Copper-Mediated Reactions of Nitriles with Nitromethanes: Aza-Henry Reactions and Nitrile Hydrations

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Supporting Information

ABSTRACT: In this study, the first aza-Henry reaction of nitriles with nitromethane in a CuI/Cs₂CO₃/DBU system is described. The process was conveniently and directly used for the synthesis of β-aminonitroalkenes 2a−x and tolerated aryl-, alkyl-, hetaryl-, alkenyl-, and alkynynitriles. The resulting aminonitroalkenes could be successfully transformed to the corresponding 2-nitroacetophenones, 2-amino-1-halonitroalkenes, 2-alkylaminonitroalkenes, or 3-nitropyridines. In the presence of H₂O, the aza-Henry reaction turned the reaction path to the nitrile hydration to exclusively yield the amides 3a−s.

β-Aminonitroalkenes are an important class of biologically active compounds which include H₂-receptor antagonists such as nizatidine and ranitidine.1 β-Aminonitroalkenes are widely used as building blocks that are useful as push−pull alkenes in applications ranging from pharmaceutical to catalysis chemistry.2 Pyrroles,3a isoxazolines,3b pyridines,3c indoles,3d,e dihydropyridiones,3e,f pyrimidiones,3f and other heterocyclic compounds3g have been synthesized from simple transformations of β-aminonitroalkenes. Furthermore, recent advances in the enantioselective hydrogenation of N-acylaminoalkenes have enabled the synthesis of valuable chiral amine derivatives. Such chiral amines can act as the key structural element in chiral diamine ligands and can be found in pharmaceuticals such as clopidogrel, oseltamivir, and asimadoline.4 β-Aminonitroalkenes have attracted great attention because they can be easily converted to α-amino acids through their respective Nef reactions.5

β-Aminonitroalkenes are typically synthesized through two conceptually different methods: the direct nucleophilic addition of nitroalkanes to aldehydes (Henry reaction) followed by amination of the resulting alkene (Scheme 1)4a and the same Henry reaction followed by the sequential pyridinium chlorochromate (PCC) oxidation and titanium-catalyzed enamination using ammonia or other amines.4b,c,6,7 Most methods for β-aminonitroalkene synthesis consist of multistep processes that combine Henry reaction of aldehydes with subsequent amination reactions. Recently, a simple and convenient method has also been reported using methyl imidates.8 The nucleophilic addition of nitroalkanes to imines (aza-Henry reaction) is a powerful tool for the preparation of β-aminonitroalkanes;7 however, the aza-Henry process, which is the most convenient and atom-economical route to synthesize β-aminonitroalkenes using nitriles, is very difficult because it is entropically unfavorable. Recently, Lee et al. reported that the Lewis acid catalyzed Blaise reaction of nitriles with zinc acetates (Reformatsky reagents) provided β-aminoketenyl esters in good yields.10 If the aza-Henry reaction of nitriles with nitromethane was possible, it would be a powerful, atom-economical, and environmentally benign route for the synthesis of β-aminonitroalkenes. In the proposed study, we report the first copper-promoted aza-Henry reaction of nitriles under mixed-base conditions.

To optimize the nucleophilic addition of nitromethane to nitriles, we selected toluonitrile as the model substrate. The reaction of nitriles with zinc acetates (Reformatsky reagents) provided β-aminoketenyl esters in good yields.10

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screening results are shown in Table 1. When the reactions were performed with a base such as C₈H₆O₃ (3 equiv) or diazabiclyclo[5.4.0]undec-7-ene (DBU) in nitromethane at 100 °C, very low conversions were observed (entries 1 and 2). When the aza-Henry reaction of 1a was attempted under mixed-base conditions, using a combined C₈H₆O₃/DBU system, the desired 2a was obtained in 14% yield (entry 3). When we also examined the metal-catalyzed reaction of 1a under mixed-base conditions, a dramatic increase in the yields of both 2a and amide 3a was observed (entry 4). The same reaction was performed in a mixed solvent system (MeNO₂-H₂O) yielding only the hydrated amide 4a (57% yield, entry 5). This remarkable result indicated that the nitro−aza-Henry reaction was highly sensitive to water; therefore, we used molecular sieves 4A and one equivalent of copper iodide, which resulted in improved yields of 2a (entries 6–8). The copper-catalyzed reaction of 1a resulted in 52% yield of 2a; however, the use of 1 equiv of both CuI and HMPA resulted in the highest yield.

With the optimized reaction conditions in hand, we investigated the substrate scope of the proposed aza-Henry reaction with substituted benzonitriles (Scheme 2). The reaction of benzonitrile (1b) afforded 2b in quantitative yield. p-Chlorobenzonitrile (1c) was also tolerated; however, the reaction with p-methoxybenzonitrile resulted in only a moderate yield. The aza−Henry reaction of o-chlorobenzonitrile and o-methoxybenzonitrile also yielded the β-aminonitroalkenes 2e and 2f in moderate to high yields, respectively, rather than the corresponding o-substituted β-nitroalkenes due to steric effects. Surprisingly, the reaction with methyl p-cyanobenzoate afforded the expected 2g in high yield along with amide 5g. Unfortunately, the aza-Henry reaction of p-nitrobenzonitrile gave 2h in low yield. Sterically hindered biphenyl and naphthonitrile resulted in low yields of products 2i and 2j, respectively. Next, we investigated the reactions of disubstituted benzonitriles. 3,4-Difluorobenzonitrile and 2,5-difluorobenzonitrile were easily converted to the corresponding amino-nitroalkenes 2k and 2l, respectively. The reaction of 3-fluoro-6-methylbenzonitrile (1m) gave 2m in good yield; however, the use of 4-bromo-2,5-difluorobenzonitrile (1n) resulted in relatively low yields. Next, we examined the aza-Henry reactions with cyanoalkanes. 2-Alkyl-2-aminonitroalkenes are difficult to prepare; however, compounds 2o–q were isolated as the free amines. Next, we investigated the aza-Henry reactions of cyanoheterocycles. Nitrile-containing heterocycles can be good precursors for a wide variety of substituted heterocycles. The reaction of 3-cyanopyridine (1r) gave alkene 2r in 52% yield; however, the reaction of 2-cyanopyridine (1s) only gave 2s in relatively low yields. The aza-Henry intermediate is responsible for the lower yield of 2s than that of 2r. 2-Pyrimidinonitrile and furonitrile also tolerated the aza-Henry reaction conditions to yield 2t and 2u, respectively. β-Aminonitroalkenes bearing 3- and 2-thiophene (2v and 2w, respectively) groups were obtained as stable crystals. Interestingly, cinnamononitrile (1x) underwent Michael addition followed by the aza-Henry reaction to yield dinitroalkene 2x. Thus, we found that the aza-Henry reactions of nitriles involving the CuI/C₈H₆O₃/DBU system were practical for the synthesis of β-aminonitroalkanes, but only in the absence of H₂O.
Next, we explored the hydration process that competed with the aza-Henry reaction of nitriles (Scheme 3). Nitrile hydration processes, leading to primary amides, are considerably useful for the direct syntheses of drugs. Adding H₂O and tuning the reaction conditions resulted in an efficient nitrile hydration. Thus, we uncovered a facile one-pot procedure to yield the corresponding primary amides from our aza-Henry reaction. The results are shown in Scheme 3. Amides were obtained in moderate to high yields, with only trace amounts of the aminoalkenes. Surprisingly, methyl 4-cyanobenzoate (1g) was also converted to 3g without the ester group hydrolysis. The reaction of 2-cyano-4′-methylbiphenyl gave the amide in high yields, although the yield of the product from the aza-Henry reaction of 1i was very low. The reactions of difluorobenzonitrile (1k) and 2-cyanopyridine (1s) gave the amides in quantitative yield.

A plausible reaction mechanism for this aza-Henry reaction was proposed on the basis of the work of Fukuyama et al. They reported the inter- and intramolecular amination of aryl halides using a combination of CuI/CsOAc. CuOAc was the active metal species, generated from CuI and CsOAc, and recent progress indicates that Cu(I) favors tetrahedral coordination. Therefore, we proposed the following reaction mechanism for the aza-Henry reaction using CuI/Cs₂CO₃/DBU (Scheme 4). In the CuI/Cs₂CO₃/DBU system in nitromethane, Cu ions weakly coordinate with nitromethane to form intermediate 4. Cs₂CO₃ then reacts with intermediate 4 to give the active intermediate 5, similar to Szymczak’s Cu(I) complex. The ligand exchange of 5 with nitrile yields intermediate 6. Then, DBU abstracts a proton from the copper-bound nitromethane to form anion 7. Intermediate 7 then undergoes intramolecular nucleophilic addition, via the 6-membered transition state, to yield 8. Thus, the aza-Henry reaction of nitriles is achieved due to both the ease forming the 6-membered transition state and the intramolecular cesium carbonate coordination. The protonation of 8 with DBUH⁺ yields the product, 2-aminonitroalkene 9. The formation of amides would result from protonating enolate 7.

Scheme 3. Copper Iodide Catalyzed Nitrile Hydration

<table>
<thead>
<tr>
<th>R¹-CN</th>
<th>MeNO₂·H₂O (1:1)</th>
<th>CuI (0.2 equiv)</th>
<th>Cs₂CO₃ (0.5 equiv)</th>
<th>DBU (2 equiv)</th>
<th>NH₂NO₂ + R¹CONH₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a(%)</td>
<td>/ 3a (87%)</td>
<td>2b (4%)</td>
<td>3b (91%)</td>
<td></td>
<td>2c (5%) 3c (94%)</td>
</tr>
<tr>
<td>2f (%)</td>
<td>/ 3f (50%)</td>
<td>2g (9%)</td>
<td>3g (90%)</td>
<td></td>
<td>2h (−) / 3h (quant)</td>
</tr>
<tr>
<td>2k (%)</td>
<td>/ 3k (94%)</td>
<td>2s (−) / 3s (94%)</td>
<td>2u (10%) / 3u (81%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scheme 4. Proposed Reaction Mechanism

Scheme 5. Transformation of β-Amino Nitroalkenes 2

The selected alkenes were easily converted to the corresponding nitroketones 13a–w quantitatively. Next, we halogenated the β-aminonitroalkenes with N-halosuccinimides. Haloalkenes are known to be good substrates for Suzuki–Miyaura coupling reactions. The reaction of 2-tolunitrile 2a with N-bromosuccinimide at room temperature without any additives.
afforded 1-bromonitroalkene 14a in 67% yield. The reaction of 2a with NCS and NIS gave 1-chloronitroalkene 15a and 1-iodonitroalkene 16a in good yield, respectively. Other 2-arylalkenes were easily converted to 2-halo derivatives 14g–16g.

We explored the transformations of β-aminonitroalkenes to other useful compounds. The free amino group of 2 was found to have low nucleophilicity, and the yields of both acetylation and carbamation were low. Thus, Lewis acid catalyzed [3 + 3] cycloaddition of 2 with substituted enals or enones afforded the functionalized pyridines 19a–d.17

In conclusion, the copper-mediated aza-Henry reaction of nitriles using a Cs2CO3/DBU mixed-base system successfully afforded the corresponding β-aminonitroalkenes. In the presence of H2O, the corresponding amides could be obtained in excellent yields.18 The synthesis of substituted pyridines using the proposed aza-Henry reaction is currently underway, and the results of which will be reported in due course.

■ ASSOCIATED CONTENT

$ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00058.

Experimental procedure and NMR spectra (PDF)

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Notes

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