TBHP to an acylimine intermediate **3**,[12] which was generated by dehydrogenation of **1**. This pathway could be ruled out, because when the reaction was carried out using *t*-BuOH as the solvent, **2a** was obtained in 80% yield as the only product and no *t*-BuOH addition product could be found.[13]

Table 2. Peroxidation of Amides 1



[a]Isolated yield.

Scheme 1. Plausible Reaction Mechanisms



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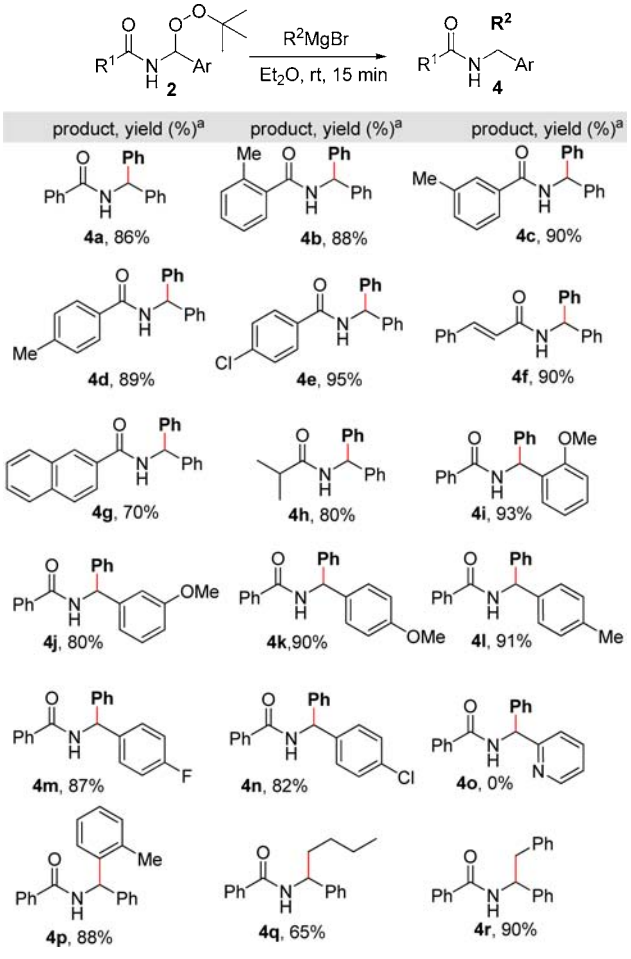
The acetal structure of the resultant compounds **2** allows it to serve as a versatile intermediate for organic synthesis.[14] When **2a** was treated with 3.0 equiv of PhMgBr in Et_2O, *N*-benzhydrylbenzamide[15] **4a** was obtained in 86% yield within 15 min at room temperature. Under the same conditions, α-substituted amides **4b**−**4n** were prepared in high yields up to 95%. One exception is that when **2q** was reacted with 3.0 equiv of PhMgBr, no product was found and all the starting material decomposed. Treatment of **2a** with 3.0 equiv of 2-MePhMgBr also gave the corresponding product in good yield (Table 3, **4p**). BuMgBr and BnMgBr also gave the desired products in 65% and 90% yield respectively (Table 3, **4q**−**4r**).

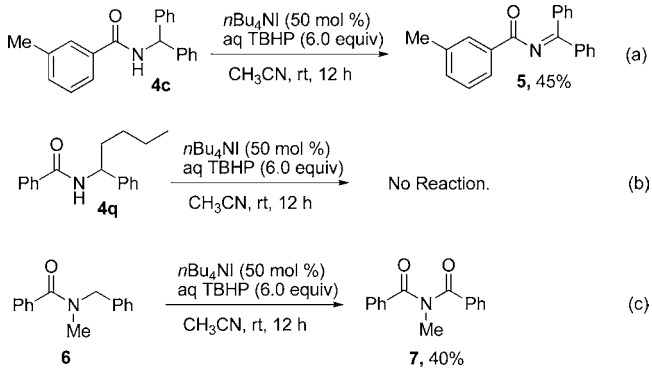
Table 3. Reaction of 2 with Grignard Reagents



[a]Isolated yield.

The peroxidative reaction of the obtained α-substituted *N*-benzylbenzamides was also examined. Interestingly, when *N*-benzhydryl-3-methylbenzamide **4c** was used as the substrate, acylimine **5** was isolated as the main product in 45% yield and 50% of the starting material **4c** was recovered (Scheme 2a). A longer reaction time and increase in amounts of TBHP used did not improve the yield of **5**. When *N*-(1-phenylpentyl)-benzamide **4q** was used, no reaction occurred (Scheme 2b). Finally, *N*-benzyl-*N*-methylbenzamide **6** was also examined, and an overoxidized product *N*-benzoyl-*N*-methylbenzamide **7** was obtained in 40% yield owing to the relatively high reactivity of **6** under oxidative conditions (Scheme 2c).

Scheme 2. Peroxidation of α-Substituted *N*-Benzylbenzamides and *N*-Benzyl-*N*-methylbenzamide



In conclusion, we have developed an efficient and practical method for the synthesis of *tert*-butylperoxyamido acetal by simple oxidative functionalization of *N*-benzylbenzamides. The reaction was carried out under mild conditions using TBHP as the oxidant and *n*-Bu_4NI as the catalyst. By treating *tert*-butylperoxyamido acetals with Grignard reagents, α-substituted amides could be prepared in high yields. Attempts to convert the obtained *tert*-butylperoxyamido acetals into other amide derivatives using different nucleophiles are still in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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