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

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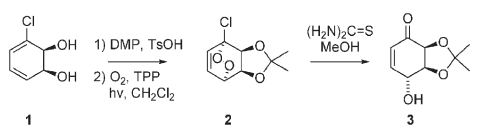
Received (in Cambridge, UK) 23rd June 2005, Accepted 2nd August 2005
First published as an Advance Article on the web 12th August 2005
DOI: 10.1039/b508815a

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 (4*R*,5*S*,6*S*)-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 acetonide protection, photo-oxygenation using $^1O_2$, 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%,[5] and '85% highest',[5] respectively. However, as implied by the epithet 'highest', we[1] and others,[6] and indeed Hudlicky[2] 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-product[7] (*vide infra*) and silica gel.[8]

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 acetate ester (Ac_2O, Et_3N, DMAP) or TBS ether (TBSOTf, 2,6-lutidine, DMAP) in various solvent systems gave very poor yields of protected products.



Scheme 1 Thiourea-mediated hydrogenolysis of endoperoxide **2** according to the method of Hudlicky.[4,5]

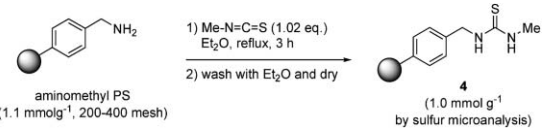
Frustrated by this situation, we envisaged that a solid-supported thiourea reagent would obviate these problems. Efficient synthesis of the parent γ-hydroxy enone **3** would be enabled because the resin-bound thiourea by-products could be simply filtered off. Moreover, protection of the alcohol function 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.

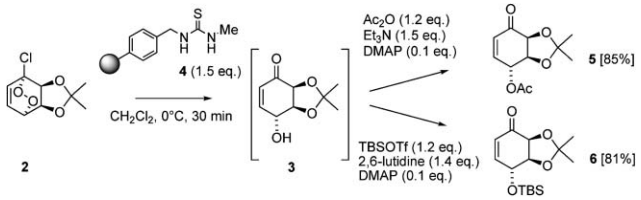
Polystyrene-bound *N*-methylthiourea **4** (~1.0 mmol g^{-1}) was obtained as free-flowing pale yellow resin beads by refluxing aminomethylated polystyrene (Aldrich, 1–2% DVB crosslinked, 200–400 mesh, 1.1 mmol g^{-1}) with 1.1 eq. of commercially available methyl isothiocyanate[10] in Et_2O followed by extensive washing with anhydrous Et_2O and drying *in vacuo* (Scheme 2).

Pleasingly, treatment of endoperoxide **2** with 1.5 eq. of resin **4** in CH_2Cl_2 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 Ac_2O, Et_3N and DMAP or TBSOTf, 2,6-lutidine and DMAP in CH_2Cl_2 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 2 Synthesis of resin-bound *N*-methylthiourea **4**.



Scheme 3 Sequential hydrogenolysis/protection of endoperoxide **2**.

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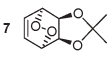
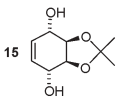
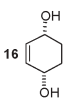
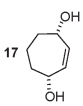
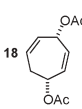
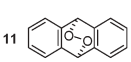
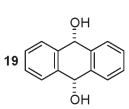
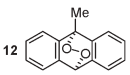
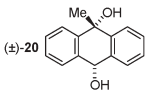
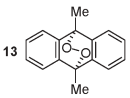
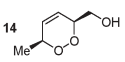
[b]*GSK Tonbridge, Old Powder Mills, Leigh, Tonbridge, Kent, UK TN11 9AN. E-mail: Inderjit.S.Mann@gsk.com*
† Electronic supplementary information (ESI) available: Preparation of resin **4** and all reactions in Scheme 3 and Table 1. See http://dx.doi.org/10.1039/b508815a

Table 1 Hydrogenolysis of endoperoxides **7–14** using resin **4**[a]

Entry	Substrate	Product	Time (h)	Yield (%)	Lit. yield (%)
1	 **7**	 **15**	2.5	98	80[13]
2	 **8**	 **16**	96	99	~75[14]
3	 **9**	 **17**	70	85	68[15]
4	 **10**	 **18**	120	77[b]	70[c11]
5	 **11**	 **19**	3	85 (77)[d]	N/A
6	 **12**	 (±)-**20**	5.5	99	92[16]
7	 **13**	No reaction[e]	—	—	N/A
8	 **14**	No reaction[e]	—	—	N/A

[a] *Reaction conditions:* resin **4** (1.5 eq.), CH_2Cl_2, RT. [b] Sequential hydrogenolysis/esterification (as Scheme 3), the diol was highly unstable. [c] Yield of unstable diol. [d] After recrystallisation from toluene. [e] Thiourea itself was also unreactive.

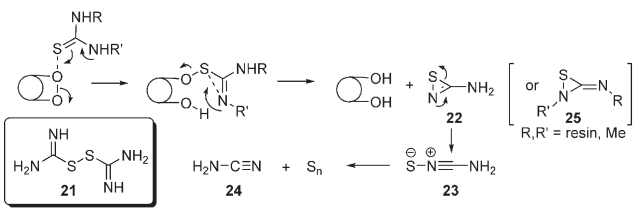
Bicyclic di-*sec*-endoperoxides **7–11** (Entries 1–5) and bicyclic *sec*,*tert*-endoperoxide **12** (Entry 6) were all reduced to the corresponding *cis*-diols in yields exceeding the best previously reported in the literature; bicyclic di-*tert*-endoperoxide **13** and monocyclic di-*sec*-endoperoxide **14** were not reduced. The diol product resulting from hydrogenolysis of cycloheptatriene **10** has been reported to be highly unstable[11] and so we employed the telescoped procedure with Ac_2O, Et_3N 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.[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,[17] strain also impacts on the rate of reaction. There does not appear to be 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).[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.[17] By contrast, diimide displays the opposite chemoselectivity in this regard, and $Pd/C/H_2$ reduces both functions.[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).[19] Phosphines and sulfides (as used in the reductive work-up of ozonolysis reactions) effect deoxygenation to give vinyl epoxides.[17]

The hydrogenolysis of endoperoxides using thiourea appears to have been first described by Schenck and Dunlap in 1956[20] and to the best of our knowledge no mechanism has been proposed. Formamidine disulfide (**21**), as formed by the electrochemical oxidation of thiourea[21] and reported to be the primary by-product of the reaction of thiourea with Br_2 or I_2,[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.[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 **22**. This ring opens to give nitrile sulfide **23** which decomposes to cyanamide **24** and elemental sulfur.[24,25] In the case of resin **4**, an analogous sequence leads to resin-bound thiaziridine **25** which is possibly the final product.[26] This mechanism accounts for the absence of sulfur precipitation when using resin **4** and the unreactivity of di-*tert*-endoperoxide **13** towards both thiourea and resin **4** because the σ^*_{O-O} orbitals are sterically inaccessible. It also implicates either nitrile sulfide **23** or cyanamide **24** as the by-product responsible for accelerating the decomposition of sensitive γ-hydroxy enone **3** in our initial studies using thiourea.



Scheme 4 Possible mechanism for the hydrogenolysis of endoperoxides by thiourea.

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]

We gratefully acknowledge the EPSRC and GSK for financial support for this work. We also thank Prof. Charles W. Rees (Imperial College) for helpful discussions during the preparation of this article.

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