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sp^3 C–H bond functionalization of methyl *n*-alkyl ketones [$MeCOC_nH_{2n+1}$ ($n = 6–8$)] as a novel method for the one-pot regioselective synthesis of 'bifunctional alkanes' with remote functional groups

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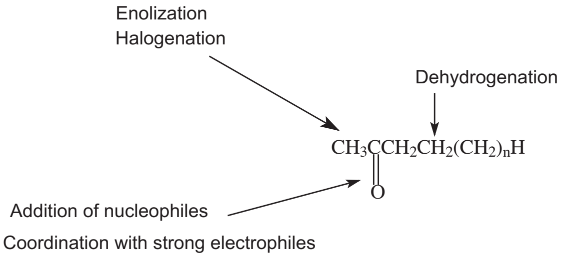
ABSTRACT

Selective one-pot functionalization of methyl *n*-alkyl ketones, $C_nH_{2n+1}COMe$ ($n = 6–8$) involving C-sp^3–H bond cleavage with CO and various nucleophilic substrates [^{i}PrOH, BuCH(Et)CH_2OH, CF_3CH_2OH, $(CF_3)(Me)CHOH$, $H(CF_2)_2CH_2OH$, HC≡CCH_2OH, furan, thiophene, and anisole] in the presence of the superelectrophilic system $CBr_4{\cdot}2AlBr_3$ has been performed for the first time.

Ketones are a broad class of organic compounds, which are produced industrially as solvents, polymers, pharmaceutical precursors, perfumes, etc.[1] In methyl *n*-alkyl ketones, there are three reaction centers, namely: CO and α- and β-C–H bonds. In contrast to α- and β-C–H bonds, the other C–H bonds in ketones are inert to both common nucleophiles and electrophiles (Scheme 1).

Transition metal complexes were shown to form chelates with ketones with the participation of ketone α- or β-C–H bonds.[2,3] While ketone sp^3 C–H bond functionalization by transition metal complexes results in chelate formation, functionalization by superelectrophiles[4] opens the unique possibility to introduce a novel functional group into the most distant position from the existing carbonyl group and to obtain regioselectively, bifunctional products of *neo*- or tertiary structures.[5–9] Prior to our studies,[7–9] only two cases of one-pot, selective sp^3 C–H bond intermolecular functionalization of monofunctional linear aliphatic compounds by superelectrophiles were reported.[5,6] One of these involved in reactions of aliphatic alcohols, ketones, and aldehydes with ozone in magic acid in SO_2ClF.[5] Primary alcohols containing tertiary or secondary C–H bonds at the γ-position, or more remote from the oxonium center, were shown to undergo insertion reactions with protonated ozone to give oxidation products in good yield. In contrast to primary alcohols, secondary C–H bonds at the γ-position of aldehydes and ketones remained unreactive toward ozone in SO_2ClF at −40 °C. Such reactions with protonated ozone occurred only with higher ketones and aldehydes.[5] In the second case, carbonylation of methyl isoalkyl ketones in excess HF-SbF_5 was shown to occur selectively at the ω-1 position to produce the corresponding acids after quenching of the carbonylation intermediate with water. However, the ketone conversions were in the range of 16–66%. The attempts to perform selective carbonylation of methyl *n*-alkyl ketones with CO in the presence of this proton superacid were unsuccessful. The reactions of linear ketones either did not occur at all or led to mixtures consisting predominantly of degradative carbonylation products with smaller numbers of C atoms in the alkyl group at the carbonyl than in the initial ketones, while the desired products were formed in only small amounts, or not at all.[6]

We have found that the use of the potent superelectrophilic complexes, $CX_4{\cdot}2AlX_3$ (X = Br or Cl) allows easy generation, not only of carbocations R^+ from alkanes RH,[10] but also carbocations



Scheme 1. Reaction centers in ketones.

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XR_1^+ (X is a functional group) from *n*-alkyl acetates[8,9] and monofunctional adamantanes.[7] In the presence of CO, cations R^+ and XR_1^+ convert spontaneously into the acyl cations RCO^+ and XR_1CO^+, respectively. In turn, the acyl cations RCO^+ and XR_1CO^+, under the action of nucleophilic substrates, produced monofunctional and bifunctional products, respectively, in which the initially present functional group remained intact.

In this Letter, we report the first case of sp^3 C–H bond functionalization of methyl *n*-alkyl ketones resulting in bifunctional products with remote functional groups. We found that at −20 °C under atmospheric CO pressure and in the presence of 50% molar excess of the superelectrophilic complex $CBr_4{\cdot}2AlBr_3$, carbonylation of methyl *n*-alkyl ketones [$C_nH_{2n+1}COMe$ ($n = 6$–8)] followed by treatment of the carbonylation products with nucleophilic agents led to the corresponding bifunctional products 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 ketones, were observed (Scheme 2).

The carbonyl group is clearly a much stronger nucleophile than an sp^3 C–H bond. However, while the interaction of the superelectrophile with a carbonyl group is reversible, C–H bond cleavage followed by acylium cation formation in the presence of CO is virtually irreversible. As a result, the less nucleophilic center can still react with the superelectrophile, even in the presence of the much stronger CO donors. Undoubtedly, the bonding of the carbonyl group to the superelectrophile not only hinders the generation of the cation, but also reduces the superelectrophilicity of the media.

We do not think that the coordination of a CO molecule to the superelectrophile in the presence of the much stronger donor carbonyl group takes place. In fact, our calculations of the mechanism of methane carbonylation with CO in the presence of superelectrophilic complexes $CX_4{\cdot}2AlX_3$ have shown that CO forms only very weak solvates with superelectrophiles, in which the bond lengths and charges are practically the same as in the free CO molecule.[11]

At −20 °C, the functionalization of methyl *n*-hexyl ketone occurred regioselectively to form products with the tertiary structures in moderate yields (Scheme 3).

Functionalizations of methyl *n*-heptyl ketone by CO in the presence of the superelectrophilic system $CBr_4{\cdot}2AlBr_3$ (E) followed by treatment of the carbonylation product with ^{i}PrOH were shown to proceed effectively both at −20 and at −10 °C, and at molar ratios [E]:[ketone] of 1.5:1 and 1.3:1, respectively. At −20 °C for 2 h, the conversion of ketone was close to 100% and a single *neo*-product $MeCOC_7H_{14}COOPr^i$ was formed. At −10 °C, the conversion and selectivity were somewhat lower.

At −20 °C, functionalizations of methyl *n*-heptyl ketone, [$C_nH_{2n+1}COMe$ ($n = 7$)] by CO and various nucleophiles (^{i}PrOH, $BuCH(Et)CH_2OH$, CF_3CH_2OH, $CF_3(Me)CHOH$, $H(CF_2)_2CH_2OH$, C_6H_5OMe, and thiophene) resulted almost exclusively in bifunctional products of the *neo*-structure, in which the functional group was located at the quaternary C atom, being the most distant from the parent carbonyl group (Scheme 4).

In this case, the new functional group was separated from the initial carbonyl by five carbon atoms. A similar tendency was observed for *n*-alkyl acetates.[7,8] The easier formation of the *neo*-products from methyl *n*-heptyl ketone with a longer alkyl chain showed that isomerization of the long-chain cation $MeCOC_7H_{15}^+$ proceeded more rapidly than isomerization of its shorter homologs.

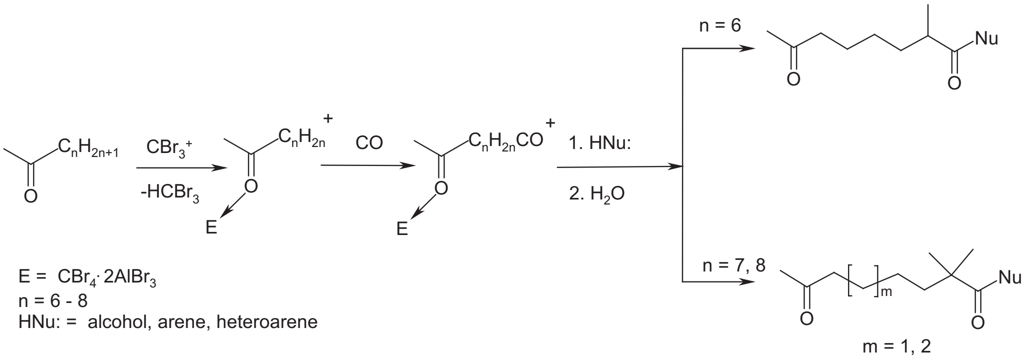
The synthesis of bifunctional aliphatic compounds with *neo* structures is of special interest because they display valuable properties, such as enhanced thermal and chemical stabilities, low freezing points, etc.[12] The content of these *neo* products was no less than ~90% in the corresponding isomeric mixtures; in some cases, other isomers were totally absent. The yields of the products with alcohols, such as ^{i}PrOH, CF_3CH_2OH, $CF_3(Me)CHOH$, $H(CF_2)_2CH_2OH$, ranged from 68% to 99%, while the yields of diketones from anisole and thiophene, and an ester from $BuCH(Et)CH_2OH$ were approximately 50%. Alongside the diketone, the alkylation product, $MeCOC_7H_{14}C_6H_4OMe$ was formed in a small amount in the reaction with anisole.

The functionalization of methyl *n*-octyl ketone by CO with ^{i}PrOH, thiophene, and anisole also occurred effectively, resulting almost exclusively in the bifunctional products of *neo* structure in good yield (Scheme 5).

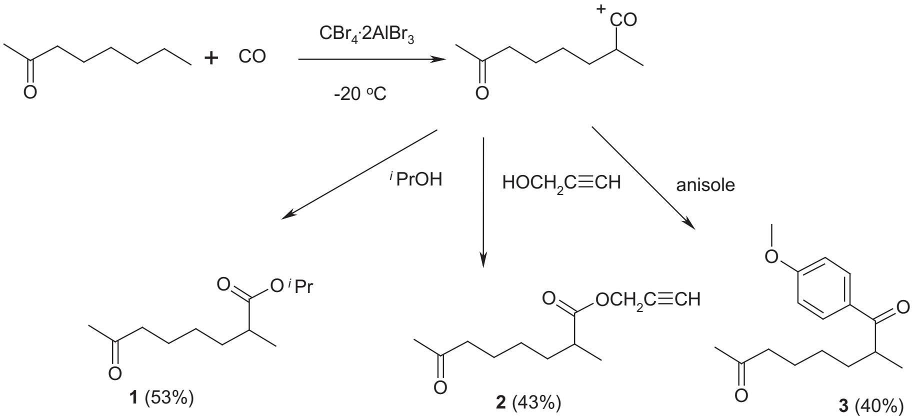
It is important to note that furan (Scheme 4) and thiophene (Scheme 5), which are very active toward electrophiles, can be successfully involved in the functionalization reactions.

This study demonstrates that in the presence of a carbonyl group, a single carbocation is generated selectively in all of the above reactions. Therefore, the corresponding acylium cation accumulates in the reaction medium, allowing for regioselective functionalization of the ketone. We believe that the site for hydride abstraction from the methyl *n*-alkyl ketone molecule is determined by two factors, namely: (1) its remoteness from the already existing carbonyl group, and (2) the stability of the carbocation generated. For ketone $MeCOC_nH_{2n+1}$ ($n = 6$), the remoteness from the carbonyl is the decisive factor leading to an isocation with a non-isomerized alkyl segment, while for ketones $MeCOC_nH_{2n+1}$ ($\geqslant 7$), the two factors work together to produce the most stable tertiary cation separated from the parent carbonyl group by four or more methylenes. The functional groups are remote from the original carbonyl by 5 ($n = 6$ or 7) and 6 ($n = 8$) carbon atoms. We believe that the different locations of the functional groups in these products are mainly due to repulsion between the carbonyl group coordinated to the electrophile and the generated carbocation, rather than to the higher stabilities of tertiary cations $C(O)C^+(Me)_2$ compared with those of $C(CO)C^+(Me)(Alkyl)$ (where alkyl = Et, Pr, etc.).

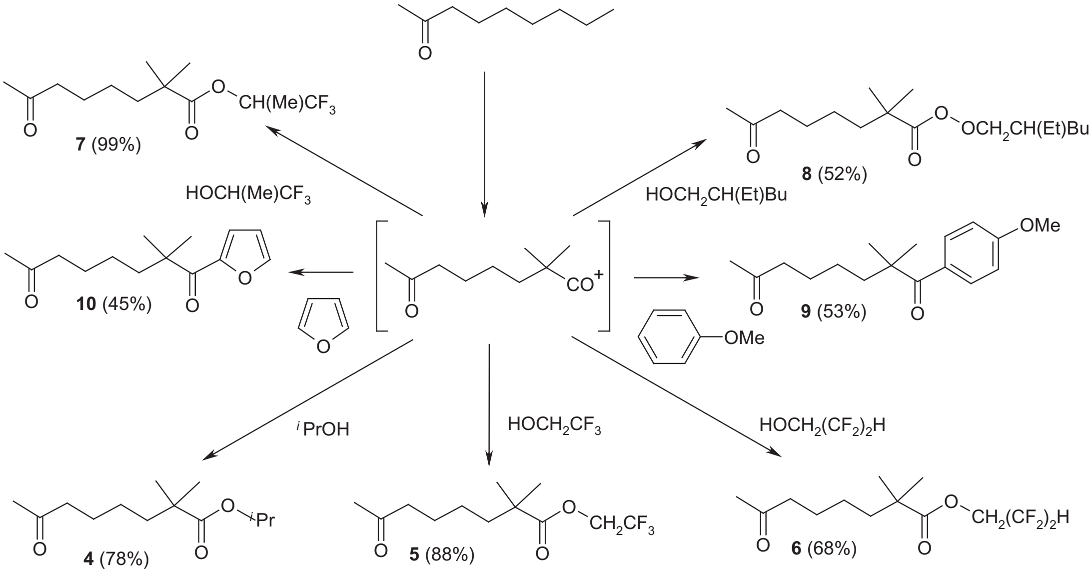
All the products obtained in this study are new. Their structures were established from ^1H, ^{13}C, and ^{19}F NMR spectra, and mass spectrometry. A typical procedure is presented.[13]



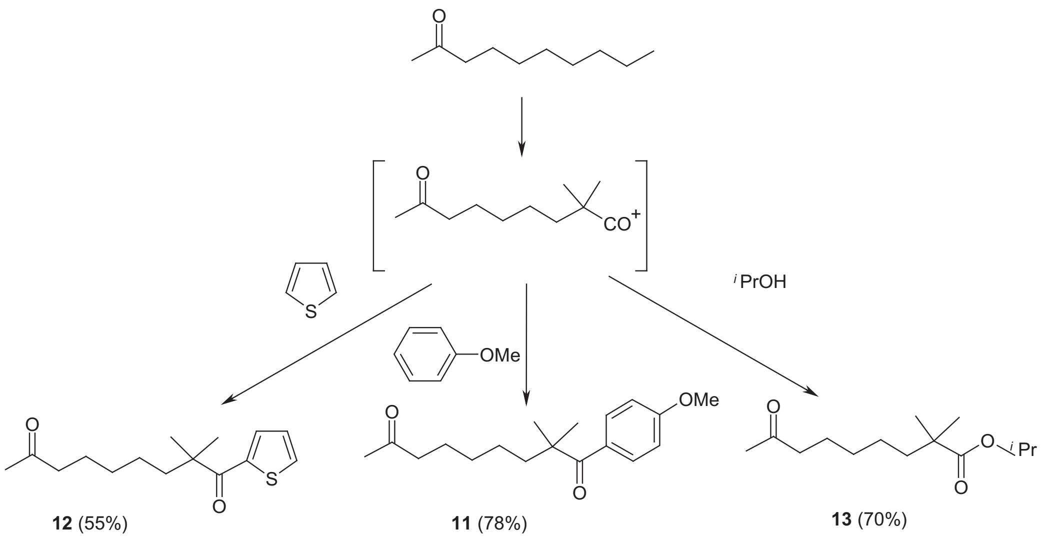
Scheme 2. One-pot functionalization of methyl *n*-alkyl ketones by $CBr_4{\cdot}2AlBr_3$.



Scheme 3. One-pot functionalization of methyl *n*-hexyl ketone.



Scheme 4. Products of the one-pot functionalization of methyl *n*-heptyl ketone.



Scheme 5. Products of the one-pot functionalization of methyl *n*-octyl ketone.

In summary, a new approach for the one-pot sp^3 C–H functionalization of methyl *n*-alkyl ketones has been demonstrated. The use of a powerful superelectrophilic complex, $CBr_4 \cdot 2AlBr_3$ makes possible the regioselective synthesis of ketones with remote functional groups. A major benefit of this approach consists of the generation, under a CO atmosphere, of an acylium cation which serves as a synthon for the one-pot synthesis of a broad series of bifunctional products from each ketone.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.164. These data include MOL files and InChiKeys of the most important compounds described in this article.

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13. *Typical procedure:* At -20 °C, under atmospheric CO pressure, methyl *n*-alkyl ketone (0.8–2.0 mmol) was added to a stirred solution of $CBr_4 \cdot 2AlBr_3$ (1.20–3.0 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 for 2–3 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 for 10–15 min at −20 °C and then left to warm to 0 °C over 20–30 min. Next, H_2O (10 mL) and $CHCl_3$ (30 mL) were carefully added to the mixture. The organic layer was separated and the remaining aqueous layer was extracted with $CHCl_3$ (10 mL). The combined organic phase was dried over Na_2SO_4. The structures of the products were established by ^1H, ^{13}C, and ^{19}F NMR, and from GC–MS spectra; conversions and isomeric ratios were determined by GC. To perform NMR measurements, all solvents and highly 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 vacuum. The yields of the products obtained were determined by ^1H NMR spectroscopy with mesitylene as an internal standard.