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Nitrosobenzene-Mediated C−C Bond Cleavage Reactions and Spectral Observation of an Oxazetidin-4-one Ring System

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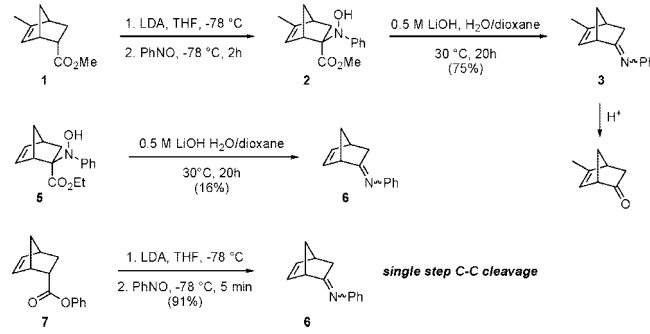
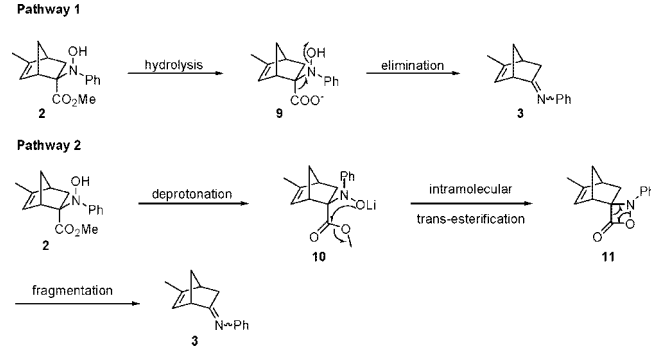
Synthetic organic chemistry is concerned with the assembly of complex chemical structures from relatively simple starting materials. Not surprisingly, processes facilitating the formation of new chemical bonds encompass a preponderance of the literature.[1] However, the inverse process of C−C bond cleavage, while synthetically desirable in many cases, poses a great challenge due to the inherent strength of the C−C bond.[2,3] Accordingly, relatively few procedures have been reported for this transformation, and those that have usually rely on transition metal catalysis.[4] In the present work, we describe a powerful, one-step oxidative C−C bond cleavage methodology for a broad range of ester and dicarbonyl substrates utilizing nitrosobenzene as an oxidant. Moreover, mechanistic studies using ReactIR spectrometry have allowed the first spectral observation of the oxazetidin-4-one ring system. This methodology marks a breakthrough over related multistep and metal-mediated procedures, providing a highly robust oxidative C−C bond cleavage protocol for a diverse array of carbonyl compounds.[5,6]

Given our long standing work in Diels−Alder chemistry, we became interested in C−C bond cleavage methodology in the context of developing a highly versatile asymmetric ketene equivalent.[7] In preliminary studies toward an asymmetric route to bicyclo[2.2.1]hept-5-ene-2-one derivatives it was found that treatment of *N*-hydroxy methyl ester **2** with LiOH provided bicyclic ketone **4** in 75% yield over two steps (after acidic hydrolysis of the imines).[8,9] Interestingly, under identical conditions *N*-hydroxy ethyl ester **5** gave the corresponding product **6** in only 16% yield. By increasing the lability of the ester it was found that direct addition of nitrosobenzene to the lithium enolate of phenyl ester **7** at −78 °C provided the corresponding *N*-phenyl imines **6**, accompanied by evolution of CO_2, within 5 min in 91% yield *in one step* (Scheme 1).

Scheme 1. Preliminary Data on Oxidative Decarboxylation



Scheme 2. Plausible Pathways for Oxidative Decarboxylation



The markedly contrasting results obtained between the related ethyl, methyl, and phenyl bicyclo[2.2.1]hept-5-ene-2-carboxylates prompted us to undertake detailed mechanistic studies. As a starting point, the conversion of *N*-hydroxy methyl ester **2** to *N*-phenyl imines **3** was examined. Two conceivable reaction pathways may exist for this transformation. Initial hydrolysis of the methyl ester of **2** would afford carboxylate intermediate **9**. Subsequent loss of CO_2 and elimination of a hydroxide ion would furnish imines **3**.[10] More interestingly, the *N*-hydroxyl group could first be deprotonated to give **10**. Intramolecular attack of the methyl ester by the oxyanion would give the highly energetic, spiro-oxazetidin-4-one intermediate **11**.[11] This strained species should spontaneously fragment, expelling CO_2, to give imines **3** (Scheme 2).[12,13]

To ascertain if the reaction proceeded through **Pathway 1** (viz. intermediate **9**), carboxylic acid **12**[14] (for preparation, see Supporting Information) was subjected to the identical conditions for which imines **3** had been obtained from *N*-hydroxy methyl ester **2** (Figure 1A). However, under these same reaction parameters **12** gave only a complex mixture of decomposition products. To verify if **Pathway 2** was indeed correct, spectroscopic observation of the oxazetidin-4-one functionality of **11** was required. However, due to the slow rate of conversion of **2** to **3**, the low concentration as well as the expected short lifetime of **11** would make detection difficult. The observation that phenyl esters are directly cleaved to yield the corresponding imine products by addition of nitrosobenzene at −78 °C suggested that under these conditions observation of the oxazetidin-4-one intermediate was feasible.

In situ ReactIR technology was employed to monitor the conversion of phenyl ester **7** to the corresponding *N*-phenyl imines **6**. As can been seen in Figure 1B (3D and 2D plots), less than 1 min after addition of nitrosobenzene to the lithium enolate of **7**, a new, sharp peak appears at 1846 cm^{-1}. The intensity of this peak gradually decreases as the cooling bath is warmed to −20 °C. Importantly, the disappearance of the 1846 cm^{-1} band is marked by the appearance of two bands at 1695 and 1679 cm^{-1} corresponding to *N*-phenyl imines **6**. We believe the new IR absorption at 1846 cm^{-1} is attributable to the existence of spiro-oxazetidin-4-one intermediate **14**. IR data of similar cyclic compounds reveal that a stretch of 1846 cm^{-1} is highly characteristic of this type of four-membered, spiro ring system.[15] Thus, we can now conclude that the conversion of **7** to **6** follows a mechanistic course analogous

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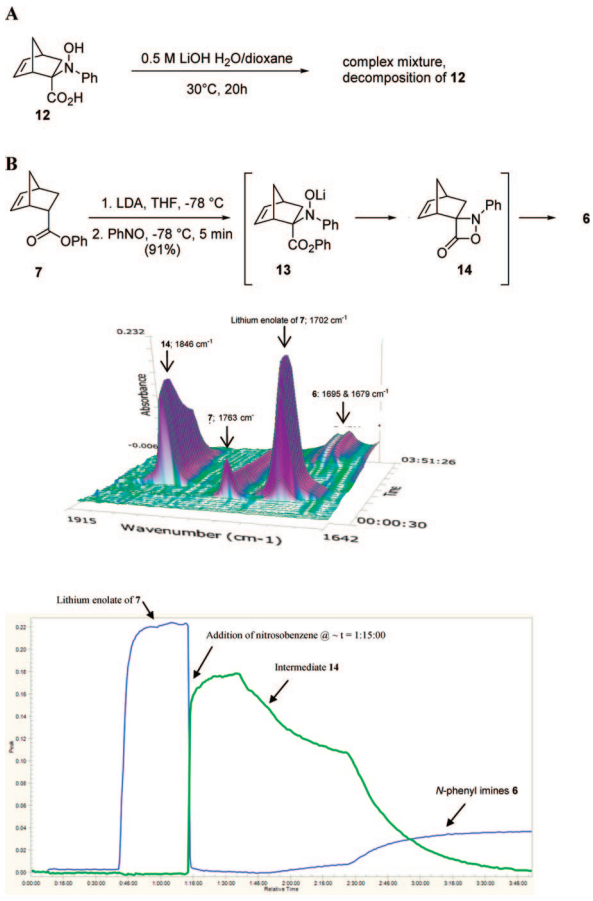


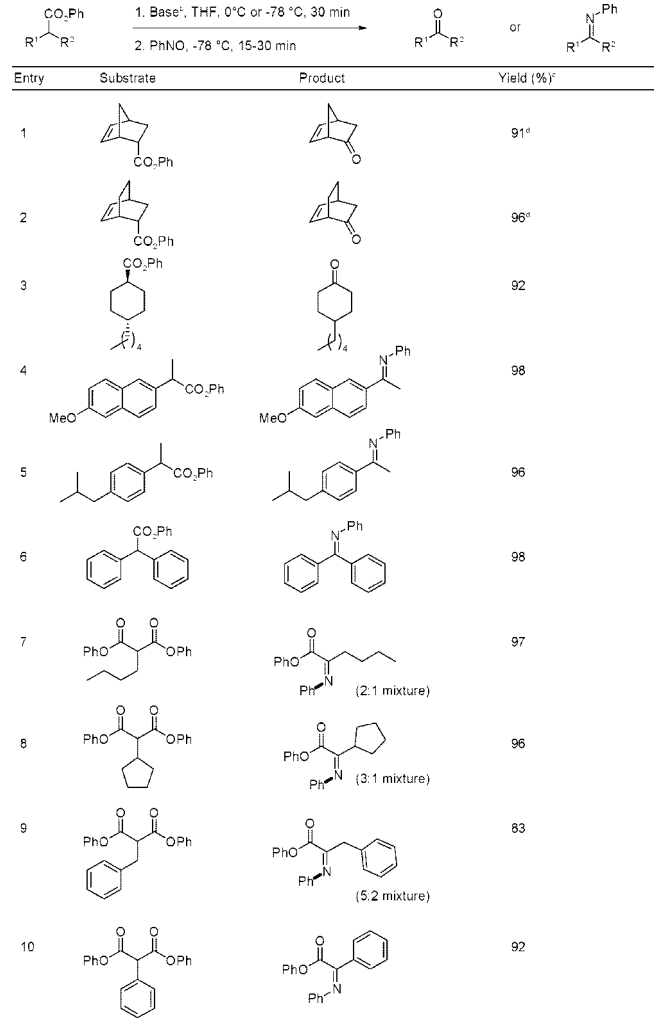
Figure 1. Control and ReactIR experiments were conducted to determine the mechanistic course of the nitrosobenzene-mediated oxidative decarboxylation reaction. (A) Control experiment showing that conversion of **2** to **3** does not follow Pathway 1. (B) 3D and 2D plots of ReactIR experiment showing Pathway 2 is correct with the first spectral observation of an oxazetidin-4-one heterocycle **14**. Immediately after addition of nitrosobenzene to the lithium enolate of **7** at −78 °C, oxazetidin-4-one **14**, having an IR stretch at 1846 cm^{-1}, is observed. As the cooling bath is gradually warmed, the disappearance of **14** is marked by the appearance of *N*-phenyl imines **6**. Note: The intensity of the line plot of **6** is reflective of only one isomer of **6**.

to **Pathway 2**. While oxazetidin-4-ones have been postulated as reaction intermediates in only a handful of synthetic and theoretical papers,[12,13,16] direct evidence for the existence of this functional group has hitherto been unreported.[17]

The reaction scope of this novel process was subsequently examined. Table 1 summarizes these results. The present method tolerates a range of bicyclic, cyclic, sp^2-sp^3, and sp^2-sp^2 α,α′-disubstituted phenyl esters to provide either ketone or imine products in generally excellent yields. In general, ketimines containing at least one sp^2 α-subsitutent were stable to silica gel while those having only sp^3 α-subsitutents (entries 1−3) were immediately hydrolyzed. Further, malonic ester derivatives could also be applied to provide the corresponding α-imino phenyl esters in uniformly high yields as well.

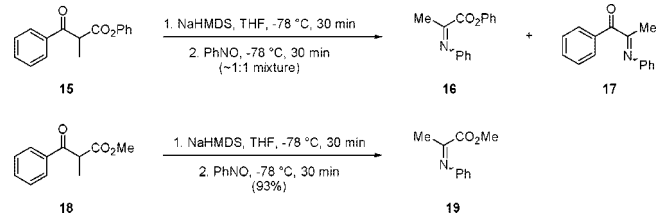
Unexpectedly, when β-keto phenyl ester **15** was subjected to the standard reaction conditions, an ∼1:1 mixture of α-imino-ester **16** and α-keto-imine **17** was obtained, presumably from attack of the aminooxy anion at either the ketone or ester functionalities (Scheme 3). Guided by our previous findings, use of the corresponding less labile β-keto methyl ester **18** resulted in exclusive cleavage of the ketone moiety furnishing α-imino-methyl ester **19** in 93% yield. Gratifyingly, this process could

Table 1. Nitrosobenzene-Mediated Oxidative Decarboxylation[a]



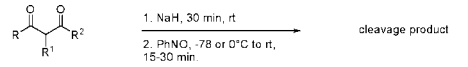
[a] Products in entries 4−10 were hydrolytically stable to SiO_2. See Supporting Information for additional details. [b] Base = LDA (lithium diisopropylamide) or NaHMDS (sodium bis(trimethysilyl)amide). [c] Isolated yield. [d] Determined by ^1H NMR with $MeNO_2$ as internal standard.

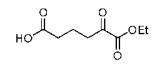
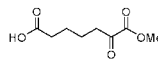
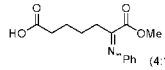
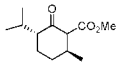
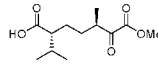
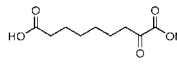
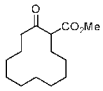
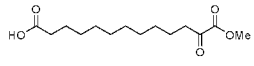
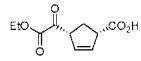
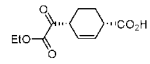
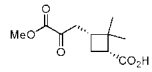
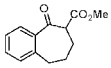
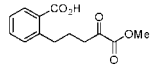
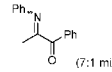
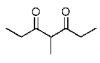
Scheme 3. Initial Results for Cleavage of β-Ketoesters



be applied to ring-opening cleavage reactions of a diverse array of mono- and bicyclic β-ketoesters to afford highly functionalized dioxo- (acidic workup) or oxo-imino acids (workup under buffered conditions) in quantitative yields (Table 2, entries 1−9). Further, a simple extension of this ketone cleavage methodology to symmetric 1,3-diketone substrates allows for a regioselective route to α-ketoimines (Table 2, entries 11−13). It should be noted that in both oxidative decarboxylation and ketone cleavage reactions spectroscopically pure compounds can be obtained after simple aqueous workup procedures obviating the need for chromatographic purification.

Table 2. Nitrosobenzene-Mediated Ketone Cleavage[a]



Entry	Substrate	Product	Yield (%)[b]
1			>95%
2			>95%
		 (4:1 mixture)[c]	85%
3			>95%
4			>95%
5			>95%
6			>95%
7			>95%
8			>95%
9			>95%
10	 R = Me, Ph		75% (R =Me) 83% (R = Ph)
11		 (7:1 mixture)	83%
12			83%
13			84%

[a] See Supporting Information for details. [b] Products in entries 1−9 were isolated after acidic workup as their crude acids which were >95% pure by ^{1}H NMR. Products in entries 10−13 were isolated after column chromatography. [c] Isolated after workup with pH 6.5 citric acid/phosphate buffer. Contains ca. 7% of the corresponding dioxo acid.

In summary, we have developed an efficient single step oxidative decarboxylation reaction of esters involving nitrosobenzene addition to the corresponding enolate. A series of control and spectroscopic experiments have elucidated the mechanism of this novel cleavage process, providing the first spectral evidence for the existence of an oxazetidin-4-one ring system. Based on these findings, this methodology could be generalized to cleavage reactions involving a wide scope of dicarbonyl compounds affording highly functionalized products in excellent yields and in short reaction times. Current work in our laboratory is aimed at expanding the full scope and applications of this new C−C bond cleavage methodology. We believe the findings from the present study will provide impetus for further research into alternative, metal-free bond fission methodologies.

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Supporting Information Available: Experimental procedures, X-ray crystallographic data, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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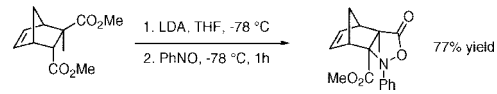

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