



Intermolecular sp^3 C–H bond functionalization of alkyl amides as a new method for the one-pot synthesis of functional neo alkyl amides with remote functional groups



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ABSTRACT

The one-pot, regioselective, remote functionalization of amides of octanoic acid [$R_2NCOC_7H_{15}$, $NR_2 = NH_2$, NEt_2 , NC_4H_8O , (morpholinyl)] via Csp^3 –H bond cleavage with CO and various nucleophiles (EtOH, i PrOH, CF_3CH_2OH , $H(CF_2)_2CH_2OH$, $C_8H_{17}SH$, Et_2NH , morpholine, furan, thiophene, and anisole) in the presence of the superelectrophilic complex, $CBr_4 \cdot 2AlBr_3$ has been performed for the first time. This methodology provides access to new synthetically challenging and promising derivatives of amides with remote functional groups of *neo*-structure. The oxidative cyclization of octanamide into a six-membered cyclic amide with the C(Me)Et group adjacent to the heteroatom using $CBr_4 \cdot 2AlBr_3$ has been demonstrated.

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Selective, one-pot, sp^3 C–H bond functionalization of an alkane unit in readily available organic compounds opens the exciting possibility for the synthesis of bifunctional compounds.^{1,2} Studies on this topic have been very active in organic chemistry over the last decade.³ Most of them are based on the applications of transition metal compounds and radical systems. In contrast, examples of intermolecular functionalization of sp^3 C–H bonds in organic compounds by superelectrophiles in the absence of transition metal compounds or radical agents are rare.^{4–11}

There are considerable distinctions between the mechanisms and product structures in the case of sp^3 C–H functionalizations initiated by different types of systems. Metal-initiating systems, as a rule, initiate the formation of linear products with a new functionality adjacent to the original functional group (the so-called 'nearest', 'adjacent' or ' α -functionalization'),³ while bifunctional products of *neo*- or tertiary structures with remote functional groups are formed in superelectrophilic reactions.^{4,5} Olah and co-workers were the first to report the hydroxylation reactions of primary alcohols containing secondary C–H bonds at the γ or a more remote position from the oxonium center, as well as higher homologs of aldehydes and ketones with ozone using FSO_3H – SbF_5 (magic acid) in SO_2ClF .⁴ Yoneda et al.⁵ found that methyl isoalkyl ketones (but not linear ketones) containing C–H bonds located at least four carbon atoms from the carbonyl group reacted selec-

tively with CO in the presence of excess HF – SbF_5 superacid resulting in carboxylic acids of *neo*-structure, after hydrolysis.

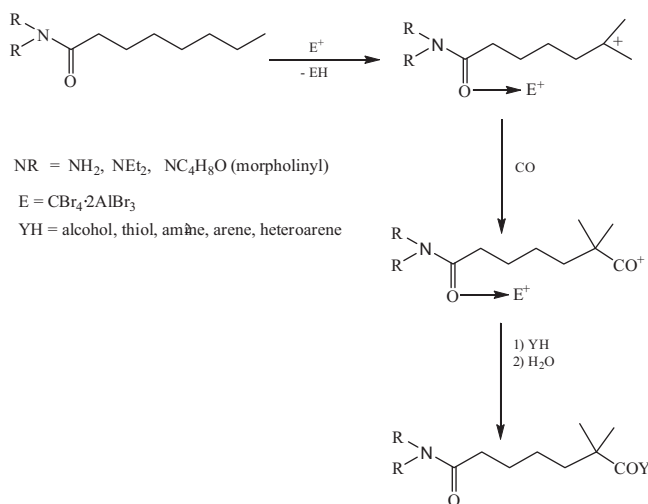
The application of the potent superelectrophilic complexes, $CX_4 \cdot 2AlX_3$ ($X = Br$ or Cl)¹² turned out to be effective for initiating sp^3 C–H cleavage and functionalization.^{6–11} We have found that these complexes, primarily $CBr_4 \cdot 2AlBr_3$, allowed easy generation, not only of carbocations from alkanes,¹³ but also carbocations from monofunctional organic compounds, such as derivatives of adamantanes,⁶ *n*-alkyl acetates,⁷ methyl *n*-alkyl ketones,⁸ and alkyl alkanoates.⁹ In the presence of CO, these cations were converted into the corresponding acyl cations, which, in turn, under the action of nucleophilic substrates, produced monofunctional and bifunctional products, respectively. In this manner, that is, in the presence of $CBr_4 \cdot 2AlBr_3$, the first functionalizations of carbonyl-containing adamantanes,⁶ alkyl acetates,⁷ methyl alkyl ketones,⁸ alkanoates,⁹ and the first bifunctionalization of bromoadamantanes¹⁰ and adamantanes¹¹ have been achieved.

In this Letter, we report the first sp^3 C–H bond functionalization of amides using the superelectrophilic complex, $CBr_4 \cdot 2AlBr_3$.¹²

Amides are an important class of organic compounds in view of their existence in peptides and proteins.¹³ Amides and diamides are widely used in plastics, rubber production, and in other fields.¹⁴ Many amide derivatives also display a broad spectrum of biological activity. For example, morpholine derivatives exhibit antimicrobial, anthelmintic, bactericidal, and insecticidal activity.¹⁵ In addition, amides can easily be converted into valuable amines and nitriles.¹³

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Scheme 1. One-pot functionalization of alkyl amides using CO and different nucleophiles.

We performed the first sp³ C–H bond functionalization of octanoic acid amides with CO and nucleophiles in the presence of CBr₄·2AlBr₃ resulting in bifunctional products with a new functional group remote from the original amide group. At –20 °C under atmospheric CO pressure, and in the presence of a 70–100% molar excess of the superelectrophilic complex, CBr₄·2AlBr₃, carbonylation of amides of octanoic acid, C₇H₁₅CONR₂ [NR₂ = NH₂, NEt₂, NC₄H₈O (morpholinyl)], followed by in situ treatment of the carbonylation products with nucleophilic agents led to the corresponding bifunctional products, as a rule, in good or moderate yields. No products of destructive functionalization, in which the number of carbon atoms in the alkyl group differed from that in the initial amide, were observed (Scheme 1).

At –20 °C and a molar ratio of [E]:[NH₂COC₇H₁₅] = 2:1, functionalization of octanamide (C₇H₁₅CONH₂) by CO and nucleophiles (ⁱPrOH, CF₃CH₂OH, C₈H₁₇SH, C₆H₅OMe, HNEt₂, morpholine, and thiophene) resulted almost exclusively in bifunctional products

of *neo*-structure, in which the functional group was located at the quaternary C atom, being the most distant from the parent carbonyl group (Scheme 2).

The reactions of NH₂COC₇H₁₅ with CO and ⁱPrOH or Et₂NH were not selective. With Et₂NH, besides the target product H₂NCO(CH₂)₄C(CH₃)₂CONEt₂ (**6**, M⁺ = 242), the product of the elimination of water from **6** was also formed (**7**, M⁺ = 224) in a similar quantity. Compounds **6** and **7** were separated by column chromatography (silica gel) using hexane/acetone (2:1) as the eluent. The total yield of **6** and **7** was 50%. The structure of **7** is currently being investigated.

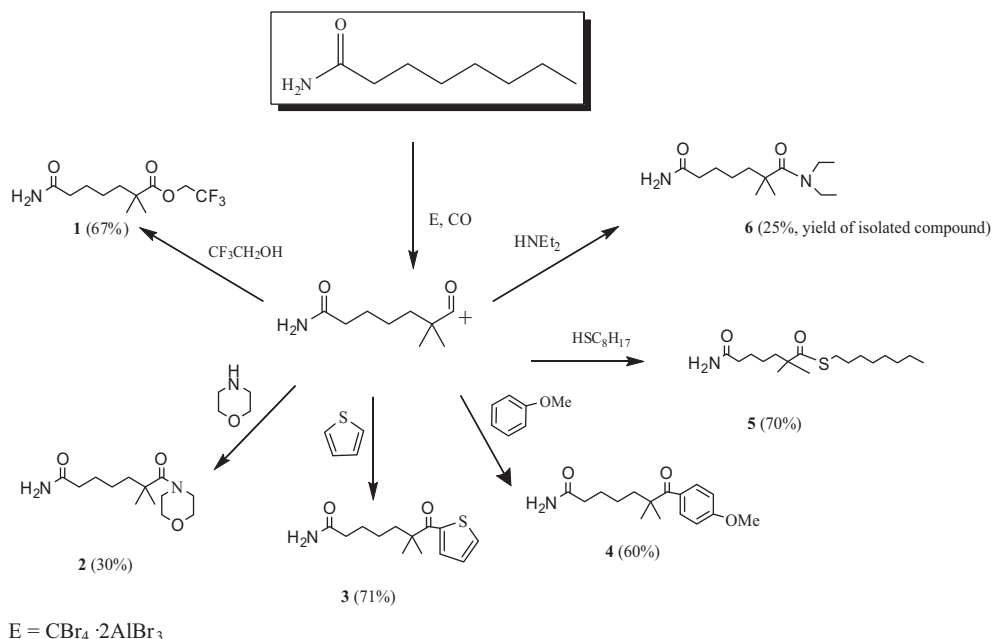
Alongside the target compounds **1–6**, in some reactions, the product of cyclization of the initial amide (**8**) was formed in a small amount. Compound **8** was obtained as the sole product in 56% yield in the reaction of NH₂COC₇H₁₅ with CBr₄·2AlBr₃ at 0 °C with or without CO. A suggested scheme for the formation of **8** involves intramolecular alkylation of the amide group by the generated carbocation followed by elimination of a proton (Scheme 3).

The formation of the most stable six-membered ring is probably the driving force for this reaction.

N,N-Diethyloctanamide also underwent regioselective C–H functionalization with CO and nucleophiles to yield bifunctional products with remote functional groups of the *neo*-structure (Scheme 4). At –20 °C (for 1 or 2 h) or at 0 °C (for 1 h), and a molar ratio of [E]:[Et₂NCOC₇H₁₅] = 2:1, the yields of products **9–14** were high with full conversion of the initial amide. In contrast to the reactions of H₂NCOC₇H₁₅ with HNEt₂ and ⁱPrOH, those with Et₂NCOC₇H₁₅ led to the corresponding target products **10** and **14** in 75% and 51% yields. The functionalization of Et₂NCOC₇H₁₅ with CO and morpholine occurred non-selectively and the product Et₂NCOC₇H₁₄CONC₄H₈O (**15**) was characterized by mass spectrometry only.

Et₂NCOC₇H₁₅ was more active than NH₂COC₇H₁₅. For example, at –20 °C and a molar ratio of [E]:[amide] = 2:1, carbonylation of these amides followed by treatment with CF₃CH₂OH resulted in **12** in 75% yield after one hour, while **1** was formed in 67% yield for 2 h.

Functionalization of the morpholinyl amide of octanoic acid was more difficult than with NH₂COC₇H₁₅ and Et₂NCOC₇H₁₅. Carbonylation at –20 °C over 2 h did not proceed with full amide conversion, in contrast to NH₂COC₇H₁₅ and Et₂NCOC₇H₁₅.



Scheme 2. Products of the one-pot functionalizations of NH₂COC₇H₁₅.

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