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Facile synthesis of *O*-acylhydroxamates *via* reaction of oxime chlorides with carboxylic acids†

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A simple and efficient method for the synthesis of *O*-acylhydroxamate derivatives from oxime chlorides and carboxylic acids was developed. The reaction affords clean and facile access to diverse *O*-acylhydroxamates in high yields (up to 85%). The chemical structure of a typical product was confirmed using single-crystal X-ray structure analysis.

Over recent decades, transition metal-catalyzed C–H activation reactions have emerged as a powerful tool in organic synthesis.[1] The functionalization of C–H bonds has a wide range of applications in, for example, the synthesis of drug molecules, natural products and the intermediates of many biologically active compounds.[2]

Among the many known C–H activation reaction substrates, *O*-acylhydroxamates are highly effective and play an important role in C–H activation reactions enabling the production of highly regioselective products (Fig. 1). In 2011, the Guimond group developed a mild rhodium(III)-catalyzed synthesis of isoquinolone and 3,4-dihydroisoquinolone *via* a C–H bond functionalization reaction between *O*-acylhydroxamates and either alkynes or alkenes.[3] Subsequently, in 2015, bulky phosphine ligands were synthesized by Li and Wang through Rh^{III}-catalyzed C–H activation and annulation reactions using 1-alkynylphosphine sulfides and *O*-acylhydroxamates.[4] In 2012, Glorius reported an annulative coupling between *O*-acylhydroxamates and allenes to synthesise 3,4-dihydroisoquinolin-1(2*H*)-ones *via* a rhodium(III)-catalyzed C–H activation reaction.[5] Subsequently, the Shi group demonstrated a controllable rhodium(III)-catalyzed C–H functionalization of *O*-acylhydroxamates with vinylidenecyclopropanes. Product selectivity was obtained through changing the directing group from C(O)NH–OPiv to C(O)NH–OBoc to afford two different major products.[6] In addition to cyclization reactions, *O*-acylhydroxamates are useful compounds that can be converted to anilines and symmetrical ureas in the presence of palladium(II) acetate or triethylamine.[7] Because of the importance of *O*-acylhydroxamates, a distinct strategy or a concise process to synthesize *O*-acylhydroxamates with diverse structural requirements is still desirable.

To the best of our knowledge, the classical approach reported for the synthesis of *O*-acylhydroxamates proceeds through an acylation reaction between hydroxamic acids and acyl chlorides under basic conditions (Scheme 1a).[7] However, this acylation reaction requires anhydrous conditions when acyl chlorides are used. On the other hand, stable and structurally diverse carboxylic acid compounds exist in many natural products, non-natural products and materials and are frequently accessible from commercial sources.[8] Inspired by these studies, we conceived a direct pathway to access *O*-acylhydroxamates from carboxylic acids (Scheme 1b). Herein, we describe the reaction of oxime chlorides with carboxylic acids under mild reaction conditions, providing convenient and efficient access to functionalized *O*-acylhydroxamate derivatives (Scheme 1b). In our protocol, the oxime chlorides[9] were

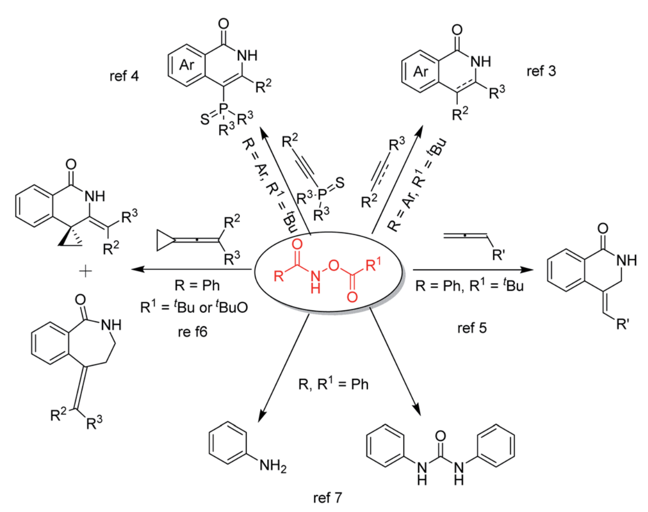

Fig. 1 Representative examples of reactions between *O*-acylhydroxamate and various reaction partners.

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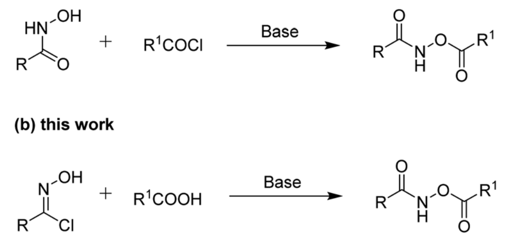
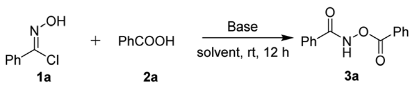


Scheme 1 (a) Classical approach and (b) our protocol for the synthesis of *O*-acylhydroxamates.

Table 1 Optimization of reaction conditions[a]



Entry	Base	Solvent	Yield of **3a**[b] (%)
1	DABCO	Dioxane	80
2	TEA	Dioxane	71
3	DBU	Dioxane	60
4	Na_2CO_3	Dioxane	31
5	NaOH	Dioxane	20
6	DABCO	Et_2O	50
7	DABCO	THF	70
8	DABCO	EtOAc	76
9	DABCO	Toluene	53
10	DABCO	CH_3CN	30
11	DABCO	DCE	60
12	DABCO	Acetone	30
13	DABCO	$CHCl_3$	45
14[c]	DABCO	Dioxane	62
15[d]	DABCO	Dioxane	81
16[e]	DABCO	Dioxane	68

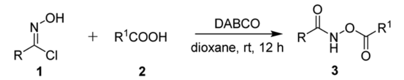
[a] Unless noted otherwise, reactions were performed with oxime chloride **1a** (0.22 mmol, 1.1 equiv.) and benzoic acid **2a** (0.2 mmol, 1 equiv.), base (0.22 mmol, 1.1 equiv.) in solvent (1.0 mL) at r.t. [b] Yield of the isolated product. [c] Reaction was carried out at 60 °C. [d] The reaction was performed at room temperature for 24 h. [e] 2 equiv. DABCO were used and the reaction was performed for 6 h.

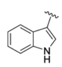
conveniently and easily synthesized in high yields from oximes using *N*-chlorosuccinimide (NCS) under mild conditions without any catalysts. In addition, the oximes could be obtained in high yields from various inexpensive aldehydes and hydroxylamine hydrochloride.

In our initial investigation, we chose phenylhydroximoyl chloride **1a** with benzoic acid **2a** as the model substrates for the optimization of the reaction conditions. The phenylhydroximoyl chloride **1a**, which can, in the presence of a base, generate nitrile oxides *in situ*, has found extensive utility in 1,3-dipolar cycloadditions for the synthesis of a wide variety of important heterocyclic compounds.[10] To our delight, the model reaction proceeded smoothly in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in dioxane at room temperature for 12 h and furnished the corresponding product **3a** in an 80% yield (Table 1, entry 1). The chemical structure of product **3a** was confirmed using single-crystal X-ray structure analysis (CCDC 1974489).[11] Subsequently, various types of base were screened, such as organic bases including TEA and DBU, and inorganic bases including Na_2CO_3 and NaOH. This revealed that DABCO was the most suitable base for this reaction (entries 2–5). To further improve the product yield, a series of different solvents were screened (entries 6–13). The results showed that product **3a** was provided in a moderate yield in Et_2O, toluene, DCE and $CHCl_3$ (entries 6, 9, 11 and 13). Whereas the product was obtained in good yields when the reaction was performed in THF or EtOAc (entries 7 and 8). The reaction can be carried out in acetone but with poorer yields than in other solvents. Furthermore, increasing the reaction temperature resulted in a slightly lower yield (entry 14). Moreover, the yield was not obviously improved when the reaction time was prolonged (entry 15). When 2 equiv. of DABCO was used for 6 h product **3a** was obtained in a moderate yield (entry 16).

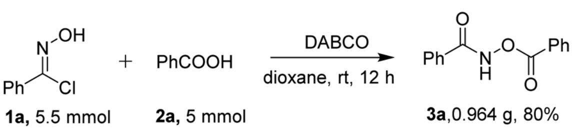
With our optimized reaction conditions in hand, the suitability of these conditions for reactions between various oxime chlorides and carboxylic acids was investigated. The results are shown in Table 2. Firstly, various substituted oxime chlorides **1** were reacted with benzoic acid **2a**. Pleasingly, regardless of the electronic properties of (electron-donating or electron-withdrawing) or the heterocyclic substituents on the R group of the oxime chloride moiety, the reaction proceeded successfully under the optimized reaction conditions, affording the corresponding products **3a–3e** (entries 1–5) in good yields (74–80%). Additionally, when an oxime chloride **1** bearing an alkyl group was reacted with benzoic acid **2a**, the corresponding product **3f** was obtained in a 69% yield. Subsequently, a number of aromatic carboxylic acids with either electron-denoting or electron-withdrawing substituents on the phenyl group reacted smoothly with phenylhydroximoyl chloride **1a** at ambient temperature under the optimized conditions. The corresponding *O*-acylhydroxamates **3g–3p** (entries 7–16) were obtained in good yields (62–74%). In these reactions, both a benzoic acid with a large sterically hindered group and a bis-substituted benzoic acid afforded the desired products **3i** and **3j** in 64% and 67% yields, respectively (entries 9 and 10). Additionally, the position of the substituent on the phenyl ring of benzoic acid **2** seemed to have a slight effect on the outcome of this reaction. For example, a *para*-bromo substrate led to a higher yield (**3o**, 70%) than the corresponding *ortho*- and *meta*-bromo substrates (**3m**, 67%; **3n**, 67%, respectively) (entries 13–15). Some heterocyclic carboxylic acids such as thiophene-2-carboxylic acid and 2-naphthoic acid could also afford the desired products in good yields. It is worth noting that an aliphatic carboxylic acid and cinnamic acid were compatible in this reaction, giving the desired products **3s** in a 70% yield (entry 19) and **3t** in a 69% yield (entry 20), respectively. This demonstrates that the reaction is not limited to only aromatic carboxylic acids. Especially, an indole-derived carboxylic acid also worked well in the reaction to furnish the corresponding *O*-acylhydroxamate **3u** in a 64% yield (entry 21). *O*-Acylhydroxamate **3u** could not be obtained through a one-step acylation reaction between

Table 2 Substrate scope for the formation of various *O*-acylhydroxamates **3**[a]

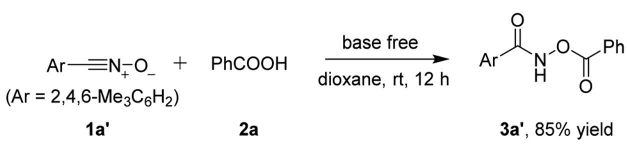


Entry	R	R^1	Yield of 3^b (%)
1	Ph	Ph	**3a**, 80
2	4-MeC_6H_4	Ph	**3b**, 74
3	4-BrC_6H_4	Ph	**3c**, 76
4	2-Furyl	Ph	**3d**, 70
5	2-Naphthyl	Ph	**3e**, 76
6	Cy	Ph	**3f**, 69
7	Ph	4-MeC_6H_4	**3g**, 68
8	Ph	4-$MeOC_6H_4$	**3h**, 66
9	Ph	4-$^tBuC_6H_4$	**3i**, 64
10	Ph	3,5-Di-Me-C_6H_3	**3j**, 67
11	Ph	4-FC_6H_4	**3k**, 74
12	Ph	4-ClC_6H_4	**3l**, 70
13	Ph	2-BrC_6H_4	**3m**, 67
14	Ph	3-BrC_6H_4	**3n**, 67
15	Ph	4-BrC_6H_4	**3o**, 70
16	Ph	4-$CF_3C_6H_4$	**3p**, 62
17	Ph	2-Thienyl	**3q**, 74
18	Ph	2-Naphthyl	**3r**, 71
19	Ph	2-Styryl	**3s**, 70
20	Ph	Cy	**3t**, 69
21	Ph		**3u**, 64

[a] Reaction conditions: oxime chloride **1** (0.22 mmol), carboxylic acid **2** (0.2 mmol), DABCO (0.22 mmol), dioxane (1 mL), at room temperature for 12 h. [b] Isolated yield.



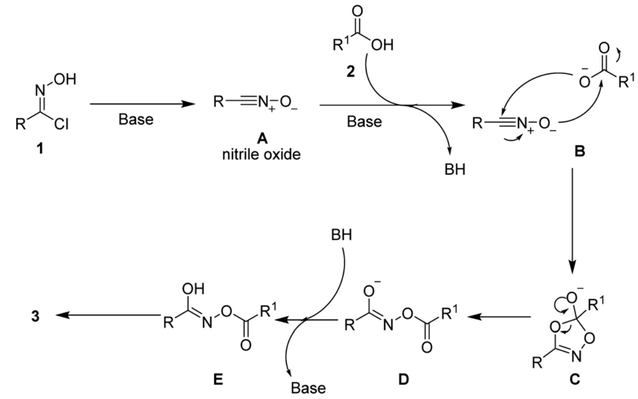
Scheme 2 Scaled-up synthesis of *O*-acylhydroxamate **3**.



Scheme 3 Reaction of isolable 2,4,6-trimethylbenzonitrile oxide (**1a′**) with benzoic acid **2a**.

a hydroxamic acid and an acyl chloride *via* the classical approach (scheme 1a).

To further highlight the utility of our method to obtain *O*-acylhydroxamates under the standard conditions, the reaction was carried out on a gram-scale between 5.5 mmol of phenylhydroximoyl chloride **1a** and 5 mmol benzoic acid **2a**. The reaction proceeded smoothly to afford the desired product **3a** without a significant loss of efficiency (0.964 g, in an 80% yield,



Scheme 4 Proposed mechanism.

Scheme 2), showing the reaction to be a practical tool for the synthesis of *O*-acylhydroxamates.

On the other hand, mesityl nitrile oxide **1a′** was stable enough to be isolated from the corresponding oxime chloride.[12] The same reaction conditions tolerated stable nitrile oxide **1a′** and it reacted with benzoic acid **2a** delivering the desired product **3a′** in an 85% yield (Scheme 3).

As shown in Scheme 4, a plausible mechanism is proposed to explain the reaction process. Firstly, the highly active nitrile oxide **A** is generated from an oxime halide under basic conditions. Then, this nitrile oxide intermediate **A** reacts with carboxylic acid **2** to afford intermediate **E**. Finally, the intermediate **E** would transform into the desired product **3** *via* keto–enol tautomerization.[13]

In conclusion, we have developed a mild, practical and efficient protocol to prepare a broad range of functionalized *O*-acylhydroxamates in high yields (up to 85%) from oxime chlorides and carboxylic acids. In addition, the methodology allows the synthesis of *O*-acylhydroxamates on a gram scale. Our approach features some advantages over previously published methods, including the easy manufacture of the start materials, being stable in air and water, having a broad tolerance of functional groups, mild reaction conditions, a simple workup and noble metal-free catalysis. Further applications of this method are presently under active investigation in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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