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Radical Solution to the Alkylation of the Highly Base-Sensitive 1,1-Dichloroacetone. Application to the Synthesis of *Z*-Alkenoates and *E,E*-Dienoates

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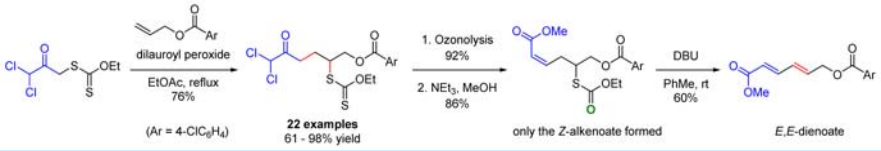
Supporting Information



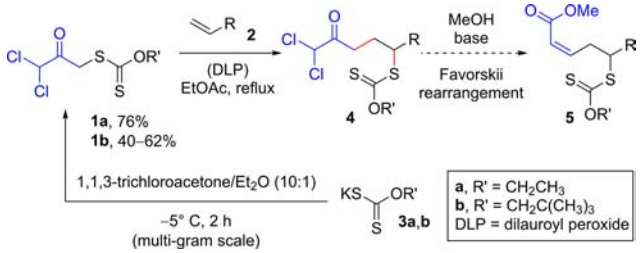
ABSTRACT: A simple radical-based route to *gem*-α-dichloroketones, relying on the degenerative addition transfer of (*S*)-[3,3-dichloro-2-oxopropyl]-*O*-ethyl dithiocarbonate (xanthate), is described. The adducts can then be converted into *Z*-enoates by exposure to Et_3N in methanol. In the case of certain substrates, it was possible to form skipped dienoic acid and methyl *E,E*-dienoates.

Olefins are a ubiquitous feature of biologically significant molecules[1] and serve as fundamental substrates for many widely exploited synthetic transformations.[2] The stereochemical configuration of the olefin, defined as *E* or *Z*, influences its biological properties and chemical reactivity.[3] While numerous methods detailing the preparation of *E*-olefins exist,[4] the synthesis of *Z*-olefins remains comparatively less well described and is often problematic.

One underutilized approach to the synthesis of *Z*-olefins is the base-catalyzed Favorskii rearrangement of *gem*-α-dihaloketones.[5] The application of this approach to the synthesis of *Z*-olefins has been restricted by difficulties associated with the requisite *gem*-α-dichloroketo unit, which is practically difficult to handle and whose preparation often involves the use of reagents that are not tolerant of a broad spectrum of functional groups.[6] The use of strongly acidic reagents[7] or highly reactive organometallic species generated at very low temperatures is often required,[8] thereby confining these chemistries to simpler molecular systems. Furthermore, the extensive sensitivity to base of 1,1-dichloroacetone has precluded approaches involving alkylation of its enolate (see discussion below).

As part of our studies on the radical additions of xanthates,[9] we have examined the addition of α-chloroacetonyl xanthate to various olefins,[10] and the success of this methodology led us to suppose that similar xanthate-transfer-based processes would allow the α,α-dichloroketo unit to be appended to a variety of alkenes via a carbon−carbon bond-forming step. The advantage of this strategy, described in Scheme 1, is that the xanthate-transfer process allows us to combine xanthate **1** with olefins such as **2** to generate adducts of the form **3** under *neutral and mild conditions*. This feature would potentially overcome difficulties previously restricting the application of the Favorskii rearrangement of α,α-dihaloketones to the synthesis of *Z*-olefins, as the former allows the α,α-dichloroketo handle to be easily incorporated into complex molecules according to a process that limits typical ionic side reactions and does not require the use of harsh reagents.

Scheme 1. Xanthate-Transfer Reaction and Favorskii Rearrangement



To assess the merits of our strategy, a simple and scalable synthesis of xanthate **1** was required. This, however, proved to be a nontrivial task, as direct substitution of commercially available 1,1,3-trichloroacetone with potassium *O*-ethyl xanthate under a variety of conditions resulted in inseparable mixtures of the mono-, di-, and trisubstituted products. After extensive experimentation, we determined that the slow addition of the xanthate salt to a large excess of 1,1,3-trichloroacetone (>10 equiv) at low temperature (−5 °C) allowed the requisite xanthate to be prepared on multigram scale and in a synthetically practical yield of 76% (Scheme 1). The xanthate salt is sufficiently basic to induce enolate formation from dichloroketone **1a**, resulting ultimately in unwanted multiple substitutions (via an oxy allyl cation analogous to **6a**; see Scheme 4 and discussion below). Hence, there is a need for the slow addition to keep the basicity as low as possible.

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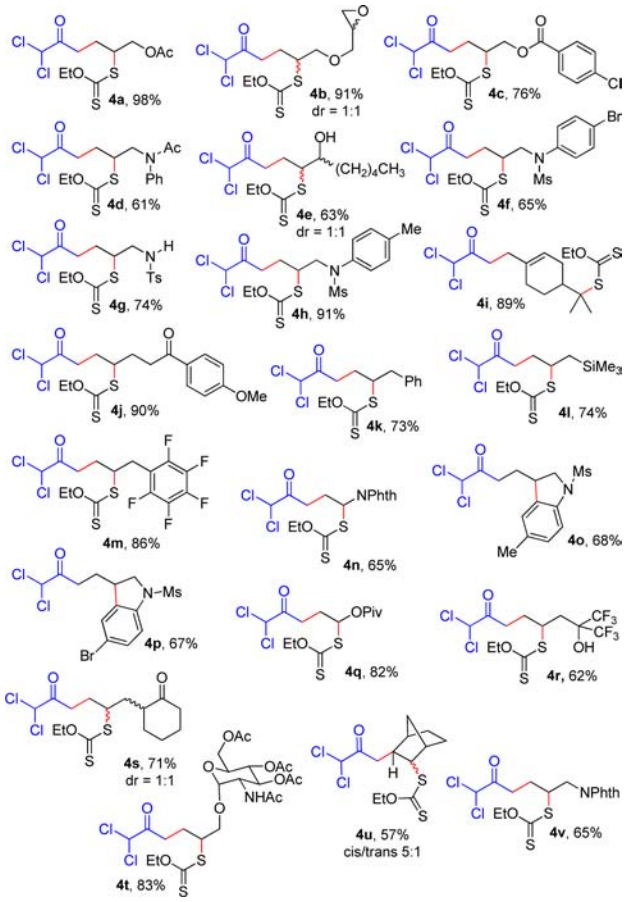
With a good stockpile of xanthate **1a** available, we set out to determine the substrate scope of the radical addition of **1** to various olefins according to the reaction manifold outlined in Scheme 1. The xanthate adducts synthesized in this way are detailed in Scheme 2; they demonstrate the broad functional group tolerance of the xanthate addition-transfer process, allowing us to generate α,α-dichloroacetonyl xanthate adducts with olefins containing esters (**4a**, **4c**), ketones (**4j**, **4s**), epoxides (**4b**), alcohols (**4e**), amides (**4d**), sulfonamides (**4g**, **4h**), imides (**4n**), halogens (**4f**, **4m**), silicon (**4l**), aromatic groups (**4k**), and highly functionalized sugars (**4t**) in good yields. Consistent with our previously established protocol,[11] compounds **4f** and **4h** could be further subjected to stoichiometric amounts of dilauroyl peroxide (DLP) in refluxing ethyl acetate at a higher dilution (0.1 M) to generate the corresponding indoline derivatives **4o** and **4p** *with no observable degradation of the α,α-dichloroketo unit*. Compound **4i** results from the addition−fragmentation to β-pinene and allows us to incorporate an olefin into the resulting adduct.[12]

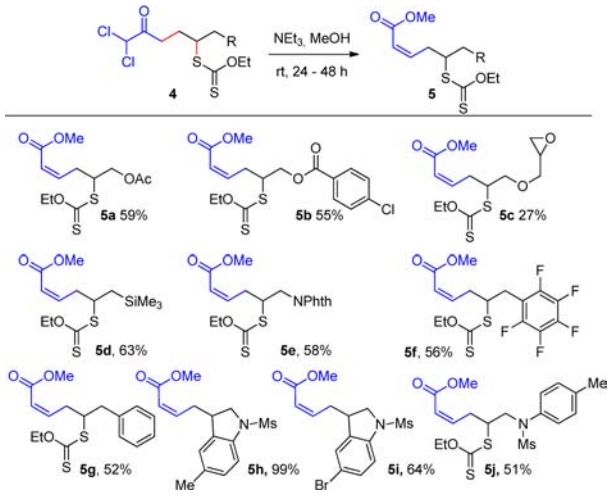
The facile generation of α,α-dichloroacetonyl xanthate adducts allowed us to turn our attention to the Favorskii chemistry of these species. We hoped to affect the transformation via a mild and simple protocol and found that the rearrangement could indeed be carried out by treating the α,α-dichloroacetonyl products with an excess of triethylamine in methanol at ambient temperature. The results of these initial rearrangements are detailed in Scheme 3 and proved to be, in every case, completely selective for the formation of the *Z*-alkene.

Scheme 2. Addition of 1a to Various Olefins[a]



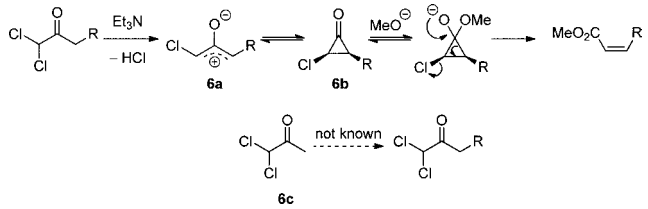
[a]Reactions performed in refluxing EtOAc in the presence of small amounts of DLP (DLP = dilauroyl peroxide).

Scheme 3. Initial Results of the Favorskii Rearrangement



The formation of the *Z*-alkenoate is presumed to be the result of the disrotatory electrocyclization of oxy allyl cation **6a** (Scheme 4) to give *cis*-disubstituted cyclopropanone **6b**.[13]

Scheme 4. Z-Olefin Formation



Reaction of the latter finally gives rise to the observed product via backside attack of the C−Cl bond. Oxy allyl cations such as **6a** are highly electrophilic and have been used in [3 + 4] cycloadditions with electron-rich dienes and heteroaromatics, especially furans.[8] It is the very easy formation of oxy allyl cation **6a**, even under extremely mild basic conditions, which complicated the synthesis of our reagent **1**. This factor has, furthermore, precluded any attempt to alkylate 1,1-dichloroacetone **6c**, a transformation that is not known, as far as we can tell. These observations make the present radical addition even more remarkable and useful, as it fills a serious gap in synthetic methodology.

The yields of the rearranged compounds obtained via our initial attempts at the Favorskii chemistry, while synthetically useful, were consistently only moderate, with the notable exception of **5h**. This compound lacks the residual xanthate moiety, and we suspected that reaction of the potentially nucleophilic thiocarbonyl group with the oxy allyl cation intermediate was responsible for the observed inefficiency of conversion. Attempts to reductively remove[14] the xanthate group prior to the Favorskii step proved to be unsuccessful, so we began to search for simple modifications to this group that would alter its ionic reactivity. Inspired by our previous work,[9] we first examined the *O*-neopentyl analogue **1b** (Scheme 1) to assess whether the increased bulk would slow the unwanted interaction with the oxy allyl cation intermediate and thus lead to a better yield of the desired Favorskii transformation.

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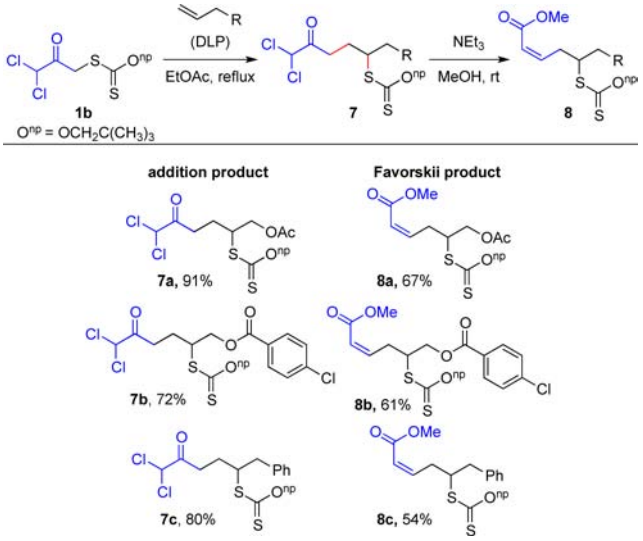
The results of the radical addition of the *O*-neopentyl xanthate **1b** to various olefins and the Favorskii rearrangements of the resulting adducts **7** are shown in Scheme 5. The poor purity of *O*-neopentyl xanthate **1b**, resulting from difficulties associated with its synthesis and purification, led to generally lower yields for its addition to olefins than was the case for the *O*-ethyl analogue **1a**, as can be seen by comparing the yields of compounds **7a** and **7b** with **4a** and **4c**.

Scheme 5. Addition of Xanthate 1b to Various Olefins and Subsequent Favorskii Rearrangement

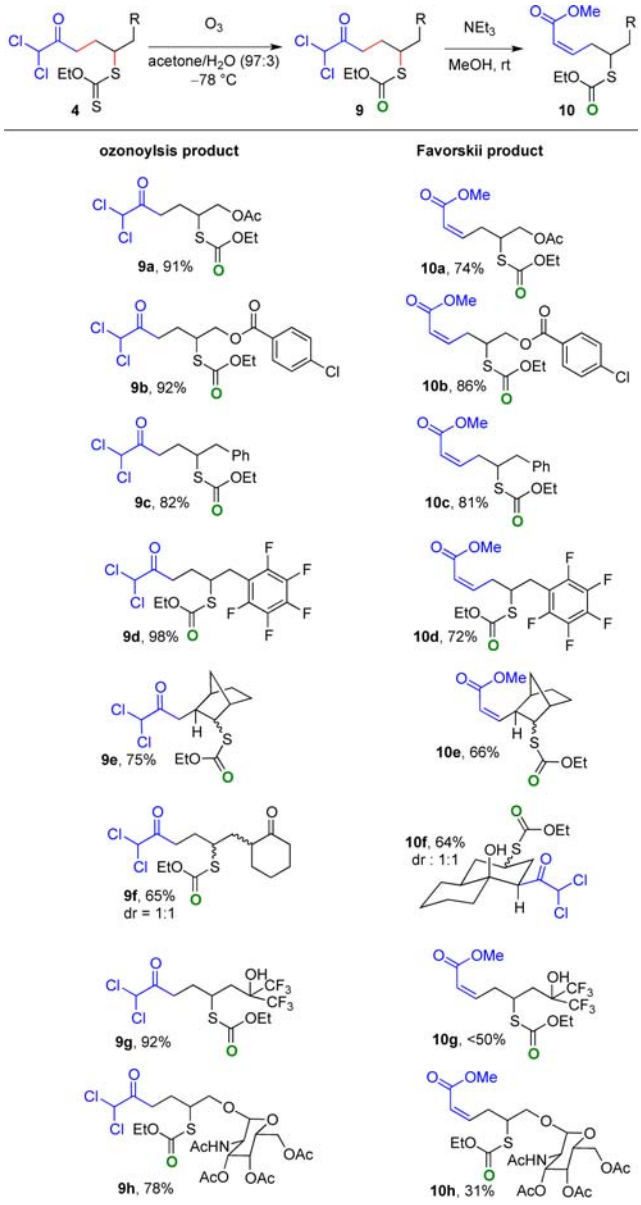


Moreover, the yields observed for Favorskii rearrangements of adducts **7** containing the *O*-neopentyl xanthate did not represent a significant improvement over analogous reactions carried out on the *O*-ethyl-containing substrates, as can be seen by comparing the yields of compounds **8a**, **8b**, and **8c** with those of compounds **5a**, **5b** and **5g**. This suggested that the neopentyl group, despite its greater bulk, was unable to attenuate the reactivity of the xanthate group and limit the undesired side reactions.

In view of these unfavorable results, we decided to replace the thiocarbonyl group with the less nucleophilic carbonyl group. We had shown that this transformation could be readily accomplished by ozonolysis.[15] The results of the ozonolysis of various xanthate adducts and the subsequent subjection of the thiocarbonates thus obtained to the Favorskii rearrangement are shown in Scheme 6.

Ozonolysis of the xanthate adducts proceeded in good yield, and crucially, the yields for the Favorskii rearrangement of the resulting thiocarbonate derivatives were consistently much higher than those seen for their xanthate analogues (as can be seen by comparing the yields of compounds **10a**, **10b**, **10c**, and **10d** with compounds **5a**, **5b**, **5g**, and **5f**). This supports our hypothesis regarding the cause of the inefficiency of the Favorskii rearrangement of the latter. Lower yields for the rearranged product were invariably observed when acidic groups were situated in such a way as to react in an intramolecular sense with the oxy allyl cation intermediate (compound **9g**). The low yield of sugar derivative **10h** is in part due to methanolysis of the acetate groups. Finally, in the case of **9f**, exposure to triethylamine resulted in ring closure to furnish bicyclic compound **10f**, isolated as an equimolar mixture of epimers

Scheme 6. Ozonolysis and Subsequent Favorskii Rearrangement on the Xanthate Adducts



Further support for our conjecture is found in Scheme 7, whereby a second radical addition[16] of the phthalimido xanthate adduct **4n** to *N*-allyl-4-chlorobenzamide allowed us to situate the residual xanthate moiety in the product **11a** further away from the oxy allyl cation intermediate, thereby resulting in a 79% yield of rearranged product **11b**. A similar situation prevailed in the rearrangement of xanthate adduct **4i** and allowed for the synthesis of the skipped diene **11c**, in which the *Z* configuration of the enone double bond was preserved in a synthetically useful yield. It is worth noting that in this case the use of methanol resulted in partial isomerization of the alkene. This is due to the higher acidity of the enolizable protons of the skipped diene in ester **11d**. In contrast, the acidity of enolizable protons in the free carboxylic acid is considerably lower and the stereochemistry of the *Z*-alkene is therefore preserved.

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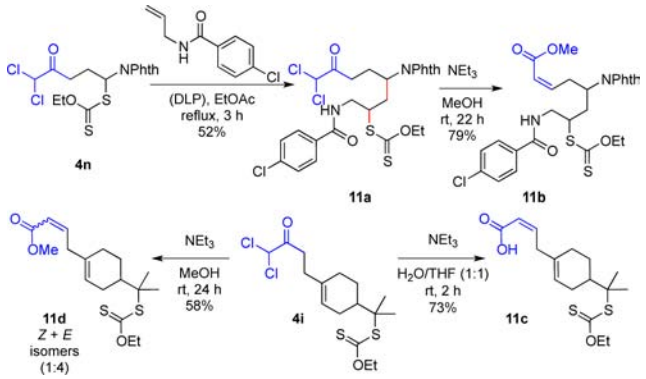
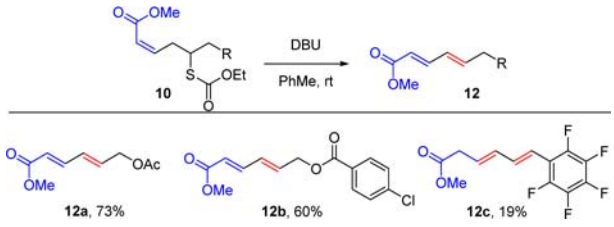
Scheme 7. Effect of Proximity to the Xanthate Residue on the Favorskii Rearrangement



The thiolcarbonate-containing enones **10a**, **10b**, and **10d** were further elaborated into dienes **12a**, **12b**, and **12c**, respectively (Scheme 8), via reaction with DBU in toluene at ambient

Scheme 8. Diene Synthesis via Elimination of the Thiocarbonate



temperature. In the case of compounds **10a** and **10b**, the enone double bond in the product was isomerized cleanly to the *E* isomer. In the case of **10d** only diene **12c** could be isolated from the reaction mixture, albeit in poor yield.

Xanthate **1a** solves indirectly, but powerfully, the problem of alkylating 1,1-dichloroacetone and provides a direct, convergent access to a large variety of functionalized α,α-dichloroketones. These, in turn, lead to the corresponding *Z*-enoates and, in some cases, to *E,E*-dienoates, thus complementing existing methods, especially the Still–Gennari and Ando variations of the Horner–Wadsworth–Emmons olefination[17] and expanding considerably the utility of the hitherto little used variation of the Favorskii rearrangement. The fact that the sensitive α,α-dichloro ketone survives the carbon–carbon bond forming process is a testimony to the extremely mild experimental conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02681.

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated with respect to the memory of Dr. Suren Husinec (Duochem).

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