

Copper-Catalyzed Alkylation of Nitroalkanes with α -Bromonitriles: Synthesis of β -Cyanonitroalkanes

Kirk W. Shimkin, Peter G. Gildner, and Donald A. Watson*

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States

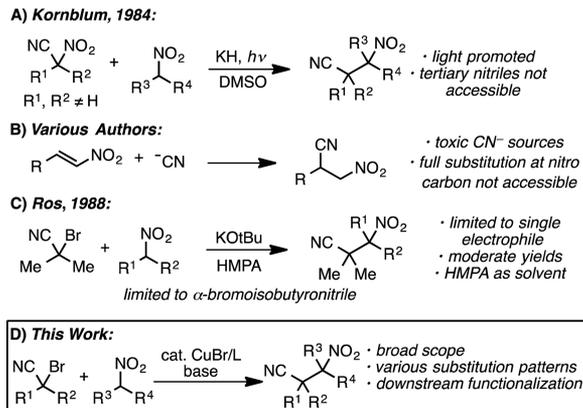
S Supporting Information

ABSTRACT: Copper catalysis now enables the efficient C-alkylation of nitroalkanes with α -bromonitriles. Using a simple and inexpensive catalyst, this process provides access to β -cyanonitroalkanes. The method is highly tolerant of various functional groups and substitution patterns. These functionally dense products serve as orthogonally masked 1,3-diamines, which can be revealed selectively for access to differentially substituted diamines. These products can also be exploited for the formation of complex cyanoalkenes and 5-aminoisoxazoles.



β -Cyanonitroalkanes are highly appealing and synthetically valuable building blocks, particularly because of their potential to serve as orthogonally masked diamines.¹ Several prior entries into β -cyanonitroalkanes have been reported, but all are limited with respect to generality (Scheme 1A–C). In 1984, Kornblum

Scheme 1. Synthesis of β -Cyanonitroalkanes



reported that nitronates could be alkylated using α -nitronitriles under photolytic conditions.² However, only fully substituted α -nitronitriles could be utilized as electrophiles, which significantly limits the accessible substitution patterns. Moreover, only simple alkyl substrates were examined, providing little evidence of functional group compatibility. β -Cyanonitroalkanes have also been accessed via the conjugate addition of cyanide to simple nitroalkenes.³ However, these reactions require the use of toxic cyanide reagents (or equivalents), and β -cyanonitroalkanes bearing full substitution at the nitro center are not accessible via this method.⁴

An alternative route for the preparation of β -cyanonitroalkanes would be alkylation of nitroalkanes with α -bromonitriles. This is attractive as α -bromonitriles are stable, readily available compounds that can be prepared on a multigram scale from aldehydes or alkyl nitriles.⁵ Although these reagents have recently

found wide use in catalytic reactions,^{6,7} their use to alkylate nitroalkanes has not been well developed. The noncatalyzed addition of nitronate anions to these reagents was studied by Ros in 1988.⁸ Although α -bromoisobutyronitrile could be used to alkylate simple, unfunctionalized nitronate anions in modest yields (36–70%), only a single example of another α -bromonitrile was reported. In this latter case, the product was formed in only 16% yield, along with significant amounts of elimination products (56%). No examples of α -bromonitriles bearing α hydrogens were reported, drawing into question the generality of the procedure.

In general, nitroalkanes are highly versatile synthetic intermediates, particularly as precursors to nitrogen containing molecules. The nitro group serves as a diverse functional handle that can undergo myriad reactions including oxidation, reduction to amines, arylation, allylation, additions to aldehydes, and conjugate additions.⁹ However, simple C-alkylation of nitroalkanes using alkyl electrophiles has been challenging, as noncatalyzed alkylation reactions are dominated by O-alkylation.¹⁰ This challenge might inform on the difficulties observed in the Ros study.

Recently, however, our group has developed inexpensive copper catalysts that allow the C-alkylation of nitroalkanes using simple alkyl halides.¹¹ In previous studies, we have shown that benzylic, heterobenzylic, and α -bromocarbonyls can serve as the electrophiles in these reactions.¹¹ Preliminary evidence suggests that these reactions proceed via stabilized radical intermediates.

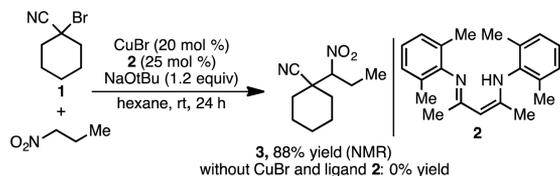
As nitrile groups can also serve as potential radical stabilizing groups, we reasoned that copper catalysis of the alkylation of nitroalkanes with α -bromonitriles might be possible. If so, this system would provide straightforward access to β -cyanonitroalkanes. In this paper, we now report that a wide range of β -cyanonitroalkanes can be accessed using this strategy.

We set out to develop a general, robust, and functional group tolerant route to β -cyanonitroalkanes. Based upon our

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mechanistic hypothesis for copper-catalyzed nitroalkane alkylation, we began by examining the alkylation of 1-nitropropane with 1-bromocyclohexanecarbonitrile (**1**). Gratifyingly, using our previously identified catalytic system for the alkylation of nitronates with benzyl halides (20 mol % CuBr, 25 mol % ligand **2**, 1.2 equiv NaOtBu),^{11a} the desired β -cyanonitroalkane was formed smoothly in excellent yield (Scheme 2). The reaction

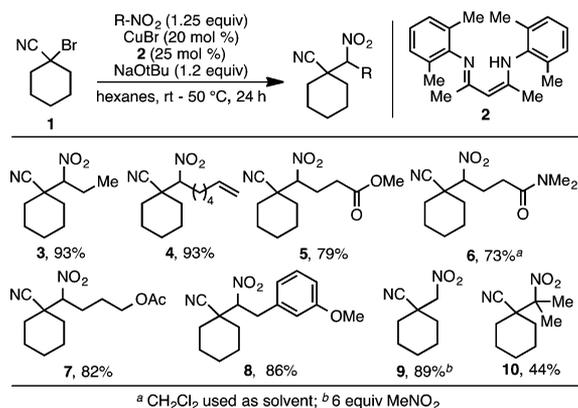
Scheme 2. Identification of Catalyst Conditions



proceeds at room temperature and uses an inexpensive, easily accessed catalyst. No product is formed in the absence of catalyst.

Further investigations revealed that the scope of this transformation is broad (Schemes 3 and 4). A variety of primary

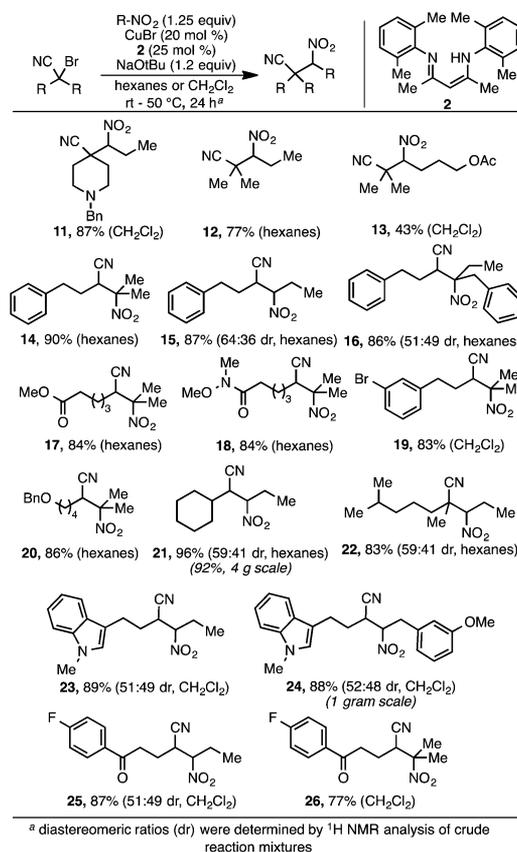
Scheme 3. Scope of the Alkylation Reaction with Respect to Nitroalkane



nitroalkanes were subjected to the reaction using 1-bromocyclohexanecarbonitrile as an alkylating reagent. Nitroalkanes bearing alkenes, amides, esters, acetates, and aryl ethers were all alkylated in good to excellent yields (**4**–**8**). Nitromethane was alkylated smoothly, although an excess of the nucleophile was required (**9**). 2-Nitropropane participated in the alkylation reaction to provide product **10** bearing two contiguous quaternary centers in moderate yield. This reaction demonstrates the ability of the alkylation protocol to form highly congested carbon–carbon bonds and potentially access sterically congested diamines. It is notable that formation of product **8** (as well as products **16**, **24**, and **28** discussed below) utilizes a nitroalkane prepared from benzylation of simple nitroalkanes using our previously developed procedure.^{11a} This serves to demonstrate how copper-catalyzed nitroalkane alkylation can be exploited to generate complexity from simple, inexpensive starting materials.

A number of functionalized α -bromonitriles were also examined in the alkylation reaction. While fully substituted α -bromonitriles often underwent smooth coupling at room temperature, secondary bromides required slightly elevated temperature (50 °C) to avoid significant production of protodebrominated starting materials. While hexanes is the solvent of choice for nonpolar substrates, dichloromethane is often superior to improve solubility in the case of more polar substrates. Basic

Scheme 4. Scope of the Alkylation Reaction with Respect to α -Bromonitriles

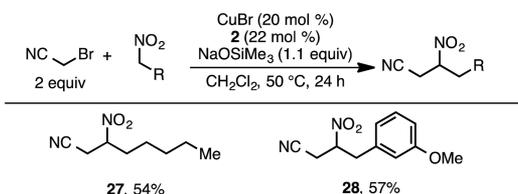


amines (**11**), esters (**17**), Weinreb amides (**18**), ethers (**20**), and ketones (**25**, **26**) proved compatible with the reaction. Product **11** is particularly notable due to its potential use as a latent triamine. Aryl bromides were also tolerated without incident (**19**), providing a convenient handle for further functionalization. Acyclic, fully substituted bromonitriles (**22**), as well as heterocycles (**23**, **24**) were tolerated under the reaction conditions. The scalability of the reaction was also demonstrated, as product **21** could be synthesized on a 4 g scale without incident.

Although the diastereoselectivity of the reaction is moderate, it should be noted that in almost all cases diastereomers were easily separated by standard column chromatography. It appears that the observed diastereomeric ratio is kinetic in origin. For example, the alkylation reaction produces compound **21** as a 59:41 mixture of diastereomers. Analysis of aliquots (NMR) shows that this ratio of products is constant over the course of the reaction. However, subjecting isolated samples of each diastereomer to mild base (sodium propynitronate) results in equilibration to a \sim 40:60 diastereomeric mixture with an opposite sense of diastereomeric enrichment.¹²

Bromoacetonitrile proved to be a particularly recalcitrant electrophile in the alkylation reaction, providing only trace amounts of product under our optimized conditions. We assume this is due to the difficulty in formation of the putative primary radical intermediate. However, a survey of reaction conditions revealed that a weaker base, sodium trimethylsilanolate, in conjunction with the use of the nitroalkane as the limiting reagent provided cyanomethylated products (**27**, **28**) in moderate yield (Scheme 5). Notably, these products, as well as many outlined in Schemes 3 and 4, are not accessible via the aforementioned

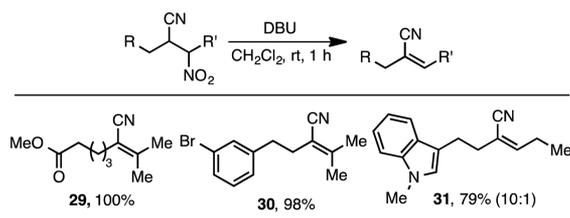
Scheme 5. Alkylation of Nitroalkanes with Bromoacetonitrile



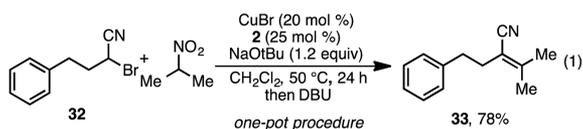
photolytic or conjugate addition methods, highlighting the complementarity of this work to existing methods.

With convenient access to β -cyanonitroalkanes in hand, we sought to investigate the reactivity of these functionally rich compounds. Exposure of the β -cyanonitroalkanes to DBU resulted in rapid formation of the corresponding cyanoalkenes in excellent yield (Scheme 6). In the case of compound 31, high selectivity for the *Z* product was observed (as determined by NOE analysis).

Scheme 6. Synthesis of Cyanoalkenes



Isolation of the β -cyanonitroalkane was not required to achieve this elimination reaction. After simply filtering the salts formed in the alkylation reaction, DBU could be added to the crude reaction mixture, providing convenient access to the cyanoalkene (eq 1).

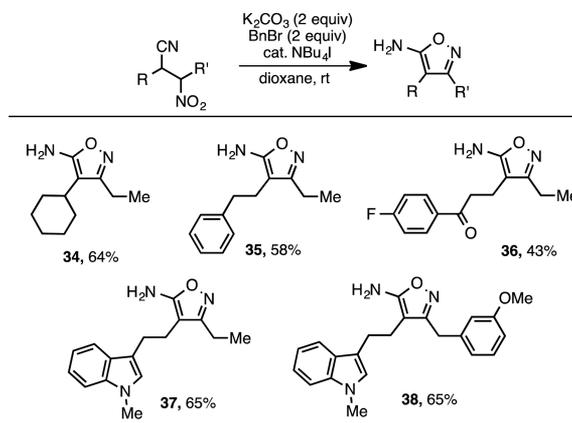


β -Cyanonitroalkanes can also be utilized in the synthesis of nitrogen-rich heterocycles. 5-Aminoisoxazoles have been accessed via the spontaneous cyclization of α -cyanooximes, but access to the oxime intermediates often requires harsh or highly toxic conditions.^{13,14} We envisioned that controlled reduction of the nitro group of our products to the oxime would allow interception of this pathway in a convergent and mild fashion. Carreira has reported a streamlined process for the conversion of nitroalkanes to oximes using benzyl bromide in the presence of tetrabutylammonium iodide.^{10,15} After optimization, we found that treatment of the β -cyanonitroalkanes under similar conditions resulted in formation of α -cyanooximes, which undergo spontaneous cyclization to form 5-aminoisoxazoles.

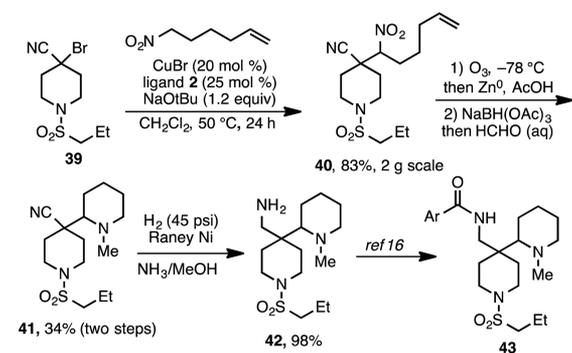
Using this method, several such heterocycles were prepared in good yield (Scheme 7). β -Cyanonitroalkanes bearing ketones (36), aryl ethers (38), arenes (35), and heteroarenes (37, 38) all cyclized smoothly, allowing a highly convergent entry into these interesting products. Importantly, β -cyanonitroalkanes may be used as a mixture of diastereomers, rendering the stereoselectivity of the nitroalkane alkylation reaction inconsequential for the preparation of 5-aminoisoxazoles.

β -Cyanonitroalkanes are exceptionally versatile in their ability to be used as latent diamines. The presence of the orthogonal nitrile and nitro groups allows simple chemoselective functional group interconversions, allowing easy access to differentially

Scheme 7. Synthesis of 5-Aminoisoxazoles



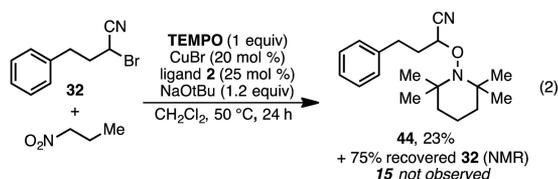
Scheme 8. Synthesis of Bispiperidine Core of GlyT1 Inhibitor 43



functionalized 1,3-diamines. To illustrate this, we targeted the synthesis of bispiperidine 42 (Scheme 8). This motif serves the core for a series of amides 43 that have recently been shown to be nanomolar inhibitors of glycine transporter 1 (GlyT1).¹⁶ This enzyme regulates glycine concentrations in the brain and has been implicated in the treatment of schizophrenia and other cognitive disorders.¹⁷

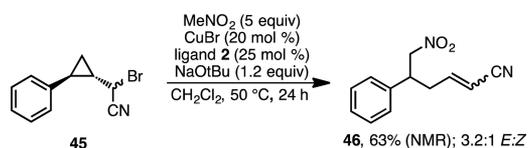
Nitroalkane 40 was accessed smoothly on a 2 g scale via our alkylation strategy. Ozonolysis using a reductive workup provided an intermediate aminoaldehyde. Sequential reductive amination and reduction of the nitrile provided amine 42,¹⁸ which is the reported intermediate for the synthesis of amides 43.¹⁶

To investigate the mechanism of the alkylation reaction, several experiments were performed. First, when the reaction was run in the presence of 1 equiv of TEMPO, a known radical scavenger, no alkylation product (15) was formed (eq 2).



Instead, only remaining starting material and 44 (the adduct of TEMPO with the starting material) were observed. This adduct likely results from the radical recombination of TEMPO with a transient α -cyano radical.¹⁹ Additionally, no alkylation was observed when the reaction was run in the presence of galvinoxyl free radical, also a known radical scavenger. These results are

Scheme 9. Fragmentation/Alkylation of the Cyclopropylcarbinyl Radical Resulting from Substrate 45



consistent with a mechanism involving transient radicals. Second, the reaction of substrate 45 results exclusively in ring-opened product 46 (Scheme 9). Fragmentation of the cyclopropane ring also suggests a radical intermediate.^{20,21} These results are consistent with the thermal redox catalysis pathway that we have previously proposed.^{11a,22}

In conclusion, we have demonstrated a facile and convergent synthesis of β -cyanonitroalkanes from nitroalkanes and α -bromonitriles. The synthesis is mild and tolerant of a variety of functional groups and substitution patterns and may be performed on the benchtop utilizing standard anaerobic technique. The densely functionalized products obtained therein may be utilized in the synthesis of various synthetically valuable targets including cyanoalkenes, 1,3-diamines, and 5- aminoisoxazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b00093](https://doi.org/10.1021/acs.orglett.6b00093).

Experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dawatson@udel.edu.

Notes

The authors declare no competing financial interest.

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