Thiol-catalysed Radical-chain Reduction of Organic Halides by Hexabutylditin in the Presence of Malonic Acid†

J. Chem. Research (S), 1998, 132–133†

Kyoung-Mahn Kim and Brian P. Roberts*

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

In the presence of a thiol catalyst and a suitable initiator, a mixture of hexabutylditin and malonic acid brings about protodehalogenation of organic bromides and iodides by a radical-chain mechanism.

Tributyltin hydride (TBTH) is a key reagent in radical-based organic synthesis.[1] The Sn—H bond is relatively weak and hydrogen-atom abstraction from TBTH by a carbon-centred radical is rapid.[2] The resulting tributylstannyl radical reacts readily at electronegative elements in a wide variety of compounds to generate new radicals and lead to chain processes. For example, alkyl bromides are readily reduced to the corresponding alkanes by TBTH, *via* the sequence of propagation reactions shown in eqns. (1) and (2). Rather than the simple reduction product R^1H, the compound R^2H resulting from the trapping of the rearranged radical $R^{2\bullet}$ is often desired [eqns. (3) and (4)]. Now the high rate of reaction (2) can become a disadvantage, because of trapping of $R^{1\bullet}$ prior to its rearrangement, and very dilute solutions have been employed or the TBTH has been added slowly to the reaction mixture using a syringe pump, in order to increase the yield of R^2H relative to R^1H. Other approaches to alleviate this difficulty have included the replacement of the TBTH with less reactive hydrogen-atom donors such as trialkylgermanes[3] or tris(trimethylsilyl)silane.[4] Alternatively, photolysis of hexaalkyldistannanes (free or polymer-supported and usually in the presence of a ketone sensitiser) have been used as sources of stannyl radicals, in conjunction with poor hydrogen-atom donors such as propan-2-ol, for non-chain reduction with rearrangement.[5,6]

$$Bu_3Sn^\bullet + R^1Br \longrightarrow Bu_3SnBr + R^{1\bullet} \quad (1)$$

$$R^{1\bullet} + Bu_3SnH \longrightarrow R^1H + Bu_3Sn^\bullet \quad (2)$$

$$R^{1\bullet} \longrightarrow R^{2\bullet} \quad (3)$$

$$R^{2\bullet} + Bu_3SnH \longrightarrow R^2H + Bu_3Sn^\bullet \quad (4)$$

Here we report the use of hexabutylditin (HBDT), together with malonic acid and a thiol catalyst, as an effective replacement for TBTH for the radical-chain reduction of organic halides. In this system the actual hydrogen-atom donor is the thiol, the concentration of which can be controlled so as to promote the formation of rearranged products without the need to work under conditions of high dilution.

After a solution in 1,2-dimethoxyethane (DME; 4 cm^3) containing 1-bromododecane (1.0 mmol), HBDT (1.1 mmol), benzenethiol (1.0 mmol), decane (*ca.* 1 mmol, as an internal reference) and azoisobutyronitrile (AIBN; 0.05 mmol) had been heated under reflux under argon for 3 h, GLC analysis showed that dodecane had been formed in 82% yield (Table 1, entry 1). The phenylthiyl radical is known[7] to displace tributylstannyl radicals from HBDT under these conditions and the dodecane is evidently formed *via* the sequence of propagation reactions shown in eqns. (5)–(7). When the amount of benzenethiol was reduced to 0.05 mmol, under otherwise identical conditions, the yield of dodecane fell correspondingly to 4% (entry 2). However, when malonic acid (1.2 mmol) was also present the yield of dodecane rose again to 84%, presumably because the carboxylic acid reacts with the Bu_3SnSPh according to eqn. (8) to regenerate the thiol,[8] which now functions as a catalyst for the reduction (entry 3). Negligible reduction takes place in the absence of benzenethiol or in the absence of AIBN (entries 4 and 5). Other thiols behaved in a generally similar way, but benzenethiol and dodecane-1-thiol were most effective. Yields of dodecane were somewhat higher in refluxing benzene solvent than in DME, although malonic acid is only very sparingly soluble in the former and the reaction mixture remains heterogeneous throughout.

$$Bu_3Sn^\bullet + RHal \longrightarrow Bu_3SnHal + R^\bullet \quad (5)$$

$$R^\bullet + PhSH \longrightarrow RH + PhS^\bullet \quad (6)$$

$$PhS^\bullet + Bu_3SnSnBu_3 \longrightarrow Bu_3Sn^\bullet + Bu_3SnSPh \quad (7)$$

$$Bu_3SnSPh + RCO_2H \longrightarrow Bu_3SnO_2CR + PhSH \quad (8)$$

A number of representative types of organic halides were reduced successfully in benzene solutions using benzenethiol as a catalyst, under the conditions specified for entry 9 of Table 1, and the results are given in Table 2. It was thought conceivable that α-bromoacetophenone (entry 4) might be reduced by a heterolytic mechanism, but in the absence of AIBN almost no acetophenone (0.4%) was formed.

The benzenethiol-catalysed reduction of 1-bromododecane by HBDT and malonic acid was also effectively initiated

Table 1 Reduction of 1-bromododecane by HBDT and malonic acid in the presence of thiols and AIBN[a]

Entry	Solvent	Thiol (mol%)[b]	Yield dodecane (%)[c]
1[d]	DME	PhSH (100)	82
2[d]	DME	PhSH (5)	4
3	DME	PhSH (5)	84
4	DME	None	0.5
5[e]	DME	PhSH (5)	2
6	DME	*tert*-$C_{12}H_{25}SH$[f] (5)	34
7	DME	MeO_2CCH_2SH (5)	74
8	DME	*n*-$C_{12}H_{25}SH$ (5)	81
9	Benzene	PhSH (5)	93
10	Benzene	*n*-$C_{12}H_{25}SH$ (5)	89

[a]Reaction mixtures consisted of 1-bromododecane (1.0 mmol), HBDT (1.1 mmol), malonic acid (1.2 mmol), decane (*ca.* 1 mmol) and AIBN (0.05 mmol) in solvent (4 cm^3) and were heated under reflux under argon for 3 h before analysis by GLC. [b]Based on 1-bromododecane. [c]By GLC using decane as internal reference. [d]Malonic acid was absent in these experiments. [e]AIBN was absent in this experiment. [f]This is the isomeric mixture of *tert*-dodecanethiols as obtained from the Aldrich Chemical Co.

*To receive any correspondence (*e-mail:* b.p.roberts@ucl.ac.uk).

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 2 Reduction of organic halides by HBDT and malonic acid in the presence of benzenethiol (5 mol%) and AIBN (5 mol%) in refluxing benzene[a]

Entry	Halide (RHal)	Yield of RH (%)
1	1-Iodododecane	95[b]
2	2-Bromoadamantane	97[b]
3	1-Bromoadamantane	95
4	α-Bromoacetophenone	99[b]
5	Ethyl 2-bromohexanoate	86
6	*p*-Bromobenzyl bromide	95[c]
7	Methyl 2-iodobenzoate	85[c,d]

[a]The reaction time was 3 h, unless stated otherwise. [b]Reaction time 1 h. [c]Benzenethiol (10 mol%) was used as catalyst. [d]DME solvent.

by di-*tert*-butyl hyponitrite[9] (5 mol% based on bromide) in benzene at 60 °C (99% yield after 2 h) or by 1,1-di-*tert*-butylperoxycyclohexane (DTBC; 5 mol%) in refluxing toluene (96% yield after 3 h).

Rearrangement of the neophyl radical **1** to the more stable 1,1-dimethyl-2-phenylethyl radical **2** is a comparatively slow process.[11] Even at relatively high temperature in a large volume of refluxing toluene (68 cm^3), reduction of neophyl bromide ($PhCMe_2CH_2Br$, 0.5 mmol) with TBTH (0.68 mmol, *ca.* 0.01 mol dm^{-3}) in the presence of DTBC initiator (5 mol% based on bromide), still gave slightly more *tert*-butylbenzene (49%) than isobutylbenzene (47%), which arises from the rearranged radical **2**. However, the reduction of neophyl bromide by HBDT and malonic acid in the presence of benzenethiol (≤1 mol%) afforded higher yields of rearranged product under conditions of much higher reagent concentration. For example, reduction of neophyl bromide (1 mmol) by HBDT and malonic acid in refluxing toluene (10 cm^3), in the presence of DTBC (5 mol%) and benzenethiol (1 mol%), gave *tert*-butylbenzene (38%) and isobutylbenzene (54%) (Table 3, entry 2). The amount of benzenethiol added corresponds to the maximum possible concentration present during the reaction and the steady-state concentration of thiol will be less than this value.

$PhCMe_2\dot{C}H_2$ **1** $\qquad$ $Me_2\dot{C}CH_2Ph$ **2**

Experimental

Benzene and DME were dried by distillation from sodium. Hexabutylditin (Aldrich) was distilled before use and stored under argon. Neophyl bromide was prepared as described in the literature;[12] other organic halides, thiols, malonic acid and tributyltin hydride were obtained commercially (Aldrich) and were used as received. AIBN (Merck–BDH) was recrystallised from dichloromethane–hexane, di-*tert*-butyl hyponitrite was prepared by the method of Mendenhall,[9b] and DTBC (Peroxid-Chemie) was obtained as a 50% w/w solution in mineral oil and was used as such.

Table 3 Reduction of neophyl bromide (1 mmol) by HBDT and malonic acid in the presence of benzenethiol and DTBC (5 mol%) in refluxing toluene[a]

Entry	Benzenethiol (mol%)[b,c]	Yield Me_3CPh (%)	Yield Me_2CHCH_2Ph (%)
1	2 (0.002)	59	39
2	1 (0.001)	38	54
3	0.5 (0.0005)	17	56

[a]Toluene (10 cm^3); reaction time 3 h. [b]Initial quantities present; these small amounts of benzenethiol were added as a standard solution in toluene. [c]Approximate molar concentrations (mol dm^{-3}) given in parentheses.

GLC analyses were carried out using a Pye–Unicam 304 gas chromatograph, equipped with a flame-ionisation detector, in conjunction with a 3 m × 4 mm bore glass column packed with 10% OV-101 on Chromosorb WHP (80–100 mesh); the carrier gas was nitrogen. Products were identified by comparison with the authentic compounds and yields were determined using decane as the internal standard.

Received, 6th November 1997; Accepted, 26th November 1997
Paper E/7/07994J

References

1 W. P. Neumann, *Synthesis*, 1987, 665; D. P. Curran, *Synthesis*, 1988, 417; C. G. Jasperse, D. P. Curran and T. L. Fevig, *Chem. Rev.*, 1991, **91**, 1237.
2 C. Chatgilialoglu, K. U. Ingold and J. C. Scaiano, *J. Am. Chem. Soc.*, 1981, **103**, 7739.
3 J. Lusztyk, B. Maillard, S. Deycard, D. A. Lindsay and K. U. Ingold, *J. Org. Chem.*, 1987, **52**, 3509.
4 C. Chatgilialoglu, *Acc. Chem. Res.*, 1992, **25**, 188; *Chem. Rev.*, 1995, **95**, 1229.
5 H. G. Kuivila and C. C. H. Pian, *J. Chem. Soc., Chem. Commun.*, 1974, 369.
6 M. Harendza, J. Junggebauer, K. Lassmann, W. P. Neumann and H. Tews, *Synlett*, 1993, 286; M. Harendza, K. Lassmann and W. P. Neumann, *Synlett*, 1993, 283; J. Junggebauer and W. P. Neumann, *Tetrahedron*, 1997, **53**, 1301.
7 G. E. Keck and J. H. Byers, *J. Org. Chem.*, 1985, **50**, 5442.
8 G. S. Sasin and R. Sasin, *J. Org. Chem.*, 1955, **20**, 387; M. Fiorenza, A. Ricci, M. Taddei, D. Tassi and G. Seconi, *Synthesis*, 1983, 640.
9 (*a*) H. Kiefer and T. G. Traylor, *Tetrahedron Lett.*, 1966, 6163; (*b*) G. D. Mendenhall, *Tetrahedron Lett.*, 1983, **24**, 451.
10 K. Matsuyama and H. Kumura, *J. Org. Chem.*, 1993, **58**, 1766.
11 J. A. Franz, R. D. Barrows and D. M. Camaioni, *J. Am. Chem. Soc.*, 1984, **106**, 3964.
12 A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, 1956, **78**, 2763.