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Superelectrophilic sp^3 C–H carbonylation of *n*-octyl acetate as a way to new bifunctional *neo*-octanes

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Carbonylation of *n*-octyl acetate in the presence of $CBr_4{\cdot}2AlBr_3$ followed by treatment with nucleophiles such as alcohols, amines or (het)arenes affords 7-acetoxy-2,2-dimethylheptanoyl-containing products.

Selective functionalization of sp^3 C–H bonds of monofunctional compounds has great synthetic potential, as it offers a solution to the problem of converting monofunctional derivatives to bifunctional compounds with distant functional groups. Finding initiating systems for such transformations presents a considerable challenge as the most functional groups have a low tolerance for highly reactive agents which are capable of cleaving unactivated sp^3 C–H bonds.

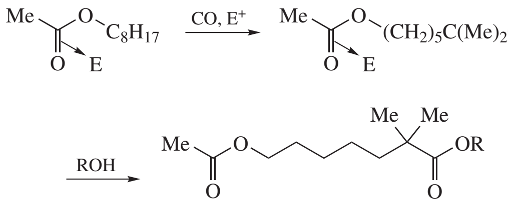
Investigations in this field started more than a century ago.[1] Up to date, the sp^3 C–H bond functionalization of monofunctional compounds mediated by radical systems,[2] compounds of transition or post transition metals,[3] and strong electrophiles[4] has been reported.[†] Over the last decade, transition metal-mediated sp^3 C–H bond functionalization has been vigorously studied. In contrast, similar reactions initiated by strong electrophiles are rare.[4] Carbonylaion of methyl isoalkyl ketones in excess HF–SbF_5 was shown to proceed selectively at $\omega - 1$ position, however, conversions of ketones amounted to 16–66%; linear ketones reacted with CO unselectively to produce desired products as minor components, if at all.[4(*c*)]

Recently, we have developed a new strategy for selective one-pot C–H bond functionalizations of alkanes,[5] including monofunctional ones.[6,7] The potent superelectrophilic complex $CBr_4{\cdot}2AlBr_3$ in organic medium allowed easy generation of carbocations XR^+ (X is a functional group) from monofunctional compounds, XRH, namely *n*-alkyl acetates[5] and monofunctional adamantanes,[6] to occur. In the presence of CO, the XR^+ cations are converted into acylium cations $XRCO^+$, which, in their turn, form bifunctional products on final treatment with nucleophiles, the original functional group remaining intact. In this approach, CO plays a crucial role because it generates a synthon suitable for one-pot synthesis of a broad variety of products depending on the nature of the nucleophile.

Functionalization of *n*-octyl acetate with CO and nucleophiles (isopropanol, morpholine and anisole) was shown to afford the bifunctional products of *neo*-structure with the acetate group $AcO(CH_2)_5C(Me)_2COY$ (Y = OPr^i, NC_4H_8O, C_6H_4OMe) in high yield.[5] In the present work, we verified the scope of this reaction by application of different nucleophiles, namely, alcohols, amines and (het)arenes.

In fact, carbonylation of *n*-octyl acetate at –20 °C under CO atmosphere (1 bar) in the presence of 70% molar excess of superelectrophilic complex $CBr_4{\cdot}2AlBr_3$ (E) for 3 h, followed by the *in situ* treatment of the carbonylation product with alcohols such as $HOCH_2CH(Et)Bu$, CF_3CH_2OH, $HO(CH_2)_3Br$, $HOCH_2C{\equiv}CH$ led to the corresponding 7-acetoxy-2,2-dimethylheptanoic esters in 63–78% yields (Scheme 1).[‡]

These products also had *neo*-structures, in which the new functional groups were located at the quaternary C-atom being maximum remote from the initial acetoxy group. The elaboration of syntheses of bifunctional aliphatic compounds having *neo*-structures is of special interest because they display valuable



R = CF_3CH_2 (75%),
$BuCH(Et)CH_2$ (75%),
$HC{\equiv}CCH_2$ (78%),
$Br(CH_2)_3$ (63%)

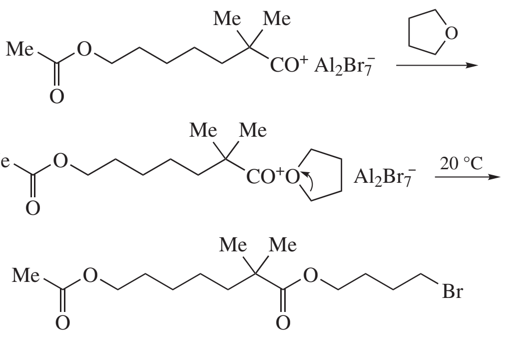
Scheme 1

[†] There are considerable distinctions between the mechanisms and the nature of products of sp^3 C–H functionalization initiated by different class systems. The radical reactions trend to occur at the weakest C–H bond. Likewise, superelectrophiles favor the formation of the more branched carbocation, even to a greater extent, thus the formation of functional products with a functional group at quaternary or tertiary C atom. Low valent transition metals, however, trend to insert into the least substituted C–H bond to give an alkylmetal hydride; as a result, linear functional products are often preferred. However, the dividing of initiating systems into three above mentioned classes is not strict, since some radical compounds act in the presence of strong acids, while some high-valent metal complexes behave as superelectrophiles.

[‡] *Typical procedure.* At –20 °C, under a CO atmosphere (1 bar), *n*-octyl acetate (1.9 mmol) was added to a stirred solution of $CBr_4{\cdot}2AlBr_3$, freshly prepared from $AlBr_3$ (6.50 mmol) and CBr_4 (3.24 mmol) in anhydrous CH_2Br_2 (2.5 ml) at room temperature. After stirring for 2.5–3 h at –20 °C under a CO atmosphere, a nucleophile was added to the *in situ* prepared carbonylation intermediate strictly under CO. The mixture was stirred additionally for 10–15 min at –20 °C and then left to warm to 0 °C over 20–30 min. Water (10 ml) and $CHCl_3$ (30 ml) were carefully added with stirring. The organic layer was separated and the remaining aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4. The structures of the products were established by ^1H, ^{13}C NMR and GC-MS spectra; conversions and isomeric ratios of products were determined by GC. To perform NMR measurements, all solvents and high volatile compounds were removed under reduced pressure and finely at 50 °C (1 Torr). In some cases, the products were purified by chromatography on silica gel. The yields of the obtained compounds were determined by ^1H NMR with mesitylene as an internal standard.

properties, such as enhanced thermal and chemical stabilities, low freezing points, *etc.*[8] The products of *neo*-structure cannot be prepared with transition metal-mediated systems.[‡]

The THF ring-opening product was formed, if $AcOC_8H_{17}$ carbonylation product reacted with THF at 20 °C under CO atmosphere (Scheme 2, for the mechanism, see ref. 9).



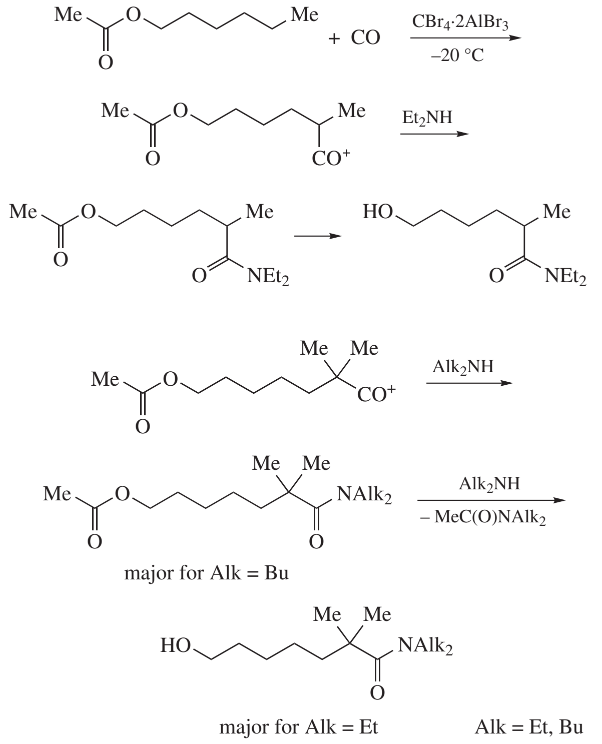
Scheme 2

The reaction proceeded regioselectively to give more than 96% of the *neo*-isomer. The yield of the target product was 72% after 20 h. Small amounts of other THF ring-opening products, $XO(CH_2)_4Y$ (X = H, Y = Br; X = $HOC_8H_{16}CO$, Y = Br; X = Y = Br) were formed as by-products.

In our experiments, the functionalization of *n*-octyl acetate occurs with good chemo- and regioselectivity. Previously, under the action of superacids, alkanes C_6–C_{10} generated mostly the products of their degradative carbonylation, resulting in compounds with different number of C-atoms in the alkyl moiety.[10] On contrast, the degradative carbonylation of alkanes C_6–C_{10} did not occur in the reactions initiated by the polyhalomethane-based superelectrophiles.[11] In this case, even at –40 °C, these alkanes are converted exclusively into carbonyl-containing products with *neo*-alkyl substituents being the two dominating isomers, $AlkC(Me)_2COOR$ and AlkC(Me)(Et)COOR.[11] Carbonylation of octane at –20 °C leads to the aforementioned isomers (Alk = C_5H_{11}) in comparable amounts. Individual carbonyl-containing products starting from C_6–C_{10} alkanes were never obtained.

The results of this work show that in the presence of the acetoxy group, an individual carbocation is generated selectively in each case. Therefore, the corresponding acylium cation accumulates in the reaction medium, leading finally to a single product. We believe that the site for hydride abstraction from the alkyl acetate molecule is dictated by two factors: (i) its remoteness from the existing functional group, and (ii) the stability of the carbocation to be generated. For *n*-octyl acetate, these two requirements lead to a compromise resulting in the formation of the most stable tertiary cation separated from the functional group by five CH_2 units. The difference in the selectivities of carbonylation of *n*-octane and *n*-octyl acetate stems from the fact that the former gives two cations that are rather similar in stability, whereas the latter is transformed into an intermediate $Me_2C^+(C_5H_{11})$ bearing the cationic center in the position that is the most remoted from the acetoxy group.

While the functionalization of *n*-hexyl and *n*-octyl acetates with CO and morpholine occurred effectively to afford the corresponding bifunctional product in 80–85% yield,[6] the treatment of their carbonylation product with Et_2NH was accompanied with the Ac–O bond cleavage in the initially formed amides to give $AcNEt_2$ and $HOC_nH_{2n}CONEt_2$ (*n* = 6 or 8). In the case of *n*-hexyl acetate, the use of three-fold excess of Et_2NH relative to E led to a mixture of $AcOC_6H_{12}CONEt_2$ and $HOC_6H_{12}CONEt_2$ in a molar ratio 4:1 (total yield 65%), while this reaction with a larger excess of Et_2NH gave rise to $HOC_6H_{12}CONEt_2$ as the only product.

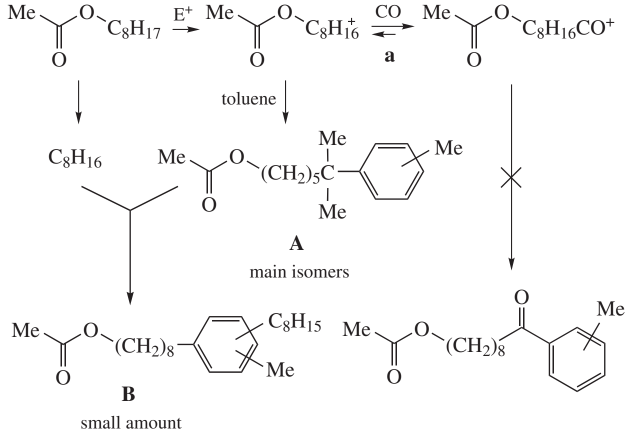


Scheme 3

Similar results were observed for *n*-octyl acetate and Et_2NH or Bu_2NH, although in the latter reaction, $HO(CH_2)_5C(Me)_2CONBu_2$ was found in trace amounts only and $AcO(CH_2)_5C(Me)_2CONBu_2$ remained as a major product (Scheme 3).

Acid-catalyzed ester cleavage has been extensively studied, and evidence has emerged suggesting that protosolvation (or electrophilic solvation) can play a role in this chemistry.[12] Thus, methyl acetate is found to be completely protonated at the acyl oxygen in superacidic $FSO_3H/SbF_5/SO_2$ solution at low temperature. However, even at –78 °C, protonated methyl acetate undergoes acyl-oxygen cleavage to give the acetyl cation and protonated methanol.[12(*c*)]

The treatment of the carbonylation product with toluene led to a mixture of toluene alkylation products (**A**) with $AcOC_8H_{16}^+$ cations, which were in equilibrium with the corresponding acylium ions (Scheme 4). Alkylation of toluene, which is less nucleophilic than anisole, occurs faster than acylation. Therefore, in spite of a shift of equilibrium **a** under CO to the right, the only alkylation is realized. Small amount of dialkylated toluenes with M⁺ 372 (**B**) was formed as by-products. The latters are the $AcOC_8H_{16}C_6H_4Me$

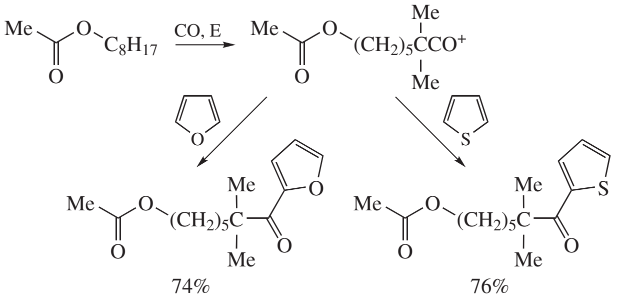


Scheme 4

alkylation products with unsaturated hydrocarbons C_8H_{16}. We did observed the formation of traces of C_8H_{14} hydrocarbons (M = 110) among the *n*-octyl acetate decomposition products. A molar ratio of [**A**]:[**B**] was ~10:1, with the conversion of $AcOC_8H_{17}$ being 92%. Thus, sp^3 C–H bond in *n*-octyl acetate transforms to C–C bond *via* alkylation of toluene.

According to MS data, two major isomers **A** (>98% of content) had *neo*-structure, because both of them contained the fragment ion *m*/*z* 133, $^+C(Me)_2C_6H_4(Me)$ (I = 100%), while a minor isomer **A** with the *m*/*z* 119, $CH(Me)C_6H_4(Me)$ (I = 100%), was probably a tertiary isomer.

Similar to the reported reaction with CO and anisole,[5] the processing of octyl acetate with CO and furan or thiophene occurs chemo- and regioselectively, in each case to give practically individual acylation products of *neo*-structure (Scheme 5).



Scheme 5

The possibility to involve in this functionalization five-membered heteroaromatics, which are very active toward electrophiles, is of interest. Thiophenes and furans are important structural fragments in many pharmaceuticals.[13] Therefore, a simple method for preparation of their new derivatives may be promising for synthesis of biologically active heteoaromatic compounds.

In summary, an 'alkane-like' strategy has been successfully used for the direct and simple one-pot functionalization of *n*-octyl acetate. This approach has provided access to new bifunctional aliphatic compounds with an acetate group, which are of interest for the synthesis of biologically active compounds and materials for industrial use.

All products obtained are novel and their structures were confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry (see Online Supplementary Materials).

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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.2011.11.010.

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