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Selective Cleavage and Tunable Functionalization of the C−C/C−N Bonds of *N*-Arylpiperidines Promoted by ^{t}BuONO

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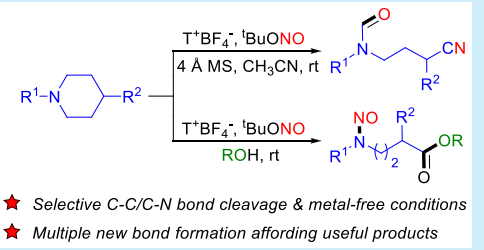
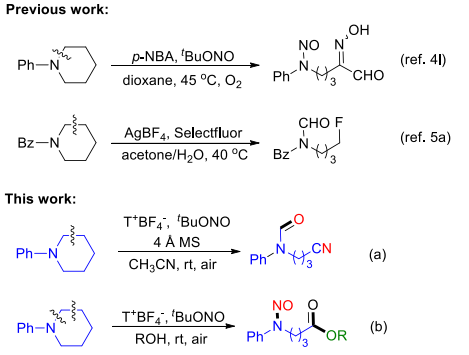
Supporting Information

ABSTRACT: In this paper, selective cleavage and tunable functionalization of the inert C−C/C−N bonds in *N*-arylpiperidines promoted by ^{t}BuONO under metal-free conditions is presented. To be specific, when the reaction was run in acetonitrile in the presence of molecular sieves, the synthetically useful acyclic *N*-formyl nitriles are formed. On the other hand, when alcohol was used as the reaction medium, the corresponding reactions afforded *N*-nitroso chain esters as dominating products via a mechanistically different pathway.



Because of its wide applications in rebuilding complex molecules that would be unapproachable from other methods, cleavage and functionalization of the inert C−C/C−N bonds represents a powerful class of chemical transformation.[1−3] Among them, the deconstructive functionalization of cyclic amines is particularly important given their ubiquity and ready availability. However, efficient accomplishment of this kind of transformation is still challenging due to the high bond dissociation energy of the inert C−C/C−N bonds.[4,5] Recent studies found that transition-metal-catalyzed C−N bond cleavage via iminium, ammonium, and/or enamine species are efficient and reliable for activateing the saturated *N*-containing compounds.[4a,b,f−j] However, some of these protocols suffer from high reaction temperature, use of expensive metal catalyst, or formation of side products due to unselective oxidation. Lately, Jia et al. disclosed some interesting multifunctionalization of the inert C−H and C−N bonds in *N*-arylazacycles via a ^{t}BuONO (TBN)-initiated radical process under metal-free conditions (Scheme 1, ref 4l). Meanwhile, it was also noted that most of the transformations reported therein were related to C−N bond cleavage, and selective cleavage of the C−C bond in unstrained cyclic amines is very limited. Very recently, Sarpong et al. disclosed the transformation of *N*-benzoyl cyclic amines into fluorine-containing acyclic amine derivatives via $AgBF_4$ promoted fluorination and cleavage of the C−C bond (Scheme 1, ref 5a).

Scheme 1. Previous Work and This Work



Inspired by the above-mentioned elegant pioneering studies, we report here a 2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate ($T^{+}BF_4^{-}$) and TBN-promoted cleavage and functionalization of the inert C−C bond in saturated cyclic amines to produce *N*-(3-cyanopropyl)-*N*-formamides with the simultaneous construction of both cyano and formamide units (Scheme 1, a). In addition, when alcohol was used as the reaction medium instead of acetonitrile, selective cleavage and functionalization of the C−N bond occurred to generate the interesting *N*-nitroso chain ester products (Scheme 1, b). Compared with literature reports, notable features of these novel protocols include (1) selective cleavage and tunable functionalization of inert C−C bond and C−N bond without using any metal catalyst and (2) multiple synthetically useful building blocks constructed in a one-pot manner.[6]

As a continuation of our interest in cyclic amine functionalization,[4i,j,7] we have initially envisioned a direct synthesis of nitroso-substituted heterocycles (**I**) through the oxidative C(sp^3)−H bond nitrosation of saturated cyclic amines by using $T^{+}BF_4^{-}$ as a generally stable oxidant[8] and TBN as an easily obtainable and convenient to handle nitrosation reagent.[4k,l,9,10] Thus, 1-phenylpiperidine (**1a**) was treated with $T^{+}BF_4^{-}$ and TBN in acetone at room temperature

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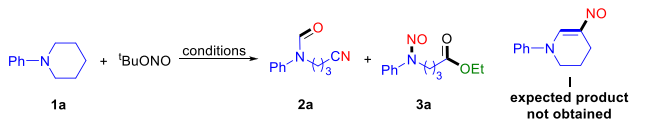
under air for 1 h. To our surprise, an unexpected product, *N*-(3-cyanopropyl)-*N*-phenylformamide (**2a**), was isolated in a yield of 10% (Table 1, entry 1). Considering the merits of this

Table 1. Optimization Studies for the Formation of 2a and 3a[a]



entry	oxidant (equiv)	additive (equiv)	solvent	yield[b] (%) 2a	3a
1	$T^+BF_4^-$ (1)		acetone	10	
2	$T^+BF_4^-$ (1)		CH_3CN	20	
3	$T^+BF_4^-$ (1)		DCE	trace	
4	$T^+BF_4^-$ (1)		DMSO	trace	
5	$T^+BF_4^-$ (1)		dioxane	trace	
6	$T^+BF_4^-$ (1)		EtOH		25
7	$T^+ClO_4^-$ (1)		CH_3CN	11	
8	T^+OTf^- (1)		CH_3CN	trace	
9	DDQ (1)		CH_3CN	trace	
10	$K_2S_2O_8$ (1)		CH_3CN	trace	
11	$T^+BF_4^-$ (1.5)		CH_3CN	31	
12[c]	$T^+BF_4^-$ (1.5)		CH_3CN	28	
13[d]	$T^+BF_4^-$ (1.5)		CH_3CN	30	
14	$T^+BF_4^-$ (1.5)	$BF_3{\cdot}Et_2O$ (1)	CH_3CN	28	
15	$T^+BF_4^-$ (1.5)	CaO (1)	CH_3CN	26	
16	$T^+BF_4^-$ (1.5)	$NaHCO_3$ (1)	CH_3CN	24	
17[e]	**$T^+BF_4^-$ (1.5)**		**CH_3CN**	**61**	
18	$T^+BF_4^-$ (1.5)		EtOH		35
19[f]	$T^+BF_4^-$ (1.5)		EtOH		33
20[g]	**$T^+BF_4^-$ (1.5)**		**EtOH**		**64**

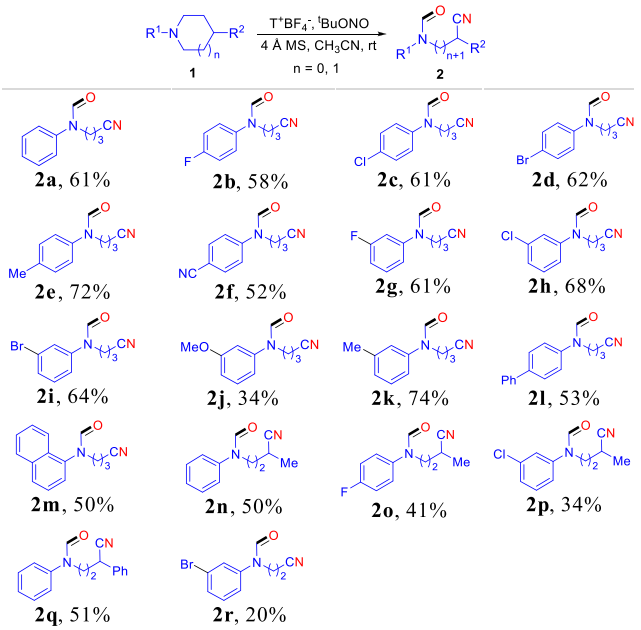
[a]Reaction conditions: 0.2 mmol of **1a**, 0.6 mmol of TBN, 1 mL of solvent, room temperature, air, 1 h. [b]Isolated yields. [c]0.4 mmol of TBN. [d]0.8 mmol of TBN. [e]In the presence of 4 Å MS (100 mg). [f]50 °C. [g]6 h.

reaction as mentioned above, we decided to screen the reaction conditions to improve the efficiency of this transformation. First, various solvents such as CH_3CN, DCE, DMSO, and dioxane were attempted (entries 2−5). Among them, CH_3CN was found to be more favorable than other solvents (entry 2 vs 1 and 3−5). Subsequently, the reaction was carried out in ethanol, and we were surprised to find that another product, ethyl 4-(nitroso(phenyl)amino)butanoate (**3a**), bearing useful nitroso and ester groups, was selectively formed in a yield of 25% (entry 6). Then different TEMPO salts as well as other kinds of oxidant were screened (entries 7−10). It turned out that $T^+BF_4^-$ is the most efficient oxidant for the formation of **2a** (entry 2). Increasing the loading of $T^+BF_4^-$ to 1.5 equiv improved the yield of **2a** to 31% (entry 11). Further studies in varying the loading of TBN did not give more positive results (entries 12 and 13). To see whether the presence of an acidic or basic additive could improve the reaction, $BF_3{\cdot}Et_2O$, CaO, and $NaHCO_3$ were used.[11] However, a slight decrease in the yield of **2a** was observed (entries 14−16). To our delight, using 4 Å molecular sieves to remove water possibly existing in the reaction system could substantially improve the yield of **2a** to 61% (entry 17), most likely due to the postulation that water is beneficial to C−N bond cleavage[4l] other than the C−C bond cleavage needed for the formation of **2a**.

After establishing an efficient synthesis of **2a**, we continued to search for reaction conditions favoring the formation of **3a** (Table 1, entry 6). For this purpose, the loading of $T^+BF_4^-$ was increased to 1.5 equiv. As a result, the yield of **3a** was improved to 35% (entry 18). In another aspect, elevating the reaction temperature from rt to 50 °C resulted in a slight reduction of efficiency (entry 19). Finally, we were delighted to find that prolonging the reaction time from 1 to 6 h improved the efficiency of this transformation considerably, and **3a** could be formed in a yield of 64% (entry 20).

With the establishment of the optimum reaction conditions, the substrate scope for the synthesis of **2** was explored. First, a number of 1-arylpiperidines **1** with different substituents attached on the phenyl ring were tested. It turned out that the corresponding reactions proceeded efficiently to afford **2a**−**k** in 34−74% yields (Scheme 2). Remarkably, functional

Scheme 2. Substrate Scope for the Synthesis of 2[a,b]



[a]Reaction conditions: 0.2 mmol of **1**, 0.3 mmol of $T^+BF_4^-$, 0.6 mmol of TBN, 4 Å molecule sieves (100 mg), CH_3CN (1 mL), rt, air, 1 h. [b]Isolated yields.

groups such as fluoro, chloro, bromo, cyano, methyl, and methoxy were well tolerated. In addition, 1-biphenyl and 1-naphthylpiperidine underwent this cascade transformation smoothly to give **2l** and **2m** in 53% and 50% yields, respectively. Second, when substrates bearing a methyl or phenyl unit on the piperidine ring were used, corresponding products **2n**−**q** could also be obtained in 34−51% yields. Third, this transformation was equally amenable to 1-arylpyrrolidine, delivering the target product **2r** in 20% yield.

Next, the substrate scope for the synthesis of **3** was studied. The results listed in Scheme 3 showed that **1** bearing different substituents on the 1-aryl unit underwent this transformation smoothly to afford **3a**−**j** in moderate to good yields. Various functional groups, from electron-withdrawing fluoro, chloro, bromo, trifluoromethyl, and cyano to electron-donating methyl, were well tolerated. Notably, **3e** and **3f** were obtained in lower yields, probably owing to electronic effect. Besides, when a chloro unit was attained at the *ortho*-position of the

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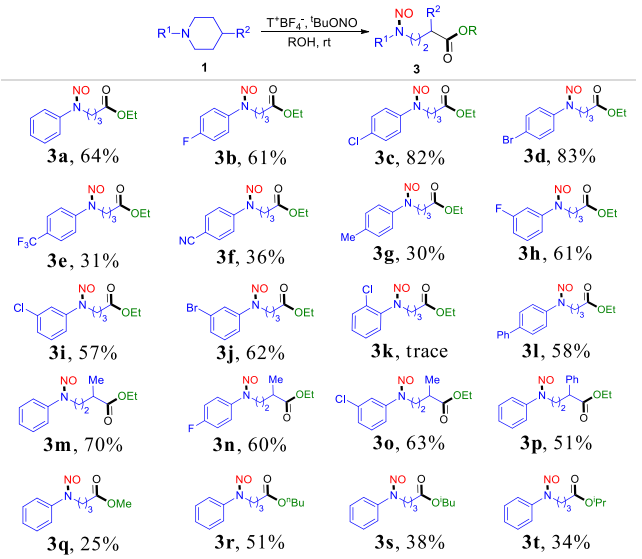
Scheme 3. Substrate Scope for the Synthesis of 3[a,b]

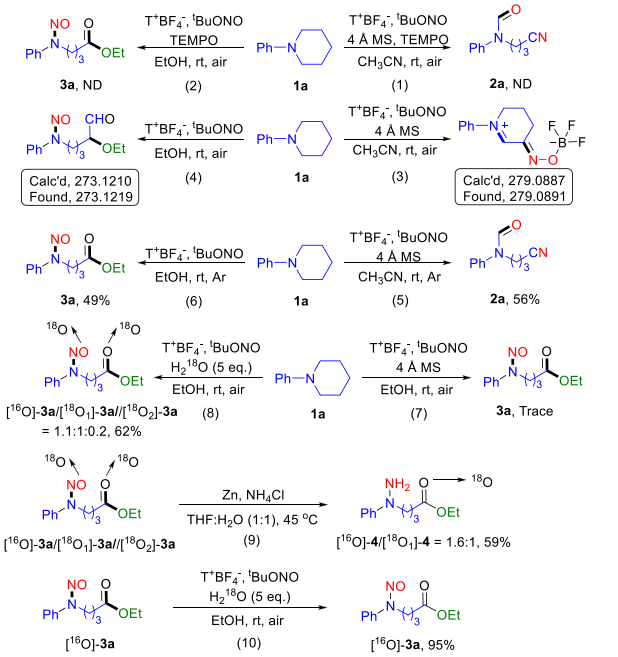


[a]Reaction conditions: 0.2 mmol of **1**, 0.3 mmol of $T^+BF_4^-$, 0.6 mmol of TBN, alcohol (1 mL), rt, air, 6 h. [b]Isolated yields.

benzene ring, the corresponding product was formed only in trace amounts, probably due to steric hindrance (**3k**). Moreover, *N*-biphenyl-substituted piperidine could be smoothly transformed into the desired product **3l** in 58% yield. In addition, substrates bearing a methyl or phenyl group on the *para*-position of the piperidine ring could also take part in this reaction to give **3m**−**p** in yields ranging from 51 to 70%. In another respect, other primary alcohols such as methanol, *n*-butanol, and 2-methylpropanol and secondary alcohols such as 2-propanol were found to be suitable substrates for this reaction, furnishing the corresponding products **3q**−**t** in moderate yields.

To gain some insight into the reaction mechanism, some control experiments were conducted. First, 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as a radical scavenger was added to the standard reaction systems for the synthesis of **2a** and **3a**. As a result, the formation of **2a** and **3a** was not detected (Scheme 4, (1) and (2)), indicating that these reactions should follow a radical pathway. Second, HRMS studies on the reaction mixture for the formation of **2a** and **3a** were conducted. A zwitterion species trifluoro(((1-phenyl-5,6-dihydropyridin-1-ium-3(4*H*)-ylidene)amino)oxy)borate (calcd, 279.0887; found, 279.0891) consisting of iminium and borate was detected, which hits the promoting effect of $T^+BF_4^-$ for the construction of **2a** (Scheme 4, (3)). On the other hand, *N*-(4-ethoxy-5-oxopentyl)-*N*-phenylnitrous amide (calcd, 273.1210; found, 273.1219) was detected in the reaction mixture leading to **3a**. This result suggests that a decarbonylation process might be involved in the formation of **3a** (Scheme 4, (4)). Third, the reactions for the formation of **2a** and **3a** were carried out under argon instead of air (Scheme 4, (5) and (6)). From these reactions, **2a** and **3a** were formed in slightly decreased yields of 56% and 49% compared with those obtained under air, indicating that the presence of molecular oxygen in air should have some effect on the formation of **2a** and **3a**. Fourth, the reaction for the formation of **3a** was implemented in the presence of 4 Å molecule sieves (Scheme 4, (7)). Under this circumstance, **3a** was obtained only in a trace amount. This result indicated that the presence of water

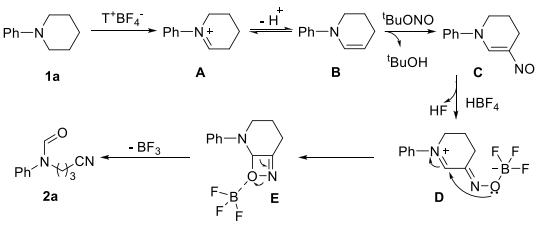
Scheme 4. Control Experiments



is crucial for the formation of **3a**. Afterward, an ^{18}O-labeling experiment with $H_2{}^{18}O$ for the preparation of **3a** was carried out (Scheme 4, (8)), from which [^{16}O]-**3a**, [$^{18}O_1$]-**3a**, and [$^{18}O_2$]-**3a** were formed in a ratio of 1.1:1:0.2 as determined by HRMS analysis (see the SI). It indicates that H_2O might not be the sole source of the oxygen atoms of nitroso and ester moieties embedded in **3a**. In trying to locate the position of the ^{18}O atom on [$^{18}O_1$]-**3a**, the 261 ion was selected and subjected to MSMS fragmentation, and the results showed the ^{18}O atom is located either on the ester or on the nitroso functional group (see the SI). Then, in order to further determine the ratio of [$C^{18}OOEt$]-**3a** and [$N^{18}O$]-**3a**, the nitroso groups in the mixture of [^{16}O]-**3a**, [$^{18}O_1$]-**3a**, and [$^{18}O_2$]-**3a** (1.1:1:0.2) were reduced to the amine unit to give [^{16}O]-**4** and [$^{18}O_1$]-**4** in a ratio of 1.6:1 as determined by HRMS analysis (Scheme 4, (9)). Thus, the ratio of [$C^{18}OOEt$]-**3a** and [$N^{18}O$]-**3a** was calculated as 2.4:1. Finally, ^{16}O-**3a** was treated with $H_2{}^{18}O$ under the standard reaction conditions (Scheme 4, (10)). The following HRMS study of the product thus obtained excludes the possibility of O atom exchange between water and functional groups (nitoso and ester) existing in **3a** as only ^{16}O-**3a** (95%) was obtained (see the SI).

On the basis of the above results and previous reports,[7a,8,12] a plausible mechanism accounting for the formation of **2a** is proposed in Scheme 5. Initially, **1a** is oxidized by $T^+BF_4^-$ to give an iminium intermediate **A**.[8] Subsequent *β*-hydrogen

Scheme 5. Proposed Mechanism Accounting for the Formation of 2a



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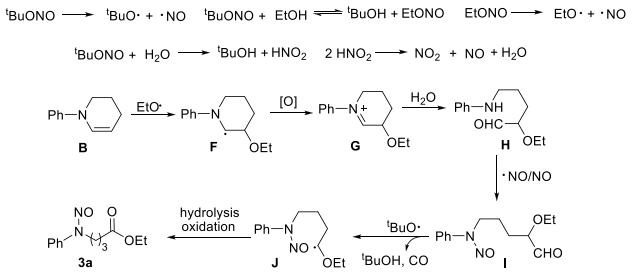
elimination occurs with **A** to produce an enamine intermediate **B**.[7a] Next, nitrosation of **B** by TBN affords intermediate **C**.[12a] In the presence of BF_3, the isomerization of **C** occurs to deliver charge-separated intermediate **D**,[12b] which then undergoes an intramolecular nucleophilic attack to form **E**. Then N−O and C−C bond cleavage of **E** occur to furnish product **2a**.[12]

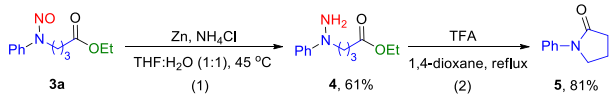
As for the formation of **3a**, it should also involve an initial in situ formation of enamine **B**. Then EtO$^{\bullet}$ generated from the reaction medium undergoes a radical addition on **B** to provide intermediate **F**.[4l,13] The following oxidation of **F** produces an iminium intermediate **G**. Then hydrolysis and C−N bond cleavage of **G** take place to afford acyclic intermediate **H**,[4l] which subsequently captures an NO or NO radical to form intermediate **I**.[14a] Next, with the aid of ^{t}BuO$^{\bullet}$, decarbonylation of **I** occurs to give radical intermediate **J**,[14b] which is hydrolyzed and/or oxidized into product **3a** (Scheme 6).[9c]

Scheme 6. Proposed Mechanism Accounting for the Formation of 3a



Finally, the synthetic applications of the products obtained above were explored. It was thus found that the nitroso group in **3a** could be conveniently reduced to an amine unit by subjecting it to zinc and NH_4Cl in THF/water to give **4** (Scheme 7, (1)). Treatment of **4** with TFA in refluxing 1,4-dioxane afforded pyrrolidone **5** in an excellent yield of 81% (Scheme 7, (2)). This is a synthetically interesting transformation as pyrolidone derivatives are known to play important roles in biological and pharmaceutical fields.[15]

Scheme 7. Synthesis of 4 and 5 from 3a



In conclusion, we have established some efficient methods to realize selective cleavage and tunable functionalization of the C−C/C−N bonds in unstrained cyclic amines by using inexpensive $T^{+}BF_4^{-}$ as a mild oxidant and easily available TBN as a sustainable nitrogen source. From these reactions, the synthetically useful acyclic *N*-formyl nitriles and *N*-nitroso chain esters were conveniently prepared. In general, these novel no-metal-catalyzed transformations, which were accomplished under mild conditions and showed good tolerance toward a variety of functional groups, are excellent complements to previously reported synthetic strategies. Further exploitation on the detailed mechanism is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00226.

Experimental procedure, characterization data, and NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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