JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Benzylation of Nitroalkanes Using Copper-Catalyzed Thermal Redox Catalysis: Toward the Facile C-Alkylation of Nitroalkanes

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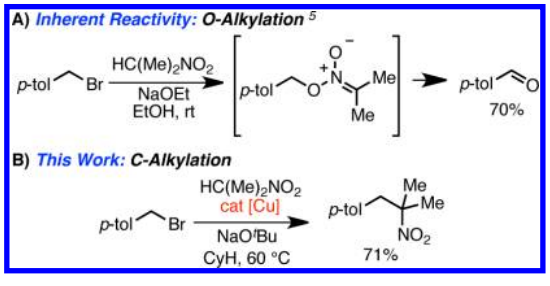
Supporting Information

ABSTRACT: The C-alkylation of nitroalkanes under mild conditions has been a significant challenge in organic synthesis for more than a century. Herein we report a simple Cu(I) catalyst, generated in situ, that is highly effective for C-benzylation of nitroalkanes using abundant benzyl bromides and related heteroaromatic compounds. This process, which we believe proceeds via a thermal redox mechanism, allows access to a variety of complex nitroalkanes under mild reaction conditions and represents the first step toward the development of a general catalytic system for the alkylation of nitroalkanes.

Nitroalkanes are ubiquitous reagents in organic synthesis. They are widely used as synthons for heterocycles, as radical precursors, and for installation of heteroatoms, including carbonyls via the Nef reaction and amines via reduction. Arguably, their most important function is as nucleophiles for C−C bond construction. Although C−C bond-formation reactions involving nitroalkanes are known, including the Henry reaction,[1] conjugate additions,[1] and Pd-catalyzed allylation[2] and arylation,[3] the alkylation of nitroalkanes with alkyl halides to form new C−C bonds remains a significant challenge. As early as 1908, failures of attempted C-alkylation reactions were first reported.[4] In 1949, Hass and Bender reported a detailed explanation for the failure: treatment of nitronate anions with a variety of alkyl halides results in O-alkylation, ultimately leading to the formation of carbonyl products via nitronic esters (Scheme 1A).[5] Only minor amounts of C-alkylated products are formed. O-Alkylation predominates with benzylic and aliphatic halides and with nitronate anions derived from nitromethane and primary and secondary nitroalkanes. The one exception is for *o*- or *p*-nitrobenzyl chlorides, which react with nitronate anions at carbon.[5] This unique reactivity was shown to proceed via an $S_{RN}1$ pathway triggered by single electron transfer (SET) from the nitronate anion to the highly electron-deficient aromatic ring.[6] However, except for this mechanistically isolated case, C-alkylation of simple nitronate anions does not occur with alkyl halides.

Scheme 1. Alkylation of Nitronate Anions



Previous methods for C-alkylation of nitroalkanes require either the formation of nitronate dianions at inconveniently low temperature (−90 °C)[7] or the use of complex 2,4,6-trisubstituted *N*-alkylpyridinium ions as electrophiles (also via an $S_{RN}1$ pathway).[8] Both methods have limitations in preparative chemistry. A procedure using readily available alkyl halides to C-alkylate nitroalkanes under mild reaction conditions would greatly expand both the preparation and utility of nitroalkanes in organic synthesis.

Here we report the first step toward a practical solution to this century-old problem. We disclose the development of conditions for the benzylation of nitroalkanes using electron-rich Cu(I) catalysts (Scheme 1B). These reactions occur at mild temperature (60 °C), employ benzyl bromides and inexpensive precatalysts, and afford high yields. These reactions likely proceed via a thermal redox catalysis pathway. Importantly, this process is general with respect to both the benzyl bromide and nitroalkane, including the use of secondary nitroalkanes. This wide scope allows preparation of many complex nitroalkanes. In addition, this method enables the facile preparation of medicinally important phenethylamines.

In considering means to effect C-alkylation of nitroalkanes, we were drawn to the potential use of radical chemistry. In addition to the aforementioned radical pathways, radicals generated from photofragmentation of alkylmercury or -cobalt compounds react with nitronate anions at carbon.[9] Although of limited synthetic utility, these reactions demonstrate that radical−anion coupling involving nitronate anions is feasible.

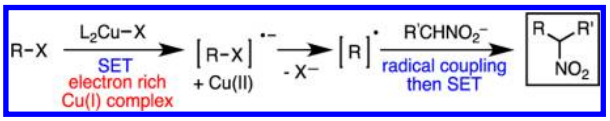
Simultaneously, we were cognizant of recent work on metal-catalyzed alkylation of carbon nucleophiles using alkyl halides.[10] Many of these reactions involve radical intermediates. We were particularly drawn to the Cu-based catalysts used in the mechanistically related atom-transfer radical addition and atom-transfer radical polymerization (ATRA/ATRP) reactions, in which Cu(I) catalysts initiate radical reactions of substituted alkenes by undergoing SET with alkyl halides bearing a wide range of radical-stabilizing groups.[11] Given the propensity of nitronate anions to undergo reactions with radical intermediates, we reasoned that a Cu-based catalyst might promote C-alkylation using readily prepared or commercially available alkyl

Received: May 10, 2012
Published: June 12, 2012

dx.doi.org/10.1021/ja304561c | J. Am. Chem. Soc. 2012, 134, 9942−9945

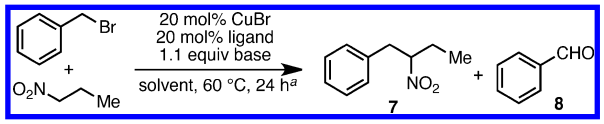
halides via a pathway involving SET followed by radical−anion coupling (Scheme 2).

Scheme 2. Cu Catalysts To Promote Nitroalkane Alkylation



We began by examining the reaction of 1-nitropropane and benzyl bromide in benzene. Under basic conditions in the absence of catalyst, only a trace of the desired product 1-phenyl-2-nitrobutane (**7**) was observed (<5% by NMR). The major product was benzaldehyde (12% by NMR; Table 1, entry 1) along with unreacted starting material. Attempts to employ catalysts derived from Pd, Co, Ni, or Fe led to similar results (data not shown). With the use of CuBr and simple ligands such as PPh_3 or bipyridyl **1** (Figure 1), a modest increase in the yield of **7** was seen (entries 2 and 3). Neutral polydentate ligands **2a** and **2b** (Figure 1), which are often very effective ligands in ATRA/ATRP reactions, were less effective (entries 4 and 5).

Table 1. Identification of Reaction Conditions



				yield (%)[b]	
entry	ligand	base	solvent	7	8
1	none[c]	KO^{t}Bu	C_6D_6	trace	12
2	PPh_3	KO^{t}Bu	C_6D_6	18	13
3	**1**	KO^{t}Bu	C_6D_6	17	19
4	**2a**	KO^{t}Bu	C_6D_6	8	14
5	**2b**	KO^{t}Bu	C_6D_6	10	2
6	**3a**	KO^{t}Bu	C_6D_6	45	8
7	**3b**	KO^{t}Bu	C_6D_6	15	22
8	**4**	KO^{t}Bu	C_6D_6	64	2
9	**5**	KO^{t}Bu	C_6D_6	3	10
10	**6**	KO^{t}Bu	C_6D_6	7	8
11[d]	**4**	KO^{t}Bu	C_6D_6	72	2
12[d]	**4**	LiO^{t}Bu	C_6D_6	0	1
13[d]	**4**	NaO^{t}Bu	C_6D_6	78	2
14[d]	**4**	NaO^{t}Bu	hexanes	85[e]	trace

[a]Unless otherwise noted, 1.15 equiv of 1-nitropropane was used. [b]NMR yields, unless otherwise noted. [c]No copper, no ligand. [d]Conditions: 1.25 equiv of 1-nitropropane, 1.2 equiv of base, 25 mol % **4**. [e]Isolated yield.

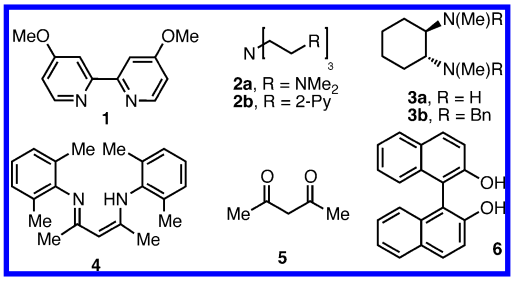


Figure 1. Examples of ligands examined in the benzylation.

In contrast, *trans-N,N′*-dimethyl-1,2-cyclohexanediamine (**3a**), which has been used in Cu-catalyzed Goldberg-type reactions[12] but is not often used in atom-transfer reactions, led to more promising results. With this ligand, **7** was obtained in 45% yield (entry 6). Efforts to optimize this ligand design were unsuccessful. However, we noted that a major byproduct was dibenzylated ligand **3b**. Independently prepared **3b** proved to be ineffective as a ligand in the reaction (entry 7).[13] Similar results were observed for other tetraalkyldiamine ligands, suggesting that the protic N−H bond of **3a** might be integral to its success; we postulated that the active catalyst might arise from deprotonation of the ligand under the reaction conditions, leading to the formation of a highly electron-rich Cu(I)−amido species.

This line of reasoning led us to examine 1,3-diketimine (nacnac) ligands. We predicted that because of the acidic nature of the nacnac backbone, a neutral Cu(I)−nacnac complex would rapidly form under the basic reaction conditions.[14] Further, the steric bulk of the nacnac architecture might prevent competitive alkylation of the ligand. With nacnac **4**, a 64% yield of **7** was obtained under the initial screening conditions. Attempts to optimize the reaction through modulation of the nacnac framework proved unsuccessful (see the Supporting Information), but further studies revealed a significant effect of the base counterion, with sodium proving to be optimal in terms of yield and ease of use (entry 12 vs 13).[15,16] Nonpolar solvents were also favored, with hexanes being the most effective in the screening reaction. Under these optimized conditions, the desired secondary nitroalkane was isolated in 85% yield on a 1 mmol scale (entry 14).[17]

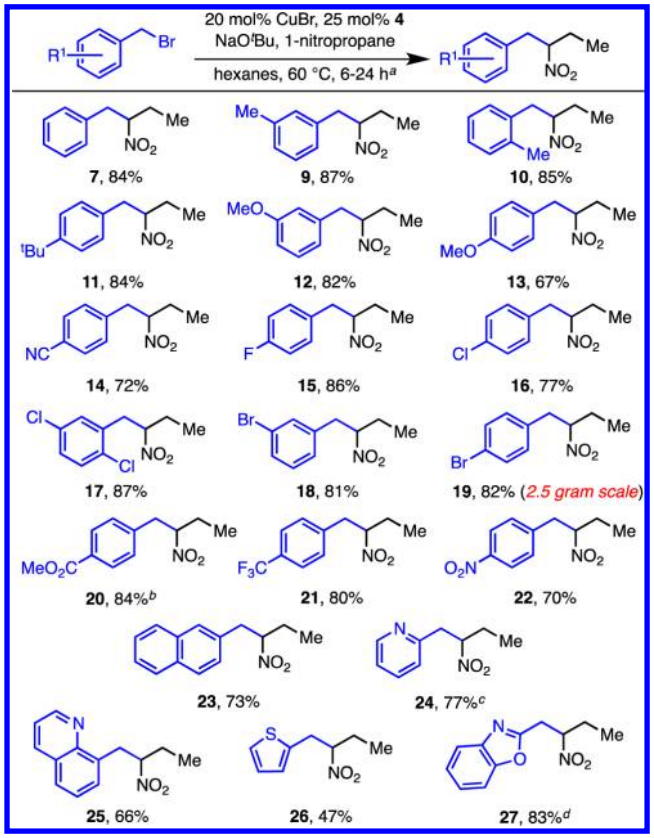
The scope of the reaction with respect to benzyl bromides is broad (Table 2). A wide range of functional groups are tolerated, including fluorides, chlorides, bromides, nitriles, esters, ethers, and trifluoromethyl groups. Both electron-rich (**13**) and electron-poor (**14**, **20**, and **21**) benzyl bromides participated equally well in the reaction. A more sterically encumbered benzyl bromide (**10**) and a polyaromatic substrate (**23**) also reacted without incident. *p*-Nitrobenzyl bromide also provided the C-alkylated product under the Cu-catalyzed reaction conditions (**22**).[5] Finally, bromomethyl-substituted heteroaromatic compounds, including pyridines (**24**), quinolines (**25**), thiophenes (**26**), and benzoxazoles (**27**), also can be used in the reaction.[18] The reaction was easily scaled; compound **19** was isolated in 82% yield from a 2.5 g reaction. In all cases, only trace aldehyde (1−5%) was observed. The major byproduct was the bibenzyl formed by dimerization of the alkylating reagent.

The reaction also enjoys wide substrate scope with respect to nitroalkanes (Table 3). Longer aliphatic nitroalkanes (**28**) and branching β to the nitro group (**29**) were tolerated. A range of functional groups on the nitroalkane proved to be compatible, including alkenes, esters, amides, and acyl-protected alcohols (**30**−**33**). Nitromethane can also be alkylated in good yield (**34**), provided that it is used in excess (7.5 equiv). Under these conditions, good selectivity for the monoalkylated product was observed; with less nitromethane, double alkylation was competitive.

Importantly, secondary nitroalkanes are also tolerated. For example, benzylation of 2-nitropropane resulted in a 71% yield of **35** (Table 3). This transformation allows direct construction of a fully substituted carbon bearing a nitrogen substituent, which remains a challenge in organic synthesis.[19] Not surprisingly, this reaction proceeded more slowly than those

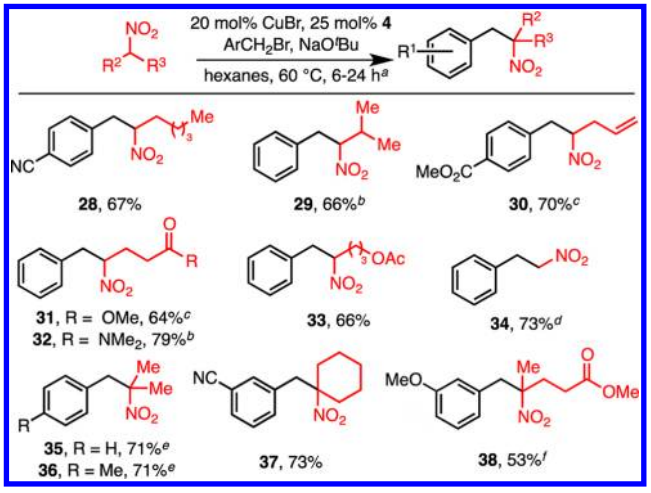
dx.doi.org/10.1021/ja304561c | J. Am. Chem. Soc. 2012, 134, 9942−9945

Table 2. Scope with Respect to Benzyl Bromides



[a]Conditions: 1 equiv of benzyl bromide, 1.25 equiv of 1-nitropropane, 20 mol % CuBr, 25 mol % **4**, and 1.2 equiv of NaO^{t}Bu, unless otherwise noted. [b]NaOMe was used as the base. [c]2.2 equiv of NaO^{t}Bu; benzene was used as the solvent, and the starting material was the HBr salt. [d]Benzene was used as the solvent, and $NaOSiMe_3$ was used as the base.

Table 3. Scope with Respect to Nitroalkanes

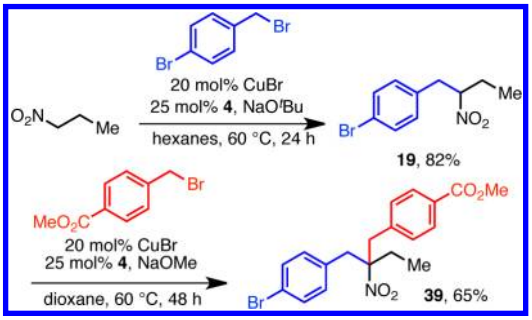


[a]Conditions: 1 equiv of benzyl bromide, 1.25 equiv of nitroalkane, 20 mol % CuBr, 25 mol % **4**, and 1.2 equiv of NaO^{t}Bu, unless otherwise noted. [b]Dioxane was used as the solvent. [c]NaOMe was used as the base. [d]20 mol % CuBr, 20 mol % **4**, 7.5 equiv of NO_2Me; dioxane was used as the solvent. [e]1.15 equiv of nitroalkane, 20 mol % **4**, 48 h; cyclohexane was used as the solvent. [f]1.15 equiv of nitroalkane with cyclohexane as the solvent and $NaOSiMe_3$ as the base; 24 h; the reaction was performed in a glovebox.

of primary nitroalkanes. Other secondary nitroalkanes can participate in the reaction, including nitrocyclohexane (**37**) and those bearing functional groups (**38**).[20]

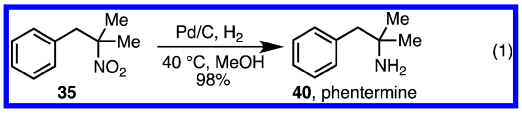
The ability of secondary nitroalkanes to participate in the reaction opens the possibility for sequential alkylations (Scheme 3). As reported above, alkylation of 1-nitropropane

Scheme 3. Sequential Double Benzylation of Nitroalkanes



with 4-bromobenzyl bromide gave nitroalkane **19** in 82% yield. Subsequent alkylation of that product with methyl 4-(bromomethyl)benzoate afforded tertiary nitroalkane **39** in 65% yield. Such sequential alkylations deliver complex nitroalkanes and amines rapidly from very simple starting materials.

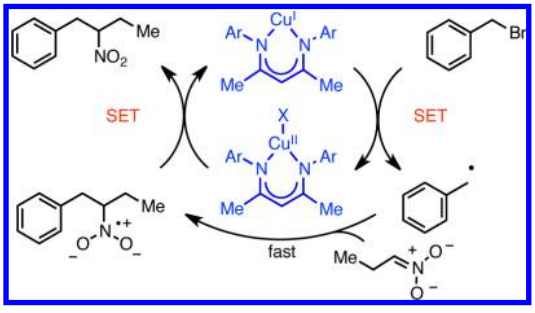
There is clear relevance of the nitroalkane products from the Cu-catalyzed benzylation to the preparation of bioactive molecules. Phenethylamines are important medicinal agents used in the treatment of obesity and other metabolic diseases.[21] These compounds can be readily prepared from β-phenyl nitroalkanes.[1] As an illustration of the utility of our catalytic process, simple hydrogenolysis of nitroalkane **35** (eq 1)



provided in high yield the tertiary amine phentermine (**40**), a clinically prescribed anorectic.[22] Phentermine is typically prepared via the Henry reaction of benzaldehyde and 2-nitropropane followed by a multistep reduction sequence[23] or via a Ritter reaction of the corresponding tertiary alcohol and subsequent hydrolysis,[24] both of which require more steps than the sequence reported herein.

We postulate that these reactions proceed via a thermal redox mechanism involving SET from the electron-rich Cu catalyst to the benzyl bromide (Scheme 4). Upon loss of halide, this process generates a neutral benzylic radical, which

Scheme 4. Possible Mechanistic Pathway



dx.doi.org/10.1021/ja304561c | J. Am. Chem. Soc. 2012, 134, 9942−9945

undergoes coupling with the nitronate anion. Electron transfer from the resulting nitronate radical regenerates the Cu catalyst. The observation of bibenzyl byproducts is consistent with an SET pathway.[25]

In summary, we have developed a catalytic system for the benzylation of nitroalkanes that utilizes readily available benzyl bromides and related heteroaromatic compounds. This protocol addresses a century-old gap in C−C bond construction and provides the first example of alkylation of nitroalkanes using readily available starting materials under mild reaction conditions. This reaction allows the conversion of simple starting materials to complex nitroalkanes, which are important synthetic intermediates in the preparation of bioactive molecules such as phenethylamines. The key to this discovery was the identification of a highly electron-rich Cu(I)−nacnac complex that can be prepared in situ and can reduce the benzyl halide to the corresponding radical. This thermally driven process clearly bears mechanistic resemblance to catalytic photoredox systems, whose synthetic utility has been elegantly demonstrated by several groups.[26,27] Efforts to apply our Cu-based system to other catalytic redox reactions and to expand the scope of the nitroalkane alkylation to other classes of alkyl halides are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The University of Delaware (UD) and the University of Delaware Research Foundation are gratefully acknowledged for funding and other support. NMR and other data were acquired at UD on instruments obtained with the assistance of NSF and NIH funding (NSF MIR 0421224, NSF CRIF MU CHE0840401, NIH P20 RR017716, NIH S10 RR02692).

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(15) In all cases, the alkylation reactions were heterogeneous, which we believe is due to the low solubility of the nitronate anions in the apolar medium. The failure of the reactions involving lithium salts likely stems from the very low solubility of the lithium nitronates.

(16) Screening reactions were set up inside a nitrogen-filled glovebox. The use of NaO^{t}Bu, because of its limited hydroscopicity relative to KO^{t}Bu, also allowed the reactions to be performed on the bench using standard Schlenk techniques. With the exception of **38**, all of the isolated yields refer to reactions run on the bench. All of the reported isolated yields are averages of at least two independent experiments.

(17) Lower catalyst loadings resulted in lower yields.

(18) In some cases, particularly those involving more polar substrates, preforming the catalyst in situ and using alternative solvents (e.g., 1,4-dioxane) or weaker bases (e.g., NaOSiMe$_3$) proved to be superior to the standard conditions. For substrates containing methyl esters, NaOMe was used as the base.

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(27) Our reactions do not require light, as similar yields were obtained in control experiments run in the dark.