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Intramolecular Rearrangement of α-Azidoperoxides: An Efficient Synthesis of *tert*-Butyl Esters

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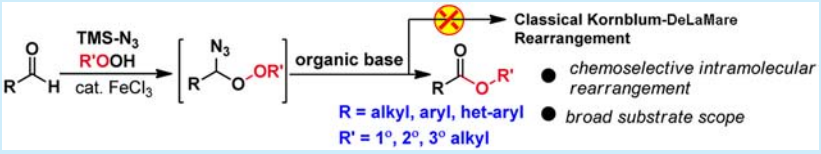
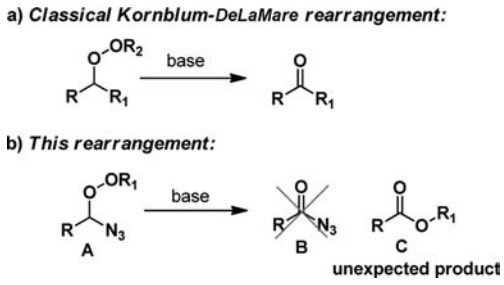
Supporting Information



ABSTRACT: An unprecedented intramolecular rearrangement of α-azidoperoxides, promoted by simple organic base to provide *tert*-butyl esters, has been presented. Further, a one-pot methodology consisting of in situ generation of the α-azidoperoxides from corresponding aldehydes followed by base-promoted rearrangement to obtain the desired ester has also been executed. Relevant mechanistic studies, to provide the proof for intramolecular alkoxy transfer, are investigated.

The identification of novel reactivity is not only more challenging but also increasingly essential to meet the ever-increasing societal demands on synthetic chemistry. Often, the discovery of new reactivity has been a consequence of investigating a hypothesis based on a known reactivity and intuition, resulting in an unexpected outcome. Kornblum and DeLaMare reported base-promoted peroxide decomposition for the synthesis of ketones.[1] On the basis of such reactivity, Kelly and co-workers suggested a synchronous peroxide cleavage and retro-aldol cleavage of endoperoxides to provide γ-hydroxy enones.[2] Toste et al. developed the enantioselective synthesis of γ-hydroxyenones by a chiral base-catalyzed Kornblum−DeLaMare rearrangement.[3] We expected an analogous reactivity of our recently synthesized new class of α-heteroperoxides **A**[4] to provide the acyl azide **B** (Scheme 1). Instead, we observed unprecedented reactivity that provides the corresponding esters **C** through an intramolecular rearrangement of the alkoxy group, thus unfolding an unrecognized opportunity for the synthesis of esters.

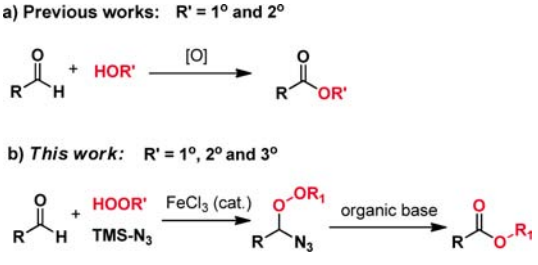
Scheme 1. Base-Promoted Decomposition of α-H-Containing Peroxides: (a) Classical Kornblum−DeLaMare Rearrangement, (b) Unprecedented Rearrangement of α-Azidoperoxides



tert-Butyl esters are of interest because of their rich applications across many fields of chemistry. This functionality has a significant advantage as a protecting group which can be readily converted to the corresponding acids under mild acidic conditions.[5] Moreover, the steric bulk of this group plays a crucial role in achieving better selectivity in many asymmetric processes.[6] Traditionally, the synthesis of *tert*-butyl esters relied primarily on the reaction of carboxylic acid and its derivatives with *tert*-butyl alcohol. However, the preparation of these hindered esters from carboxylic acids and other precursors is more complicated than from other esters.[7] Considerable attention has been paid to the synthesis of such esters via alkoxycarbonylation of aryl halides, and many attractive processes have been developed.[7h,8] However, the use of toxic carbon monoxide, a crucial raw material in this process, is a limitation. Further, these reactions are limited to aromatic substrates only.[8]

Recently, oxidative esterification of aldehydes has been considered as an interesting strategy for the synthesis of esters (Scheme 2a).[9−12] Although large varieties of esters of primary

Scheme 2. Oxidative Esterification of Aldehydes



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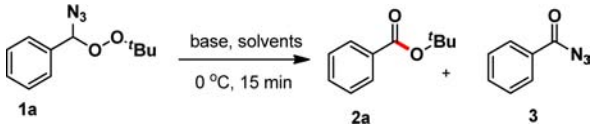
and secondary alcohols have been successfully prepared using these methods, the synthesis of *tert*-butyl ester still remained a challenge. In this regard, copper-catalyzed oxidative esterification of aldehydes with dialkyl peroxides is notable.[10] However, organocatalyzed anodic oxidation[11] or Pd-catalyzed hydrogen transfer[12] of aldehydes for the synthesis of esters also failed to provide the *tert*-butyl esters. Therefore, the development of a novel, user-friendly approach for the synthesis of *tert*-butyl esters from corresponding aldehydes would be highly useful.

We started the investigation of base-promoted decomposition of α-azidoperoxide to acylazide (**3**) choosing azido(*tert*-butylperoxy)methyl)benzene (**1a**) as a model substrate and TMEDA as base in dichloromethane solvent.[13] Encouragingly, the decomposition of α-azidoperoxide gave the formation of *tert*-butyl benzoate (**2a**) as the major product, and benzoylazide (**3**) was formed as the minor product. The reaction shows a highly chemoselective "O−O" bond breaking (over "N−N_2" bond), which drives such rearrangements to occur. We began optimization of the reaction conditions using different bases and solvents at 0 °C as shown in Table 1. We found that ethyl

Table 1. Optimization of the Reaction Conditions



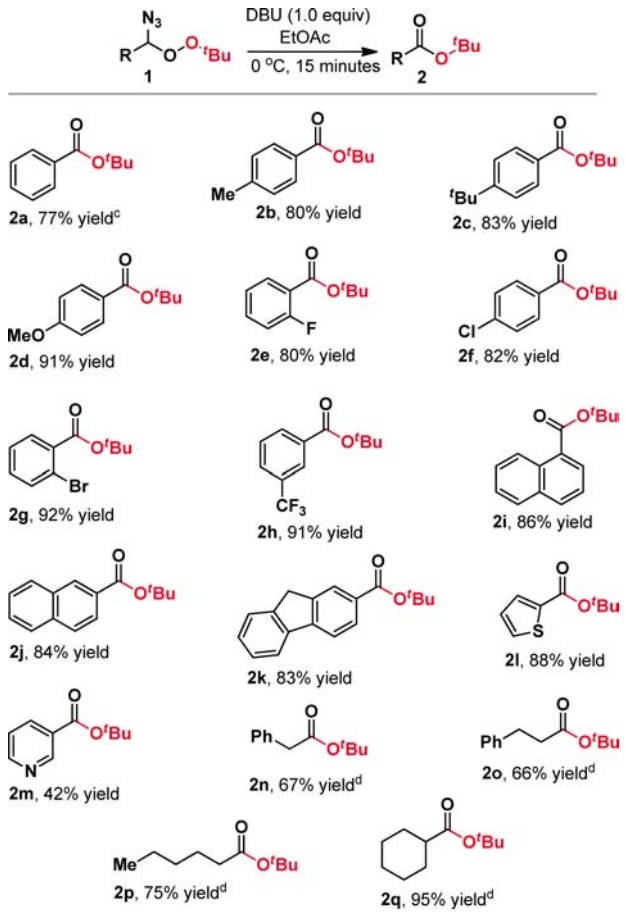
entry	base	solvent	2a[a] (%)	2a:3[b]
1	TMEDA	CH_2Cl_2	68	1:0.21
2	TMEDA	toluene	62	1:0.21
3	TMEDA	EtOAc	71	1:0.16
4	NEt_3	EtOAc	57	1:0.17
5	*i*-Pr_2EtN	EtOAc	18	1:0.40
6	pyridine	EtOAc	1	1:10.0
7	**DBU**	**EtOAc**	**83** (77)[c]	**1:0.12**
8	DBU	CH_2Cl_2	60	1:0.34
7	DBU	toluene	72	1:0.12
8	DBU	THF	66	1:0.12
9	DBU	CH_3CN	38	1:0.59
10	DBU	1,4-dioxane	72	1:0.08

[a]^{1}H NMR yield of the reaction mixture using DMSO as an internal standard. [b]Ratios were determined using ^{1}H NMR of the reaction mixture. [c]Yields (in parentheses) after column chromatography.

acetate was the superior solvent in the presence of TMEDA as base (entries 1−3). Then several organic bases were used, and DBU was found to be the best in terms of selectivity as well as yield of *tert*-butyl benzoate (**2a**). All these reactions were found to be completed within 15 min at 0 °C. We then began carrying out the reaction in different solvents (entries 7−10), taking DBU as the suitable base. Changing the solvent to dichloromethane, toluene, THF, acetonitrile, and 1,4-dioxane led to a decrease in the yields of the reaction. Finally, the optimum reaction conditions were determined as the combination of DBU (1 equiv) as base and ethyl acetate as solvent at 0 °C.

Having optimized the reaction conditions, we extended the esterification to a variety of α-azidoperoxides to synthesize *tert*-butyl esters. As shown in Scheme 3, aryl esters (**2a−h**) containing electron-donating and electron-withdrawing functional groups were synthesized with excellent yields. Azidoperoxides with electron-rich substituents like methyl, *tert*-butyl, and methoxy reacted smoothly to provide the corresponding esters

Scheme 3. Scope of Azidoperoxides for *tert*-Butyl Ester Synthesis[a,b]



[a]Azidoperoxide (**1**, 1.0 mmol) and DBU (1.0 mmol) in EtOAc at 0 °C, stirred for 15 min. [b]Isolated yield after column chromatography. [c]Compound has low boiling point.[14] [d]Reaction was carried out at room temperature for 3 h for the aliphatic α-azidoperoxides **1n−q**.

(**2b−d**). Yields of the reaction were not affected when esters containing electron-withdrawing functional groups like fluoro, chloro, bromo, or trifluoromethyl were used (**2e−h**). Azidoperoxides prepared from naphthaldehyde and fluorene carboxaldehyde reacted even smoothly to furnish the desired esters (**2j** and **2k**, respectively). Esterification of heteroaromatic azidoperoxides are equally effective for the current process (**2l** and **2m**). Notably, a wide range of alkyl α-azidoperoxides efficiently undergo such base-promoted rearrangement under optimized conditions (**2n−q**). In contrast to the known method, our metal-free method provides a novel range of substrates that complements existing metal-catalyzed methods.

After successful synthesis of *tert*-butyl esters from azido peroxides, a one-pot, sequential azidoperoxidation of aldehydes followed by decomposition was carried out to furnish the *tert*-butyl esters (Scheme 4). Aromatic, heteroaromatic, and aliphatic *tert*-butyl esters were synthesized at room temperature with moderate to good yields.

After successful synthesis of tertiary butyl esters, we turned our attention to investigate the applicability of primary and secondary alkyl-protected azidoperoxides in this transformation, and the results are summarized in Scheme 5. The ethyl-protected peroxide (**1r**) afforded the corresponding ester (**2r**) in good yield. Similarly, the isopropyl ester (**2s**) was obtained from the

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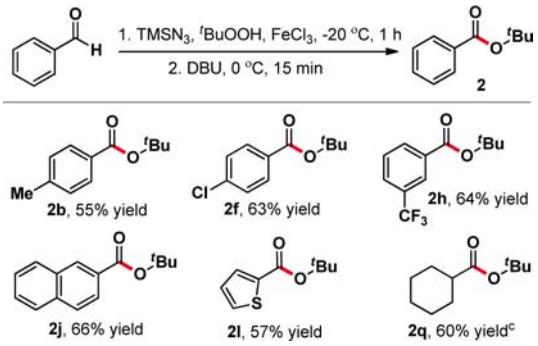
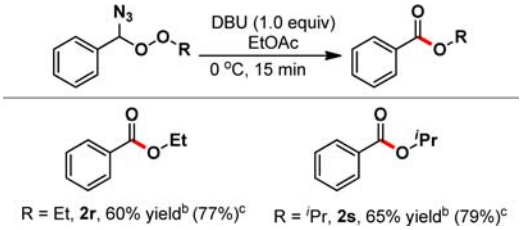
Scheme 4. Synthesis of *tert*-Butyl Esters from Aldehydes[a,b]



[a]Step 1: Aldehyde (1.0 mmol), $TMSN_3$ (2.5 equiv), ^{t}BuOOH (5.5 [M] in decane, 1.0 equiv), and $FeCl_3$ (10 mol %) in anhydrous dichloromethane at −20 °C stirred for 1 h, then $FeCl_3$ was filtered. Step 2: Reaction mixture and DBU (1.0 equiv) in EtOAc at 0 °C, stirred for 15 min. [b]Isolated yield after column chromatography. [c]Reaction was carried out at room temperature for 12 h in the second step for the aliphatic ester **2q**.

Scheme 5. Synthesis of Primary and Secondary Alkylesters.[a]



[a]Isolated yield after column chromatography. [b]Compounds have low boiling point.[15] [c]The yields based on the ^{1}H NMR spectroscopy of the reaction mixture using anisole as an internal standard are shown in parentheses.

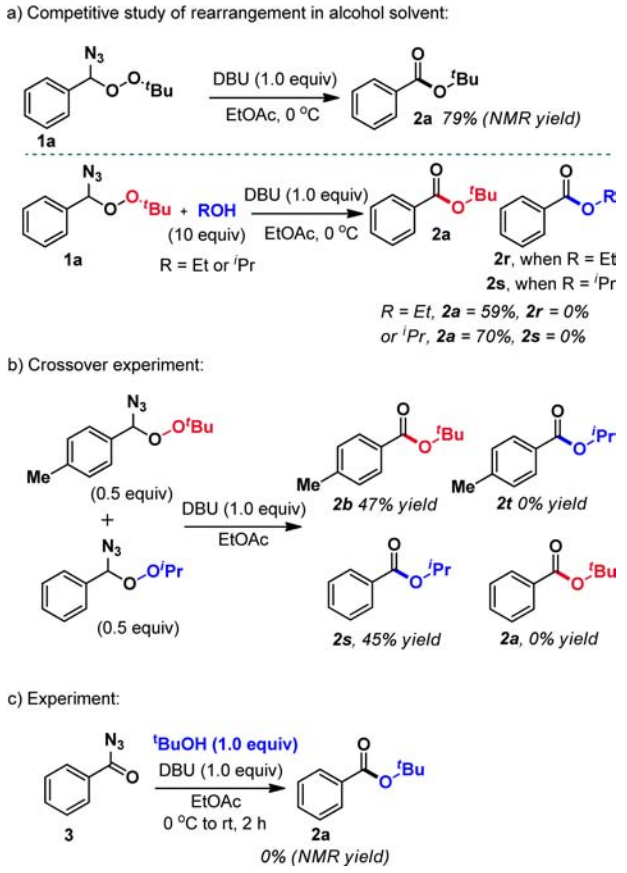
corresponding azidoperoxide (**1s**). The relative lower yields are assigned due to the volatility of these esters.[15]

To gain insight into the reaction mechanism and to establish the intramolecular nature of the reaction, a competitive study was performed as shown in Scheme 6a. α-Azidoperoxide (**1a**) was treated in the presence of 10 equiv of ethanol and 2-propanol in separate reactions maintaining the standard reaction conditions. If the reaction is intermolecular, then ethyl benzoate (**2r**) and isopropyl benzoate (**2s**) should be formed through intermolecular alkoxy transfer from ethanol or 2-propanol, respectively. However, there was no trace of ethyl benzoate or isopropyl benzoate in the reaction mixture as observed on the basis of the ^{1}H NMR studies of the reaction mixture (see the Supporting Information). Instead, tertiary benzoate (**2a**) was obtained in 59% and 70% yields for the respective reactions. These results indicate an intramolecular 1,2-migration of the alkoxy group in the α-azidoperoxide (**1a**).

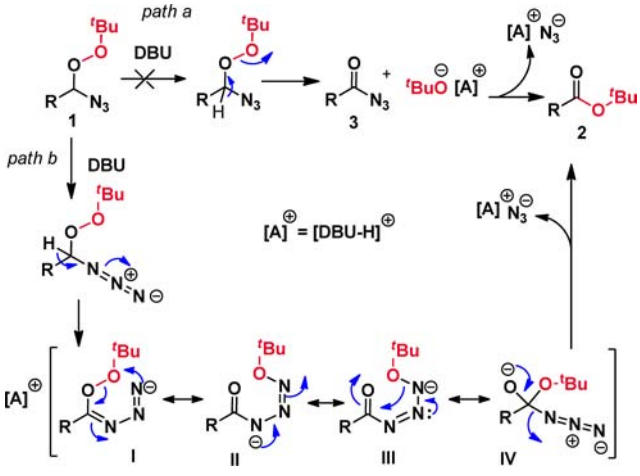
Further, a crossover experiment was followed to confirm the intramolecularity of these reactions as shown in Scheme 6b. Azidoperoxides (**1b**) bearing *tert*-butyl peroxide and **1s** bearing isopropyl peroxide were mixed and treated with 1.0 equiv of DBU. As expected, no cross product (e.g., **2t** and **2a**, respectively) was observed in the respective reaction mixture.

Based on the results of our preliminary mechanistic investigations and recently reported denitrogen of azide,[16] we propose a reaction mechanism as depicted in Scheme 7. Potentialy, there could be two possible paths for the current

Scheme 6. NMR Study for the Investigation of Reaction Mechanism



Scheme 7. Proposed Reaction Mechanism



ester synthesis via base-promoted decompostion of α-azidoperoxides. Abstraction of α-hydrogen of the azidoperoxide leads to the direct decomposition of the peroxide bond, which provides acylazide (**3**) and alkoxide ion (path a). Further, the exchange of azide moiety of **3** with alkoxide ion generates the esters. On the other hand, abstraction of α-hydrogen of the azidoperoxide leads to a resonance-stabilized intermediate **I** (path b). Then, an intramolecular 1,2-alkoxy migration of **I**, via the peroxide bond breakage, followed by cleavage of the C−N bond (intermediate **IV**) affords the desired ester. However, on the basis of the control studies, it is probably going through the latter path.

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In conclusion, we have developed an unprecedented intramolecular rearrangement of α-azidoperoxides for the synthesis of esters. Esters of primary, secondary, and most importantly tertiary alcohols can be generated starting from the corresponding α-azidoperoxides. Further, a one-pot methodology for the synthesis of *tert*-butyl esters from the corresponding aldehydes has also been developed. This provides an alternative approach to the synthesis of *tert*-butyl ester. Preliminary mechanistic investigations revealed that intramolecular alkoxy transfer occurs. Further investigations and applications of these unusual rearrangements are being actively pursued in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra for all products. 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.

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