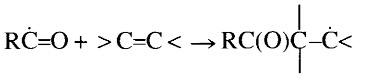
Homolytic aldol reactions: thiol-catalysed radical-chain addition of aldehydes to enol esters and to silyl enol ethers

Hai-Shan Dang and Brian P. Roberts*

Christopher Ingold Laboratories, Department of Chemistry, University College London, 20 Gordon Street, London, UK WC1H 0AJ

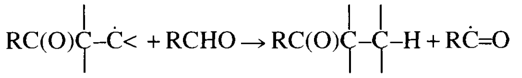
Thiols catalyse the radical-chain addition of primary aldehydes to enol esters and to silyl enol ethers to give aldol derivatives in good yields under mild conditions.

The intermolecular radical-chain addition of an aldehyde to an alkene to give a ketone[1] (hydroacylation) was first studied by Kharasch and co-workers[2] nearly 50 years ago. The usefulness of this reaction in synthesis was extended by Patrick,[3] who showed that good yields could often be obtained from the addition of primary aldehydes (RCH_2CHO) to certain electron-deficient alkenes (*e.g.* α,β-unsaturated ketones and dialkyl maleates). However, a major problem with the radical-chain pathway [reactions (1) and (2)] remains the inefficiency with which the acyl radical adduct **1** abstracts hydrogen from the aldehyde [reaction (2)]. A modern adaptation, which circumvents this difficulty and has been used successfully for both inter- and intra-molecular hydroacylation, is to use a selenoester in conjunction with tributyltin hydride instead of the aldehyde, when reaction (2) is replaced by the pair of more rapid reactions (3) and (4).[4–6]

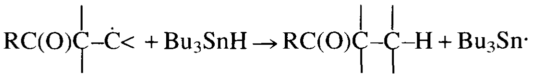


$$R\dot{C}{=}O + {>}C{=}C{<} \longrightarrow RC(O)\overset{|}{\underset{|}{C}}{-}\dot{C}{<} \qquad (1)$$

1



$$RC(O)\overset{|}{\underset{|}{C}}{-}\dot{C}{<} + RCHO \longrightarrow RC(O)\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}H + R\dot{C}{=}O \qquad (2)$$



$$RC(O)\overset{|}{\underset{|}{C}}{-}\dot{C}{<} + Bu_3SnH \longrightarrow RC(O)\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}H + Bu_3Sn\cdot \qquad (3)$$

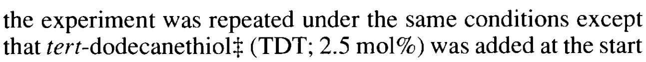
$$Bu_3Sn\cdot + RC(O)SePh \longrightarrow R\dot{C}{=}O + Bu_3SnSePh \qquad (4)$$

The RC(O) group behaves in many ways like the R_3Si group and we have shown recently that radical-chain hydrosilylation of alkenes is catalysed by thiols.[7] This result, along with consideration of the various factors that influence the rates of hydrogen-atom transfer reactions[8] and the previous observation that thiols catalyse the radical-chain decarbonylation of aldehydes,[9] suggests that thiols should also catalyse the hydroacylation of alkenes. Here we report experimental confirmation of this prediction and we describe the application of thiol-catalysed hydroacylation of enol esters and of silyl enol ethers to provide a radical-chain route to aldol derivatives (Scheme 1).

A solution in dry dioxane (2.5 cm^3) containing freshly distilled butanal **2a** (5.0 mmol), isopropenyl acetate **3b** (2.5 mmol) and di-*tert*-butyl hyponitrite[10] initiator (TBHN, 0.063 mmol, 2.5 mol% based on alkene) was heated at 60 °C and stirred under argon for 1.5 h. A further 2.5 mol% of TBHN was then added and heating was continued for a further 2 h. Methyl benzoate was added as an internal standard, volatile material was removed at room temperature under reduced pressure (10–15 Torr) and the residue was examined by ^1H NMR spectroscopy. Only a small amount (8% yield based on **3b**) of the aldol addition product **4** had been formed.† However, when the experiment was repeated under the same conditions except that *tert*-dodecanethiol‡ (TDT; 2.5 mol%) was added at the start of the reaction and also with the second portion of TBHN, the yield of **4** increased to 58%. The hydroacylation evidently follows a radical-chain mechanism involving thiol catalysis; the proposed propagation cycle, in which steps (*b*) and (*c*) replace the direct abstraction of hydrogen from the aldehyde, is shown in Scheme 2. Of the thiols investigated as catalysts, TDT and methyl thioglycolate ($HSCH_2CO_2Me$; MTG) proved to be the most suitable and generally higher yields of the aldol adducts were obtained using the latter catalyst. For example, when the addition of butanal to isopropenyl acetate was repeated with MTG (2 × 2.5 mol%) as catalyst, the yield increased to 67% and with MTG (2 × 5 mol%) it was 80% (Table 1, entry 4).

The thiol-catalysed hydroacylation of a number of enol esters and silyl enol ethers with primary aldehydes was investigated and selected results are summarised in Table 1. The products were readily purified by flash chromatography on silica gel and the isolated yields were generally good. Similar results, but with somewhat lower yields, were obtained using hexane (entries 7 and 8).

The thiol-catalysed hydroacylation is generally very clean and the material balance (yield **4** + unreacted **3**) was ≥95% in most reactions. Production of trace amounts of a radical-scavenging inhibitor during the reaction (possibly related to the

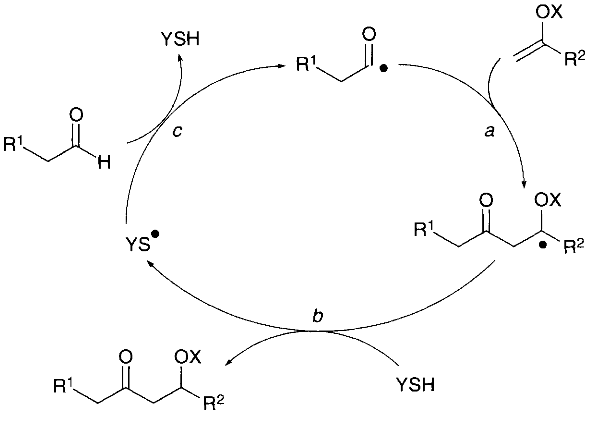


2a $R^1 = Et$
b R^1 = hexyl
c $R^1 = Pr^i$

3a $R^2 = H$; X = Ac
b $R^2 = Me$; X = Ac
c $R^2 = Bu^t$; X = Ac
d $R^2 = Bu^t$; $X = Bu^tMe_2Si$
e $R^2 = Me$; $X = (EtO)_2P(O)$
f $R^2 = H$; X = Bu

4

Scheme 1 *Reagents and conditions*: i, TBHN initiator, thiol catalyst, 60 °C, 3 h



Scheme 2

Table 1 Results of selected hydroacylation reactions at 60 °C initiated with TBHN in dioxane[a]

Entry	Aldehyde[b] **2**	Alkene **3**	Thiol (mol%)[c]	Conditions[d]	Yield **4**[e] (%)
1	**a**	**a**	TDT (5)	A	81 (74)
2	**a**	**b**	TDT (5)	B	58
3	**a**	**b**	MTG (5)	B	67
4	**a**	**b**	MTG (10)	B	80 (67)
5	**b**	**b**	MTG (10)	B	79 (63)
6	**c**	**b**	MTG (10)	B	68 (59)
7	**a**	**c**	TDT (5)	C[f]	45
8	**a**	**c**	TDT (5)	C	53
9	**a**	**c**	TDT (5)	B	61
10	**a**	**c**	TDT (5)	D	64
11	**a**	**c**	Octane-1-thiol (5)	B	55
12	**a**	**c**	Adamantane-1-thiol (5)	B	56
13	**a**	**c**	MTG (5)	B	67
14	**a**	**c**	MTG (10)	B	90 (83)
15	**a**	**d**	MTG (10)	B	65 (52)
16	**a**	**e**	MTG (10)	B	36 (29)
17	**a**	**f**	MTG (10)	B	66 (58)

[a] Unless stated otherwise. [b] 2 equiv. based on alkene. [c] Total amount based on alkene. [d] A = the alkene in dioxane was added during 2 h using a syringe pump; B = half the TBHN and half the thiol was added at the start of the reaction, the remainder of each was added after 1.5 h; C = all the TBHN and thiol was added at the start of the reaction; D = TBHN (*ca.* 1 mol%) and thiol (*ca.* 1 mol%) were added at the start of the reaction, the remainder of each dissolved in dioxane was added during 2 h using a syringe pump. [e] Determined by ^{1}H NMR spectroscopy; isolated yields given in parentheses. Satisfactory spectroscopic and analytical data were obtained for all adducts. [f] In hexane.

formation of α,β-unsaturated carbonyl compounds by elimination from the aldol adducts) is probably responsible for the incomplete consumption of alkene under the conditions used. Further optimisation of the reaction conditions should lead to increased conversion of **3** and, thus, to increased yields of **4**.

Reaction of butanal with vinyl acetate **3a** under the usual conditions gave an 8 : 1 mixture of **4** with the 'dimeric' product formed by addition of **1** to a second molecule of alkene before H-atom transfer from the thiol. However, when the alkene was added slowly to the reaction mixture using a syringe pump, the ratio **4**:dimer increased to 12 : 1 and the yield of **4** was 81% (entry 1).

The classic aldol addition of an enol or enolate derivative to an aldehyde or ketone is one of the key reactions for carbon–carbon bond formation; it is a heterolytic process and acids or bases (Brønsted or Lewis) are often present. The complementary thiol-catalysed radical-chain addition reaction described here, although certainly more limited in scope, takes place in non-polar solvents under mild, neutral conditions.

We thank the EPSRC for support.

Footnotes

† TBHN decomposes cleanly to form *tert*-butoxyl radicals and nitrogen;[10] in the absence of TBHN no **4** was produced.

‡ This is the mixture of isomers of *tert*-$C_{12}H_{25}SH$ obtained from Aldrich.

References

1 C. Walling, *Free Radicals in Solution*, Wiley, New York, 1957, pp. 273–278; E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970, pp. 152–154; C. Walling and E. S. Huyser, *Org. React.*, 1963, **13**, 91; B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, 1986, pp. 72–73.

2 M. S. Kharasch, W. H. Urry and B. M. Kuderna, *J. Org. Chem.*, 1949, **14**, 248.

3 T. M. Patrick Jr., *J. Org. Chem.*, 1952, **17**, 1009, 1269.

4 D. Crich and S. M. Fortt, *Tetrahedron*, 1989, **45**, 6581.

5 D. L. Boger and R. J. Methvink, *J. Org. Chem.*, 1989, **54**, 1779; 1992, **57**, 1429; *J. Am. Chem. Soc.*, 1990, **112**, 4003, 4008.

6 C. E. Schwartz and D. P. Curran, *J. Am. Chem. Soc.*, 1990, **112**, 9272; M. P. Astley and G. Pattenden, *Synlett*, 1991, 335.

7 H.-S. Dang and B. P. Roberts, *Tetrahedron Lett.*, 1995, **36**, 2875.

8 B. P. Roberts and A. J. Steel, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2155; B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, in the press.

9 E. F. P. Harris and W. A. Waters, *Nature*, 1952, **170**, 212; K. E. J. Barrett and W. A. Waters, *Faraday Discuss. Chem. Soc.*, 1953, **14**, 221.

10 H. Kiefer and T. G. Traylor, *Tetrahedron Lett.*, 1966, 6163; G. D. Mendenhall, *Tetrahedron Lett.*, 1983, **24**, 451.

Received, 5th July 1996; Com. 6/04705J