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Toluene as a novel carrier of xanthates—preparation, use and surrogate of *S*-tri- and di-chloromethyl xanthates

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ABSTRACT

Toluene has been identified as a novel carrier of xanthates. Their corresponding fragmentative precursors proved to behave efficiently in radical group transfer reactions. As examples, unprecedented *S*-tri/di-chloromethyl xanthates could be prepared, isolated and further used in radical additions to olefins. Their precursors (de-aromatized toluene upon which is grafted, at one end, a tri/di-chloromethyl-group and, at the other end, a dithiocarbonyl group) can also be used directly in the transfer of both groups to olefins. The re-aromatizing loss of toluene by radical initiated fragmentation of the precursors brings thus new opportunities to the chemistry of xanthates, exemplified here in the intermolecular additions to olefins of new *S*-tri/di-chloromethyl xanthates.

Introduction

The transfer of alkyl residues to olefins is a very useful tool offered by radical chemistry.[1–3] In the case of trichloromethyl radical transfer, the use of trichloromethyl bromide is most certainly very efficient.[4] Other sources of trichloromethyl radical are known, such as chloroform and tetrachloromethane,[5] although more difficult to activate due to stronger C–X (X = Cl, H) bond dissociation energy. The advantageous, desulfitative use of trichloromethanesulfonyl chloride over tetrachloromethane in halogen atom-transfer radical addition, discovered in 1952,[6] has been studied and extended to other reagents recently.[7]

In general, alkyl radical transfers may advantageously be performed from the xanthate analogues of alkyl halides.[8–10] Even though they usually need to be prepared (by substitution of halide with *O*-alkyl xanthate salt), the advantages they offer as alternative reagents warrant the long standing interest they have demonstrated over the years. However, to the best of our knowledge, no *S*-tri- nor *S*-dichloroalkyl xanthate has been described so far.

As part of a synthetic route to novel fungicides, we became interested in trichloromethyl radical transfers. What is more, we planned in particular for an intermediate skeletal rearrangement before termination of our radical chain process. As can be seen from Figure 1,[8] this is one advantage that a xanthate such as **1**, (a *S*-trichloromethyl-xanthate if R- would be trichloromethyl-) would offer over the sources cited above, due to the longer lifetime of the radical **4**. Indeed, the propagation by transfer of the xanthate group to **4** via **5** may be fast, but it is reversible, radical **4** being therefore continuously regenerated from **5**, during the time of the reaction.

This obviously leaves the opportunity for the intermediate radical **4** to be diverted from its normal course. The use of xanthates offers this exact opportunity to run the radical chain under thermodynamic control, where standard reagents such as bromotrichloromethane

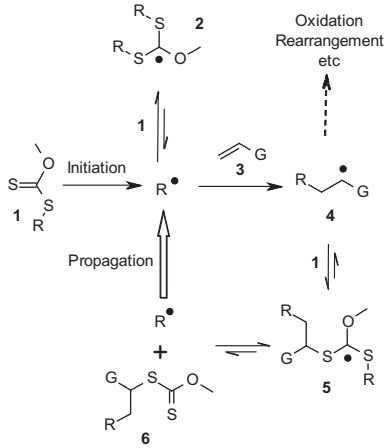

Figure 1. A typical xanthate chain reaction, with a reversible propagation step.

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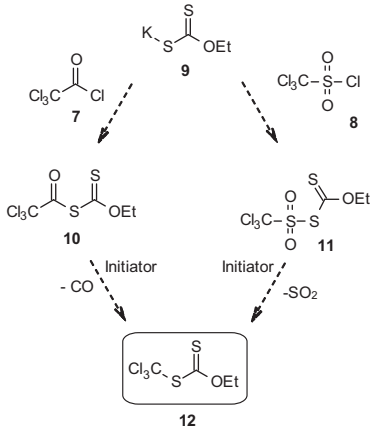


Figure 2. Approaches to **12** directly inspired from the literature.

sometimes limit the outcome of a radical transfer reaction to kinetic products.[11] Another advantage is the possible oxidation of intermediate radical **4** by the initiator peroxide when used as a stoichiometric oxidant (Radical-Polar cross-over reaction). For these two reasons, we became very interested in the synthesis and use of a *S*-trichloromethyl xanthate such as **12**.

Contrary to *S*-trichloromethyl xanthates, *S*-trifluoromethyl xanthates were prepared over a decade ago,[12–14] and we planned to follow the same steps for accessing **12**. Alongside the decarbonylative approach, the analogous desulfonylative transformation may also, *a priori*, open an access to the generation of **12** (Fig. 2).

Before reporting on the use of **12** advantageously for intermediate radical/cation rearrangements, we would like to report in this Letter the preparation of *S*-di- and *S*-tri-chloromethyl xanthates, as well as the direct use of surrogates via an aromatizing fragmentation concept hitherto unprecedented in the chemistry of xanthates.

Results and discussion

The preparation of *S*-trichloromethyl xanthate **12** as according to plans proved unsuccessful. Our efforts to approach it as depicted in Figure 2 failed in delivering any desired *S*-trichloroacetyl xanthate **10** or *S*-trichlorosulfonyl xanthate **11**. Their isolation being obviously very difficult due to high intrinsic reactivity, we attempted to decarbonylate **10** in situ, as in the precedented case of trifluoromethyl xanthate. But this one-pot approach, as well as the in situ desulfonylation of **11**, failed to deliver any desired product **12**. We then looked for less obvious accesses to **12**, ideally by using a more stable, isolable precursor than **10** or **11**.

As part of a long standing interest in little known rearomatizing chemistry,[15] we were aware of the existence of bromide **13**, described in 1997 (Fig. 3).[16] We then surmised that its substitution by potassium *O*-alkyl xanthate salts should deliver stable *S*-trichloromethyl xanthate precursors such as **15** or **16**. Similarly, the dichloromethyl analogue **14** would give an access to *S*-dichloromethyl xanthate precursor **17**. We planned to duplicate the

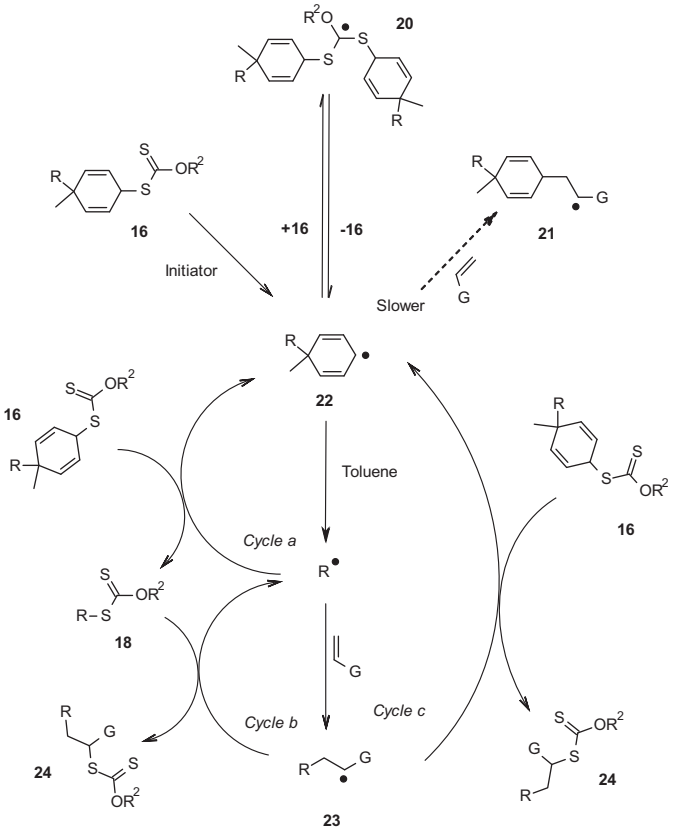


Figure 4. Design of surrogates and/or precursors of di/tri-chloromethyl xanthates.

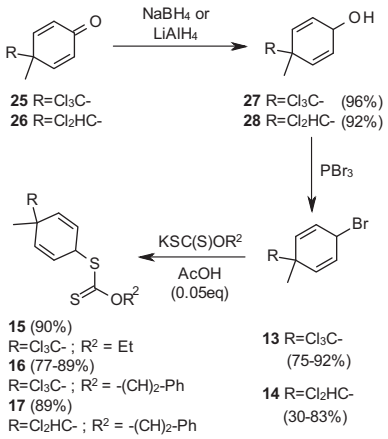


Figure 5. Synthesis of **15**, **16** and **17**.

chemistry to deliver both *S*-tri- and *S*-di-chloromethyl xanthates **18** and **19**.

As depicted in Figure 4, we indeed envisaged that after initiation, starting from example from the trichloromethyl analogue

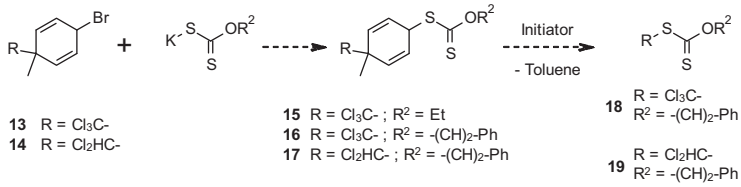


Figure 3.

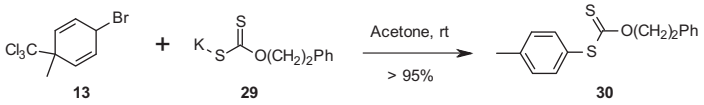


Figure 6. Issue in the synthesis of **16**.

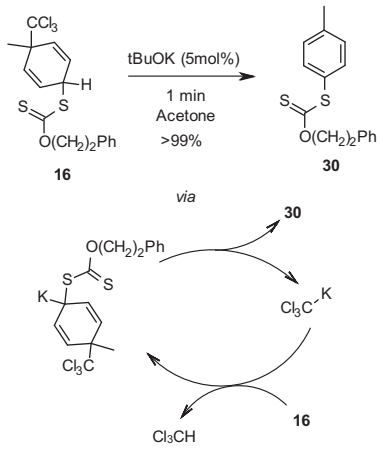


Figure 7.

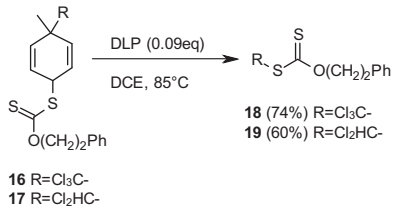
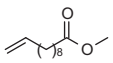
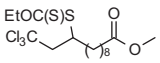
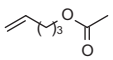
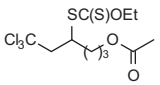
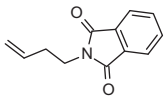
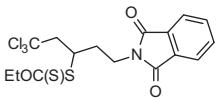
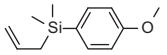
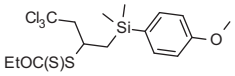
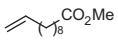
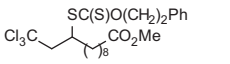
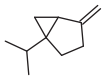
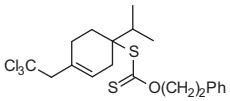
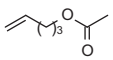
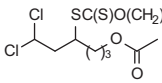
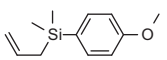
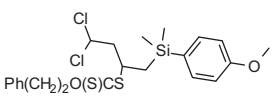


Figure 8. The efficiency of cycle a (Fig. 4).

16, a re-aromatizing fragmentation to toluene and trichloromethyl radical **R**· should happen very fast, and propagation (Cycle a) should lead to **18**. In the absence of olefin, **18** should be isolable. But more interestingly, if this fragmentation is performed in the presence of an olefin, and is taking place faster than addition of **22** to the olefin, **16** might then not be a precursor of *S*-trichloromethyl xanthate **18** but potentially a surrogate of it. The radical **R**· (here, Cl_3C·) would still have the choice to add on xanthate **16**, and generate in situ **18**, which would then enter Cycle b. But **R**· could add as well directly on the olefin to give **23**, which would propagate to **24** by addition to **16** (cycle c), without the intermediacy of *S*-trichloromethyl xanthate **18**. If the reaction would be channelled mainly through cycle c, this might open new opportunities to the chemistry of xanthates, especially in terms of relative stabilities of **R**· versus **23** for efficient propagation, as will be discussed in the perspectives.

The preparations of **15**, **16** and **17** were initiated following literature steps to the known bromide **13**,[16] from commercially available **25**, and the sequence was duplicated from commercially available **26** (Fig. 5). Reduction of **25** with $NaBH_4$, and of **26** with $LiAlH_4$, led to alcohols **27** and **28** with good yields, no purification being required. Bromination to **13** was performed several times from **27**, and always with good yields (75–93%), but only twice from **28**, once with similar yield as for **27**, unfortunately on larger scale with only 30% yield. This step was not optimized but the crude taken as such to the next step (both **13** and **14** seem quite

Table 1
Direct reactions of surrogates **15**, **16** and **17** with olefins

	Xanthate	Olefin	Product	Yield (%)
1	**15**			55
2	**15**			63
3	**15**			60
4	**15**			75
5	**16**			65
6	**16**			59
7	**17**			55
8	**17**			44

Conditions:[21] Lauroyl peroxide (7.5–22%), DCE (1 M), 80 °C, 90–270 min.

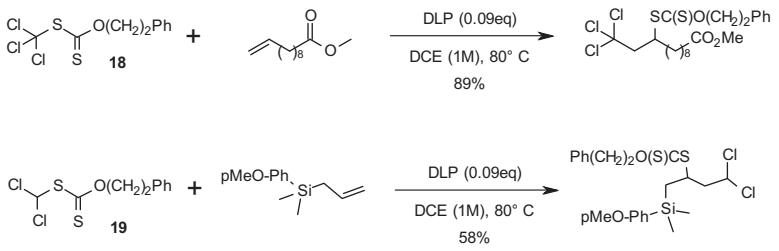


Figure 9.

sensitive to hydrolysis, already on TLC plates, and probably would not stand a chromatography column). Straightforward substitution with the commercially available xanthate salt **9** afforded **15** and with the xanthate salt **29**[17] afforded solid, shelf-stable **16** and **17** with good yields after purification. For a cheaper and large scale access, **25** can be prepared from the Zincke reaction of p-cresol with CCl_4 in the presence of $AlCl_3$,[18] and **26** can be prepared by the abnormal Reimer–Tiemann reaction of *p*-cresol with chloroform and NaOH.[19]

The use of 5% of AcOH in converting **13** to **16** turned out to be crucial for deciding the outcome of the reaction. Indeed, our first attempt to convert **13** to **16** led unexpectedly to aromatized xanthate **30** in excellent yield (Fig. 6).

Even though the quantitative NMR of xanthate salt **29**, prepared as reported in the literature,[17] showed excellent purity (>99%), we could only explain this result by the catalytic decomposition of the desired xanthate **16** by traces of a strong base, putatively residual *t*BuOK or $PhCH_2CH_2OK$, coming from the preparation of **29**. In order to avoid this side reaction, we then ran the same substitution in the presence of 5% of acetic acid and successfully got the desired xanthate **16** with yields varying between 77% and 89%. With **16** in hand, its instability towards catalytic amounts of a strong base could be confirmed by running the catalytic decomposition on purpose (Fig. 7).

To our great delight, the direct use of **15**, **16** and **17** as surrogates of **12**, **18** and **19** proved successful, and reacted as hoped with unactivated olefins with acceptable yields (Table 1). As can be seen from entry 6, the formation of a 6-membered ring from sabinene supports our initial thoughts that the intermediate radical (formed by addition of trichloromethyl radical to sabinene) is allowed enough time to rearrange towards the thermodynamic product, as sabinene has been known to be used exactly for this purpose (under kinetic conditions, a five membered ring would have been obtained).[20]

To answer whether the reaction goes via in situ intermediacy of *S*-di/tri-chloromethyl xanthates such as **18** and **19**, we wanted to observe if those species are actually present during the reaction. Cycle a was then performed independently by radical initiated fragmentation-recombination (Fig. 8) in the absence of an olefin to deliver **18** with an isolated yield of 74% after purification, and from **17** to deliver dichloromethyl- **19** with 60% yield.

With the now available analytical details of both **18** and **19**, we can ascertain that none of **18** could be detected while monitoring the reactions of **16** with olefins. Xanthate **18** is then not accumulating, and if formed at all, it would then be under steady-state conditions, below our LC/MS detection thresholds. This is not true for xanthate **19**, which was seen accumulating, for example up to 50% during the reaction of **17** with an olefin (entry 8, Table 1), before being consumed in turn to the desired product. This makes close to certain the fact that a significant part at least of **17** was channelled through cycles a then b when reacted with an olefin.

Without much surprise, cycle b works out also very well when ran independently. Both **18** and **19** reacted directly with olefins and delivered adducts faster, and with better yields than did their surrogates **16** and **17** (Fig. 9).

Even though by these experiments we have shown that both cycles a and b are efficient when ran independently, we still ignore what fraction, if any, of the starting materials passes through cycle c.

Conclusion and perspectives

S-Trichloromethyl xanthate **18** and *S*-dichloromethyl xanthate **19** were prepared and isolated here for the first time. Both add efficiently to olefins in a typical chain transfer reaction. But more importantly, their isolation is not necessary as their respective precursors, **15**, **16** and **17**, are giving the same products when reacted with olefins. Our objective to prepare trichloromethyl xanthate to allow for intermediate radicals to rearrange was also demonstrated to be efficient, as from the reaction of **16** with sabinene. From this result, we are confident that **16** can be used to deliver thermodynamic products of special interest to us for the preparation of biologically active ingredients, or be used in radical-polar crossover reactions to allow for intermediate cationic rearrangements. This will be reported in due time.

Clarification that cycle c is operating would also be important. Evaluating efficiency of cycle c could come for example by identifying a xanthate carried by toluene, that would transfer **R**· efficiently to an olefin whereas the direct **R**SC(=S)OR^2 would not, for example if **R**· is less stable than radical **23**. If possible, and if we can experimentally favour cycle c, consequences for xanthate chemistry might be quite large.

Indeed, the novel aromatizing fragmentation concept described in this Letter might break the propagation constraint, which is, that in order to get the reversible propagation forward (as in Fig. 1), the radical **R**· transferred to the olefin has to be at least as, and preferably more stable than, intermediate radical **4** coming from its addition to the olefin. As can be seen in Figure 4, the radical **22** formed by breaking of the C—S bond of **16** is not the one that is transferred to the olefin. It is a relatively stable radical (secondary, bis-allylic) and we can assume that it will be generated quite easily in most cases, but due to the highly exergonic, aromatizing fragmentation to toluene, it might produce in turn significantly less stable **R**·. If a couple of obvious kinetic conditions are met, the propagation would still be brought forward via cycle c, even with unstable R·. How much of this hypothesis is false will be evaluated in a near future.

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21. *Information on procedures:* Compound **27** was prepared as described in Plieninger, H.; Keilich, G. *Chem. Ber.* **1958**, *91*, 1891. Compound **28** was prepared as **27**, but using $LiAlH_4$ instead of $NaBH_4$. Compound **13** was prepared as described in Ref. 16, omitting the drop of Pyridine and using DCM as solvent. Compound **14** was prepared as **13**. Compound **15** was prepared as follows: To a solution of **13** (4.72 mmol) in acetone (19 mL) was added EtOC(=S)SK (1.05 equiv, 4.956 mmol) in one portion. The resulting suspension, which turned immediately light yellow, was stirred for 5 min before being concentrated under reduced pressure. The solid residue was dissolved into dichloromethane and washed twice with water. The combined aqueous phases were extracted once with dichloromethane, the combined organic phases were then dried on solid sodium sulfate, filtered and concentrated under reduced pressure. The resulting pale brown oil (2 g) was purified by column chromatography (60 g silica gel, pure heptane as eluent) and 1.41 g (4.241 mmol) of compound **15** (2 diastereoisomers) was isolated as a light yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.41–1.45 (2× t, 3H) 1.49–1.57 (2× s, 3H) 4.59–4.77 (m, 2H) 4.95–5.06 (2× m, 1H) 6.03–6.19 (m, 4H) Compounds **16** and **17** were prepared in an analogous fashion as **15**, the only difference being the addition of 0.05 equiv of AcOH prior to the addition of $Ph(CH_2)_2OC(=S)SK$. Compound **18** or **19** was prepared as follows: To a 1 M solution of **16** or **17**, (respectively), in dichloroethane under Argon, at 80 °C, is added 0.09 equiv of dilauroyl peroxide. More portions of it may be required every 90 min if the reaction is not complete. When the reaction is over, the solvent is evaporated and the products (**18** or **19**, respectively) are isolated from column chromatography (Eluant: gradient from pure heptane to 19:1 Heptane/ethyl acetate). *Reactions of **15**, **16**, **17**, **18** or **19** with olefins, typical procedure:* To a 1 M solution of xanthate **15**–**19** in dichloroethane under Argon, is added 1–1.5 equiv of olefin. The mixture is heated at 80 °C before 0.075 equiv of dilauroyl peroxide is added. More portions of it may be required every 90 min if the reaction is not complete. When the reaction is complete, the solvent is evaporated and the products are isolated under pure form from column chromatography.