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Convergent access to ketones, vinyl esters and vinyl bromides by a tin-free radical addition-intramolecular hydrogen atom transfer†

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Xanthate-mediated intermolecular radical addition, hydrogen atom transfer and sulfonyl radical elimination have been efficiently combined in a new convergent synthesis of ketones and substituted olefins.

The xanthate-mediated intermolecular radical addition has emerged as a powerful synthetic tool.[1] This process allows the efficient addition of a carbon-centered radical to an unactivated olefin and thus the creation of a new carbon–carbon bond under mild, essentially neutral conditions. Recently, this methodology has been successfully combined with the β-elimination and α-scission of alkylsulfonyl radicals[2] resulting in interesting tin-free allylation,[3] vinylation,[4] azidation[5] and acylation[6] reactions.

It seemed interesting to see if the use of xanthates as the radical precursors and the β-elimination of sulfonyl radicals could be combined with an intramolecular 1,5-hydrogen atom abstraction into a synthetically useful process. Internal hydrogen abstractions have found occasional applications in organic synthesis, sometimes with spectacular results.[7] We took inspiration from a study by Phillips and Whitham, who found that, under the action of benzoyl peroxide, δ-unsaturaterd β′-hydroxysulfones rearranged into ε-ketosulfones in modest to good yield, as outlined in Scheme 1.[8]

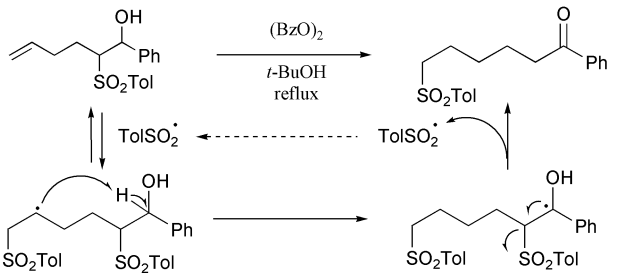
Our concept is displayed in Scheme 2. Peroxide mediated addition of xanthate **1** to olefin **2** leads to another xanthate **4**, which can fragment back to intermediate radical **3** through a reversible radical addition-fragmentation sequence. The possibility of continuous regeneration of radical **3** should allow the desired intramolecular abstraction leading to radical **5** to occur eventually. Rapid β-elimination of a methylsulfonyl radical then gives adduct **6** and, in cases where X represents a hydroxy group, this is followed by tautomerisation into the corresponding ketone **7**. The methylsulfonyl radical collapses into a molecule of sulfur dioxide and a methyl radical which is capable of propagating the chain. The required olefins **2** are readily obtained by alkylation and reduction of the corresponding ketosulfones.

Indeed, when a solution of xanthate **1a** and olefin **2a** in 1,2-dichloroethane was heated to reflux under an inert atmosphere and treated with lauroyl peroxide, a smooth reaction occurred to give the expected diketone in 81% yield (Table 1).‡ No tetralone, resulting from cyclization of the intermediate radical onto the aromatic ring, was formed.[9] In contrast to the observations of Phillips and Whitham, who found that only the *threo* isomer underwent the sequence depicted in Scheme 1, we encountered no such limitation. This reflects the importance of the relative long life of intermediate radical **3** in allowing hydrogen abstraction even from the less favourable *erythro* epimer.

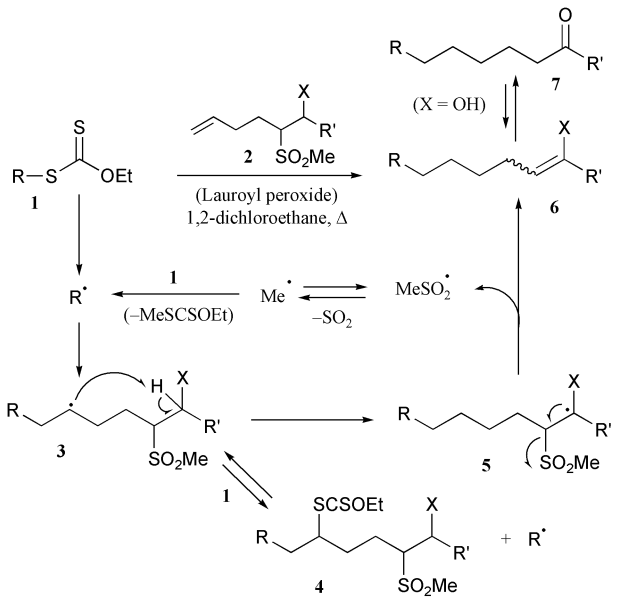
The same transformation was accomplished using various combinations of olefins and xanthates, as illustrated by the examples compiled in Table 1. In the reaction between xanthate **1a** and olefin **2b**, we isolated a significant amount of *p*-methoxyacetophenone (34%) in addition to the desired ketone **7b**. Clearly in this case, intermolecular abstraction of the labile tertiary benzylic hydrogen competes with the addition of the radical to the terminal olefin. Various useful functional groups can be introduced through the xanthate portion; in the case of **7d**, the ready creation of a quaternary centre is worthy of note.

Placing a suitable substituent on the oxygen would prevent the conversion into a ketone and would lead to the regioselective formation of an enol derivative instead. We found that although addition to the TBS-protected hydroxysulfone **2c** took place smoothly, the intermediate enol silyl ether did not survive the experimental conditions and only ketone **7e** was isolated in 57% yield. In contrast, the corresponding acetate **2d** provided the more robust enol acetates **6a** and **6b** in moderate yield.[10]

In a further extension, we applied the sequence to bromosulfone **2e** which resulted in the formation of vinyl bromides in satisfactory yield. Hydrogen abstraction is more favoured than intramolecular transfer of the bromine atom.[11] It is worth underlining the compatibility of bromides with the xanthate



Scheme 1 Whitham's rearrangement.



Scheme 2 General reaction manifold.

† Dedicated with respect to Professor Gordon Whitham.

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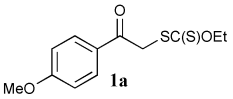
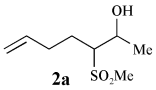
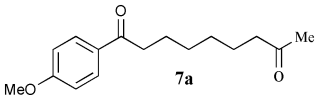
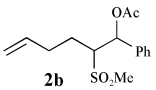
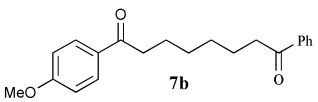
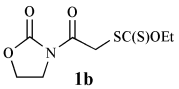
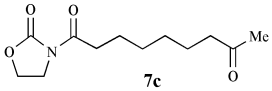
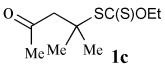
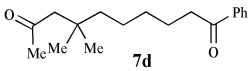
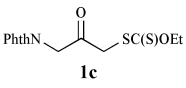
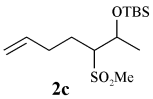
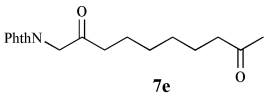
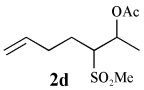
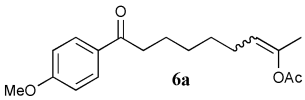
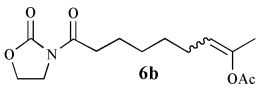
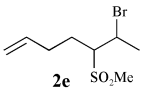
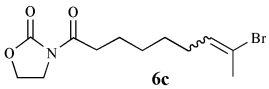
Table 1 Synthesis of olefins **6** and ketones **7**

Entry	Xanthate **1**	Olefin **2**	Product **6** or **7**	Yield
1	 **1a**	 **2a**	 **7a**	81%
2	**1a**	 **2b**	 **7b**	53%[a]
3	 **1b**	**2a**	 **7c**	73%
4	 **1c**	**2b**	 **7d**	58%
5	 **1c**	 **2c**	 **7e**	57%
6	**1a**	 **2d**	 **6a**	38% *Z*:*E* 65:35
7	**1b**	**2d**	 **6b**	43% *Z*:*E* 65:35
8	**1b**	 **2e**	 **6c**	65% *Z*:*E* 25:75

[a] 4-Methoxyacetophenone was also isolated in 34% yield.

based system for radical generation and capture. Such bromides would not survive stannane based radical chemistry. Vinyl bromide are useful starting materials in a plethora of organometallic reactions.

In summary, this preliminary study has shown the possibility of performing an intermolecular addition to an unactivated olefin followed by an intramolecular hydrogen abstraction leading to the ultimate removal of the xanthate from the product and the regioselective introduction of a remote ketone function or a vinyl acetate or bromide. Many of the products obtained would be tedious to prepare by more conventional routes. Finally, no tin or other heavy metals are involved in the process, which uses cheap, readily available starting materials and reagents

Notes and references

‡ Typical procedure: to a solution of xanthate **1a** (105 mg, 0.38 mmol, 1.0 equiv.) and olefin **2a**(112 mg, 0.58 mmol, 1.5 equiv.) in refluxing degassed 1,2-dichloroethane (2 mL) was added lauroyl peroxide (DLP) (15.1 mg, 0.038 mmol, 0.1 equiv.) under N_2 atmosphere. DLP (15.1 mg, 0.038 mmol, 0.1 equiv.) was added every hour until complete consumption of the starting material. 80% DLP was needed to complete the reaction. The reaction was cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate–petroleum ether: 2:8) gave diketone **7a** (106 mg, 81%) as colourless crystals (mp 64–65; ethanol). ^{1}H NMR (400 MHz; $CDCl_3$) δ ppm: 7.94 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.91 (t, J = 7.3 Hz, 2H), 2.43 (t, J = 7.4 Hz, 2H), 2.13 (s, 3H), 1.72 (tt, J = 7.3, 7.3 Hz, 2H), 1.59 (tt, J = 7.4, 7.4 Hz, 2H), 1.40–1.32 (m, 4H).^{13}C NMR (100 MHz; $CDCl_3$) δ ppm: 209.3, 198.8, 163.4, 130.3, 130.2, 113.7, 55.5, 43.5, 38.2, 29.9, 29.2, 29.0, 24.4, 23.7; IR (CCl_4, cm^{-1}): 2932, 2854, 1719, 1682, 1601, 1257, 1170. Calc. for $C_{16}H_{22}O_3$ (%): C,73.25, H, 8.45. Found (%): C,73.29; H, 8.53.

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