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Cerium(IV) Ammonium Nitrate Mediated Three-Component α-Allylation of Imine Surrogates

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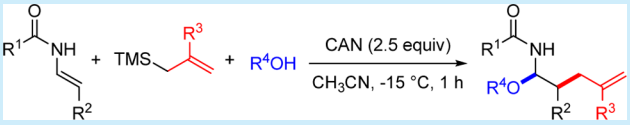
Supporting Information

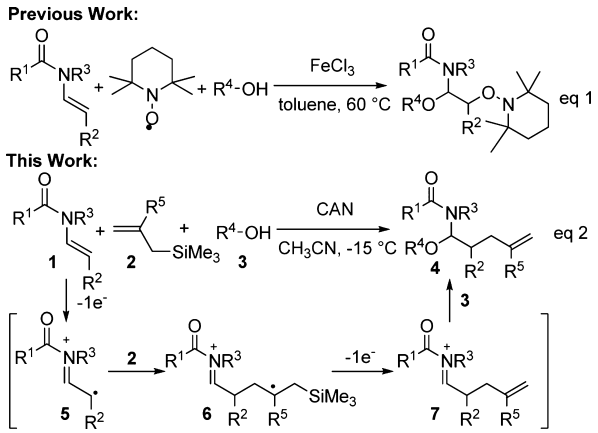
ABSTRACT: A general and practical CAN-mediated oxidative radical α-coupling reaction of various imine surrogates with allylsilanes has been described. This multicomponent process affords β-allylated α-carbamido ethers as stable imine precursors in respectable yields under mild conditions.



N-Carbamoyl α-allylated imine is a privileged chemical scaffold that is found in nitrogen-containing natural compounds such as spirolides, pinnatoxins, pteriatoxins, nodimines, and spiroprorocentrimines.[1] In addition, since *N*-carbamoylimines can be employed in various transformations, they are valuable as versatile synthetic intermediates for the preparation of β-allylated α-substituted amines.[2] However, despite their importance, few efficient syntheses exist in the literature. Mainly because of their inherent instability (hydrolysis, imine−enamine tautomerization), the traditional methods through condensation of aldehydes and carbamates were not well suited to their preparation.[3] The indirect approach based on the α-allylation of imines[4,5] or β-allylation of enamines[6] was not successful. Therefore, development of a simple and efficient method for the synthesis of *N*-carbamoyl α-allylated imine is highly desirable. In continuation of our interest in the α-alkylation of imines from stable and valuable enecarbamates,[7,8] we envisaged that a β-umpolung addition of enecarbamates to allylic nucleophiles might provide an effective alternative approach to access these α-allylimines. Here, we describe a novel α-allylation of imines which is achieved through cerium ammonium nitrate (CAN) mediated direct allylation of enecarbamates involving a radical-cationic domino process.[7,9]

In the past decades, extensive efforts have been devoted to the development of efficient oxidative[10] α-allylation of 1,3-dicarbonyls[11] and carbonyls.[12,13b] In this field, MacMillan et al.[13] have developed a direct and enantioselective α-allylation of carbonyls via singly occupied molecular orbital (SOMO) catalysis.[13,15] This approach involves a one-electron oxidation of a catalytically generated chiral enamine[14] that reacts with an allylsilane.[13] Based on our previous work concerning the $FeCl_3$-catalyzed enantioselective α-oxyamination of enecarbamates (Scheme 1, eq 1),[7a] and inspired by seminal work by Thomson[12] and MacMillan,[13,15,16] we hypothesized that oxidative radical reaction of enecarbamates would enable to access to a range of α-allylated imines (Scheme 1, eq 2).[14,17] Indeed, a well-selected oxidant should be able to initiate the single-electron transfer (SET) oxidation of enecarbamate **1** to generate the electron-deficient radical cation **5** (Scheme 1, eq 2).[18] Trapping of this intermediate by an appropriate allylsilane radicophile **2** could give rise to a new radical **6**, while a second

Scheme 1. Oxidative Three-Component Reaction of Enecarbamates[6a] and Rational Design for α-Allylation of Carbamoylimines



oxidation and a subsequent elimination of the silyl group could afford the desired *N*-carbamoyl α-allylated iminium **7**. Then, the alcohol **3** present in the reaction media would react with **7** to furnish β-allylated α-amido ether **4** as a stable precursor of **7**.[7,19]

To realize a three-component radical/ionic domino process,[7,9] some intrinsic problems might be encountered. Indeed, a strong oxidant with high single-electron transfer should be used to oxidize selectively the enecarbamate **1**[20] without touching the allylsilane **2**[21] and alcohol **3**. Following our previous work on the $FeCl_3$-catalyzed oxidative process,[7a,22] we initially examined the reaction of (*E*)-propenylbenzylcarbamate (**1a**), allyltrimethylsilane (**2a**), and ethanol (**3a**) with $FeCl_3$ as the oxidant (Table 1). Unfortunately, no reaction took place even with 2 equiv of $FeCl_3$ **8** in the presence of $NaNO_2$ and O_2 (entries 1 and 2). Since the oxidation potential of cerium(IV) is higher, we next examined ceric ammonium nitrate (CAN, **9**) as oxidant in our system.[23,24] Detailed mechanistic analysis of

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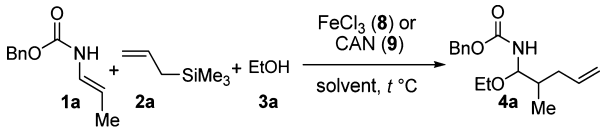
Table 1. Survey of Reaction Conditions for the CAN-Promoted Three-Component Radical/Cationic Reaction



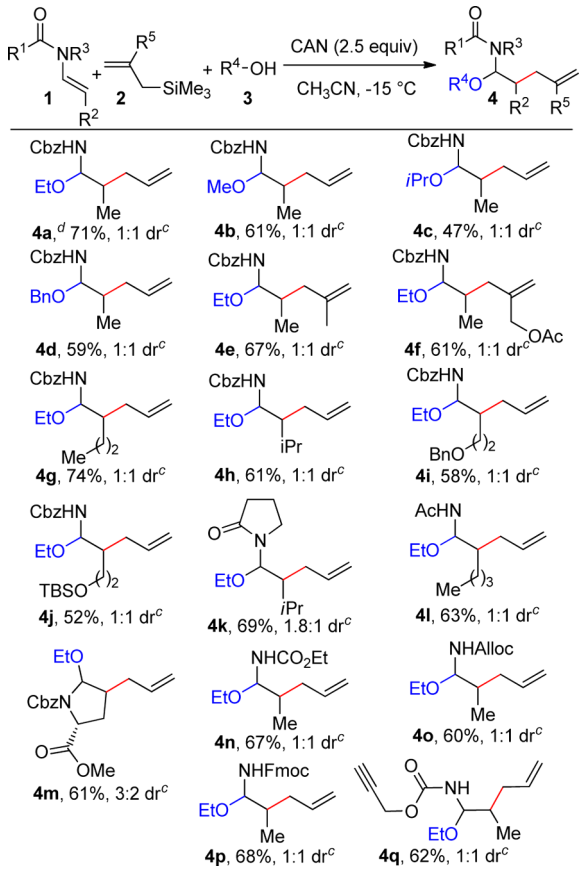
entry	Ox (x equiv)	solvent	temp (°C)	2a (x equiv)	3a (x equiv)	yield[a,b] (%)
1	**8** (0.3)	MeCN	60	3	15	*c*
2	**8** (2)	MeCN	60	3	15	*c*
3	**9** (3)	MeCN	20	3	15	*d*
4	**9** (3)	MeCN	0	3	15	63[e]
5	**9** (2.5)	MeCN	−15	3	15	65[e,f]
6	**9** (2.5)	MeCN	−30	3	15	64[e]
7	**9** (3)	MeCN	0	3		*c,e*
8	**9** (2.5)	MeCN	−15	1.5	15	20[e]
9	**9** (2)	MeCN	−15	3	15	54[e]
10	**9** (2.5)	EtOH	−15	3	15	28[e,g]
11	**9** (2.5)	DME	−15	3	15	27[e]
12	**9** (2.5)	toluene	−15	3	15	<5[e]
13	**9** (2.5)	DMF	−15	3	15	<5[e]

[a]Reaction conditions: enecarbamate (**1a**) (0.1 mmol), **2a**, **3**, and **8** or **9**, c = 0.1 M. [b]Isolated yield after column chromatography. [c]**1a** was recovered. [d]Benzylcarbamate, polymer, and benzyl(ethoxypropyl)-carbamate were isolated. [e]A solution of **1a** in 1 mL of solvent was slowly added over 1 h to a solution of **2a**, **3a**, and **9** in 1 mL of solvent. [f]With 0.1 or 5 mmol of **1a**. [g]Benzyl(ethoxypropyl)carbamate was also isolated.

CAN-promoted enantioselective α-alkylation of aldehydes[16] showed that the presence of H_2O[13,15] was vital to reach excellent activity in promoting the solubility of CAN. As such, the amount of alcohol could be beneficial to the oxidative process envisaged. However, our first attempts were largely unsuccessful (Table 1, entry 3), giving mainly products derived from direct degradation, polymerization, and isomerization of **1a**. This suggested that the CAN acts more as a Lewis acid catalyst than an oxidant. To overcome this issue, one must ensure that the oxidation can occur before the side reactions of **1a**. One way to do this is to add slowly the enecarbamate to a solution containing allylsilane, EtOH, and CAN in CH_3CN, guaranteeing that a small amount of **1** is exposed to oxidant.[25] Indeed, this experimental condition afforded the β-allyl α-carbamoyl ether **4a** as a 1:1 mixture of diastereomers in decent yield (Table 1, entry 4). Although no significant improvement of yield was observed below 0 °C (Table 1, entries 5 and 6), the temperature of −15 °C was kept for the rest of our optimization. Then, a series of individual reactions was carried out with different amounts of allylsilane **2a**, CAN **9**, and ethanol (**3a**), as well as various solvents (Table 1, entries 8−13). The best results were obtained using 2.5 equiv of CAN and 3 equiv of **2a** in CH_3CN (entry 5). It should be pointed out that no reaction took place in the absence of ethanol, and only starting materials were recovered (entry 7). This seems to confirm our assumption that the role of ethanol is not limited to trap the iminium but also increases the solubility of CAN via the formation of the ate complex.[16] Finally, scale up proved to be straightforward; product **4a** was prepared on a 5 mmol scale in the same yield as reported with a 0.1 mmol scale (entry 5).

With optimal conditions in hand, we next investigated the scope of the reaction with representative alcohols and allylic radicophiles. In all cases, the β-allylated α-amidoethers **4a−f** were obtained in acceptable yields (Scheme 2). Aliphatic alcohols with different steric properties such as methanol (**3b**)

Scheme 2. CAN-Catalyzed α-Allylation of Enamide Derivatives



[a]Reaction conditions: enecarbamate (**1**) (0.2 mmol), allylsilane (**2**) (0.6 mmol), CAN (0.50 mmol), **3** (3.0 mmol), c = 0.10 M at −15 °C. [b]Isolated yield after column chromatography. [d]dr determined by ^{1}H NMR analysis of the crude mixtures. [e]With allylstannane (**2b**).

and 2-propanol (**3c**) participated in the reaction, albeit the latter one gave a relatively lower yield (Scheme 2, **4b** and **4c**). In addition, the benzyl alcohol (**3d**), which is known to be sensitive toward oxidation,[26] was successfully engaged in this three-component radical/cationic process. When the allylstannane (**2b**)[27] was used instead of **2a**, the desired product **4a** was isolated with a slightly better yield. Allylsilanes with alkyl substituents at the β-carbon reacted well with **1a** to give the corresponding branched β-allyl α-carbamoyl ethers **4e** and **4f** in 67 and 61% yield, respectively. The reaction scope was also examined with respect to the enecarbamates. Various enecarbamates and enamides bearing linear or branched alkyl chains were all compatible leading to the respective α-allylated imine precursors **4g−q** in good yields (Scheme 2). Since hydrogenolysis of *N*-Cbz-protected aminoethers seems tricky without touching double bonds, other carbamate protecting groups were tested in this radical/ionic process. As described in Scheme 2, ethyl, propargyl, allyl, or 9-fluorenylmethyl carbamates afforded allylated products **4n−q** in respectable yields, providing an access to orthogonally protected homoallyl amines.[28b] Moreover, we were pleased to observe a high degree of functional group tolerance under these conditions. In fact,

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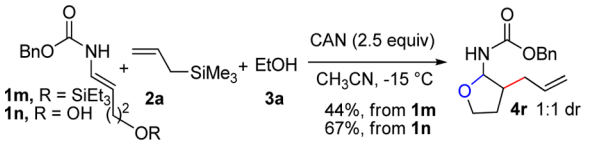
various acid- or oxidation-labile groups such as benzyl ether (**4i**) and silyl ether (**4j**) remained intact during the reaction, further highlighting the mildness of this method.[26,29] Nonetheless, more labile silane functional groups such as TES-protected enecarbamate **1m** underwent the desired β-allylation with a concomitant deprotection and cyclization in spite of the large excess of ethanol used in the process (Scheme 3).[30] The

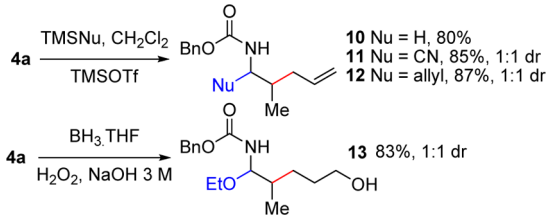
Scheme 3. Synthesis of β-Allyl α-Aminotetrahydrofurans



same product was isolated in a better yield when the unprotected alcohol **1n** was employed instead. This provides a rapid access to β-allyl α-aminotetrahydrofuran **4r**, an important intermediate in the synthesis of furoindolines.[31] It is also noteworthy that the terminal double and triple bonds were untouched in the CAN-promoted allylation (Scheme 2, **4o** and **4q**). We found that the reaction of tertiary cyclic or acyclic enamides afforded products **4m** and **4k**, respectively, in slightly better yields. Finally, the β-substituted enantiopur enecarbamate **4m** was successfully engaged in this oxidative process yielding to a 3:2 mixture of diastereomers in 61% yield.

To demonstrate the synthetic utility of the resulting β-allylated α-amidoethers, **4a** was converted into four common functional groups, showing the versatility of our imines precursors (Scheme 4). Reduction using triethylsilane and

Scheme 4. Synthetic Transformations of β-Allylated α-Amido Ethers 4



TMSOTf as acid to trigger the formation of *N*-acyliminium intermediate resulted in 80% yield of **11**. The cyanation and allylation of **4a** could be also carried out using Lewis acid to afford the β-allylated α-amidonitrile **11** and α–β-allylated **12**, respectively. This terminal olefin is ideally placed for various metal-catalyzed aminations[32] and can also serve as an anchorage point for selective transformations.[28] As illustration in Scheme 4, a hydroboration/oxidation reaction was performed, thus offering easy access to valuable 1,5-heptanolamine in acceptable yield.[33]

In summary, we have developed an approach toward the synthesis of highly functionalized β-allyl α-carbamoyl-ether derivatives via a CAN-mediated intermolecular allylation/intermolecular hemiaminalization reaction. The scope of this process shows wide tolerance of functional groups on the enecarbamates and on the allylsilane derivatives. The ready accessibility of the *N*-carbamoyl α-allylated imines makes the current methodology particularly attractive in organic synthesis.[1,2] Further work to use this oxidative radical β-allylation of enecarbamates for the synthesis of natural products is ongoing, and this work will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all new compounds are provided. 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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