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2-Quinolinecarboxaldehyde: an unusual partner in the Henry reaction and subsequent elimination

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ABSTRACT

2-Quinolinecarboxaldehyde participates in a standard Henry reaction when combined with a nitroalkane and catalytic amounts of base. However, water is not readily eliminated from the resulting β-nitro alcohol intermediate to form the expected nitroalkene. Instead, the elimination of nitrous acid is observed furnishing an unexpected ketone product.

Nitroalkenes are useful intermediates in organic synthesis and can generally be prepared from the dehydration of a β-nitro alcohol, which in turn can be synthesized from the aldol-like reaction of a nitroalkane and an aldehyde, also known as the Henry reaction (Scheme 1).[1] The Henry reaction is known to be catalyzed by both bases and acids, and the subsequent formal elimination of water can be induced thermally or promoted by the addition of other reagents, such as dicyclohexylcarbodiimide (DCC) or methanesulfonyl chloride (MsCl).[2]

During our ongoing synthetic efforts in drug discovery, we sought to utilize the nitroalkene intermediate to access primary and secondary carbinamines.[3] Toward that end, we employed the microwave-mediated method described by Texier-Boullet and coworkers, which allows for the rapid isolation of nitroalkenes.[4] Using this protocol, we isolated nitroalkenes derived from simple cyclic aldehydes in a straightforward manner. However, when 2-quinolinecarboxaldehyde was used, an *unexpected methyl ketone product* was isolated instead of the expected nitroalkene (Scheme 2). This unprecedented transformation piqued our interest; herein we present the results from our preliminary efforts to explore the scope and gain some understanding of this reaction.

The method by Texier-Boullet and coworkers calls for the dissolution of the aldehyde in the nitroalkane with no additional solvent and use of piperidine as the catalyst. The reaction is then stirred for approximately 10 min under microwave heating.[5] These conditions were employed when we made our initial observation of a ketone product instead of a nitroalkene; however, analysis of these reactions by LC–MS showed the presence of multiple species, and the isolated yield was quite variable. We attribute these erratic outcomes to the lack of solvent and the viscous nature of the reactions. An additional complication was the occasional observation by LC–MS of Mannich-type products that appeared to incorporate the piperidine catalyst to form β-nitro amines. These observations prompted us to explore conditions utilizing solvents, in order to facilitate efficient mass transport; furthermore, we chose to employ 1,1,3,3-tetramethylguanidine (TMG) instead of piperidine, since it is also known to catalyze the Henry reaction and is unlikely to form Mannich-type products.[6]

We monitored our initial optimization reactions by LC–MS and observed that in general these reactions very cleanly and rapidly (minutes) show consumption of aldehyde to generate a β-nitro alcohol intermediate, which is followed by slow (hours) formation of the final ketone products (Table 1). The β-nitro alcohol intermediate appears to form easily in all of the solvents we examined; however, only in the less polar solvents of dichloroethane and toluene did the intermediate readily disappear to afford the ketone product (entries 1–5).[7] Additional catalyst did not seem to lead to a more efficient reaction (entries 6 and 7). However, the

Scheme 1. Standard Henry reaction followed by dehydration.

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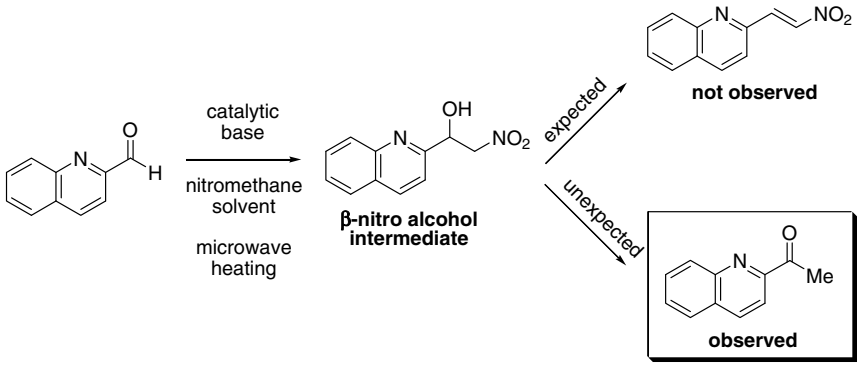
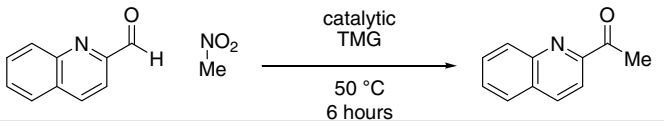


Scheme 2. Expected versus unexpected elimination products of a β-nitroalcohol derived from 2-quinolinecarboxaldehyde.

Table 1
Optimization of the reaction conditions



Entry	Solvent	Concn (M)	Catalyst loading (%)	Yield[a] (%)
1	Toluene	0.5	10	21
2	Dichloroethane	0.5	10	21
3	Methanol	0.5	10	0[b]
4	Ethyl acetate	0.5	10	0[b]
5	Acetonitrile	0.5	10	0[b]
6	Toluene	0.5	20	22
7	Dichloroethane	0.5	20	21
8	Toluene	0.1	10	0[b]
9	Dichloroethane	0.1	10	0[b]
10	Toluene	2.0	10	37
11	Dichloroethane	2.0	10	30

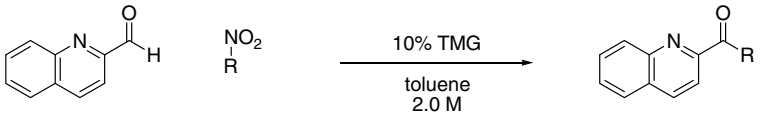
[a] Average of two HPLC yields based on a calibrated internal standard.
[b] No product was observed by HPLC; however, significant nitro alcohol intermediate was observed.

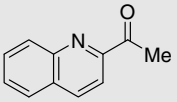
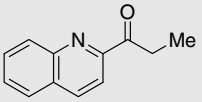
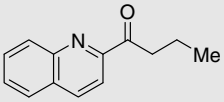
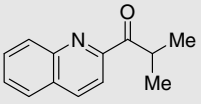
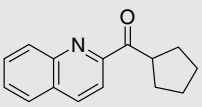
transformation is sensitive to concentration and a dilute reaction performed at 0.1 M did not proceed past intermediate formation (entries 8 and 9), while conducting the reaction at 2.0 M led to the highest HPLC yields (entries 10 and 11).

Next we chose to examine the scope of nitroalkanes that can be employed in this unique transformation. We were pleased to discover that when 2-quinolinecarboxaldehyde and nitromethane are combined in the presence of 10% TMG in 2.0 M toluene, the desired methyl ketone can be isolated in 45% and 60% yield at 50 and 110 °C, respectively (Table 2, entries 1 and 2).[8] Both nitroethane and nitropropane can be utilized to furnish the ethyl (63% yield) and propyl (37% yield) ketones (entries 3 and 4). Secondary nitroalkanes react more sluggishly and 2-nitropropane affords the *i*-propyl ketone in only 19% yield, while similarly nitrocyclopentane leads to only 16% isolated yield of the corresponding ketone (entries 5 and 6).

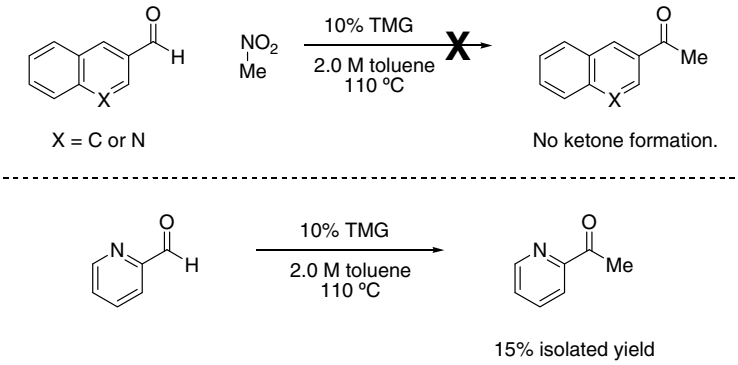
We were curious to verify whether or not this unexpected transformation was indeed uniquely effective for 2-quinolinecarboxaldehyde. Employing our optimized reaction conditions with 2-napthaldehyde and 3-quinolinecarboxaldehyde did not lead to

Table 2
Scope of nitroalkanes in ketone formation

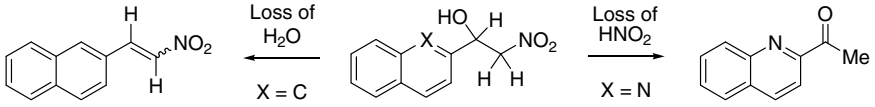


Entry	Nitroalkane	Temperature (°C)	Product	Yield[a] (%)
1		50		45
2		110		60
3		110		63
4		110		37
5		110		19
6		110		16

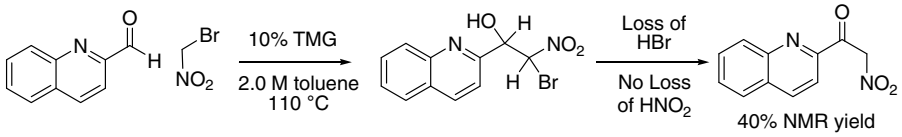
[a] Average of two isolated yields.



Scheme 3. Structural analogues of 2-quinolinecarboxaldehyde do not lead to a ketone product (top); 2-pyridinecarboxaldehyde does furnish a ketone product (bottom).



Scheme 4. Substrate-dependent elimination leading to different types of products.

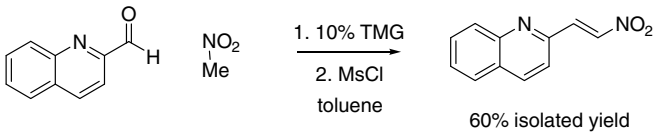


Scheme 5. Use of bromonitromethane to access a nitromethyl ketone.

any analytical evidence (LC–MS or NMR) of methyl ketone formation (Scheme 3, top); however, when 2-pyridinecarboxaldehyde was employed, 2-acetylpyridine was isolated, albeit in low yield (Scheme 3, bottom).[9]

With these observations in hand, it is apparent that the substrate-dependent formation of either nitroalkenes or ketones from a β-nitro alcohol can be explained by two different elimination reactions (Scheme 4). Thus the standard dehydration reaction yields the expected nitroalkene; however, the formal elimination of nitrous acid ultimately furnishes the ketone. While we do not fully understand the role of the nitrogen atom in the 2-quinoline scaffold, clearly it facilitates the loss of HNO_2 over that of H_2O.[10]

We were intrigued by this apparent reversal in elimination propensity between water and nitrous acid; however, we do not believe that the presence of the quinoline nitrogen confers excellent elimination ability to HNO_2. When we examined bromonitromethane under our reaction conditions, we observed the formation of a nitromethyl ketone and were unable to acquire any evidence of HNO_2 elimination (Scheme 5). We believe this compound to be derived from the elimination of HBr from the standard β-nitro alcohol intermediate. Finally, we have been able to direct the β-nitro alcohol intermediate derived from 2-quinolinecarboxaldehyde and nitromethane toward the nitroalkene product by inducing the formal elimination of water by addition of MsCl.[2c,d]



Scheme 6. Reaction with MsCl leads to nitroalkene formation.

Thus after the putative formation of a mesylate leaving group, 2-nitro-vinylquinoline can be smoothly generated in 60% yield (Scheme 6).

In summary we have shown that 2-quinolinecarboxaldehyde can smoothly undergo the standard Henry reaction with a variety of nitroalkanes. However, instead of the typical loss of water to yield nitroalkenes, an apparent loss of nitrous acid is observed, furnishing ketone products. We do not believe that HNO_2 elimination is a particularly facile process and it is clearly not the preferred path when a substrate capable of eliminating HBr is employed. While the standard elimination of water is not readily observed, the addition of MsCl allows for the formation of the expected 2-nitro-vinylquinoline. We continue to study the mechanistic aspects of this unique transformation as well as try to extend this reaction to an aldehyde substrate other than 2-quiniolinecarboxaldehyde. We hope to report the results of these investigations in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.044.

References and notes

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2. (a) MacNevi, C. J.; Moore, R. L.; Liotta, D. C. *J. Org. Chem.* **2008**, *73*, 1264–1269; (b) Calmes, M.; Escale, F.; Didierjean, C.; Cazals, G.; Martines, J. *Tetrahedron: Asymmetry* **2007**, *18*, 2491–2496; (c) Franck, X.; Fournet, A.; Prina, E.;

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4. Ayoubi, A. A.-E.; Texier-Boullet, F.; Hamelin, J. *Synthesis* **1994**, 258–260.
5. The actual temperatures were not provided. Microwave powers of between 200 and 400 W were used.
6. For examples of TMG-catalyzed Henry reactions, see: (a) Luzzio, F. A.; Ott, J. P.; Duveau, D. Y. *J. Org. Chem.* **2006**, 5027–5030; (b) Hanessian, S.; Desilets, D.; Bennani, Y. L. *J. Org. Chem.* **1990**, *55*, 3098–3103.
7. The reactions performed with more polar solvents such as methanol, ethyl acetate, and acetonitrile do furnish product after approximately 24 h of heating.
8. 2-Quinolinecarboxaldehyde (200 mg, 1.27 mmol, 1.00 equiv) and the corresponding nitroalkane (3.82 mmol, 3.00 equiv) were combined in toluene (636 μL, 2.00 M) in a microwave vial containing a teflon coated magnetic stir bar at room temperature under air. 1,1,3,3-Tetramethylguanidine (16.1 μL, 0.127 mmol, 10.0%) was added and an immediate color change was observed. The vial was sealed and the reaction mixture heated with stirring at either 50 °C or 110 °C until no starting material or intermediate was observed by LC–MS. The reaction mixture was cooled to room temperature, quenched with sodium bicarbonate, and extracted with dichloromethane. The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in dichloromethane and purified by column chromatography (80% hexanes/20% ethyl acetate) or (80% dichloromethane/20% ethyl acetate).
9. Nitroalkene product was not observed (LC–MS and NMR) in any of these reactions.
10. It has been suggested that elimination of nitrous acid can only occur when acidic protons are present, beta to the nitro group. For other examples of HNO_2 loss in synthetic chemistry, see: (a) Ballini, R.; Bosica, G.; Fiorini, D.; Righi, P. *Synthesis* **2002**, 681–685; (b) Ballini, R.; Bosica, G.; Fiorini, D.; Gil, M. V.; Palmieri, A. *Synthesis* **2004**, 605–609.