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Chemo- and regioselective remote functionalization of nonanamides *via sp*^{3} C–H bond cleavage under superelectrophilic conditions

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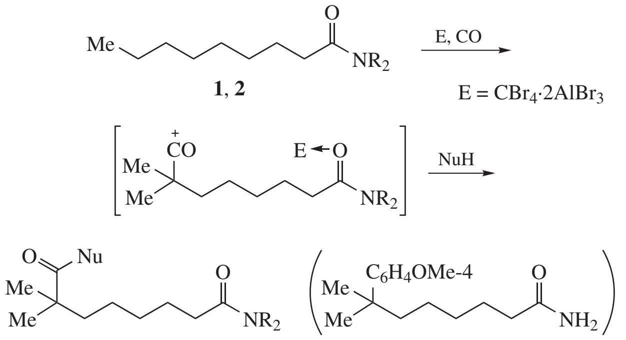
Treatment of nonanamides $C_8H_{17}C(O)NR_2$ (R = H or Et) with superelectrophilic complex $CBr_4 \cdot 2AlBr_3$ under CO atmosphere followed by quenching with nucleophiles NuH cleanly gives 7-methyl-7-(Nu-carbonyl)octanamide bifunctional derivatives.

Selective, one-pot *sp*^{3} C–H bond functionalization of an alkane unit is an important trend of organic synthesis.[1–3] Most of such methods are based on the applications of transition metal compounds and radical systems as initiators. Examples of intermolecular functionalization of *sp*^{3} C–H bonds by superelectrophiles on using proton superacids were limited by two works.[4,5]

The application of the potent superelectrophilic complexes $CX_4 \cdot 2AlX_3$ (X = Br or Cl) turned out to be effective for *sp*^{3} C–H cleavage and functionalization of alkanes[6] and functional organics.[7–11] Such complexes, primarily $CBr_4 \cdot 2AlBr_3$, provided easy oxidative generation of carbocations from alkanes[6] and even from monofunctional organic compounds.[7–12] In the presence of CO, these cations were converted into the corresponding acylium cations which under the action of nucleophilic substrates yielded monofunctional[6] and bifunctional products,[6–12] respectively.

Here we report the first *sp*^{3} C–H bond functionalization of nonanamides $C_8H_{17}C(O)NR_2$ (R = H or Et) **1**, **2** using 100% molar excess of complex $CBr_4 \cdot 2AlBr_3$, carbon monoxide (1 bar, 0 °C) and nucleophiles leading to bifunctional products in good or moderate yields (Scheme 1).[†]

In the case of nonanamide **1** and nucleophiles [EtOH, CF_3CH_2OH, $H(F_2C)_2CH_2OH$, $C_8H_{17}SH$, PhOMe, $HNEt_2$ and thiophene] bifunctional products of the *neo*-structure were obtained, in which the functional group was located at the quaternary C atom, being the most distant from the parent carbonyl group.



1, **2**

3a–g, **4a–e**

5

1, **3** R = H
2, **4** R = Et

Product	Nu	Yield	Product	Nu	Yield
3a	EtO	48%	**4a**	EtO	90%
3b	CF_3CH_2O	89%	**4b**	CF_3CH_2O	89%
3c	$H(F_2C)_2CH_2O$	67%	**4c**	$H(F_2C)_2CH_2O$	57%
3d	2-thienyl	50%	**4d**	2-thienyl	62%
3e	$C_8H_{17}S$	73%	**4e**	2-furyl	42%
3f	Et_2N	25%			
3g	4-MeOC$_6$H$_4$	24% (+ 36% of **5**)			

Scheme 1

The reaction of amide **1** with CO and anisole led to the mixture of acylation (**3g**) and alkylation (**5**) products in ratio depending on reaction conditions. These products were separated by column chromatography. Compound **5** was also obtained in a low yield in reaction of the amide with anisole in the absence of CO. The reaction with *N*,*N*-diethylamine proceeded non-selectively giving the target diamide **3f** (*m*/*z* 256 [M]$^+$) along with two by-products, *i.e.* the product of dehydratation of **3f** (*m*/*z* 238 [M]$^+$) and the cyclization product of the initial amide (*m*/*z* 155 [M]$^+$) in a molar ratio *ca.* 3:1.1:1, respectively. The target diamide **3f** was isolated by column chromatography.

The amide group is clearly a stronger nucleophile than an *sp*^{3} C–H bond. The reason why the less nucleophilic center reacts with the superelectrophile, even in the presence of much stronger CO donors, and the reason for the regioselective formation of the *neo*-products were discussed previously.[8] Anyway, the successful reaction proceeding requires an excess of superelectrophile.

N,*N*-Diethyl nonanamide **2** underwent similar chemo- and regioselective C–H functionalization (see Scheme 1). At 0 °C for 1 h and a molar ratio [E] : [**2**] = 2:1, as a rule, the yields of

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[†] *Typical procedure*. At 0 °C, under CO atmosphere (1 bar), the amide (0.7–2.0 mmol) was added to a stirred solution of $CBr_4 \cdot 2AlBr_3$ [(1.2–1.4)–(3.0–4.0) mmol, respectively], freshly prepared from $AlBr_3$ and CBr_4 in the molar ratio 2:1 in anhydrous CH_2Br_2 (1–2 ml) at room temperature. After stirring at –20 °C for 2 h or at 0 °C for 1 h under a CO atmosphere, a nucleophile was added to the *in situ* prepared carbonylation intermediate strictly under CO. The addition of furan, thiophene, anisole was carried out at –20 °C. The mixture was stirred at –20 °C for 0.5 h and then left to reach room temperature. Next, H_2O (10 ml) and $CHCl_3$ (30 ml) were carefully added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 ml). The combined organic extracts were washed with H_2O until neutral reaction and dried over Na_2SO_4. The structures of the products were established by ^{1}H, ^{13}C, ^{19}F NMR, and from GC-MS spectra; conversions and isomeric ratios were determined by GC. To perform NMR measurements, all solvents and volatile compounds were removed under reduced pressure. In some cases, to remove by-products, the product was washed with a suitable solvent and repeatedly dried *in vacuo*. In some cases, the product was purified by column chromatography (silica gel) using hexane–acetone (2:1) as the eluent. The yields of the products were determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard.

bifunctional products **4a**–**e** were high with full conversion of the initial amide.

The synthesis of new long chain derivatives of amides with remote functional groups is of special interest because these products are expected to possess valuable properties, such as enhanced thermal and chemical stabilities, low freezing points, *etc*. and some of them seem to be promising for practical use.[13] A branched chain amide, *viz*. *N*,*N*-di(2-ethylhexyl) isobutylamide, showed improved separation of the desired actinide constituents like ^{239}Pu and ^{233}U over the fission products as compared with linear amides.[14]

There are considerable distinctions between the mechanisms and product structures in the case of *sp*^{3} C–H functionalizations initiated by superelectrophiles systems and metal complexes.[1–3] In the presence of a superelectrophile, the most stable cations form preferably,[15] and due to the repulsion of positive charges, the carbocation, and hence the new functional group tends to be the most distant from the already existing functional group. On the contrary, in metal-initiating reactions, an original functionality first coordinates to the metal center thus facilitating the *sp*^{3} C–H bond functionalization. Since these processes require the direct interaction between the metal complex and the C–H bond, the steric environment around the reaction center is a crucial factor in determining whether the process is possible. For this reason, less hindered primary *sp*^{3} C–H are funtionalized preferably to form linear products with new functionality adjacent to an original functional group (so-called the nearest, adjacent or α-functionalization).[1–3] For example, metal initiated intermolecular functionalization of the methyl group of amide to form linear products with new functionality adjacent to an original functional group was described.[16]

Interestingly, the functionalization of amides **1**, **2** as well as alkyl acetates,[8] methyl ketones[9] and alkanoates[10] occurred with good regioselectivity, while it is impossible to obtain individual carbonyl-containing products starting from C_6–C_{10} alkanes. In fact, under the action of proton superacids, even propane carbonylation proceeded non-selectively, and only polyhalomethane additives improved selectivity of the reaction.[17] *n*-Alkanes C_6–C_{10} in proton superacids furnish mostly the products of their degradative carbonylation.[18] The degradative carbonylation of alkanes C_6–C_{10} does not occur when polyhalomethane-based superelectrophiles are used[19] affording carbonyl-containing products with *neo*-alkyl substituents, mostly AlkC(Me)$_2$C(O)OR and AlkC(Me)(Et)C(O)OR, as two dominating isomers (*cf*. ref. 10).

All the products obtained in this study are new. Their structures were established from ^{1}H, ^{13}C and ^{19}F NMR spectra, and mass spectrometry (for details, see Online Supplementary Materials). In summary, a new approach to the one-pot *sp*^{3} C–H functionalization of amides has been demonstrated. The use of the potent superelectrophilic complex, CBr$_4$·2AlBr$_3$ makes it possible to perform the one-pot chemo- and regioselective synthesis of new family of compounds with remote functional groups.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.03.015.

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