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COMMUNICATION

α-Amination of keto-nitrones *via* Multihetero-Cope rearrangement employing an imidoyl chloride reagent†

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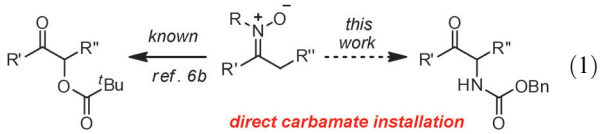
α-Aminations of ketone-derived nitrones have been developed *via* [3,3]-rearrangement of the intermediates generated upon condensation with imidoyl chlorides. Careful reagent selection provides synthetically attractive amino protecting groups. The enediamide or α′-carbamoyl enamide products can be hydrolyzed to the desired carbonyl, or exposed to electrophiles for further α-functionalization.

α-Amino carbonyls are ubiquitous in organic chemistry. Creation of this functional group *via* C_α–N bond construction is a central challenge in organic synthesis that has received considerable attention in the literature.[1] The electrophilic α-amination of enolates and their equivalents is in principle a direct, efficient method for α-amino carbonyl synthesis and significant work on this problem has been reported. Azodicarboxylates are especially prominent N(+)-sources that have been widely and effectively applied to this reaction, including asymmetric variants,[2] but come with several drawbacks. Atom inefficiency, explosion hazard,[3] and typically harsh or multistep deprotection protocols to reveal the amine somewhat counterbalance the favourable reactivity profile. Thus, an argument can be made that an important but often-overlooked component of the electrophilic α-amination problem lies in the "packaging" of the amine product. Previous studies by our group made use of a weak N–O bond for electrophilic amination methodology,[4] and we questioned whether this tactic could be harnessed to provide convenient nitrogen protecting groups (*e.g.* Boc, Fmoc, Cbz) concomitantly upon α-amination. The purpose of this communication is to report a [3,3]-rearrangement of imidoyl nitrones providing α-amination products with synthetically-attractive amino protecting groups.

[3,3]-Sigmatropic rearrangements are important reactions for the reliable introduction of various functionality in complex settings.[5] Multihetero-[3,3]-rearrangements, such as those of *N*-alkyl-*N*-acetoxyenamines, are an important subclass.[6] Coates and Cummins were the first to develop this rearrangement as a method for α-functionalization: treatment of *N*-^{t}Bu nitrones with acyl chlorides provide α-acyloxy carbonyls (eqn (1)).[6b]

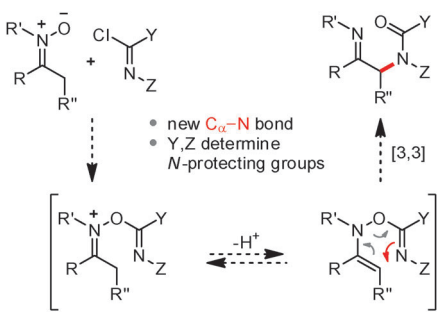
Extension of this strategy to achieve α-amination has been scarcely pursued. The use of an imidoyl chloride rather than an acyl chloride in the condensation with a keto-nitrone afforded α-amido ketone products in two preliminary investigations.[7] The imidoyl electrophiles used (Y, Z = Ph *or* Y = Ph, Z = Me (Scheme 1)) provided *N*-Ph/Me-benzoylamino products that would be difficult to convert to the free α-amino ketones.



(1)

In formulating a reaction design for an α-amination that proceeds with concurrent generation of synthetically-attractive protecting groups, we envisioned that a [3,3]-rearrangement involving an appropriately functionalized imidoyl chloride reagent could be useful (Scheme 1). Herein, we disclose an α-amination protocol for keto-nitrone substrates *via* [3,3]-rearrangement. The α-amino products obtained are conveniently configured as benzyl carbamates (NH–Cbz). An unexpected deprotonation event occurs with acyl migration to furnish enediamide or α′-carbamoyl enamide products dependent on the α-proton availability on the nitrone substrate (*vide infra*).

The requisite keto-nitrones were prepared *via* hydroxylamine/ketone condensation.[8] A variety of enolizable ketones were employed with aryl, alkyl, and cyclic substrates providing varied yields (13–88%) of nitrone product.[9] These compounds are stable to SiO_2 chromatography and can be stored in a freezer indefinitely. The Cbz-protected trifluoromethyl imidoyl chloride **1** was synthesized *via* the published two step route.[10]



Scheme 1 α-Amination *via* multiheteroatom [3,3]-rearrangement.

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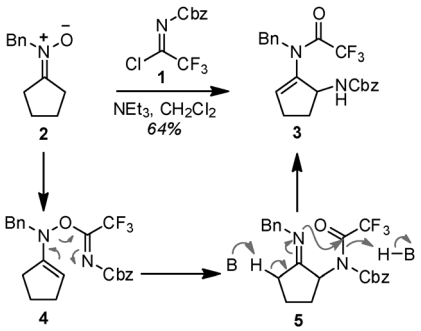
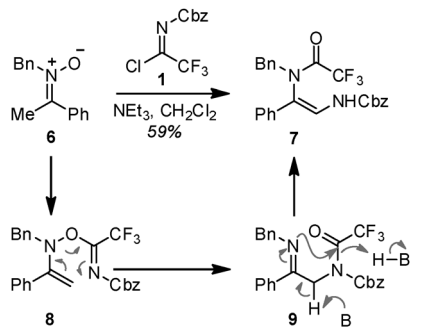


Scheme 2 Initial result and proposed mechanism.

The reaction of cyclopentanone-derived nitrone **2** and the imidoyl chloride **1** in the presence of Et_3N at 0 °C led to rapid and complete reagent consumption. Analysis of the crude reaction mixture showed formation of an α′-carbamoyl enamide product (**3**), rather than the anticipated α-amino imine or ketone (Scheme 2). This was rationalized *ex post facto* by a 1,4-trifluoroacetyl migration/proton transfer[6a] of the initial [3,3]-imine product (**5** → **3**, Scheme 2). At this time it is unclear whether the system is under kinetic or thermodynamic control, although the formation of α′-carbamoyl enamide products (deprotonation at the less-hindered site) suggests a kinetic scenario. Equimolar quantities of nitrone and reagent **1** treated with 2.0 equiv. triethylamine provided the optimal results for this transformation when run in CH_2Cl_2 at 0 °C. The reaction was usually complete within 30 min.

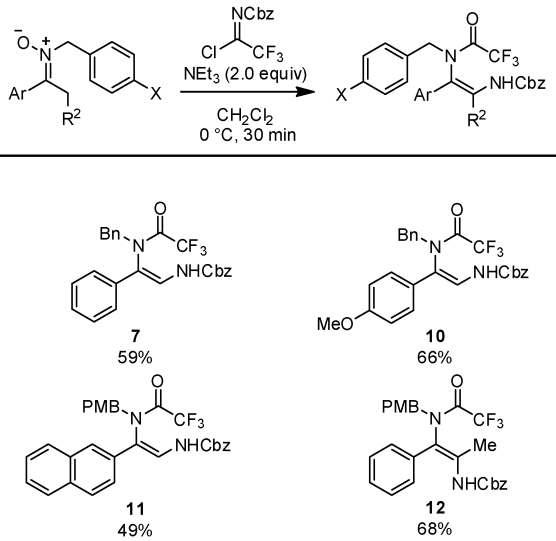
A divergence in reactivity was observed when acetophenone-derived nitrone **6** was subjected to identical conditions. In the absence of an α′-enolizable proton, terminal deprotonation occurred at the α-site furnishing the enediamide product (**9** → **7**, Scheme 3).

With optimized conditions in hand and two product classes identified, we explored the scope of the [3,3]-rearrangement/α-amination. Nitrones derived from acetophenone derivatives provided moderate yields ranging from 49–66% (**7**, **10–12**, Table 1). The enediamide moiety was formed exclusively in the (*Z*)-configuration. When a propiophenone-derived nitrone was used, the product geometry was reversed (**12**), presumably due to increased $A^{1,3}$-strain introduced by the methyl substituent (*vs.* –H). Cyclic nitrones also performed well in the [3,3]-rearrangement (Table 2). Cyclopentyl and cyclohexyl substrates provided α′-carbamoyl enamides in 64–78% yields (**3**, **13–16**). The use of a 4-^{t}Bu-cyclohexanone derived nitrone decreased the yield and provided minimal diastereoselectivity (**17**).



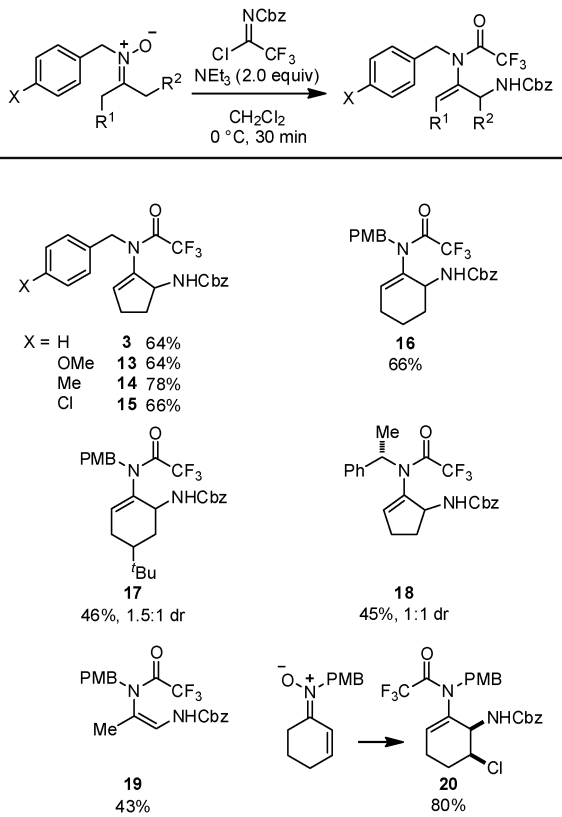
Scheme 3 Divergent reactivity with aryl nitrone.

Table 1 Aryl nitrone scope[a,b,c]



[a] All reactions: $[\mathbf{1}]_0$ = 0.1 M. [b] Yields of isolated products. [c] See Supporting Information for more details.

Table 2 Cyclic/alkyl nitrone scope[a,b,c]



[a] All reactions: $[\mathbf{1}]_0$ = 0.1 M. [b] Yields of isolated products; dr determined by ^{1}H NMR spectroscopy. [c] See Supporting Information for more details.

The nitrone *N*-benzyl protecting group was varied, using the cyclopentyl core as a model. Several substituted benzyl nitrones were examined, with the tolyl group providing the highest yield (**14**). A chiral nitrone derived from (*S*)-α-methyl

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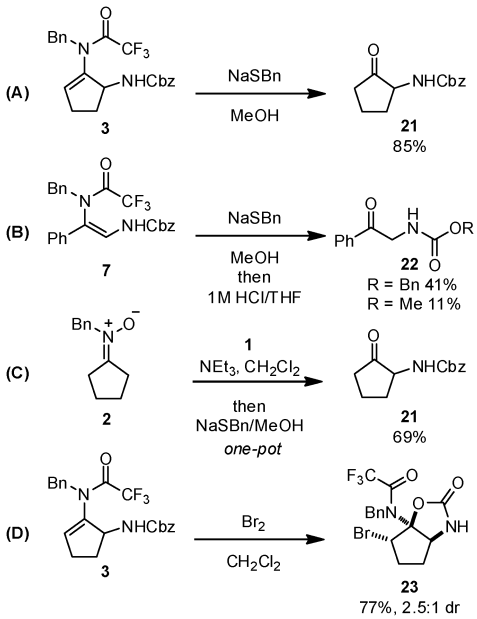

Scheme 4 Secondary transformations.

benzylamine was synthesized and tested,[11] but chirality transfer was poor (**18**).

The acetone-derived nitrone provided the enediamide **19** rather than the isomeric α′-carbamoyl enamide. In this case and other examples reported with diminished yields, competing reactions producing unknown byproducts account for the mass balance. The cyclohexenone-derived nitrone displayed unique reactivity wherein the chloride byproduct was incorporated yielding *cis*-β′-chloro-α′-carbamoyl enamide **20**.

Both the enediamide and α′-carbamoyl enamide products are resistant to hydrolysis and survive acidic or basic aqueous workup; however, after extensive screening of conditions, basic hydrolysis was realized upon treatment with freshly prepared sodium benzylthiolate in MeOH. Subjecting the enamide **3** to these conditions cleanly provided the Cbz-protected α-amino ketone **21** in 85% yield (**A**, Scheme 4). Enediamide product **7** was also hydrolyzed upon thiolate exposure and subsequent acidic workup. In this case, partial tranesterification occurred providing the methoxy-carbamyl protected α-amino ketone as a minor product (**B**, Scheme 4). A one-pot procedure taking nitrone starting material directly to the Cbz-protected α-amino ketone **21** was also realized by treating the crude reaction product from the [3,3]-α-amination with NaSBn/MeOH. This sequence resulted in a yield of 69%, significantly higher than the analogous two-step process (**C**, Scheme 4).

The enamide in both product classes provides opportunities for further α-functionalization. Exposure of enamide **3** to Br_2 provided hemiaminal oxazolidinone **23** from bromination-debenzylation (**D**, Scheme 4).

In conclusion, we have developed an α-amination of keto-nitrones *via* multiheteroatom-[3,3]-rearrangement. This reaction provides enediamide or α′-carbamoyl enamide products based on the enolizable sites on the substrates employed. Upon basic hydrolysis, carbonyl functionality may be revealed providing a new method for carbonyl α-amination. Ongoing studies in our laboratory are focused on extending this method to aldo-nitrones and development of an asymmetric variant.

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