Polystyrene-supported N-methylthiourea: a convenient new reagent for the hydrogenolysis of bicyclic endoperoxides†

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The single-step preparation of a polystyrene-bound N-methylthiourea 4 and its use for the hydrogenolysis of bicyclic endoperoxides is described.

During the course of ongoing studies towards the total asymmetric synthesis of Amaryllidaceae alkaloids via retro-Cope elimination,1 we required an efficient preparation of (4R,5S,6S)-γ-hydroxy enone 3. Hudlicky and others have shown that this enone is a versatile intermediate for the syntheses of various cyclitols, conduritols and related compounds.2,3 It is generally prepared from enantiomerically pure cis-diol 1 (a commercially available Pseudomonas putida oxidation product of chlorobenzene) by acetone protection, photo-oxygenation using 1O2, and then thiourea-mediated hydrogenolysis of the intermediate bicyclic endoperoxide 2 (Scheme 1).

The best reported yields for these 3 steps are by Hudlicky: 95%,4 93%,4 and 85% highest,5 respectively. However, as implied by the epithet ‘highest’, we1 and others,6 and indeed Hudlicky7 have found that this sequence is generally compromised by the capricious nature of the thiourea-mediated hydrogenolysis for which yields of 40–75% are typical. During attempted optimisation it became apparent that the variability of this step, which proceeds cleanly by TLC, can be accounted for by rapid decomposition of the product once the crude reaction mixture is concentrated to dryness and during any subsequent filtration/chromatography on silica gel. Clearly, the product is sensitive towards a thiourea by-product8 (vide infra) and silica gel.9

We reasoned that in situ protection of the sensitive γ-hydroxy enone 3 would circumvent these issues. However, thiourea has very limited solubility in non-alcoholic organic solvents and attempted ‘in situ’ protection of γ-hydroxy enone 2 as an aceto ester (Ac2O, Et3N, DMAP) or TBS ether (TBSOTf, 2,6-lutidine, DMAP) in various solvent systems gave very poor yields of protected products.

Frustrated by this situation, we envisaged that a solid-supported thiourea reagent would obviate these problems. Efficient synthesis of the parent γ-hydroxy enone 3 would be enabled because the resin-bound thiourea by-products could be simply filtered off. Moreover, protection of the alcohol function directly following filtration, in a ‘telescoped’ process,9 would be possible because of the wider solvent compatibility of the resin.

Herein, we describe a facile method for preparation of the first solid-supported N-methylthiourea reagent 4 and its application to the hydrogenolysis of endoperoxide 2 and other bicyclic endoperoxides. Some observations on the scope and mechanism of thiourea-mediated endoperoxide hydrogenolysis are also presented.

Polystyrene-bound N-methylthiourea 4 (≈1.0 mmol g−1) was obtained as free-flowing pale yellow resin beads by refluxing aminomethylated polystyrene (Aldrich, 1–2% DVB crosslinked, 200–400 mesh, 1.1 mmol g−1) with 1.1 eq. of commercially available methyl isothiocyanate10 in Et2O followed by extensive washing with anhydrous Et2O and drying in vacuo (Scheme 2).

Pleasingly, treatment of endoperoxide 2 with 1.5 eq. of resin 4 in CH2Cl2 at 0 °C for 30 min followed by filtration and solvent evaporation afforded γ-hydroxy enone 3 in near quantitative yield. Moreover, if a pre-cooled solution of Ac2O, Et3N and DMAP or TBSOTf, 2,6-lutidine and DMAP in CH2Cl2 was added by cannula directly to the filtrate, γ-acetoxy- and γ-siloxy enones 5 and 6 could be obtained directly in overall yields of 85% and 81%, respectively (Scheme 3).

To explore the scope of this method we employed resin 4 for the hydrogenolysis of a series of endoperoxides 7–14 (Table 1).

Scheme 1 Thiourea-mediated hydrogenolysis of endoperoxide 2 according to the method of Hudlicky.3,5

Scheme 2 Synthesis of resin-bound N-methylthiourea 4.

Scheme 3 Sequential hydrogenolysis/protection of endoperoxide 2.

† Electronic supplementary information (ESI) available: Preparation of resin 4 and all reactions in Scheme 3 and Table 1. See http://dx.doi.org/10.1039/b508815a
Bicyclic di-sec-endoperoxides 7–11 (Entries 1–5) and bicyclic sec,tert-endoperoxide 12 (Entry 6) were all reduced to the corresponding cis-diols in yields exceeding the best previously reported in the literature; bicyclic di-tert-endoperoxide 13 and monocyclic di-sec-endoperoxide 14 were not reduced. The diol product resulting from hydrogenolysis of cycloheptatriene 10 has been reported to be highly unstable\textsuperscript{11} and so we employed the telescoped procedure with Ac\textsubscript{2}O, Et\textsubscript{3}N and DMAP (cf. for acetate 5, Scheme 3) to obtain the stable diacetate 18 in this case (Entry 4).

Interestingly, hydrogenolysis of anthracene derived endoperoxide 11 (Entry 5) has not been reported previously despite the utility of the product diol 19 which was obtained as an inseparable mix of cis and anti isomers by reduction of anthraquinone using 9-BBN.\textsuperscript{12}

Inspection of Scheme 3 and Table 1 reveals that the time required to effect complete hydrogenolysis varies significantly as a function of endoperoxide structure. Inductive effects appear to impact significantly: cf. a reaction time of 30 min for chloro-substituted endoperoxide 1 (Scheme 3) vs. 2.5 h for the des-chloro analogue 7 (Entry 1) vs. 96 h for the des-chloro, des-dioxy analogue 8 (Entry 2). The degree of substitution of the termini of the peroxide linkages also appears to be decisive: di-sec- and sec,tert-anthracenyl endoperoxides 11 and 12 react in 3 and 5.5 h respectively whereas di-tert-analogue 13 is inert (Entries 5–7). As reported previously for hydrogenolyses conducted using thiourea itself,\textsuperscript{17} strain also impacts on the rate of reaction. There does not appear to be a dramatic difference between the [2.2.2] and [3.2.2] systems, cf. bicyclic endoperoxide 8 (96 h) vs. 9 (70 h), but the lack of reactivity of monocyclic endoperoxides like 14 has been attributed to low ring-strain (Entry 8).\textsuperscript{17}

Also apparent from Table 1 is the synthetically valuable chemoselectivity profile that resin 4 shares with thiourea itself: allowing the hydrogenolysis of endoperoxides in the presence of alkenes.\textsuperscript{17} By contrast, diimide displays the opposite chemoselectivity in this regard, and Pd/H\textsubscript{2} reduces both functions.\textsuperscript{18} Metal hydrides generally display the same chemoselectivity as thiourea but additionally reduce carbonyl functions preferentially, making them unsuitable for many applications (e.g. 2 → 3, Scheme 3).\textsuperscript{19} Phosphines and sulfides (as used in the reductive work-up of ozonolysis reactions) effect deoxygenation to give vinyl epoxides.\textsuperscript{17}

The hydrogenolysis of endoperoxides using thiourea appears to have been first described by Schenck and Dunlap in 1956\textsuperscript{20} and to the best of our knowledge no mechanism has been proposed. Formamidine disulfide (21), as formed by the electrochemical oxidation of thiourea\textsuperscript{21} and reported to be the primary by-product of the reaction of thiourea with Br\textsubscript{2} or I\textsubscript{2},\textsuperscript{22} cannot be the final by-product of this process given that just 1 eq. of thiourea is required for the reaction. Moreover, Balci has noted that elemental sulfur can precipitate in these reactions.\textsuperscript{23} The following mechanism seems plausible (Scheme 4).

For thiourea, initial attack by the sulfur on an oxygen of the weak O–O bond gives a sulfenate intermediate which then fragments to give the product diol and thiazirine.\textsuperscript{22} The ring opens to give nitrile sulfide as the by-product responsible for accelerating the decomposition of sensitive \(\gamma\)-hydroxy enone 3 in our initial studies using thiourea.

\begin{table}

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<th>Entry</th>
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</table>

\textsuperscript{a} Reaction conditions: resin 4 (1.5 eq.), CH\textsubscript{2}Cl\textsubscript{2}, RT. \textsuperscript{b} Sequential hydrogenolysis/esterification (as Scheme 3), the diol was highly unstable. \textsuperscript{c} Yield of unstable diol. \textsuperscript{d} After recrystallisation from toluene. \textsuperscript{e} Thiourea itself was also unreactive.

Table 1 Hydrogenolysis of endoperoxides 7–14 using resin 4

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In summary, polystyrene-supported N-methylthiourea 4 has been shown to be a useful reagent for the hydrogenolysis of bicyclic endoperoxides and for sequential hydrogenolysis/alcohol protection.27

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Notes and references
7 This is also consistent with our failure to obtain any product by conducting the photo-oxygenation reaction with in situ thiourea, see: C. Kaneko, A. Sugimoto and S. Tanaka, Synthesis, 1974, 876–877.
8 Successful chromatography of γ-hydroxy enone 3 on silica gel has however been reported (ref. 5).
9 Process chemists use the term ‘telescoped’ for processes in which sequential chemical reactions (that were previously carried out in different solvents) are performed in a single batch of solvent to minimise costly solvent evaporation then recharging.
27 Thiourea has been used as an odourless alternative to dimethylsulfide during the reductive work-up of alkene ozonolysis reactions. Resin 4 may also be useful in this regard: D. Gupta and R. S. D. Soman, Tetrahedron, 1982, 38, 3013–3018.