OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Sequential Reduction of Nitroalkanes Mediated by CS_2 and Amidine/Guanidine Bases: A Controllable Nef Reaction

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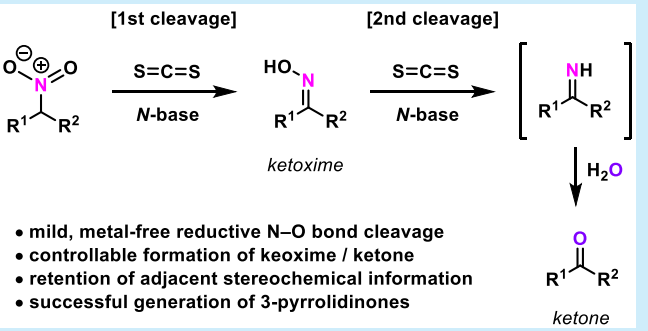
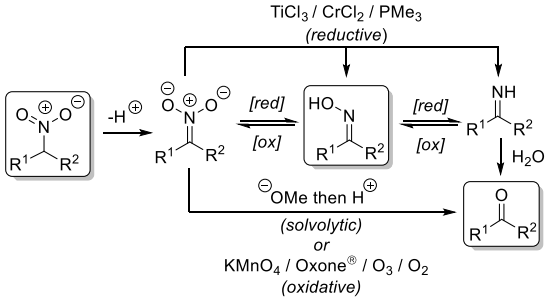
Supporting Information

ABSTRACT: In this letter, we describe a mild, functional group-tolerant reductive Nef reaction that utilizes CS_2 and an amidine or guanidine base to sequentially cleave N−O bonds. These conditions transform secondary nitroalkanes to ketones via an isolable oxime with minimal erosion at labile stereogenic carbons, show excellent compatibility with groups sensitive to oxidizing or reducing conditions, display good scalability, and are well-suited for generating useful 3-pyrrolidinone motifs from readily accessible 1,3-dipolar cycloaddition products.



The Nef reaction is a convenient method to convert readily available primary and secondary nitroalkanes into the corresponding aldehydes and ketones.[1] The classic Nef reaction, reported in 1894, involves the basic treatment of a nitroalkane precursor to form a nitronate intermediate, which is then hydrolyzed to the carbonyl-containing product using a strong acid.[2] The harsh nature of these original conditions has led to great interest in the development of modified protocols with a broader scope and functional group compatibility (Scheme 1). For example, oxidative Nef methods are a popular

Scheme 1. General Pathways for the Nef Reaction



strategy for obtaining carbonyl-containing compounds from the nitronate intermediate using reagents such as $KMnO_4$,[3a,b] H_2O_2,[3c,d] O_3,[3e] and O_2.[3f] In contrast, reductive protocols typically proceed via a stepwise N−O bond cleavage to an oxime, followed by a second reduction event and imine hydrolysis. Within this latter class of Nef reactions, the $TiCl_3$-mediated McMurry protocol is quite popular,[4a,b] but other reductants, including $CrCl_2$,[4c] trimethylphosphine,[4d,e] and iron powder,[4f] have been reported. Nonetheless, stereochemically complex substrates, especially those with labile stereocenters, are still challenging. Despite these useful protocols, when a Nef-type reaction became necessary for the development of a medicinally relevant class of nitro-pyrrolidines (vide infra), we found all of the above protocols to be either ineffective or not robust enough to pursue for scale-up. Herein we report a mild, functional group-tolerant reductive Nef reaction that uses CS_2 and either an amidine or guanidine base to transform 2° nitroalkanes to ketones with a minimal loss of stereochemical information adjacent to the nitro group, even at very labile stereogenic carbons.[5] Other advantages include the lack of stoichiometric metal reductants, compatibility with groups sensitive to oxidizing or reducing conditions, scalability, and excellent suitability for the late-stage functionalization of complex molecules.

Efforts to identify mild Nef chemistry were inspired by bioactive 3-hydroxypyrrolidines (see Scheme 3, vide infra), which exhibit a range of important antifungal,[6] anticancer,[7] antihypertensitive,[8] and glucosidase inhibitory activities.[9] More recently, this class of compounds has received attention as promising drug candidates for the treatment of cystic fibrosis.[10] An efficient method to construct enantioenriched 3-hydroxypyrrolidines involves 1,3-dipolar cycloadditions of azomethine ylides (derived from glycine) and nitroalkenes, followed by the Nef reaction and reduction of the resultant ketone. However, efforts to transform nitro groups of heavily functionalized pyrrolidines proved challenging under traditional Nef conditions, particularly when several labile asymmetric centers were present.[4c,11] Prior to this work, the only successful

Received: August 22, 2019

DOI: 10.1021/acs.orglett.9b02987
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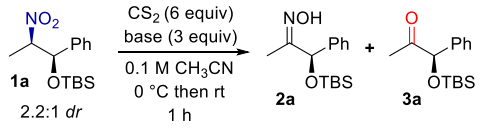
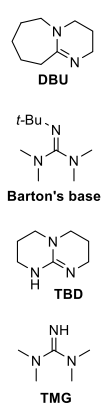
conversion of these motifs was achieved using an excess amount of an undesirable chromium(II) reductant.

To address this challenge, we took inspiration from old reports from Oae[12] and Barton[13] describing the use of CS_2 to reductively cleave the N−O bond of amine oxides and conjugated nitronates to furnish amines and α,β-unsaturated aldoximes, respectively. Initial investigations focused on treating a *tert*-butyl(dimethyl)silyl (TBS)-protected Henry product **1a** with CS_2 and a nitrogenated base (Table 1).

Table 1. Optimization of CS_2-Mediated Reductive Nef Reaction[a]





entry	base	2a	3a	1a
1	Et_3N	8%	nd	90%
2	DIPA	nd	nd	95%
3	DBU	4%	53%	nd
4[b]	DBU	60% (2.1:1 *dr*)	32%	nd
5	Barton's base	trace	38%	46%
6[c]	TBD	75% (5.7:1 *dr*)	5%	20%
7	TMG	42% (1.4:1 *dr*)	5%	53%
8	DBU/Barton's base[d]	7%	63%	nd
9[e]	DBU/Barton's base[d]	8%	76%	nd

[a]Reactions were performed on a 0.1 mmol scale. Yields were determined by NMR using mesitylene as an internal standard. [b]Reaction was stirred for 5 min at 0 °C. [c]Reaction was stirred for 30 min at 0 °C. [d]1.5 equiv of each base was used. [e]Reaction was run in 0.01 M CH_3CN.

Encouragingly, oxime **2a** was noted using Et_3N (entry 1), albeit in low conversion. *N*,*N*-Diisopropylamine (DIPA) gave no reaction (entry 2); however, the more basic 1,8-diazabicyclo[5.4.0]-undeca-7-ene (DBU) resulted in a 53% yield of **3a**, along with 4% of **2a** (entry 3). Decreasing the temperature to 0 °C for 5 min gave a mixture of **2a** and **3a** (entry 4) in good mass balance, suggesting that the poor mass balance in entry 3 results from inefficient oxime-to-imine conversion or competing imine hydrolysis to the ketone. Interestingly, highly basic 2-*t*-butyl-1,1,3,3-methylguanidine (Barton's base (BB)) gave a 38% yield of **3a** and 46% yield of remaining **1a**; only a trace amount of **2a** was noted (entry 5). This result implied that the rate of the second reductive N−O bond cleavage event is faster than the formation of the oxime with this sterically hindered base. In contrast, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) retarded the rate of the second reduction to furnish a 75% yield of **2a** with excellent mass balance (entry 6). The selective reduction of nitroalkanes to oximes, valuable building blocks for amides (via Beckmann rearrangement)[14] and heterocycles (via metal-mediated cyclizations),[15] is an attractive feature of this chemistry; other methods employ stoichiometric, toxic metal salts ($SnCl_2$, $TiCl_3$)[16] or require carefully controlled hydrogenation.[17] The use of 1,1,3,3-tetramethylguanidine (TMG) as the base inhibits the second reduction step (entry 7), similar to TBD. A combination of DBU and BB improved the yield of **3a** to 63% (entry 8). Finally, we found that dilution (from 0.1 to 0.01 M in CH_3CN) minimized the degradation of the imine[18] under the reaction conditions (entry 9) to give the optimal conversion of **1a** to **3a** in 76% yield.

The yield of ketone **3a** can be maintained without dilution, provided that the temperature and reaction progress are carefully monitored (Figure 1) to prevent the rate of imine

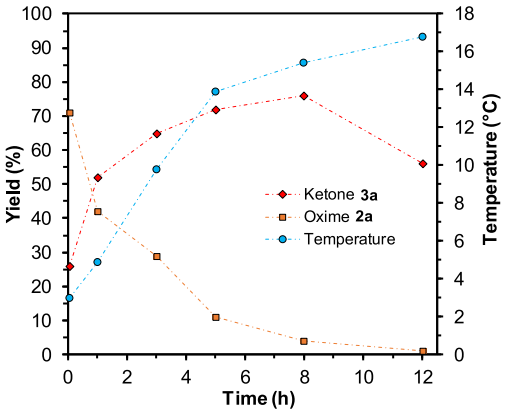
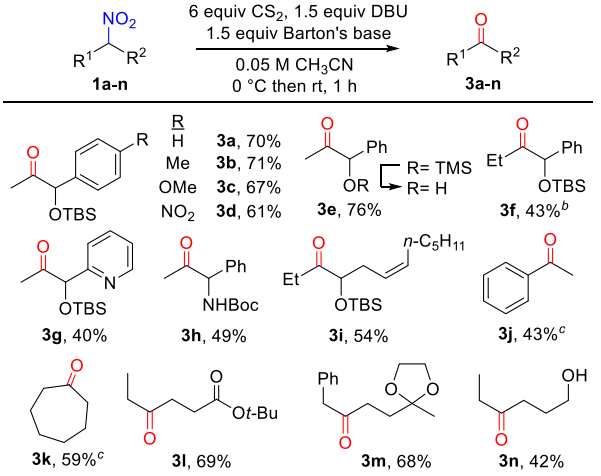


Figure 1. Reaction profile of CS_2-mediated Nef reaction with **1a** (0.1 mmol, 1 equiv) CS_2 (6 equiv), DBU (1.5 equiv), Barton's base (1.5 equiv), and 0.1 M CH_3CN. Yields were determined by NMR using mesitylene as an internal standard.

degradation from surpassing that of the conversion of oxime to imine. The instability of the imine makes it difficult to quantify in situ; thus samples were quenched with H_2O to hydrolyze the imine intermediate at each time point and the amount of ketone determined. Figure 1 clearly indicates that a balance between increasing temperatures to drive conversion and minimizing the destabilization of the imine intermediate is important to obtain ketone **3a** in high yield.

With optimized conditions in hand for the conversion of nitroalkane **1a** to the ketone **3a**, the scope of the reductive Nef reaction for 2° nitroalkanes was investigated (Scheme 2). Reactions were conducted at room temperature (rt) (1 h) and in 0.05 M CH_3CN. A variety of TBS-protected Henry products **1a−d**, containing electronically diverse aromatic rings, were well-tolerated to yield the ketones in 61−71% yield. It is worth noting that the aromatic NO_2 group in **1c** was not affected

Scheme 2. Scope of CS_2-Mediated Nef Reaction[a]



[a]Reported yields are of isolated material on a 0.2 mmol scale. [b]17% oxime and 16% **1f** were detected by ^1H NMR. [c]Yield was determined by NMR using mesitylene as an internal standard due to the volatility of the product.

DOI: 10.1021/acs.orglett.9b02987
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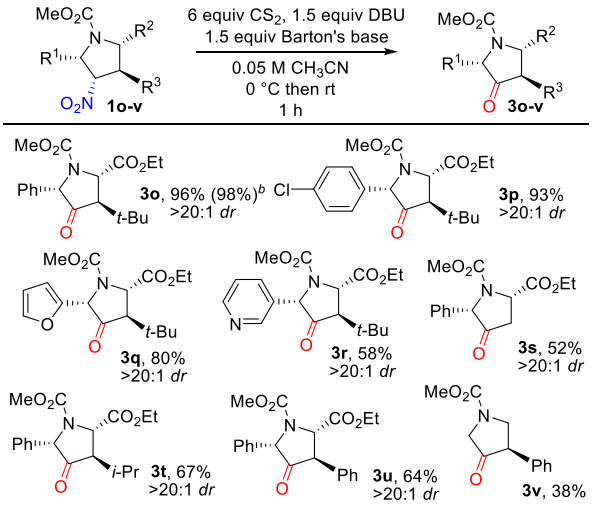
under the reaction conditions. TMS-protected Henry product **1e** furnished α-hydroxy ketone **3e** in 76% yield after in situ deprotection during acidic hydrolysis. Increased sterics in **1f** retarded the reaction, yielding **3f** in 43% yield; the remainder of the mass balance included oxime (17%) and **1f** (16%). The ability to tolerate amines was demonstrated by the presence of a pyridine in **1g** to furnish ketone **3g**;[19] a substrate bearing an acidic N−H bond (*aza*-Henry product **1h**) was also successful in delivering α-amino ketone **3h**. An alkene, which could be sensitive to oxidative Nef conditions, was tolerated in **1l** to give **3l** in 69% yield. Low-molecular-weight nitroalkanes **1j,k** and functional groups traditionally sensitive to oxidative or reductive conditions, including esters (**1l**), ketals (**1m**), and alcohols (**1n**), gave the desired ketones **3j−n**.

We were pleased to find that applying our conditions to stereochemically rich nitropyrrolidines **1o−v**, generated by 1,3-dipolar cycloaddition, resulted in the efficient production of 3-pyrrolidinones **3o−v** (Scheme 3), useful precursors to

Scheme 3. Nef Reactions on Nitropyrrolidines[a]

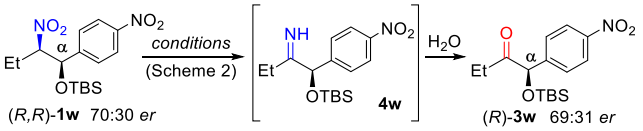


[a]Reported yields are of isolated material on a 0.2 mmol scale. [b]1 mmol scale.

bioactive 3-hydroxy-pyrrolidines. When R^3 = *t*-Bu, 3-pyrrolidinones **3o−q** were obtained in excellent 80−96% yield due to the increased stability of the imine intermediate. Furan and pyridine substituents were well-tolerated to furnish **3q** and **3r** in good yield. The removal of the *t*-Bu group flanking the $-NO_2$-bearing carbon did result in a lower 52% yield of **3s**, but improvements with **3t,u** suggest that the steric environment of the $-NO_2$ affects the stability of the imine intermediate. Thus further improvements in yields are expected if imine decomposition is avoided (Figure 1). The low yield of pyrrolidinone **3v** is due to product instability. Importantly, in every case where the pyrrolidinone bears multiple epimerizable stereogenic centers, no formation of any other diastereomer was observed by ^{1}H NMR (>20:1 *dr*).

The preservation of stereochemical information at epimerizable stereocenters in acyclic nitroalkanes was also investigated (Scheme 4). A Cu-catalyzed asymmetric Henry reaction gave a 70:30 enantiomeric ratio (*er*) of the *syn* diastereomer; TBS protection furnished **1w**.[20] The treatment of **1w** under the standard condition (Scheme 2) confirmed the stereoretention at the α carbon, highlighting that these mild

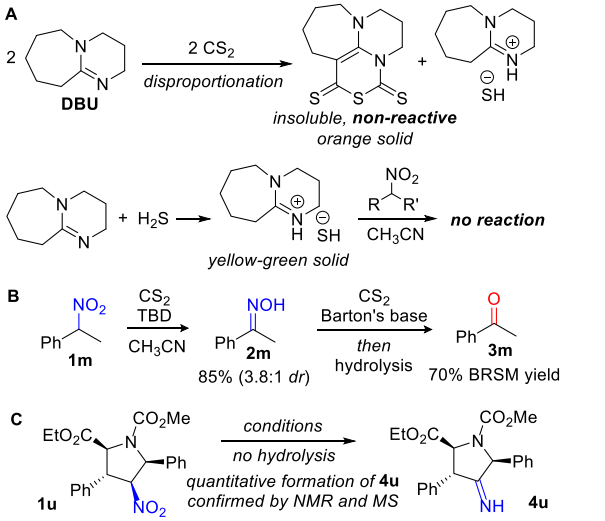
Scheme 4. Stereoretention in CS_2-Mediated Nef Reaction



reaction conditions tolerate acidic, enolizable stereocenters present in intermediates such as **4w**.

The conversion of 1° nitroalkanes to aldehydes or carboxylic acids is challenging, perhaps due to the lowered stability of the nitronate intermediate.[4e,21−23] Before embarking on efforts to apply our conditions to 1° nitroalkanes, the mechanism of this unusual transformation was explored. A base−CS_2 adduct was first considered as the species responsible for the initial N−O bond cleavage. DBU has been reported to undergo disproportionation with CS_2 to generate a cyclic carbamic carboxylic trithioanhydride and a $[DBU-H]^+SH^-$ ionic pair (Scheme 5A, top).[24] However, the independent preparation of

Scheme 5. Mechanistic Evidence of CS_2-Mediated Nef Reaction



this adduct for use in the Nef reaction gave no oxime or ketone, suggesting that the DBU−CS_2 complex is not responsible for the observed reactivity (Scheme 5A). However, several clues as to the mechanism were obtained by the careful monitoring of reaction progress using a variety of spectroscopic techniques. Important observations areas follows: (1) Both steric effects and base strength are critical, but the relative importance of these factors differ for the first versus the second reductive N−O cleavage steps, (2) S=C=O is a byproduct, (3) oxime is observed even in the absence of H_2O, and (4) ketone is observed only in the presence of H_2O. Moreover, evidence of the intermediacy of the oxime was provided by subjecting isolated oxime **2m** to CS_2-mediated conditions to generate the ketone **3m** upon hydrolysis (Scheme 5B). The isolation of the stable imine intermediate **4u** prior to hydrolysis (Scheme 5C) further supports the hypothesis that the reaction occurs via the sequential reductive cleavage of the N−O bonds.

Taken together, these observations led us to propose the mechanism in Figure 2. DBU is both basic and unhindered enough to deprotonate the acidic, sterically congested proton of nitroalkane **a** to generate nitronate anion **b** and the

DOI: 10.1021/acs.orglett.9b02987
Org. Lett. XXXX, XXX, XXX−XXX

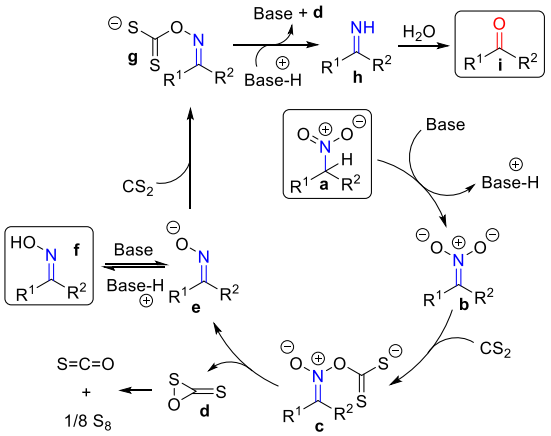


Figure 2. Proposed mechanism for CS_2-mediated Nef reaction.

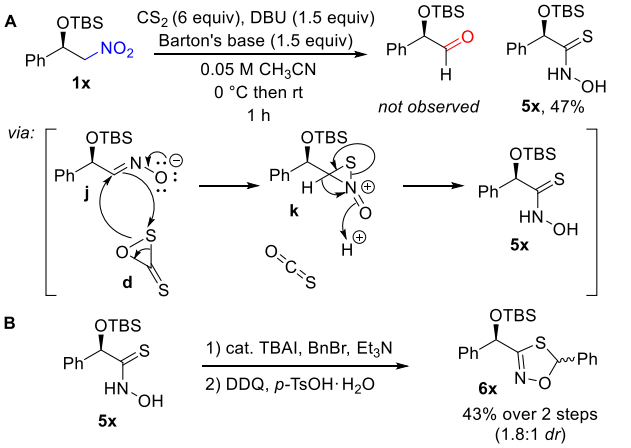
conjugate acid of DBU. The attack of the nitronate **b** on CS_2 furnishes intermediate **c**; the elimination of dithiiranone **d** cleaves the first N−O bond to deliver oxime anion **e**, which protonates to furnish oxime **f**, the first key intermediate that can be observed and isolated. Evidence of **d** was provided by the headspace analysis of the reaction mixture, showing the presence of S=C=O, a reported disproportionation product resulting from the decomposition of dithiiranone.[12,13,25]

Depending on the base used in the first deprotonation, reduction can be stopped at oxime **f** with good selectivity. Bases bearing N−H bonds, such as TBD and TMG, enable the deprotonation of **a** to furnish **f**; however, the further deprotonation of **f** is disfavored, significantly slowing the rate of the second reduction event (see Table 1) due to H-bonding donor/acceptor interactions that stabilize the oxime−base adduct.[26] In contrast, the equilibrium with BB favors oxime anion **e**, which attacks a second molecule of CS_2 to furnish **g**. The loss of **d** and the protonation of the imine anion yield **h**. We suspect the imine **h** is "protected" in situ by the reaction with excess CS_2[27,28] due to its stability toward hydrolysis to give the desired ketone **i**.

The mechanism in Figure 2 has several important implications for the further development of this reductive Nef reaction. First, it suggests that the conversion of the nitroalkane to oxime may be amenable to catalytic conditions if off-cycle reactions between CS_2 and DBU (Scheme 5A, top) and BB (tetramethylthiourea was observed as a byproduct) can be avoided. Second, the formation of byproduct **d** explains why the initial efforts to transform 1° nitroalkanes into aldehydes were unsuccessful. Oxime anion **j** (Scheme 6A) may react with dithiiranone **d** to give **k** and extrude S=C=O. This species rapidly rearranges to thiohydroxamic acid **5x**, which was isolated in 47% yield in the reaction of 1° nitroalkane **1x**. Bruice has reported that **d** can act as a sulfur transfer agent in the reaction with electron-rich olefins.[29] The observation of **5x** not only supports the existence of **d** but also can be harnessed to synthesize unique *S,N,O*-containing heterocycles. A sequential *S*-alkylation/oxidative cyclization developed by Pierce[30,31] enabled the efficient conversion of thiohydroxamic acid **5x** to 1,4,2-oxathiazole **6x** in 43% yield over two steps (Scheme 6B).

In conclusion, this letter describes the development of a mild and controllable Nef reaction that achieves the sequential reduction of 2° nitroalkanes to generate ketoximes or ketones using CS_2 as the reducing agent while avoiding stoichiometric

Scheme 6. Reaction with Primary Nitroalkane 1x and 1,4,2-Oxathiozole Synthesis



amounts of metal reductants. The chemistry is amenable to a variety of sensitive functional groups and excels in retaining stereochemical information at labile chiral centers. Evidence of the reductive mechanism is provided by isolating products of the first and second N−O reduction steps. This new method provides convenient access to 3-pyrrolidinones from 1,3-dipolar cycloaddition adducts, which can then be transformed to biologically important 3-hydroxypyrrolidines.[4c]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02987.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The NMR facilities at UW-Madison are funded by the National Science Foundation (NSF; CHE-9208463, CHE-9629688) and National Institutes of Health (NIH; RR08389-01). The Q-Exactive mass spectrometer was acquired with funds from an NIH-S10 award through the National Institutes of Health (NIH-1S10OD020022-1). We thank Steve Dougherty, Bradley Greiner, Jianguo Ji, and Jeff Kallemeyn for helpful discussions and experimental support. AbbVie sponsored and funded the study. AbbVie and the University of Wisconsin-Madison contributed to the design and participated in the

DOI: 10.1021/acs.orglett.9b02987
Org. Lett. XXXX, XXX, XXX−XXX

collection, analysis, and interpretation of data and in the writing, reviewing, and approval of the final publication.

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