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A novel method for protection and deprotection of the carbonyl groups in 1,2-indanedione by conversion to dioxa-dithiapropellanes

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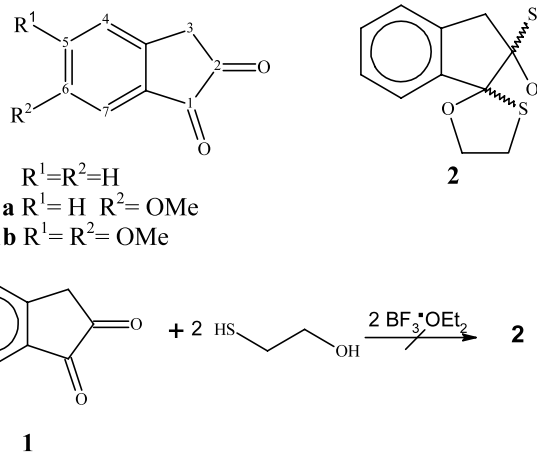
Abstract—1,2-Indanedione reacts with two equivalents of 2-mercaptoethanol to produce, instead of the expected 1,2-bis(1,3-oxathiolane), a dioxa-dithia[4.4.3] propellane. Other 1,2-indanediones produce analogous compounds. The protecting groups are removed at room temperature with NBS in aqueous acetone, to produce the original diketone.

Since the discovery of the fluorogenic reaction between 1,2-indanedione **1** and amino acids in 1998,[1] there has been an increased interest in the chemistry of 1,2-indanediones, particularly as potential fingerprint reagents.[2] In another study, dione **1** was converted to *cis* (1*S*,2*R*)-indanediol as the first stage of a synthesis of a leading HIV protease inhibitor, Crixivan.[3] Addition reactions and dianionic Cope rearrangements of **1**,[4] as well as condensation with dimethylaniline,[5] have also been reported recently. In continuation of our comprehensive study towards improved fingerprint reagents (for earlier work see Refs. 2b,c,f), it became necessary to protect the carbonyl groups of 1,2-indanedione and its analogs, to allow acylation or sulfonylation on the aromatic ring. While protection and deprotection of carbonyl groups is a common strategy in organic synthesis, it is much less common with vicinal diketones, particularly when the products might be acid-sensitive. We planned to convert the diketone **1** into its bis(1,3-oxathiolane) derivative **2** by reaction with 2-mercaptoethanol (Scheme 1), which could be easily removed afterwards.[6] Reaction of dione **1** with excess of 2-mercaptoethanol, in the presence of two equivalents of $BF_3{\cdot}OEt_2$, produced a 69% yield of a single product, which was not the expected **2**, but its isomer, the 2,10-dioxa-5,7-dithia[4.4.3]propellane **3**. The propel-



Scheme 1.

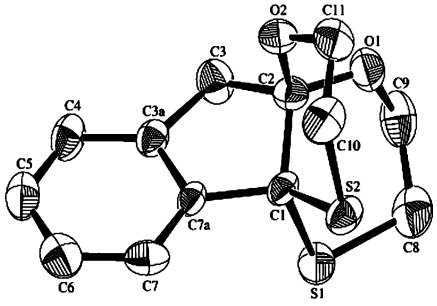


Figure 1. ORTEP drawing of propellane **3**; ellipsoids enclose 50% probability.

Keywords: 1,2-indanedione; mercaptoethanol; dioxa-dithiapropellanes; 1,3-oxathiolanes; protection; deprotection.
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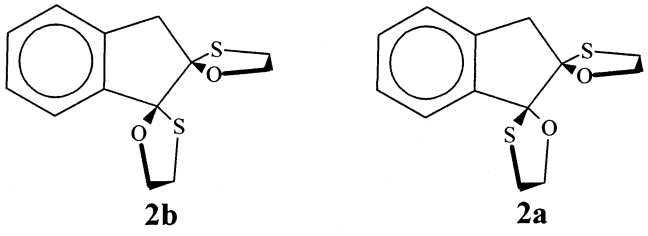
lane-type structure was deduced from the ^{1}H NMR spectrum in solution, and has been unequivocally confirmed by X-ray crystallographic analysis. In **2** the oxathiolane hetero-atoms would be either *syn* or *anti* (**2a** and **2b**, respectively), and the methylene protons on C3 should be anisotropic, producing an A_2B_2 pattern. A similar spectrum would have been exhibited by the unsymmetrical propellane **4**. The C3 protons of the product **3**, however, displayed a sharp singlet at 3.33 ppm corresponding to either of the symmetrical propellanes, **3** and **5**. XRD measurements established the structure as **3** (Fig. 1). A plausible reaction mechanism is depicted in Scheme 2. Under similar conditions, but without a catalyst, only one equivalent of mercaptoethanol adds to the dione, producing the monooxathiolane **6** with the 'protection' on C1, as confirmed by XRD (Fig. 2). On the other hand, in the presence of only one equivalent of $BF_3{\cdot}OEt_2$, the isomeric oxathiolane **7** is the predominant product, accompanied by some **3**. This finding is in accordance with Dimitroff and Fallis' report on monooxathiolane formation, in the reaction between 1,2-cyclopentanedione and mercaptoethanol, in the presence of *p*-TsOH.[7] It is somewhat surprising though, that the first carbonyl group to react with mercaptoethanol without a catalyst was that at C1, since the carbonyl group at C2 in 1,2-indanedione is more susceptible to nucleophilic attack.[2g,8]

6-Methoxy-1,2-indanedione **1a**, and 5,6-dimethoxy-1,2-indanedione **1b**, gave analogous propellanes (**3a** and **3b**, respectively) under similar conditions. In a typical reaction $BF_3{\cdot}OEt_2$ (2 equivalents) is added dropwise to a refluxing solution of **1** in dry ether, to provide 69% of the dioxa-dithiapropellane **3**. When the reaction is carried out in refluxing ether, with one equivalent of mercaptoethanol without a catalyst, **6** is obtained in 40% yield.

Under the relatively mild conditions that would remove the oxathiolane protection,[9] the dioxa-dithiapropellanes are cleaved to give the starting diketones. Thus, reac-



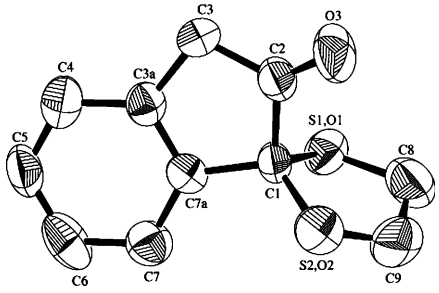
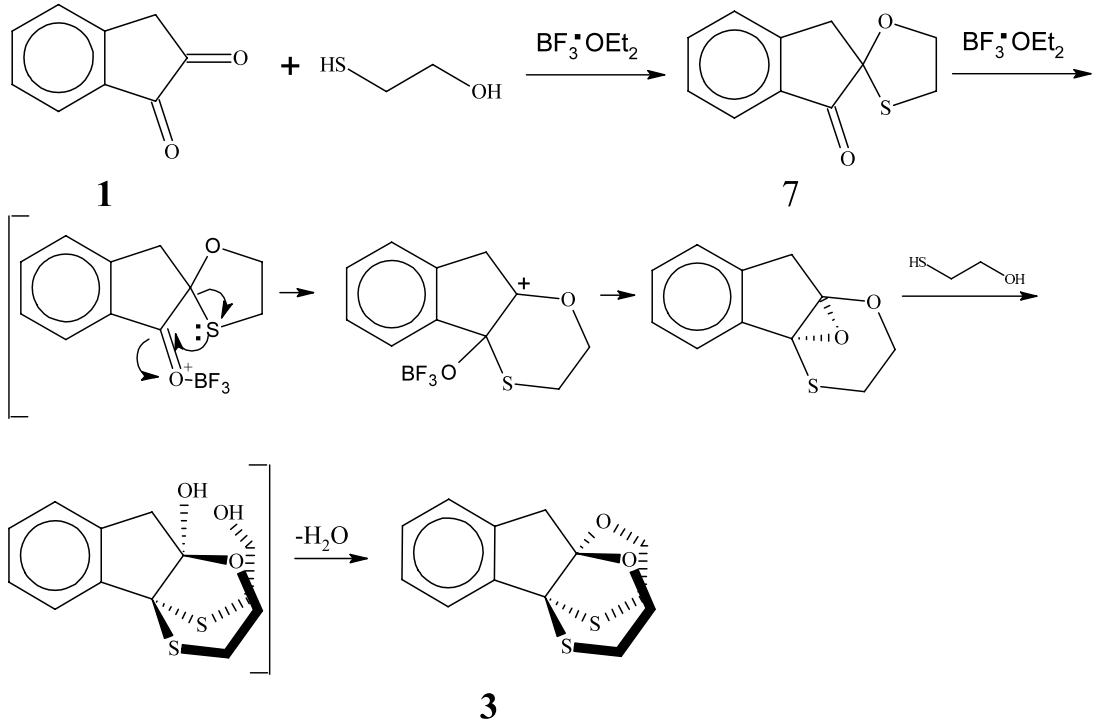
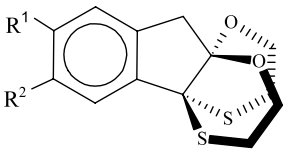


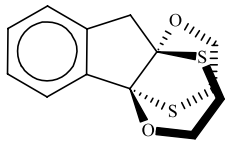
Figure 2. ORTEP drawing of oxathiolane **6**; ellipsoids enclose 50% probability.



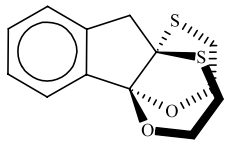
Scheme 2.



3 $R^1=R^2=H$
3a $R^1=H$ $R^2=OMe$
3b $R^1=R^2=OMe$



4



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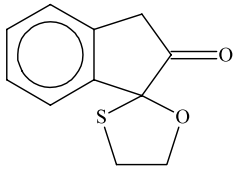
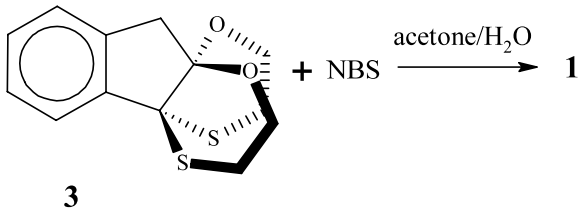


6

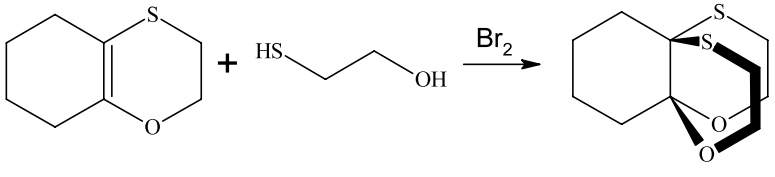
tion with NBS in aqueous acetone converts **3** to 1,2-indanedione **1** in 80% yield (Scheme 3). The monooxathiolane **6** reacts similarly.

A related propellane, 2,10-dioxa-5,7-dithia[4.4.4]propellane, was previously described by Fjeldskaar and Skattebøl[10] (Scheme 4). It is interesting that despite the different conditions for generating the two propellanes, the hetero-atoms in both systems are identically aligned. The formation of hexaoxapropellanes by the reaction between ethylene glycol and vicinal cyclic diketones was described by Erez and Fuchs, but the isomeric bis[1,3-dioxolane] was also obtained.[11]

The new compounds were characterized[12] by elemental microanalyses, IR, ^1H, ^{13}C NMR, MS, and by XRD.[13] No attempt was made at this stage to optimize the yields. The precursor 1,2-indanediones (**1**, **1a**, and **1b**) were prepared according to Joullie et al.[2g]



Scheme 3.



Scheme 4.

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12. **Data for the new compounds**. **Compound 3**: yield 69%, colourless plates, mp 174–176°C (from methanol), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.60 (m, 1H), 7.29–7.26 (m, 3H), 4.43 (ddd, $J=11.9$, 7.2, 2.6 Hz, 2H), 3.98 (ddd, $J=11.9$, 7.2, 2.6 Hz, 2H), 3.33 (s, 2H), 2.76 (ddd, $J=13.6$, 7.2, 2.6 Hz, 2H), 2.51 (ddd, $J=13.6$, 7.2, 2.6 Hz, 2H). Crystallographic data (Fig. 1): $C_{13}H_{14}O_2S_2$, monoclinic, space group Cc with $a=7.349(1)$, $b=23.912(6)$, $c=14.728(3)$ Å, $\beta=104.05(2)°$, $V=2510.7(9)$ Å^3 and $Z=8$.
Compound 3a: yield 48%, colourless plates, mp 189–193°C (from methanol), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, $J=8.2$ Hz, 1H), 7.16 (d, $J=2.6$ Hz, 1H), 6.82 (dd, $J=8.2$, 2.6 Hz, 1H), 4.43 (ddd, $J=11.9$, 7.2, 2.6 Hz, 2H), 3.99 (ddd, $J=11.9$, 7.2, 2.6 Hz, 2H), 3.84 (s, 3H), 3.26 (s, 2H), 2.76 (ddd, $J=13.6$, 7.2, 2.6 Hz, 2H), 2.52 (ddd, $J=13.6$, 7.2, 2.6 Hz, 2H).
Compound 3b: yield 43%, colourless prisms, mp 197–199°C (from methanol), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (s, 1H), 6.85 (s, 1H), 4.4 (ddd, $J=12.6$, 7.1, 2.3 Hz, 2H), 3.99 (ddd, $J=12.6$, 7.1, 2.3 Hz, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.26 (s, 2H), 2.78 (ddd, $J=13.6$, 7.1, 2.3 Hz 2H), 2.51 (ddd, $J=13.6$, 7.1, 2.3 Hz, 2H).
Compound 6: yield 40%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.57 (m, 1H), 7.40–7.37 (m, 2H), 7.31–7.27 (m, 1H), 4.75–4.68 (m, 1H), 4.57–4.50 (m, 1H), 3.76 (d, $J=21.5$ Hz, 1H), 3.58–3.50 (m, 1H), 3.48 (d, $J=21.5$ Hz, 1H), 3.44–3.36 (m, 1H), Crystallographic data (Fig. 2): $C_{11}H_{10}O_2S$, orthorhombic, space group $P2_12_12_1$ with $a=9.247(1)$, $b=16.061(2)$, $c=6.769(1)$ Å, $V=1005.3(2)$ Å^3 and $Z=4$.
Compound 7 was obtained as a thick oil, which could not be fully purified. The spectroscopic data agree with the isomeric oxathiolane structure **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (br.d, $J=8.0$ Hz, 1H), 7.63 (dt, $J=7.6$, 1.2 Hz, 1H), 7.44–7.38 (m, 2H), 4.72–4.65 (m, 1H), 4.44–4.37 (m, 1H), 3.62 (d, $J=9.6$ Hz, 1H), 3.54–3.46 (m, 1H), 3.50 (d, $J=9.6$ Hz, 1H), 3.36–3.28 (m, 1H).
13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 196209 and 196210. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).