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N,S-Dimethyldithiocarbamyl oxalates as precursors for determining kinetic parameters for oxyacyl radicals†

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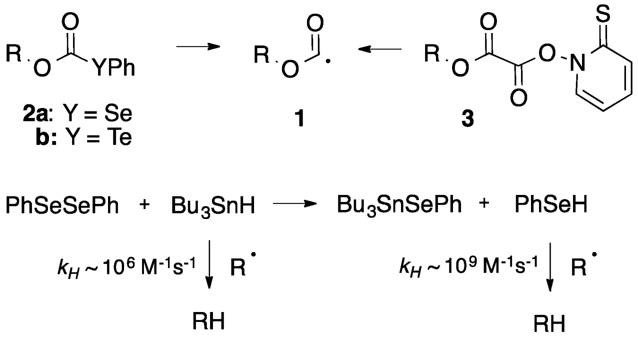
N,S-Dimethyldithiocarbamyl oxalates (e.g. 6, 10) are novel, readily prepared precursors to alkyloxyacyl radicals 1 that are more suitable for kinetic studies than existing precursors; 10 has allowed the determination of accurate rate data for the cyclization of the butenyloxyacyl radical 5 (k_c = 1.2 × 10^7 s^{-1} at 21 °C).

Methods for the generation of carbon-centred free radicals abound.[1] Halides, arylselenides, aryltellurides, xanthates, pyridinethioneoxycarbonyl (PTOC, Barton)[2] esters and dithiocarbamyl (Kim) esters,[3] while most commonly used, form just a subset of the chemical toolbox available to the practitioner when considering the use of radical chemistry in synthesis.[1]

Despite this, there are still some classes of carbon-centred radical for which no robust precursors have been reported. Oxyacyl radicals (**1**) are one such class of radical.[4] To date only phenylselenide (**2a**),[5] phenyltelluride (**2b**)[6] and PTOC oxalate (**3**)[7] precursors have appeared in the literature (Scheme 1), and these have their own specific limitations and drawbacks. For example, studies using tellurides (**2b**) and PTOC oxalates (**3**) are complicated by photochemical instability,[7,8] while the former (**2a**) can be contaminated with traces of diphenyl diselenide,[9] which for the purposes of synthesis can often present no real disadvantage, however for those of us interested in determining accurate rate data, this contaminant provides some significant challenges. Diphenyl diselenide is known to react rapidly with chain-carrying reagents such as tributyltin hydride to afford benzeneselenol (Scheme 1).[9] This impurity reacts some three orders of magnitude faster as a hydrogen atom donor than the intended stannane,[10] and even undetectable levels of diphenyl diselenide contamination can skew the interpretation of the kinetic data.



Scheme 1

With this in mind, we recently reported the use of high-level computational techniques for the determination of kinetic data for the 5-*exo* and 6-*endo* modes of ring closure of a series of substituted acyl and oxyacyl radicals.[4] While the calculated rate constants (k_c) for the cyclization of the acyl radicals (*e.g.* **4**) were in good agreement with available experimental data (Scheme 2), we reported that the oxyacyl system (**5**) cyclizes with a rate constant of 8 × 10^7 s^{-1} (80 °C) using G3(MP2)-RAD, well over an order of magnitude faster than that reported by Newcomb (4 × 10^6 s^{-1}),[7] based on data provided by Bachi.[5] We argued that this discrepancy was largely the result of PhSeSePh contamination during the experiments performed by Bachi, a situation acknowledged by Newcomb when he concluded that "one must be aware of the fact that generation of PhSeH from small impurities of PhSeSePh or from photolysis can be problematical".[7]

In search of a more robust oxyacyl radical precursor appropriate for kinetic studies, we explored the possibility that "Kim esters" derived from oxalic acid may be suitable for this purpose.[3]

We now report that alkyl *N,S*-dimethyldithiocarbamyl oxalate esters (*e.g.* **6**) are readily prepared compounds that generate oxyacyl radicals under photochemical conditions. In addition, these novel precursors have allowed us to kinetically "recalibrate" the cyclization

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† Electronic supplementary information (ESI): Experimental details for the preparation of **6** and **10**. General protocol for kinetic experiments. ^{1}H and ^{13}C NMR spectra of compounds **6** and **10**. See DOI: 10.1039/c4cc06132b

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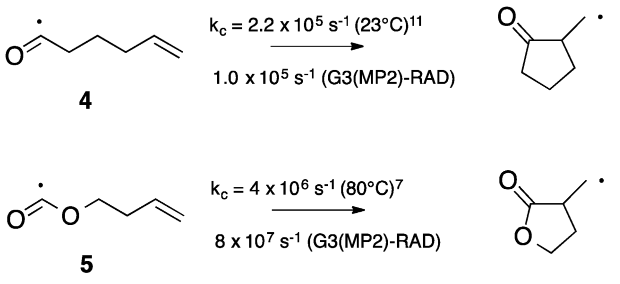


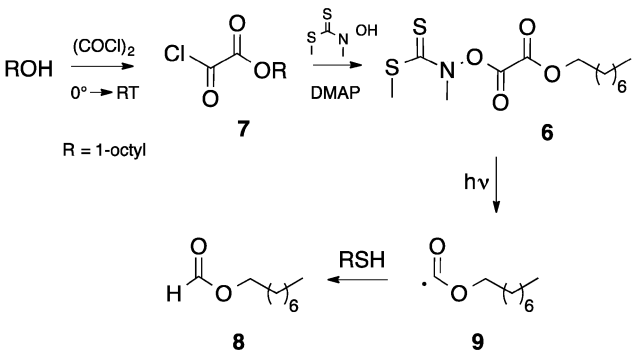
Scheme 2

of **5**; the value of k_c reported herein is in excellent agreement with our previously reported calculations.

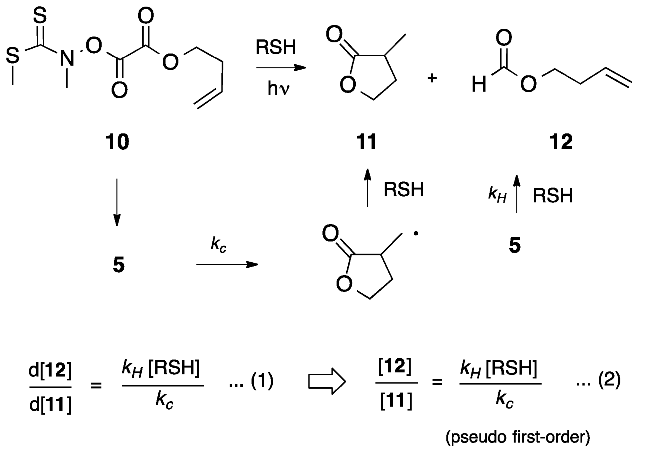
N,*S*-Dimethyldithiocarbamyl esters (Kim esters) were developed by Kim as more robust precursors for alkyl radicals than the corresponding pyridinethioneoxycarbonyl (PTOC) esters reported by Barton a few decades ago,[3] and we have successfully employed these precursors on several occasions.[12,13] Guided by this previous work, 1-octanol was stirred in oxalyl chloride overnight. Following removal of the solvent *in vacuo*, the residue, presumed to be the chloride **7** was dissolved in dichloromethane and further reacted with *N*-hydroxy-*N*,*S*-dimethyldithiocarbamate[3] and a catalytic amount of DMAP in dichloromethane to afford **6** in 94% yield (Scheme 3). The dithiocarbamate **6** was not stable to chromatography, however, in our hands, with the correct stoichiometry and careful workup, **6** could be isolated with excellent purity.†

When a solution of **6** and *tert*-dodecanethiol (RSH, 0.6 M), in benzene, was irradiated in a Rayonet photochemical reactor (350 nm) for one hour, we were delighted to observe the quantitative formation of 1-octyl formate (**8**) by GC analysis and direct comparison with an authentic standard; presumably **8** is formed from the intermediate oxyacyl radical **9**. This outcome demonstrates the synthetic utility of this novel radical precursor.

We next turned our attention to the cyclization of the 3-butenyloxyacyl radical **5**. The dithiocarbamyl precursor **10** was prepared in identical manner to **6** from 3-butenol and was isolated in 85% yield.† Given that the rate constant (k_H) for hydrogen transfer from tributyltin hydride to an oxyacyl radical **1** has been previously reported,[7] initial experiments were carried out under photochemical conditions (Rayonet) in benzene using **10** and Bu_3SnH. Disappointingly, these experiments provided reaction mixtures that were difficult to analyse by GC because of broad overlapping signals that we ascribed to tin-based byproducts. Consequently, an alternative kinetic paradigm was required.



Scheme 3



$$\frac{d[\mathbf{12}]}{d[\mathbf{11}]} = \frac{k_H\,[\mathrm{RSH}]}{k_c} \quad \ldots (1) \quad \Rightarrow \quad \frac{[\mathbf{12}]}{[\mathbf{11}]} = \frac{k_H\,[\mathrm{RSH}]}{k_c} \quad \ldots (2)$$

Scheme 4

To our delight, when this reaction was repeated using *tert*-dodecanethiol as the source of hydrogen atom, GC analysis of the crude reaction mixture revealed cleanly the formation of methylbutyrolactone **11** and butenylformate **12** by comparison with authentic samples (Scheme 4). When repeated with a tenfold excess of thiol (pseudo first-order conditions) in benzene (21 °C) at the concentrations listed in Table 1, ratios of [**12**]/[**11**] consistent with radical chemistry (Scheme 4) were observed (Table 1). The relative rate constant k_H/k_c is obtained by linear regressional analysis of the data in Table 1 (Fig. 1) and application of the integrated rate equation (eqn (2)).

Inspection of Fig. 1 reveals excellent linearity ($R^2 = 0.996$) and confirms the validity of eqn (2); a value of the relative rate constant (k_H/k_c) of 0.59 ± 0.02 is obtained. Determining a value for k_c requires knowledge of the rate constant for hydrogen atom transfer (k_H) from *tert*-dodecanethiol (RSH); unfortunately this rate constant has not been determined for oxyacyl radicals **1**.

It is well established that unlike acyl radicals, oxyacyl radicals are not stabilised by resonance, as evidenced by IR spectroscopy and computational studies.[11,14] It is somewhat surprising therefore that the reported value of k_H for radicals **1** reacting with Bu_3SnH ($1.1 \times 10^6\ M^{-1}\ s^{-1}$, 80 °C)[7] is almost identical to that for acyl radicals (*e.g.* **4**).[15] On the basis of

Table 1 Relative rate data (21 °C) for the ring closure of the butenyloxyacyl radical **5** in benzene. Reactions performed under pseudo first-order conditions in *tert*-dodecanethiol (RSH)

[RSH] (M)	[**12**]/[**11**][a]	k_H/k_c (M^{-1})	k_c[b] (s^{-1})
0.43	0.27	0.63	1.1×10^7
0.75	0.41	0.55	1.2×10^7
1.20	0.64	0.53	1.3×10^7
2.00	1.09	0.55	1.3×10^7
2.50	1.46	0.58	1.2×10^7
3.00	1.76	0.59	1.2×10^7

[a] Average of three experiments. [b] Spot value calculated from eqn (2) (see text).

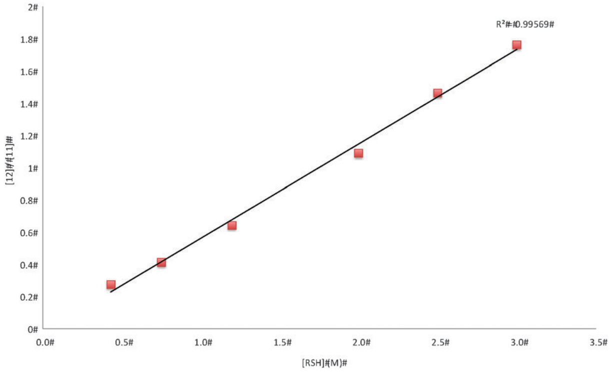


Fig. 1 Dependence of [**12**]/[**11**] on *tert*-dodecanethiol concentration at 21 °C for the cyclization of **5** in benzene.

relative radical stabilities,[14] we would expect **5** to react significantly faster with *tert*-dodecanethiol than its acyl counterpart (**4**). CCSD(T)/aug-cc-pVDZ calculations reported previously suggest that **5** is about 45 kJ mol^{-1} less stable than **4**.[14] Applying this same methodology to other radicals reveals that a primary alkyl radical (*e.g.* ethyl) is about 55 kJ mol^{-1} less stable than an acyl radical, while a vinylic radical (*e.g.* ethylenyl) is calculated to be about 98 kJ mol^{-1} less stable than **4** at CCSD(T)/aug-cc-pVDZ.§ These data, in turn, suggest that an oxyacyl radical such as **5** is more similar in reactivity to a primary alkyl radical than an acyl radical. Importantly, **5** would not be expected to react with a rate constant of an acyl radical (too slow), or a vinyl radical (too fast).

With this in mind, we suggest that **5** abstracts hydrogen atom from *tert*-dodecanethiol with a similar rate constant (k_H) to that of a primary alkyl radical, namely $6.8 \times 10^6\ M^{-1}\ s^{-1}$ at 21 °C.[16]¶ With this assumption, our value of k_H/k_c leads to:

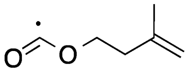
$$k_c = 1.2 \times 10^7\ s^{-1}\ (21\ ^\circ C).$$

This value of k_c is in excellent agreement with our calculated (G3(MP2)-RAD) value of $1.5 \times 10^7\ s^{-1}$ (21 °C)[4] and significantly faster than the value reported previously.[7]

Not only are we delighted with the agreement between our calculated and experimental data, this study provides further validation of our computational methodology for determining rate data and also suggests that our assumption regarding k_H for oxyacyl radicals is approximately correct.

Alternatively, using our calculated value of k_c, we can determine a value for k_H of $7 \times 10^6\ s^{-1}$, slightly (but not significantly) higher than the value used earlier based on the experimental value for a primary alkyl radical (*vide supra*).

Finally, we are now in a position to revisit the work of Bachi and Bosch and provide a more robust value for k_H for Bu_3SnH reduction of **1** by the application of eqn (2). While the authors report data for the ring-closure of **5**, product ratios are reported in neat Bu_3SnH.[5] Consequently, it is difficult to determine reliable reagent concentrations and, from them, to calculate rate constants. On the other hand, more robust data are provided for the cyclization of the related radical **13**. Using the reported product ratio and average value of $[Bu_3SnH]$,[5] together with our value of k_c ($2.7 \times 10^7\ s^{-1}$, 80 °C)[4] for **13**, we suggest that $4.6 \times 10^6\ M^{-1}\ s^{-1}$ (80 °C) is a more appropriate value for k_H when tributyltin hydride reacts with oxyacyl radicals **1**. This value for k_H is well aligned with that for a primary alkyl radical reacting with Bu_3SnH, namely $6.4 \times 10^6\ M^{-1}\ s^{-1}$ (80 °C).[18]



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Notes and references

§ This work.

¶ This is k_H for a primary alkyl radical (5-hexenyl) reacting with *tert*-butylthiol (ref. 16). While many workers have assumed that *tert*-dodecanethiol reacts with the same rate constant as *tert*-butylthiol, we have recently verified, in independent work, that the two reagents react with primary alkyl radicals with rate constants (k_H) within experimental error of each other (ref. 17).

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