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Nitrosocarbonyl–Henry and Denitration Cascade: Synthesis of α-Ketoamides and α-Keto Oximes

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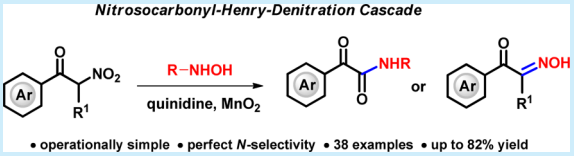
Supporting Information

ABSTRACT: An unprecedented Henry reaction of in situ generated nitrosocarbonyl intermediates and concomitant denitration cascade has been developed. The reaction is catalyzed by organic base at room temperature offering α-ketoamides, a demanding scaffold for drug discovery, in high yields. An alteration of substitution pattern also produced α-keto oximes, a high-value synthon. The protocol features operational simplicity and broad substrate scope.

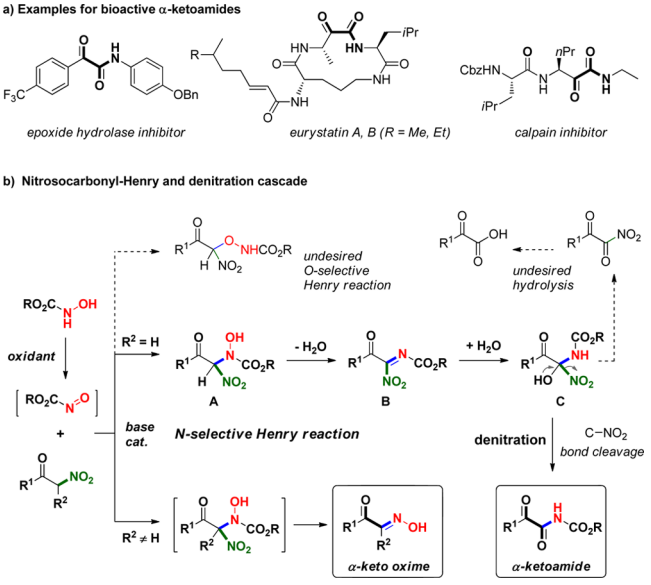


Nitrosocarbonyl intermediates and the derivatives thereof have occupied a prominent position in contemporary organic synthesis.[1] They are very reactive and versatile prototypes of ambident electrophiles allowing construction both C–N and C–O bonds from a single source. In this context, chemists have compiled a reaction compendium that includes nitrosocarbonyl aldol, ene, Diels–Alder, and other types of cycloaddition reactions.[2−4] Despite these accomplishments, heretofore, the reaction of nitroalkanes with nitrosocarbonyl compounds, the so-called nitrosocarbonyl-Henry reaction, remains elusive, which is the quintessence of this report.[5]

α-Ketoamides represent an important structural motif found in numerous natural products and bioactive molecules (Scheme 1a).[6] They also serve as useful synthetic intermediates for various transformations.[6,7] Consequently, synthetic endeavors toward this scaffold are in high demand and remain a focus of general interest.[6−9] We envisaged that Henry reaction of substituted nitroalkane with in situ generated nitrosocarbonyl intermediate could be a convenient transformative alternative to access this scaffold (Scheme 1b, R^2 = H). The product **A** thus obtained through the Henry reaction may undergo a water elimination–addition sequence to give densely substituted hemiaminol **C**, which will trigger a denitration[10] reaction to produce the desired product α-ketoamide. However, formation of the competing *O*-selective nitroso-Henry reaction and the undesired hydrolysis as depicted in Scheme 1b poses significant challenges to this strategy. Additionally, a mild oxidation cycle for in situ generation of nitrosocarbonyl intermediate is crucial to overcome the decomposition of substrate. Herein, we report an unprecedented nitrosocarbonyl Henry reaction en route to α-ketoamides (R^2 = H) and α-keto oximes ($R^2 \neq$ H) catalyzed by cinchona alkaloid at room temperature (Scheme 1b). It is worth noting that, similar to α-ketoamides, α-keto oximes are also key building blocks for the synthesis of diverse heterocyclic frameworks.[11]

We commenced our investigation using keto-substituted nitroalkane **1a** as a model substrate and commercially available hydroxamic acid **2a** as a precursor of nitroso intermediate

Scheme 1. Bioactive α-Ketoamides and Reaction of Nitroalkanes with Nitrosocarbonyl Intermediates



(Table 1). A solution of **2a** was slowly injected into a mixture of **1a** and MnO_2 oxidant in THF at room temperature under the influence of various base catalysts (10 mol %). However, the reaction was unfruitful for commonly employed tertiary amines such as DBU, NEt_3, and DABCO (entries 1–3). The breakthrough came when cinchona alkaloid cinchonidine was considered. To our satisfaction, the reaction proceeded with complete *N*-selectivity, rendering the desired α-ketoamide **3a** in 34% isolated yield. When the catalyst was changed to quinidine, the yield increased to 78% (entry 5). Screening of other solvents and oxidant gave inferior results (entries 6–9). Control experiments revealed that the presence of both the

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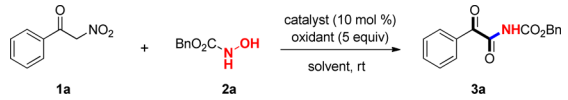
Table 1. Optimization of Reaction Conditions for the Synthesis of α-Ketoamides[a]



entry	solvent	oxidant	catalyst	yield[b] (%)
1	THF	MnO_2	DBU	*c*
2	THF	MnO_2	NEt_3	*c*
3	THF	MnO_2	DABCO	*c*
4	THF	MnO_2	cinchonidine	34
5	**THF**	**MnO_2**	**quinidine**	**78**
6	CH_3CN	MnO_2	quinidine	30
7	DCE	MnO_2	quinidine	trace
8	MeOH	MnO_2	quinidine	trace
9[d]	THF	CuCl, Py, O_2	quinidine	48
10	THF		quinidine	*c*, *e*
11	THF	MnO_2		*c*

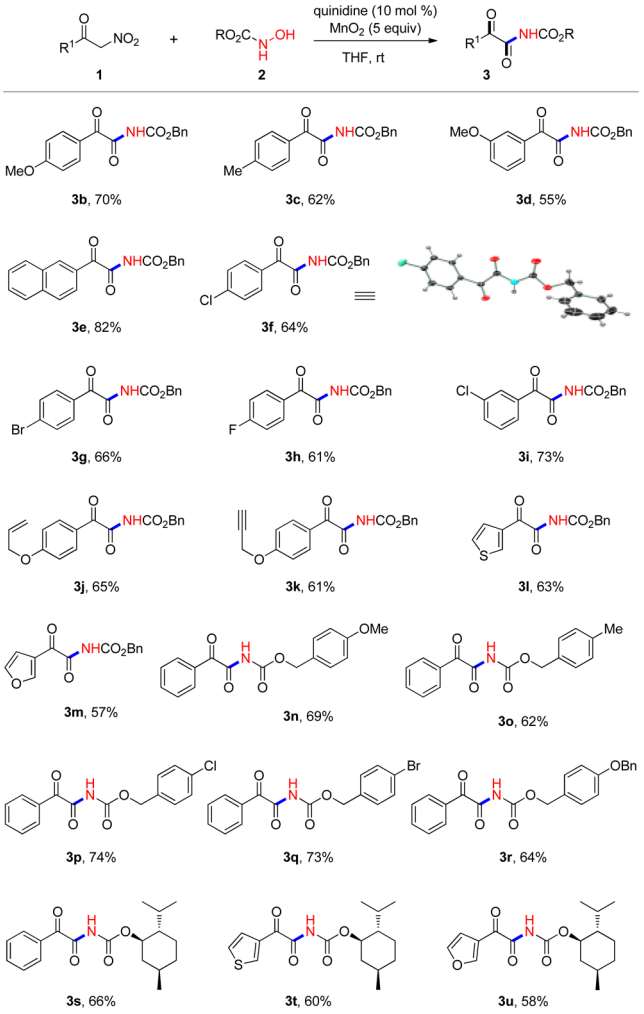
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), catalyst (0.1 equiv), MnO_2 (5 equiv), solvent (3 mL), 48 h. [b]Isolated yield. [c]No reaction with the recovery of **1a**. [d]CuCl (0.1 equiv), pyridine (Py, 0.2 equiv), O_2 balloon. [e]No reaction with recovery of **1a** and **2a**. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. DABCO: 1,4-diazabicyclo[2.2.2]-octane; DCE: 1,2-dichloroethane.

quinidine catalyst and the MnO_2 oxidant is mandatory, and the reaction was ineffective in the absence of either of them (entries 10 and 11).

With the optimized conditions in hand, the scope of the α-ketoamide synthesis was then explored (Scheme 2). The reaction is quite general. Various keto-substituted nitroalkanes having electron-donating and -withdrawing substituents (**1b–i**) uniformly delivered the desired products in good yields (55–82%). Compound **3f** was crystallized, and the structure was unambiguously confirmed through X-ray analysis.[12] Interestingly, the reaction tolerates various functional groups; alkene (**3j**) and alkyne (**3k**) groups were unaffected. Heterocyclic systems are also compatible to the reaction conditions, producing **3l,m** in 63% and 57% yields, respectively. Substitutions at the hydroxamic acid moiety were also explored to furnish **3n–r** in 62–74% isolated yields. Notably, (−)-menthol-derived hydroxamic acid also efficiently participated in this reaction, and chiral α-ketoamides **3s–u** were obtained in good yields.

Interestingly, when a higher homologue of nitroalkane **4a** (R_2 = Me) was exposed to optimized reaction conditions in the presence of Cbz-substituted hydroxamic acid **2a** (R = Bn), α-keto oxime **7a** was obtained exclusively (Scheme 3). The formation of oxime product can be rationalized on the basis of the *N*-selective nitroso-Henry reaction en route to compound **5** followed by C–NO_2 bond cleavage (Scheme 3). This conjecture was corroborated by the fact that the reactions of nitroalkane **4a** with other hydroxamic acids, Troc-NHOH (**2b**) and Boc-NHOH (**2c**), also produced the same product **7a** but in diminished yields (70% and 52%, respectively). This fortuitous finding encouraged us to explore the reaction further. To our delight, a series of nitroethanes and nitropropanes reacted smoothly to produce substituted α-keto oximes in high yields (52–80%, Scheme 3). The functional group compatibility of this reaction is impressive. The reaction can be performed in the presence of various halogens (**7e–i,n**), nitrile (**7j**), acetal (**7k**), and double bond (**7l**) functionalities without any difficulties. The mild reaction conditions are also

Scheme 2. Scope of α-Ketoamide Synthesis[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), quinidine (0.1 equiv), MnO_2 (5 equiv), THF (3 mL), 48 h. Isolated yield.

suitable for heterocyclic systems, furnishing furyl- (**7o**), benzofuryl- (**7p**), and thienyl-substituted (**7q**) α-keto oximes in good yields (60–66%). Furthermore, only *E*-oximes are selectively formed in this reaction, and crystal structures of **7a** and **7q** also support this observation.[12] It is important to emphasize that traditional α-keto oxime syntheses are usually performed under acidic conditions.[13] In contrast, our protocol operates under catalytic basic conditions.

To highlight the synthetic utility of this protocol, we have performed the reaction on a gram scale (Scheme 4). With only 10 mol % catalyst loading under the optimized conditions, the gram-scale *N*-selective nitrosocarbonyl-Henry reaction of **1e** with **2a** proceeded smoothly, and the corresponding product **3e** was isolated in comparable yield (76%). Additionally, compound **3e** was also exquisitely reduced with $NaBH_4$, rendering β-hydroxy-α-amino alcohol **8** in excellent yield (Scheme 4).

In conclusion, we have described a Henry reaction of in situ generated nitrosocarbonyl intermediates with keto-substituted nitroalkanes and the subsequent denitration cascade. The reaction is catalyzed by cinchona alkaloid quinidine and proceeds at room temperature to deliver α-ketoamides in high yields with nitromethane derivatives (up to 82%). When

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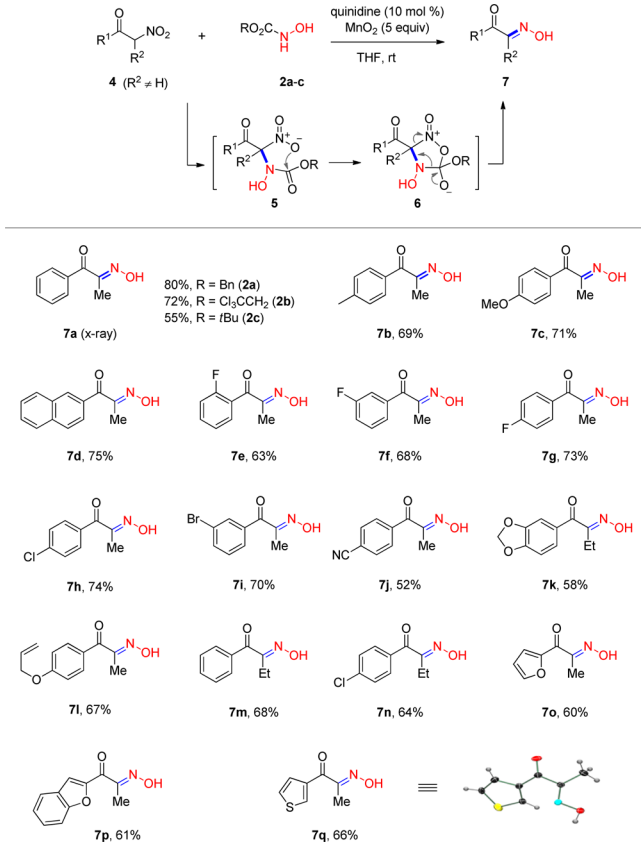
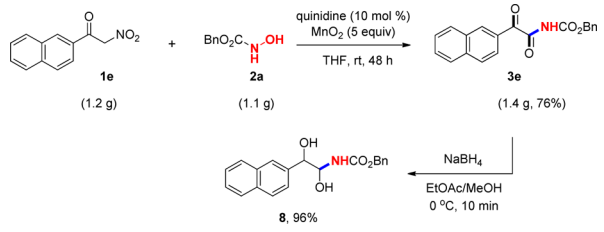
Scheme 3. Synthesis of Oximes via Nitrosocarbonyl-Henry Reaction[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), quinidine (0.1 equiv), MnO_2 (5 equiv), THF (3 mL), 48 h. Isolated yield.

Scheme 4. Gram-Scale Reaction and Post-functionalization



higher homologues of nitromethane derivatives were employed, selective formation of α-keto oximes was accomplished (up to 80% yield). The protocol is operationally simple, scalable, and displays broad substrate scope with high functional group compatibility. Additional studies of nitrosocarbonyl chemistry for organic synthesis are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00482.

Complete experimental details and characterization data for the prepared compounds (PDF)
Crystallographic data for **3f** (CIF)
Crystallographic data for **7a** (CIF)
Crystallographic data for **7q** (CIF)

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Notes

The authors declare no competing financial interest.

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