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A very mild and selective method for O-benzoylation of hydroxamic acids

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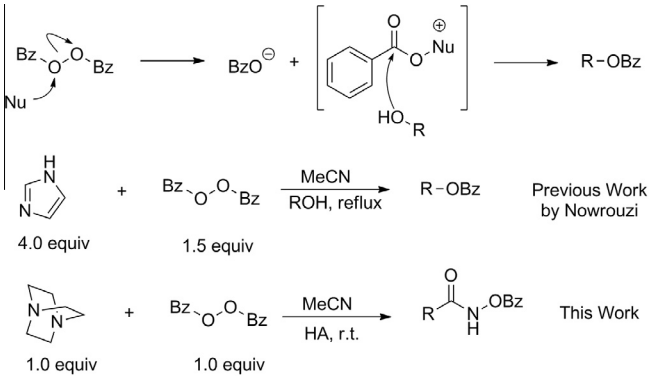
ABSTRACT

Selective O-benzoylation of hydroxamic acids is achieved by the treatment of BPO and DABCO. Aliphatic alcohols are not reactive under these conditions. Various radical or oxidation sensitive functional groups are compatible with this protocol, and no anhydrous reagents or solvents are required for the high yields of the benzoylations.

O-Acylated hydroxamic acids (HAs) and hydroxyl amines have found broad applications in organic synthesis. Owing to the unique nature of the N—O single bond, HA derivatives have served as building blocks for heterocyclic compound synthesis,[1] stoichiometric oxidants for olefin di-functionalization,[2] nitrogen sources for cross coupling reactions[3] and more recently, as precursors for molecular HNO production.[4] Given the nucleophilicity and Lewis basicity of the heteroatoms, it is not surprising to find that O-acylated HAs also play important roles in transition metal catalysis: HAs are efficient nucleophiles for metal catalysed allylic substitution reactions[5] and they are excellent directing groups in aromatic C—H activation.[6] In principle, O-acylated HAs can be prepared by reacting HAs with various acylation reagents; however, such transformations are typically carried out at low temperature for prolonged time to avoid over acylations and other side reactions. In particular, when multiple hydroxyl groups are present in the same substrate, a protection–deprotection process is usually necessary for the optimal yields. To address these problems, we herein disclose an alternative approach for selective O-benzoylations of HAs by a reagent that is conveniently prepared from benzoyl peroxide (BPO) and diazabicyclo[2,2,2]octane (DABCO).

The peroxide bond of BPO is susceptible to reductive cleavage and the resulting product is capable of transferring the attached benzoyl group to various alcohols (Scheme 1). Indeed, one of such protocols has been reported by Nowrouzi et al. for the benzoylation of alcohols and phenols by reacting 4 equiv imidazole with BPO in MeCN at reflux temperature.[7] Although this condition is suitable for converting phenols as well as primary and secondary alcohols to the corresponding ester, it is not ideal to acylate HAs because the benzoate product of HA can undergo a Lossen rearrangement at high temperature in the presence of a base. We envisioned that other nitrogen nucleophiles with enhanced nucleophilicity should be able to cleave the peroxide bond at lower temperature and the resulting intermediate may exhibit distinct activities towards different types of hydroxyl groups.

To test the hypothesis, we first used protected hydroxylamine **1a** as a model substrate to screen suitable conditions for the proposed benzoylation (Table 1). When DABCO was added to a



Scheme 1. Benzoyl peroxide as an acyl donor for esterification.

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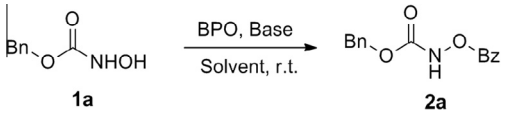
Table 1
Optimization of benzoylation conditions[a]



1a 2a

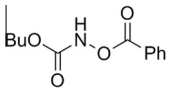
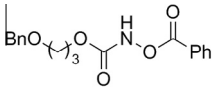
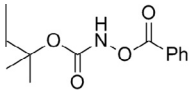
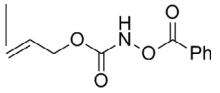
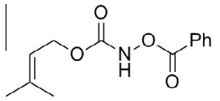
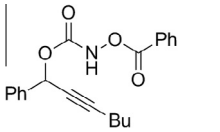
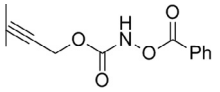
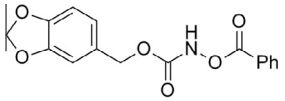
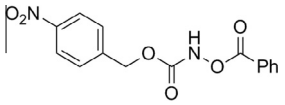
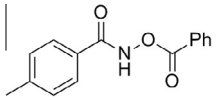
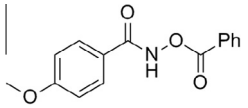
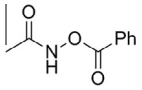
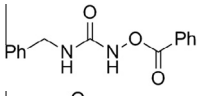
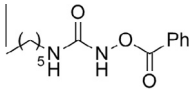
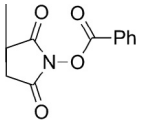
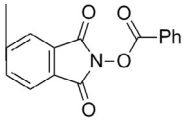
Entry	Solvent	Base	Yield[b] (%)
1	MeCN	DABCO	63
2	MeCN	Lutidine	0
3	MeCN	Pyridine	0
4	MeCN	DMAP	56
5[c]	MeCN	DABCO	55
6	THF	DABCO	50
7	DCM	DABCO	46
8	Toluene	DABCO	54
9	DMF	DABCO	0[d]
10	DMSO	DABCO	0[d]
11	MeCN	DABCO	90[e]

[a] Unless specified otherwise, reaction was performed with 0.20 mmol **1a**, 1.0 equiv of BPO and 1.0 equiv of DABCO in 1.0 mL solvent for 1 h.
[b] Isolated yield.
[c] 0.40 mmol of BPO and 0.40 mmol of DABCO were used.
[d] BPO was completely consumed.
[e] Reaction time was 3 h.

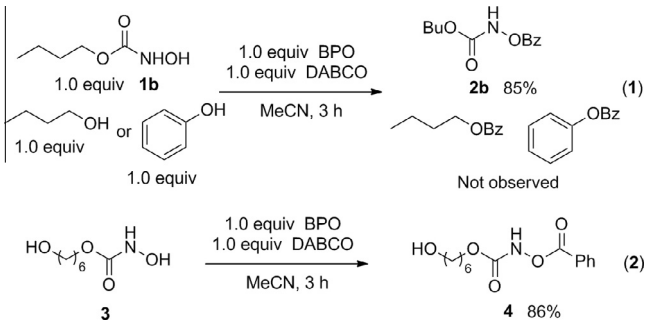
reaction mixture containing **1a** and BPO in MeCN, the desired product was rapidly formed within a minute, accompanied by immediate disappearance of the BPO (Table 1, entry 1). Although pyridine and lutidine failed to give any benzoylation product under the same conditions, dimethylaminopyridine (DMAP) did produce **2a** in decent yield, indicating that the nucleophilicity of the nitrogen atom was one of the determining factors for the success of benzoylation (Table 1, entries 2–4). The quantity of BPO and DABCO only had a marginal effect on the acylation, as the yield of **2a** was not improved by 2 equiv of both reagents. Since the reagent formation involves initial nucleophilic attacks, we also explore the solvent polarity effects on the benzoylation (Table 1, entries 6–10). Reactions carried out in common solvents such as THF, DCM and toluene all gave inferior yields compared to that in MeCN; polar aprotic solvents, such as DMF and DMSO, completely shut down the reaction, even though the BPO was fully consumed in the reaction mixture. The optimal yield was obtained when the reaction time was extended to 3 h in MeCN with 1 equiv of BPO and 1 equiv of DABCO. It is worth noting that, no anhydrous reagents or solvent was necessary for obtaining the high yield, and the reaction can be performed under an air atmosphere.

With the optimal conditions in hand,[8] we evaluated the generality of this benzoylation reaction with different HAs and the results are summarized in Table 2. Generally speaking, the O-benzoylation of protected hydroxyl amines gave good to excellent yields under standard conditions (Table 2, entries 1–9). Even though BPO can potentially act as an oxidant and radical initiator, our current method is compatible with a variety of functional groups including alkenes, alkynes and aromatics with electron-donating or electron-withdrawing substituents. As expected, HAs of both aromatic and aliphatic origins were converted to the corresponding benzoate under the same conditions (Table 2, entries 10–12). The versatility of the reagent was also demonstrated by benzoylation of benzylamine- and hexylamine-derived *N*-hydroxyurea. We were pleased to find that the additional nitrogen atom caused no interference to the acyl transfer reaction and the BPO/DABCO combination provided the benzoate products in 76% and 95% yields, respectively (Table 2, entries 13 and 14). To further broaden the substrate scope, we extended the optimized conditions to *N*-hydroxysuccinimide and *N*-hydroxyphthalimide; and the reactions proceeded smoothly to afford the desired esters in excellent yields (Table 2, entries 15 and 16).

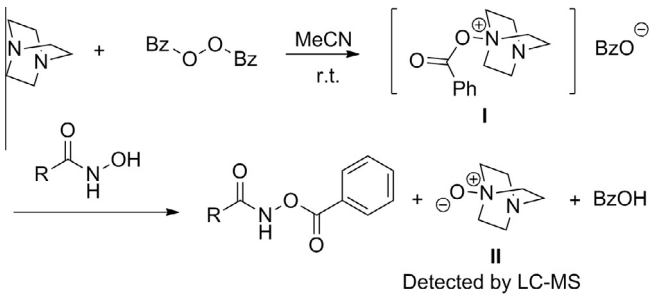
Table 2
Synthesis of hydroxamic acid benzoate by BPO/DABCO[a]

Entries	Benzoate product		Yield[b] (%)
1		**2b**	87
2		**2c**	92
3		**2d**	93
4		**2e**	93
5		**2f**	79
6		**2g**	88
7		**2h**	71
8		**2i**	87
9		**2j**	81
10		**2k**	73
11		**2l**	91
12		**2m**	73
13		**2n**	76
14		**2o**	95
15		**2p**	84
16		**2q**	91

[a] HA 0.20 mmol, 1.0 equiv of BPO and 1.0 equiv of DABCO in 1.0 mL MeCN for 1 h.
[b] Isolated yields.



Scheme 2. Selectivity between hydroxamic acid and aliphatic alcohols.



Scheme 3. A plausible mechanism for the benzoylation.

A notable advantage of our current protocol is the high selectivity for HA hydroxyl groups over aliphatic alcohols and phenols: butanol, benzyl alcohol, menthol and phenol are not reactive under the optimal conditions. We performed a competition reaction between equal amount of 1-butanol/phenol and **1b** in the presence of BPO/DABCO (Scheme 2, Eq. 1); and we found that **2b** was the sole product and there was no butyl benzoate or phenol benzoate formed in the reaction mixture. Such selectivity was retained for more complex substrate **3**, which has a pendant hydroxyl group and a protected hydroxylamine group within the same molecular scaffold. The only product isolated from benzoylation reaction was **4** and no acylation on the aliphatic alcohol was detected. This observation is attributed to the different pK_a of the hydroxyl groups: the acidic HA hydroxyl proton is readily removed by DABCO and the resulting oxygen anion is more nucleophilic than regular aliphatic alcohols.

A plausible mechanism for the benzoylation of the HAs is illustrated in Scheme 3. An initial nucleophilic attack by DABCO generates intermediate **I** as an acyl donor, which is responsible for the subsequent esterification reactions. Upon deprotonation, the oxyanion of HA acts as an acceptor for the benzoyl group in intermediate **I**; and DABCO *N*-oxide **II** is released as a byproduct. This mechanistic scheme is supported by the detection of **II** by LC–MS and explains the inactivity of pyridine and lutidine in the benzoylation reaction.

In summary, we have developed a mild and selective method for the benzoylation of protected hydroxylamines and HAs. The combination of DABCO and BPO produces a reagent that is capable of transferring a benzoyl moiety to various *N*-hydroxyl groups at room temperature and the rapid consumption of BPO allows radical and oxidation sensitive functional groups intact during the acylation process. The reaction conditions are very robust and require no anhydrous chemicals or inert atmosphere to secure good yields.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.009.

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8. *A representative procedure for the synthesis of benzoate* ***2a****:* To a test tube charged with a stir bar, 0.20 mmol of **1a** and 0.20 mmol of BPO were sequentially added MeCN 1.0 mL and 0.20 mmol of DABCO. The resulting reaction mixture was stirred at room temperature for 3 h and diluted by addition of EtOAc, the organic layer was briefly washed by saturated aqueous sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. The bulk solvent was removed in vacuo, and the residue was purified by silica gel flash chromatography to afford product **2a** 48.8 mg, 90% yield.