Nitroso Aldol Reactions

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The Electrophilic α-Amination of α-Alkyl-β-Ketoesters with In Situ Generated Nitrosoformates**

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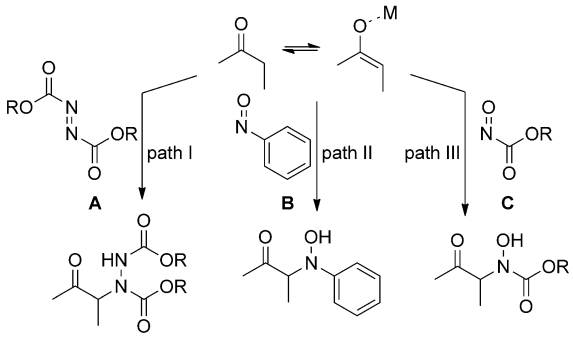
amination · copper · electrophilic addition · nitroso compounds · oxidation

α-Amino acids represent an important structural motif in organic chemistry and the importance of α-amino acids as principal building blocks of peptides and proteins for biological systems as well as bioactive small molecules is widely recognized. Accordingly, the development of efficient strategies for the construction of α-amino acids and other α-amino carbonyl compounds has been a long-standing challenge in synthetic organic chemistry. One of the most conceptually simple and direct ways to access α-amino carbonyl compounds is the electrophilic α-amination reaction, which directly introduces a nitrogen atom to the α-position of CH-acidic carbonyl substrates.[1]

Despite the obvious appeal of this synthetic method, direct α-aminations are still a challenging task, and their application is still limited by the sparse availability of suitable electrophilic nitrogen sources. Accordingly, the vast majority of known α-aminations—both directly applied to activated carbonyl compounds as well as using enol ethers, enolates, and enamines as substrates—rely on the use of a single class of amination reagents, namely azodicarboxylates **A** (Scheme 1). The obtained twofold carbamate-protected hydrazine products (path I) can be further derivatized to give a variety of different products, but the conversion to simple α-amino carbonyl compounds requires the cleavage of the N–N hydrazine bond and often rather drastic reductive conditions.

As an alternative to azodicarboxylates, nitroso compounds (R–N=O) may serve as electrophilic amination reagents. Nitrosobenzene (**B**), for example, can be regarded as an aza analogue of benzaldehyde, and its N-selective nitroso aldol reaction gives rise to N-substituted hydroxylamines (path II). The reaction of nitrosobenzene with enolates was extensively studied by Yamamoto and Momiyama and the outcome, especially with regard to N- versus O-selectivity (i.e., nitroso aldol versus aminooxygenation) proved to be highly dependent on the exact reaction conditions.[2] Even in cases where good N-selectivity can be achieved, however, the synthetic utility of the aryl hydroxylamine products is unfortunately quite limited due to the difficult removal of the aromatic N-substituent. The nitroso aldol reaction of nitrosoformates **C**, on the other hand, would result in much more easily manipulated and thus synthetically more versatile carbamate-protected N-substituted hydroxylamines (path III). The group of Read de Alaniz has now presented the first example of the N-selective nitroso aldol reaction using these previously unstudied nitrosoformates.[3] It is also noteworthy that the corresponding O-selective nitroso aldol reaction was published almost simultaneously.[4]



Scheme 1. Strategies for the electrophilic α-amination of carbonyl compounds.

In contrast to bench-stable nitrosobenzene (**B**), acyl nitroso compounds, such as nitrosoformates **C** are highly reactive transient species, which are generally produced by the in situ oxidation of *N*-hydroxycarbamate precursors.[5] Nitrosoformates and other acyl nitroso species have been studied quite extensively in hetero-Diels–Alder and ene reactions, but have not been used previously as substrates for nitroso aldol reactions.[6] The new N-selective nitrosoformate aldol reaction relies on the aerobic oxidation of readily available *N*-hydroxycarbamates using Cu^{I} catalysis, which had been previously developed by the authors,[7] while, independently, Whiting, Shea, and co-workers had reported a similar Cu^{II}-catalyzed oxidation.[8] Now, CuCl (5 mol%) and Cu(OTf)$_2$ (5 mol%) were combined as a mixed catalyst system with no added ligands in MeOH to effect the mild and efficient aerobic oxidation of *N*-hydroxycarbamates **1** to nitrosoformates **2** (Scheme 2). In addition, the same copper catalysts also act in a synergistic fashion as a Lewis acid to

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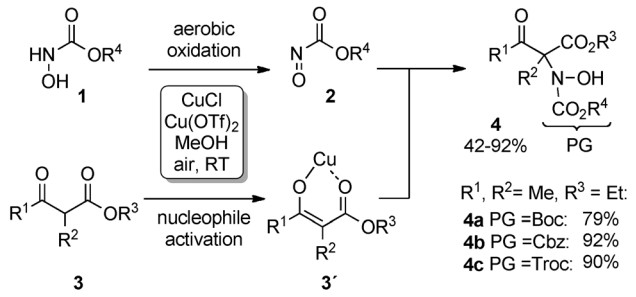
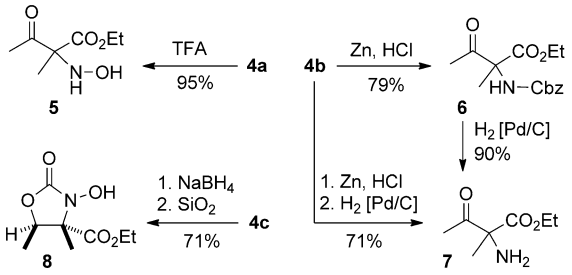
activate β-ketoesters **3** through the formation of chelated Cu enolates **3′**, although no mechanistic details have been reported yet. The following nitroso aldol reaction proceeds with high N-selectivity to give the desired *N*-hydroxycarbamates **4** in high yields.



Scheme 2. α-Amination of α-alkyl-β-ketoesters by means of Cu-catalyzed oxidation and an N-selective nitroso aldol reaction. R^1 = alkyl, aryl; R^2,R^3 = alkyl; R^4 = Bn (PG = Cbz), *t*Bu (PG = Boc), CH_2CCl_3 (PG = Troc), 9-fluorenylmethyl (PG = Fmoc), $CH_2CHMe(o\text{-}O_2NC_6H_4)$ (PG = Nppoc).

The reaction succeeds under operationally simple conditions, employs only cheap and readily available catalysts and starting materials, and stands out due to its very broad substrate scope. Aliphatic (R^1 = Me, Et, Bn), branched (R^1 = *i*Pr), and electron-rich as well as electron-poor aromatic (R^1 = Ar) substrates **3** bearing different α-alkyl substituents (R^2 = Me, Et, Bn) and ester groups (R^3 = Me, Et, allyl, *t*Bu) all reacted smoothly with a variety of hydroxycarbamates **1** to give the products **4** in uniformly high yields exceeding 70%. Hydroxycarbamate products **4**, even those bearing allyl or vinyl groups, were completely stable towards the mild oxidative reaction conditions. Slightly lower yields were reported only for very bulky (R^2 = *i*Pr) or certain cyclic substrates, which also displayed a greater degree of O-selective side reactions. These side products, however, were easily removable by column chromatography and thus, a wide array of highly substituted products bearing all common, orthogonally labile N-protecting groups was readily available in a convenient one-pot fashion. Very low catalyst loadings of 1 mol% CuCl and $Cu(OTf)_2$ still enabled a 82% yield of **4c** in a gram-scale experiment, although the reaction took 10 days to reach completion. Interestingly, a substrate lacking the α-alkyl substituent (R^2 = H) reacted under N–O heterolysis and incorporation of the MeOH solvent into the α-position.

To highlight the synthetic utility of the hydroxycarbamate products **4**, a number of important derivatization reactions were carried out (Scheme 3). The removal of N-protecting groups (e.g. Boc) to provide hydroxylamines **5** was straightforward. Most importantly, however, cleavage of the N–O bond could be realized with Zn in 2 N HCl to give N-protected amines like **6** and accordingly, in a two-step deprotection sequence, free amines like **7** in good overall yields. As such, the nitrosoformate aldol reaction proved highly competitive with the known azodicarboxylate route towards amino compounds. A transformation specific for hydroxycarbamates **4** was realized by the diastereoselective reduction of the keto group and a subsequent cyclization to give oxazolidinone **8**, which is an illustrative example for the use of the products in the synthesis of heterocycles.



Scheme 3. Derivatization of nitroso aldol products **4**.

In conclusion, the use of nitrosoformates as electrophilic nitrogen sources constitutes a significant extension of the previously known N-selective nitroso aldol reactions. Products with a wide variety of substituents are now easily available and the carbamate protecting groups offer a versatile handle for further transformations. The reaction is facilitated by an exceptionally mild and selective aerobic oxidation protocol for the in situ formation of the reactive nitroso species using a mixed Cu^I/Cu^{II} catalyst system, which also acts as a Lewis acid catalyst for the activation of the β-ketoester substrates. As the reaction also works to some degree using either CuCl or $Cu(OTf)_2$ alone,[3] and aerobic oxidations to nitrosoformates have been developed for both systems,[7,8] further mechanistic investigations regarding the exact nature of the different catalytically active species, also with regard to a possible Lewis acidic activation of the nitrosoformate electrophiles themselves, are still desirable. Giving the highly reactive nature of acyl nitroso compounds, further examples of their use as versatile amination and/or oxygenation reagents can probably be expected in the future. Also, in light of the progress in the field of Cu-catalyzed enantioselective α-functionalizations, for example, with chiral bisoxazoline ligands in very closely related systems,[4,9] further development into an enantioselective reaction might be possible.

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[1] For reviews on electrophilic α-aminations, see: a) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364–4372; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292–4300; b) E. Erdik, *Tetrahedron* **2004**, *60*, 8747–8782; c) C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem.* **2004**, 1377–1385; d) P. Dembech, G. Seconi, A. Ricci, *Chem. Eur. J.* **2000**, *6*, 1281–1286.

[2] a) N. Momiyama, H. Yamamoto, *Org. Lett.* **2002**, *4*, 3579–3582; b) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360–5361.

[3] D. Sandoval, C. P. Frazier, A. Bugarin, J. Read de Alaniz, *J. Am. Chem. Soc.* **2012**, *134*, 18948–18951.

[4] M. Baidya, K. A. Griffin, H. Yamamoto, *J. Am. Chem. Soc.* **2012**, *134*, 18566–18569.

[5] G. W. Kirby, H. McGuigan, J. W. M. Mackinnon, D. McLean, R. P. Sharma, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1437 – 1442.
[6] For reviews on the chemistry of nitroso and nitrosocarbonyl compounds, see: a) B. S. Bodnar, M. J. Miller, *Angew. Chem.* **2011**, *123*, 5746 – 5764; *Angew. Chem. Int. Ed.* **2011**, *50*, 5630 – 5647; b) W. Adam, O. Krebs, *Chem. Rev.* **2003**, *103*, 4131 – 4146.
[7] a) C. P. Frazier, J. R. Engelking, J. Read de Alaniz, *J. Am. Chem. Soc.* **2011**, *133*, 10430 – 10433; b) C. P. Frazier, A. Bugarin, J. R. Engelking, J. Read de Alaniz, *Org. Lett.* **2012**, *14*, 3620 – 3623.
[8] D. Chaiyaveij, L. Cleary, A. S. Batsanov, T. B. Marder, K. J. Shea, A. Whiting, *Org. Lett.* **2011**, *13*, 3442 – 3445.
[9] M. Marigo, K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1405 – 1407; *Angew. Chem. Int. Ed.* **2003**, *42*, 1367 – 1369.

