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Chemoselective Reduction: Xanthates as Traceless Precursors of Polyfunctionalized α,α-Dichloroketones

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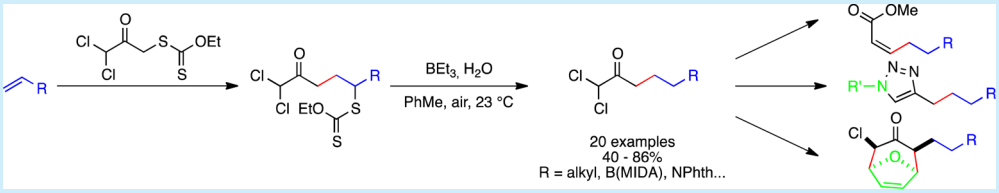
Supporting Information

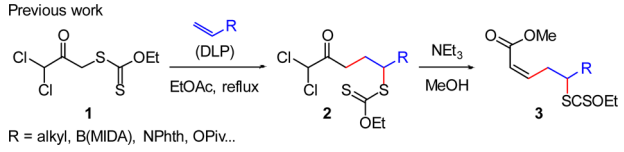


ABSTRACT: The use of $BEt_3 \cdot H_2O$ has allowed the chemoselective reductive dexanthylation in the presence of the very fragile α,α-dichloroketone motif. This has solved a major hurdle in our approach to this important, but hitherto grossly understudied, family of compounds and opened access to a number of very useful synthetic transformations.

Selective functional group interconversions are essential operations in organic synthesis. They can represent a severe hurdle when very fragile moieties are present in the target molecule. We recently reported a new, mild route to α,α-dichloroketones.[1] Despite their remarkable and unique synthetic utility, these compounds have so far remained understudied, largely because of a lack of suitable synthetic methods allowing the synthesis of more functionalized structures. Their high sensitivity toward basic conditions has frustrated most approaches, and only the simplest members have been accessible hitherto. We have exploited the ability of xanthates to mediate intermolecular radical additions to unactivated alkenes under mild, *neutral* conditions to access a large array of α,α-dichloroketones.[2] Thus, by adding xanthate **1** to various olefins, we were able to insert the Cl_2HCOCH_2- motif into a broad variety of polyfunctionalized olefins and to obtain more complex α,α-dichloroketones of general structure **2** (Scheme 1). Furthermore, this study allowed us to investigate more extensively their unusual Favorskii rearrangement leading to *Z*-alkenoates **3**.[3]

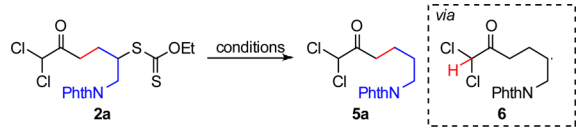
Nevertheless, although the xanthate group is needed for the C−C bond formation, its removal from the final structure was desirable since it is usually not wanted in the final product and was found in some cases to interfere with the Favorskii rearrangement.

Scheme 1. Synthesis of α,α-Dichloroketones via Xanthate Radical Addition Transfer and Their Favorskii Rearrangement[1]



Unfortunately, all our attempts to remove this group via classical reductive dexanthylation methods failed. This transformation usually proceeds through a radical pathway. Hydrogen atom donors can be Barton's reagent (hypophosphorous acid in the presence of triethylamine),[4] tris(trimethylsilyl)silane,[5] or even isopropanol.[6] Under these conditions, however, a fast degradation of the α,α-dichloroketone motif was observed (Table 1, entries 1−3). Monitoring by ^1H NMR spectroscopy showed the disappearance of the characteristic peak at $\delta \approx 5.8$ ppm, with the monodechlorinated derivative being the only detectable product in the complex mixtures. These reagents were clearly unable to accomplish a chemoselective reduction. In the case of the isopropanol/peroxide system, which seemed the most promising from the outset, the electron transfer from the ketyl

Table 1. Reductive Dexanthylation of 1,1-Dichloroketo Adducts



entry	conditions	yield (%)
1	H_3PO_2, NEt_3, (AIBN), 1,4-dioxane	*a*
2	lauroyl peroxide, *i*PrOH	*a*
3	$(Me_3Si)_3SiH$, (AIBN), PhMe	*a*
4	BEt_3 (4 equiv), H_2O (10 equiv), air,[b] PhMe (0.03 M)	65
5	BEt_3 (4 equiv), H_2O (10 equiv), air,[c] PhMe (0.1 M)	72
6	BEt_3 (4 equiv), air,[c] PhMe (0.1 M)	*a*
7	BEt_3 (1.2 equiv), H_2O (3 equiv), air,[c] PhMe (0.1 M)	*d*

[a]Degradation. [b]Introduction with a syringe pump over 24 h. [c]Reaction in an open flask. [d]Incomplete conversion.

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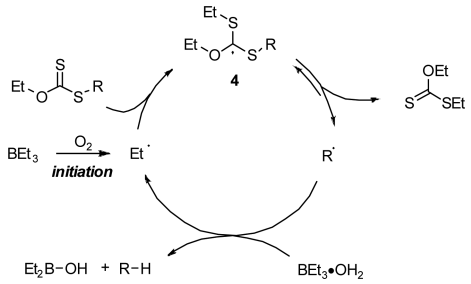
radical, $Me_2C^{\bullet}-OH$, to the electrophilic dichloroketone moiety proved too effective and competed with the desired dexanthylation. Electron-transfer from electron-rich ketyl radicals to electrophilic haloketones and esters is indeed well documented.[7]

We clearly required a reducing system involving radicals that were better able to discriminate between the thiocarbonyl of the xanthate and the electrophilic dichloroketone moiety, as well as being unable to reduce the latter through electron transfer. We therefore turned our attention to the Et_3B/H_2O/air combination, first described by Wood et al. as a replacement for stannane in the Barton–McCombie deoxygenation of alcohols via their xanthate derivatives. They namely showed that iodides and secondary *O*-alkyl xanthates can be selectively reduced with a water–trialkylborane complex in the presence of air. Furthermore, this system proved to be highly chemoselective, other halogenated alkyl derivatives remaining essentially untouched under these conditions.[8]

Considering the mechanism of this process (Scheme 2), we also expected a good chemoselectivity in the reduction of adducts

Scheme 2. Proposed Mechanism for the Reductive Dexanthylation with $BEt_3{\cdot}H_2O$[8a]



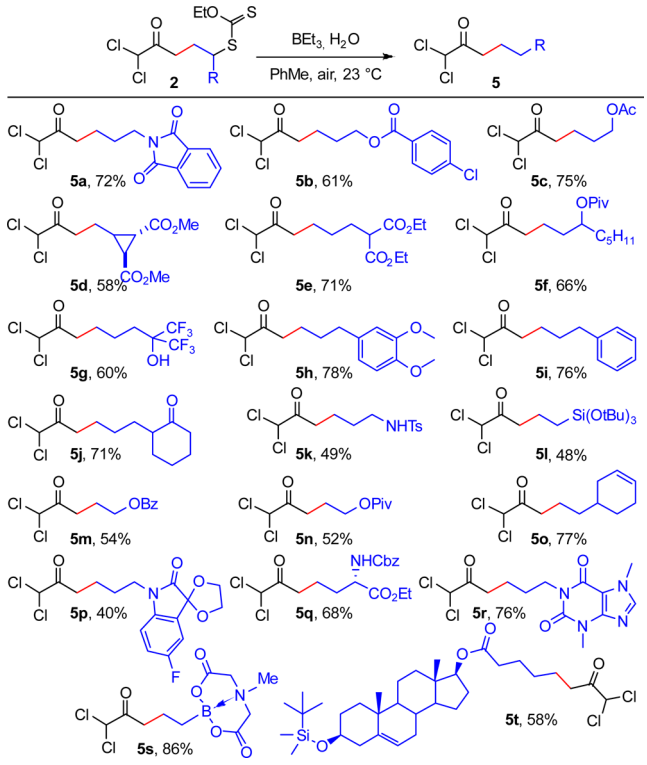
2. The ethyl radicals, formed by auto-oxidation of BEt_3, do not readily abstract a chlorine atom, in contrast to tin, phosphorus, or silicon centered radicals, nor are they sufficiently electron-rich to reduce the dichloroketone motif by electron transfer (this would lead to highly unstable ethyl cation). However, they react rapidly with the highly radicophilic thiocarbonyl of the xanthate to give intermediate **4**, which then fragments into alkyl radical $R^{\bullet}$. Hydrogen atom abstraction from the water–triethylborane complex finally provides the desired reduced compound RH and a new ethyl radical to propagate the chain. It is worth noting that the scission of the C–S bond in the type of xanthates we are using (*S*-alkyl-*O*-ethyl xanthates) is much easier than cleavage of the C–O bond in xanthates of the Barton–McCombie type (*O*-alkyl-*S*-methyl xanthates).

When we applied the Wood conditions to xanthate **2a**, using an excess of triethylborane, water, and air, the latter being introduced slowly via a syringe pump, we were pleased to find that the desired dexanthylated product **5a** could be isolated in 65% yield (Table 1, entry 4). A brief optimization of the reaction conditions was performed, leading to the conclusion that water was necessary to avoid degradation of the dichloroketone (Table 1, entry 6). In fact, Newcomb was able to show that the presence of water raised the efficiency of the hydrogen atom abstraction by about 4-fold (2.0×10^4 M^{-1} s^{-1} compared to 0.4×10^4 M^{-1} s^{-1} for the hydrogen atom abstraction from BEt_3).[9] In our case, this feature seems to be crucial since intermediate radical **6**, if not captured sufficiently rapid, can also evolve by internal abstraction of the remaining hydrogen atom (highlighted in red) in the dichloroketone motif.

We also observed that the concentration can be advantageously raised at least up to 0.1 M, thus reducing the solvent volume, and that the reaction can simply be performed in an open flask (Table 1, entry 5). Finally, we attempted to reduce the amount of triethylborane since, according to the mechanism in Scheme 2, the reaction should require only slightly more than one equivalent. Nevertheless, the conversion was incomplete and degradation was observed (Table 1, entry 7). This again could be explained by too slow capture of the intermediate radical and the consequent interference by internal hydrogen atom abstraction. The triethylborane is also partly destroyed by auto-oxidation, with the ethyl radicals reacting directly with the oxygen present, and these side reactions compete with the desired chain.[10]

These optimized conditions were applied to a large variety of derivatives and proved to be quite general with yields ranging from 40 to 86% depending on the substrates. Esters **5b–e**, malonate **5f**, free alcohol **5g**, aromatic substituents **5h–i**, or ketones such as compound **5j** are tolerated. Likewise, sulfonamide derivative **5k** underwent the reaction. More stabilized radicals were also reduced as shown by products **5l–n**, although the reaction seems to be less efficient (Scheme 3).

Scheme 3. Reductive Dexanthylation of Various Substrates



This could be ascribed to the propensity of the more stable radical to have a longer lifetime (i.e., slower reduction rate) favoring the intramolecular hydrogen abstraction on the dichloroketone moiety, which leads to degradation. Finally, more decorated compounds, such as fluoroisatin **5p**, amino acid **5q**, caffeine derivative **5r**, boronic ester **5s**, or steroid **5t** are accessible in moderate to good yields. In some cases, because of solubility problems, toluene was replaced by acetonitrile. This seems to have no significant influence on the reduction, as already reported in the literature.[8b]

With these new compounds in hand, the investigation of their versatile reactivity now becomes simpler. One interesting feature

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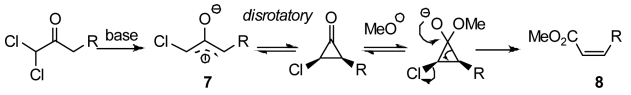
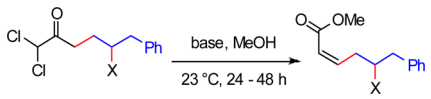
of α-chloro ketones is to form an oxyallylic cation under basic conditions. In the case of α,α-dichloroketones, we have shown that even triethylamine is basic enough to deprotonate and form oxyallyl cation **7** (Scheme 4).[1] This species undergoes a disrotatory electrocyclization and furnishes the *Z*-alkenoate **7** after addition of methanol and fragmentation.[3b,11]

Scheme 4. Mechanism of the Favorskii Rearrangement of α,α-Dichloroketones



The influence of the xanthate group could thus be investigated on a model substrate (Table 2). We previously reported that if

Table 2. Influence of the Substitution on the Favorskii Rearrangement

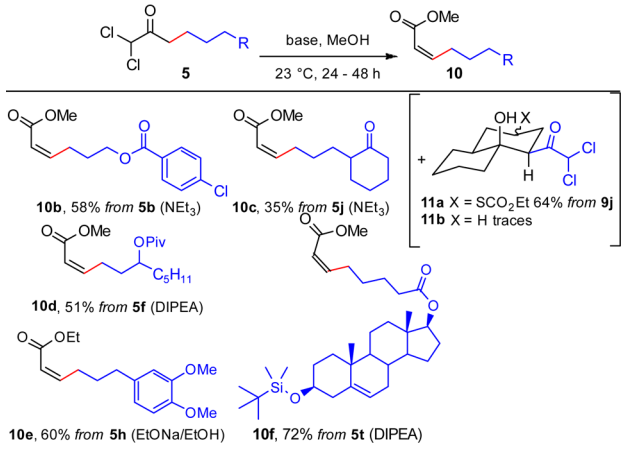


entry	X	base	yield (%)
1	SCSOEt (**2i**)	NEt_3	52
2	SCO_2Et (**9i**)	NEt_3	81
3	H (**5i**)	NEt_3	49 (**10a**)
4	H (**5i**)	DIPEA	58 (**10a**)

the xanthate group is still present, it can interact with the oxyallyl cation, and yields remain moderate (Table 2, entry 1). Conversion of the xanthate into the less nucleophilic thiolcarbonate **9i** by ozonolysis of the thiocarbonyl group all but suppresses this interaction and increases significantly the efficiency of the reaction (Table 2, entry 2). However, we were somewhat disappointed to see again a drop-off in the yields on the dexanthylated product **5i** (Table 2, entry 3). Replacement of triethylamine by the more sterically hindered Hünig's base improved the yield to 58% (Table 2, entry 4).

A few other α,α-dichloroketones were subjected to the same conditions and furnished *Z*-alkenoates **10b–f** in moderate yields (Scheme 5). In the case of compound **5j**, we were surprised to find the predominant formation of the Favorskii rearrangement ester **10c**, in stark contrast to its thiocarbonate precursor **9j**,

Scheme 5. Favorskii Rearrangement of Reduced Derivatives

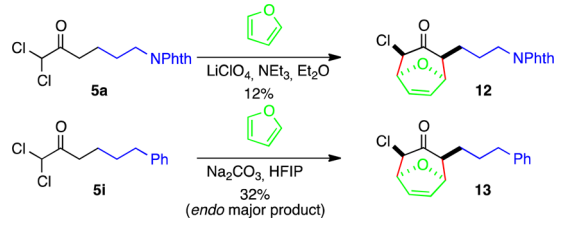


which, under the same conditions, gave rise to decaline **11a** as the main product.[1] The dithiocarbonate group presumably promotes the intramolecular aldol reaction through a Thorpe–Ingold effect. Finally, triethylamine in ethanol was not sufficient to induce the formation of ethyl ester **10e** from α,α-dichloroketone **5h**, and sodium ethoxide in ethanol had to be employed.

Another way to take advantage of the cationic intermediate **7** is to trap it by a [4 + 3]-cycloaddition reaction. This transformation, extensively studied by Föhlisch and his collaborators, furnishes bridged α-chlorocycloheptanones in intra-[12] or intermolecular fashion.[13] However, this reaction is generally in an unfavorable competition with the Favorskii rearrangement.[14] Indeed, to favor the oxyallyl intermediate, a strong dissociating protic solvent such as trifluoroethanol is usually employed. Nevertheless, this solvent can still attack the intermediate to form a *Z*-alkenoate, and the alternative use of lithium perchlorate and triethylamine in diethyl ether has been recommended.[15] However, examples bearing polar substituents are scarce, probably because of the low availability of the starting materials.

Two attempts were made to prepare the bridged seven-membered ring. Under Föhlisch's conditions, compound **12** could be isolated but only in poor yield, along with degradation products (Scheme 6). The reaction was then attempted on

Scheme 6. [4 + 3]-Cycloaddition Reactions with Furan



compound **5i** in hexafluoroisopropanol[16] with sodium carbonate yielding to the *endo* product **13** as the major diastereoisomer, as would be expected from literature precedent.[13] Under these conditions, no product of the Favorskii rearrangement could be detected in the crude mixture.

Although unoptimized, this reaction, when coupled with the present possibility of introducing numerous different substituents on the α,α-dichloroketones, represents a versatile route to bridged seven-membered rings.

The reactivity of α,α-dichloroketones is not restricted to the formation of oxyallyl intermediates. Indeed, it has been shown that these geminal dihaloketones can act as precursors of 1,4-substituted 1,2,3-triazoles.[17] This metal-free alternative to the Huisgen dipolar cycloaddition (now commonly called the "click reaction") proceeds under mild conditions in two steps. The corresponding hydrazone is first formed and is then treated with an amine under basic conditions to produce the desired triazole. Interestingly, this strategy developed by Sakai leads selectively to the 1,4-substituted triazole.[17a] In a recent study, Westermann optimized the reaction and studied extensively the type of amines that can be involved. However, the difficult access to α,α-dichloroketones restricted considerably the scope of the hydrazone partners. Only six simple α,α-dichloroketones were examined, including the trivial 1,1-dichloroacetone and α,α-dichloroacetophenone.[17b]

We subjected a few of the dexanthylated α,α-dichloroketones **5** to the Sakai reaction and were pleased to obtain various 1,2,3-triazoles **14a–d** (Scheme 7). It is thus now possible to vary much more broadly the hydrazone partner and to access polyfunction-

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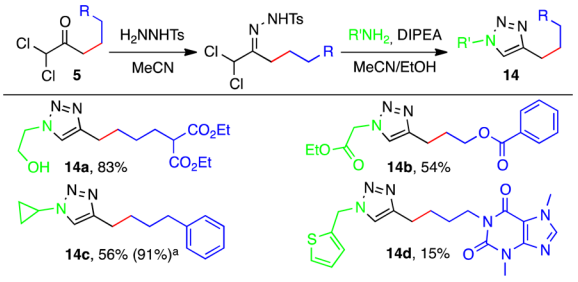
Scheme 7. Synthesis of 1,2,3-Triazoles via the Sakai Reaction

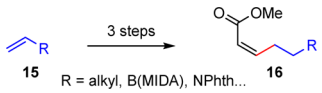


[a]The amine is used as the limiting reagent.

alized 1,4-substituted triazoles. In the case of compound **14c**, the reaction was also performed with the amine as the limiting reagent, and these conditions proved to be far more efficient. The caffeine derivative **14d** is particularly interesting since three different heterocyclic subunits can be assembled, without any use of metal catalysis, even if the reaction conditions still need to be optimized. The removal of the xanthate group is crucial since it very readily undergoes aminolysis and would thus interfere with the Sakai sequence.

In summary, by exploiting the observations of Wood and coworkers, we have succeeded in overcoming the difficult problem of chemoselective reductive dexanthylation. We now have in hand a robust sequence to access a large array of polyfunctionalized α,α-dichloketones. In addition to expanding significantly the scope of processes such as the Sakai and [4 + 3]-cycloaddition reactions and many others that can now be examined, this new development provides a convenient means of accomplishing a highly desirable synthetic transform, namely, the conversion of alkenes **15** into the higher unsaturated esters **16** with the valuable *Z*-configuration (Scheme 8). Such a transformation would be more complicated to accomplish by traditional approaches, as it would normally require reagents generally incompatible with sensitive functionality.

Scheme 8. Conversion of Alkenes 15 into Higher *Z*-Alkenoates 16



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02636.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is respectfully dedicated to the memory of Prof. István E. Markò (Université Catholique de Louvain).

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