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Triethyl Phosphite/Benzoyl Peroxide Mediated Reductive Dealkylation of *O*-Benzoylhydroxylamines: A Cascade Synthesis of Secondary Amides

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Abstract: A new triethyl phosphite/benzoyl peroxide (BPO) mediated system has been developed for the synthesis of secondary amides with good to excellent yields in a single step. This unprecedented cascade process involves sequential reduction of N−O bond and benzoylation followed by dealkylation of N−C bond of *O*-benzoylhydroxylamines (*O*-BHA). The methodology is versatile as it tolerates a variety of aromatic and aliphatic *O*-BHA as substrates to access secondary amides.

The amide bond (−CO−NH−) is an essential functional group in chemical synthesis, biology, and drug discovery.[1] Due to the prevalence of amides in both natural and unnatural materials, many synthetic protocols have been developed.[2,3] The classical methods of preparation of secondary (2°) amides include the reaction of amines with carbonyl derivatives[4] and hydroamination of alkynes.[5] Despite these developments,[3–5] current trends on 2° amide syntheses are being focused on direct transamidation of unactivated amides & amidation of alkyl esters (entry A, Figure 1),[6] reaction between readily accessible phenyl thiocarbamates and Grignard reactants (entry B, Figure 1),[7] aerobic oxidative couplings of alcohols and amines[8] and oxidation of benzylamines to benzamides under metal[9] and metal-free conditions.[10] Recently, Lei et. al., reported an efficient Bu_4NI-catalyzed oxygen-centered radical addition between acyl peroxides and isocyanides for the synthesis of 2° amides (entry C, Figure 1).[11]

The development of efficient protection/deprotection routes is crucial in organic synthesis. Mainly the reactivity of amines can be a challenge when synthesizing the essential building blocks, thus requiring protection/deprotection during a chemical conversion.[12–15] *O*-Benzoylhydroxylamine **1** (*O*-BHA), readily available electrophilic aminating reagents and an umpolung of a nitrogen atom, has attracted much attention among the research communities.[16–18] The nitrogen umpolung properties can be fine-tuned through structural modifications.[16] Some of the strategies developed to date rely upon electrophilic amination of alkenes and alkynes using *O*-BHA as electrophilic aminating reagents.[18] Recently, Bode *et. al.*, have documented few protocols for the amide bond formation using *O*-hydroxylamines

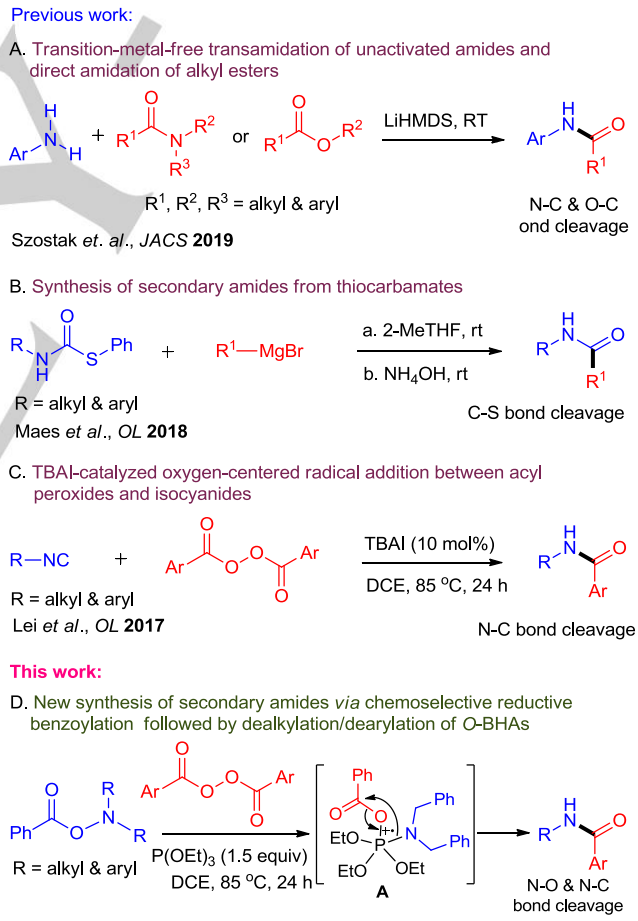
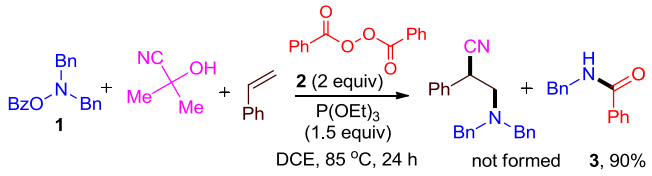


Figure 1. Recent progress in secondary amide formation and our approach.

and monofluoro acylboronates under mild conditions.[19] However, in some of the cases, the synthesis of amides and protection/deprotection of amines requires different stoichiometric amounts of poisoning reagents and harsh reaction conditions.[7,12–15,19] Due to current interest in the electrophilic amination leading to amide synthesis,[16–19] we herein report an

efficient, straightforward, and operationally simple protocol for the synthesis of secondary amides *via* sequential reduction, benzoylation followed by dealkylation of *O*-benzoylhydroxylamines (entry D, Figure 1).

Initially, we were interested in the electrophilic amination of styrene using acetone cyanohydrin as CN source and *O*-BHA **1** as a nitrogen electrophile.[20] Thus, when the reaction was carried out using triethyl phosphite as promoter and benzoyl peroxide (BPO) **2** as an oxidant in dichloroethane (DCE) as solvent at 85 °C, unexpectedly, 2° amide **3** was obtained in 90% yield (Scheme 1).



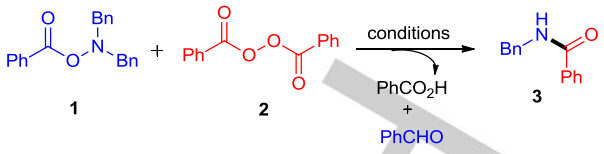
Scheme 1. Electrophilic amination and cyanation of styrene.

Encouraged by this result, *O*-BHA **1**[22] and BPO **2** were chosen as representative reactants for further optimization of the reaction. In the presence of triethyl phosphite in DCE at 60 °C, reductively dealkylated 2° amide **3** was indeed obtained in 62% yield, along with benzaldehyde (44%) and benzoic acid (90%) as side products (Table 1, entry 1). A significant increase in yield of **3** (94%) could be realized when the temperature was increased to 85 °C (entry 2). However, a slight decrease in yield was observed when the temperature was further increased to 95 °C (entry 3). Reducing the amounts of $P(OEt)_3$ and BPO to 1 and 1.5 equiv, respectively, resulted in a lower yield of **3** (80% & 65%; entries 4 & 5). Surprisingly, the reaction failed with other oxidants like TBHP and DMSO (entries 6 & 7). The effect of other phosphorus sources like $P(OiPr)_3$, and $P(OPh)_3$ was also examined, which gave a moderate yield (50 & 66%) of 2° amide **3** (entries 8 & 9), while no reaction occurred with other bases such as Et_3N, Cs_2CO_3, Na_2CO_3 or KO^{t}Bu. The reaction also failed with other organic solvents (CH_3CN, and 1,4-dioxane). Finally, to establish the role of BPO and $P(OEt)_3$, we carried out some control experiments in the absence of BPO, $P(OEt)_3$ or with other phosphorus sources (entries 12 & 13). The reaction, however, failed to give 2° amide **3** in these cases.

In order to determine its substrates scope, various symmetrically substituted *O*-BHAs **1**, **4**–**13** having alkyl, benzyl, allyl, and aryl groups were subjected to reactions under optimized conditions (Scheme 2). Evidently, good to excellent yields (71–94%), of 2° amides **3**, **14**–**22**, were obtained in most cases, indicating that the reaction is not sensitive to electronic effects. However, the present dealkylation strategy afforded the lower yield (56%) in the case of aromatic hydroxylamine **13**.

Next, unsymmetrically substituted *O*-BHAs **24**–**27** were subjected to reaction under the optimized condition. Interestingly, the reaction proceeded smoothly to afford the corresponding 2° amides **3**, **15**, **28** & **29** in 91, 83, 80 and 76% yields, respectively. This result has shown that the reaction proceeds *via* preferential defurfurylation and deethylation over debenzylation reductive processes (Schemes 3).

Table 1. Optimization of the reaction conditions[a].



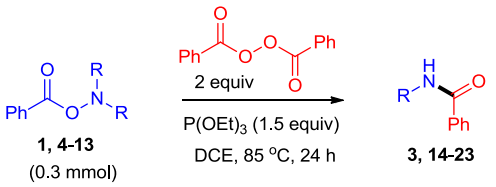
Entry	Oxidant	Base	Temp (°C)	Yield of **3** (%)[b]
1	BPO	$P(OEt)_3$ 1.5 equiv	60	62 (30)[c]
2	BPO	$P(OEt)_3$ 1.5 equiv	85	94
3	BPO	$P(OEt)_3$ 1.5 equiv	95	90
4	BPO	$P(OEt)_3$ 1.0 equiv	85	80
5	BPO[d]	$P(OEt)_3$ 1.5 equiv	85	65
6	TBHP	$P(OEt)_3$ 1.5 equiv	85	nr
7	DMSO	$P(OEt)_3$ 1.5 equiv	85	nr
8	BPO	$P(OiPr)_3$ 1.5 equiv	85	50
9	BPO	$P(OPh)_3$ 0.5 equiv	85	66
10	-	$P(OPh)_3$ 1.5 equiv	85	nr
11	BPO	-	85	nr
12	BPO	$O=P(OEt)_3$ 1.5 equiv	85	nr
13	BPO	$O=P(Ph)_3$ 1.5 equiv	85	nr

[a] Reaction conditions: 1 (1 equiv), BPO (2 equiv), $P(OEt)_3$ (1.5 equiv), DCE, 85 °C, 24 h. [b] isolated yield. [c] RT, [d] BPO (1 equiv), nr = no reaction.

In the case of cyclic protected hydroxylamines such as pyrrolidin-1-yl benzoate **30** and morpholinobenzoate **31**, it was strangely found that the reaction provided 3° amides **32** & **33** in 91 and 87% yields, respectively,) *via* the simple reductive process only (Scheme 4).

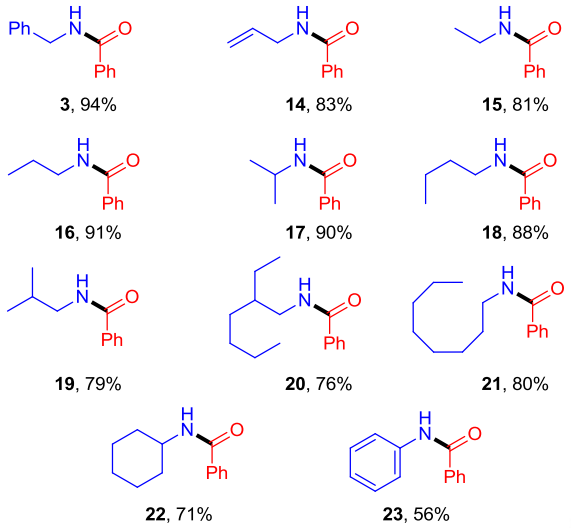
Finally, we decided to test the behavior of mono protected *O*-BHA such as *N*-(1-phenylethyl)-*O*-benzoylhydroxylamine **34**. In this case, the reaction afforded the benzoylated product **28** in 66% yield exclusively *via* simple reduction, without undergoing the dealkylation process (Scheme 5). This result suggests that the reductive benzoylation is facile and precedes dealkylation step, leading to the formation of 2° amides (Schemes 4 & 5).

To demonstrate its scalability and practicality, we performed the reaction of *O*-BHA **1** at the 2.0 g scale, for 24 h under standard conditions, which afforded **3** in 91% yield, with no significant decrease in reaction efficiency. To extend its scope further, a “one-pot” experiment was carried out directly from dibenzylamine instead of **1** that gave the amide **3** in moderate yield (63%) along with some complex mixture.



symmetrical *O*-benzoylhydroxylamines

R = benzyl (**1**), allyl (**4**), ethyl (**5**), ^{n}propyl (**6**), ^{i}propyl (**7**), ^{n}butyl (**8**), ^{i}butyl (**9**), bis(2-ethylhexyl)amine (**10**), ^{n}octyl (**11**), cyclohexyl (**12**) & phenyl (**13**)

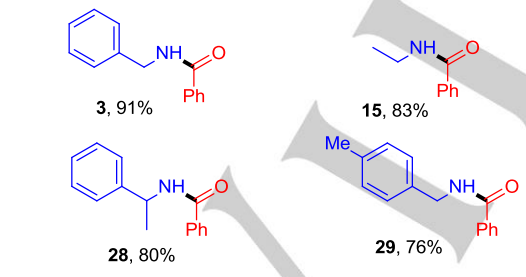


Scheme 2. Substrates scope for the reductive benzoylation followed by dealkylation of *O*-BHA.

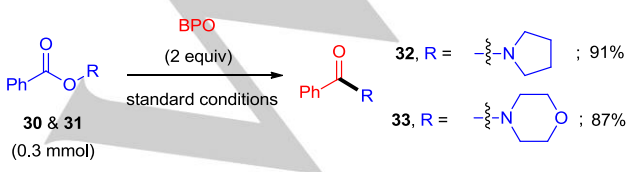
24, R^1 = Bn, R^2 = furan-2-ylmethyl ; **25**, R^1 = Et, R^2 = furan-2-ylmethyl

26, R^1 = α-Me-benzyl, R^2 = furan-2-ylmethyl

27, R^1 = Et, R^2 = 4-MeC_6H_4-CH_2-



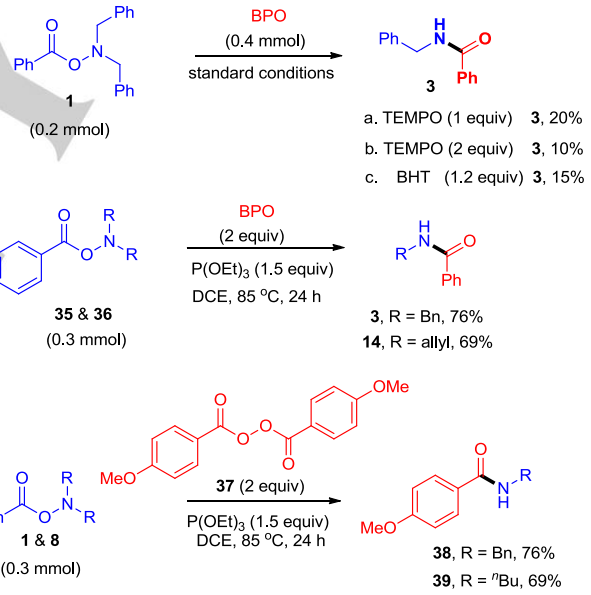
Scheme 3. Substrates scope for the unsymmetrical *O*-BHAs.



Scheme 4. Substrates scope for the synthesis of 3° amides.

Scheme 5. Reductive benzoylation for the synthesis of secondary amide.

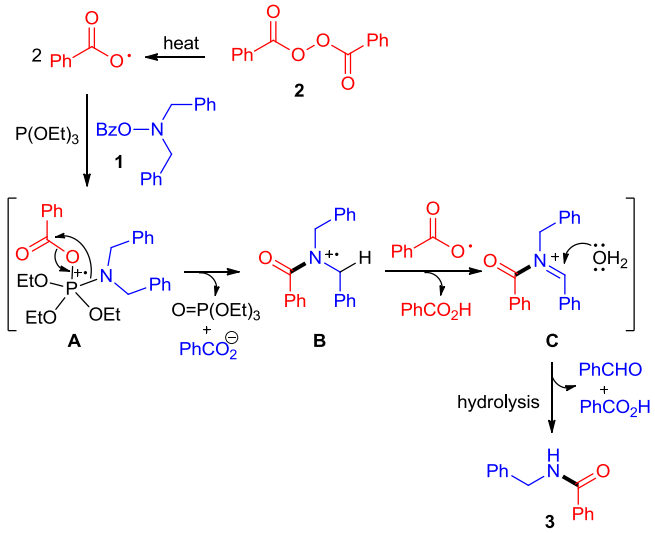
In order to get an insight into the reaction mechanism, we performed the following control experiments: (i) Firstly, when TEMPO and BHT was employed in varying amounts (1 & 2 equiv) and (1.2 equiv), respectively, in the reaction, a significantly decreased yield of **3** was obtained in both cases, thereby indicating that the reaction probably proceeds by a radical pathway; (ii) Further, when *O*-4-methoxy-BHAs **35** & **36** were employed as substrates under optimal conditions, 2° amides **3** and **14** were produced in 76% and 69% yield, respectively; (iii) Finally, the reaction of *O*-BHA **1** & **8** with 4-methoxybenzoic peroxyanhydride **37** was conducted under the optimized conditions, that afforded the corresponding 2° amides **38** & **39** in 76%, and 69% yields, respectively. These results clearly establish that benzoyl groups in 2° amides **3**, **14**, **38** & **39** have come from the corresponding BPO **2** & **37** respectively (Scheme 6).



Scheme 6. Control experiments for mechanistic studies.

Based on our experimental results and literature precedence,[18,20,21] a plausible mechanism for the cascade reductive benzoylation and dealkylation of *O*-benzoylhydroxylamine **1** is outlined in Scheme 7, although a detailed mechanism remains unclear. We believe that, first of all, a redox process sets in when *O*-benzoylhydroxylamine **1** undergoes reaction with equimolar amount of $P(OEt)_3$ and BPO producing a phosphorus cation radical species **A**. Subsequently, species **A** can possibly undergo intramolecular migration to provide nitrogen cation radical **B** with the concomitant removal of $O{=}P(OEt)_3$. This is then followed by abstraction of hydrogen radical by benzoate radical from another equivalent of BPO leading to the formation of an iminium ion **C**. This upon

hydrolysis furnishes the 2º amide **3** along with $PhCO_2H$ and PhCHO as by-products (Scheme 7).



Scheme 7. Plausible reaction mechanism.

In summary, we have developed, for the first time, a simple protocol involving triethyl phosphite/benzoyl peroxide (BPO) mediated C−N bond formation that provides for the synthesis of a variety of 2º amides. This novel cascade reaction proceeds *via* reductive benzolylation and dealkylation of *O*-benzoylhydroxylamines. The salient features of the methodology are: (1) metal-free synthesis; (2) easily accessible starting materials and inexpensive reagents; (3) good functional group tolerance and (4) high yields of secondary amides. We believe that this operationally simple and mild process would serve as a useful method that will find tremendous applications in the chemical synthesis of widely occurring natural products and medicinal chemistry.

Acknowledgements

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Keywords: *O*-Benzoylhydroxylamines 1 • 2º Amides 2 • Cascade 3 • Reductive 4 • Dealkylation 5

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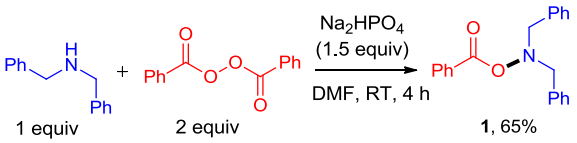

Entry for the Table of Contents

Key Topic: Secondary amides synthesis

Triethyl Phosphite/Benzoyl Peroxide Mediated Reductive Dealkylation of *O*-Benzoylhydroxylamines: A Cascade Synthesis of Secondary Amides

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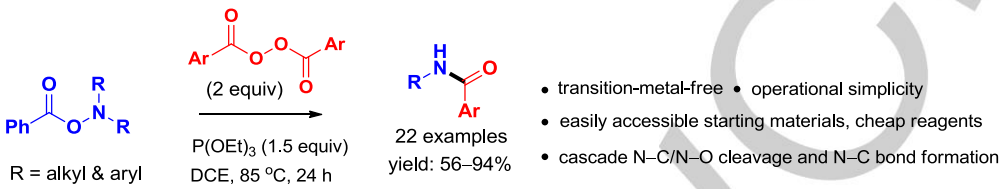

An efficient and operationally simple protocol for the synthesis of 2° amides *via* reductive benzoylation dealkylation of *O*-benzoylhydroxylamines (*O*-BHA), by using triethyl phosphite as a reducing agent and benzoyl peroxide as an oxidizing agent is described.

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