Pergamon

Tetrahedron Letters, Vol. 36, No. 9, pp. 1391-1394, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00007-0

Novel Syntheses of Dithiosalicylide

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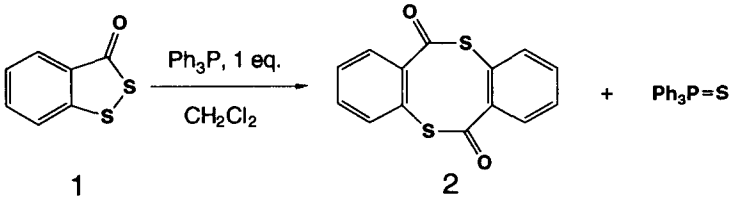
Abstract: Treatment of 3H-1,2-benzodithiol-3-one or 3H-1,2-benzodithiol-3-one 1-oxide with triphenylphosphine affords a good yield of dithiosalicylide. These reactions provide practical methods for the preparation of interesting cleft-shaped molecules.

Dithiosalicylides are an interesting class of conformationally rigid, cleft-shaped molecules.[1,2] The inversion barrier between the two enantiomeric boat conformers of the eight-membered ring in dithiosalicylides has been measured at ~25 kcal/mol.[1] Because structurally well-defined molecular clefts[3] have potential applications in the areas of molecular recognition, self assembly and catalysis, we were interested in devising an efficient synthesis of dithiosalicylides. Existing methods for preparation of these molecules are not, in general, practical and high yielding[1,4,5]

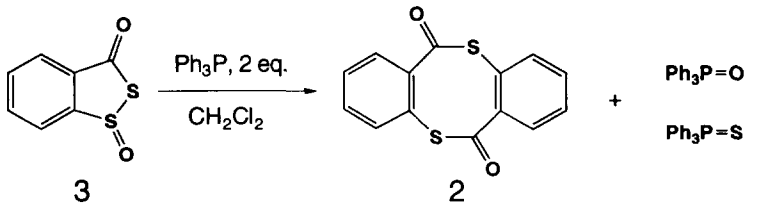
We find that treatment of 3H-1,2-benzodithiol-3-one (**1**) with triphenylphosphine (1 eq.) at room temperature in dichloromethane results in a slow reaction (168 hours) that provides a good yield of dithiosalicylide (**2**, Scheme 1).[6] Triphenylphosphine sulfide is identified as a byproduct of this reaction.[6]



1 2

Scheme 1

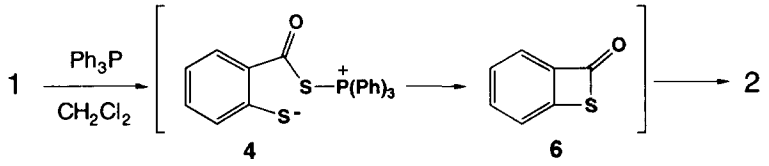
Interestingly, we find that treatment of 3H-1,2-benzodithiol-3-one 1-oxide[7] (**3**) with triphenylphosphine (2 eq.) in dichloromethane at room temperature results in a *rapid* reaction that also provides a good yield of dithiosalicylide (**2**, Scheme 2).[8] Triphenylphosphine sulfide and triphenylphosphine oxide are observed as byproducts of this reaction.[8] The reaction of **3** with triphenylphosphine is complete in 15 minutes, whereas, under identical conditions, the reaction of **1** with triphenylphosphine remains incomplete even after seven days. The marked difference in the reaction rates of these two substrates with triphenylphosphine clearly indicates that, although triphenylphosphine is known to deoxygenate sulfoxides,[9] for the reaction shown in Scheme 2, we can rule out a mechanism involving triphenylphosphine-mediated reduction of **3** to **1**, followed by triphenylphosphine-mediated dimerization of **1**. Thus, our qualitative rate data clearly indicates that treatment of **1** and **3** with triphenylphosphine leads to formation of dithiosalicylide (**2**) via two mechanistically distinct pathways.[10]



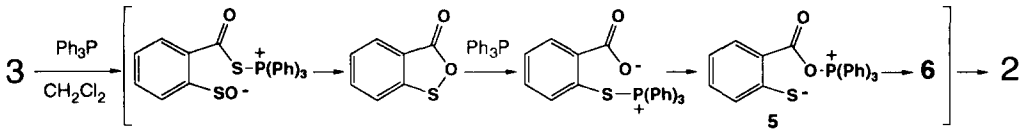
Scheme 2

The formation of **2** from the reactions of **1** and **3** with triphenylphosphine may occur via dimerization of zwitterionic species **4** and **5** respectively (Schemes 3 and 4), or through dimerization of benzothiet-2-one species **6**. It is known that **6** is unstable and dimerizes readily to yield **2**.[5] Evidence for reactive intermediates such as **4**, **5** or **6** in these reactions is provided by the observation that both reactions yield significant quantities of the methanolysis product **7**, when performed in methanol or mixtures of dichloromethane and methanol.[11] Benzothiet-2-one **6** is known to yield **7** upon reaction with methanol.[5, 4d]

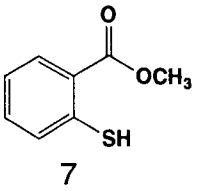
We anticipate that the reactions described herein represent mild and general methods for the preparation of various dithiosalicylides. We currently are using these methodologies in the preparation of novel, functionalized molecular clefts and cavities.



Scheme 3



Scheme 4



Acknowledgements: We thank Jeff Dannaldson and Saeid Behroozi for technical assistance and Professor Alan Schwabacher for a helpful discussion.

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6. In a typical reaction, 3H-1,2-benzodithiol-3-one (**1**, Aldrich Chemical Co., 100 mg, 0.6 mmol) and triphenylphosphine (156 mg, 0.6 mmol, 1 eq.) were stirred in dichloromethane (6 ml, distilled) under nitrogen at room temperature. After 168 hours, the light yellow solution was evaporated to dryness under reduced pressure to yield a yellow-white solid. The products were purified on a silica gel column (15:85 ethyl acetate:hexane). Dithiosalicylide (**2**) was obtained as a white solid (50 mg, 62%) which was recrystallized from chloroform:hexane to yield white crystals (m.p. 181-182°C, lit. m.p.[4e] 176-177°C). ^{1}H NMR ($CDCl_3$) : δ 7.35 (m, 4H), 7.25 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 197.3, 142.5, 135.6, 131.2, 131.0, 126.5, 125.2. (corresponds with literature data[5]). The triphenylphosphine sulfide byproduct of this reaction was isolated by column chromatography and compared to an authentic sample (Aldrich Chemical Co.) using thin layer chromatography, NMR and GC mass spectroscopy.

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8. Typical reaction conditions are as reported above,[6] except that two equivalents of triphenylphosphine (based on moles of **3**) were used. The reaction is complete in 15 minutes and provides a 67% yield of **2**. The byproducts of this reaction, triphenylphosphine oxide and triphenylphosphine sulfide, were isolated by column chromatography and compared with authentic samples (Aldrich Chemical Co.) using thin layer chromatography, NMR and GC-mass spectroscopy.

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10. Importantly, we find that the reaction of **1** with triphenylphosphine is NOT catalyzed by the addition of triphenylphosphine oxide. This means that a mechanism involving triphenylphosphine-mediated sulfoxide deoxygenation of **3** followed by triphenylphosphine-mediated, triphenylphosphine oxide-*catalyzed* dimerization of **1** is *not* possible for the reaction shown in Scheme 2. In addition, we find that treatment of **3** with only *one* equivalent of triphenylphosphine yields the usual products **2**, triphenylphosphine oxide and triphenylphosphine sulfide; however the starting material is not completely consumed even after long reaction times. The reduction product **1** is not observed in this reaction.

11. 3H-1,2-benzodithiol-3-one (**1**, 400 mg, 2.4 mmol) and triphenylphosphine (624 mg, 2.4 mmol, 1 eq.) were stirred in distilled methanol (24 ml) under nitrogen at room temperature. After 50 hours, the triphenylphosphine sulfide precipitate was removed by vacuum filtration and the filtrate was evaporated to dryness under reduced pressure to yield a yellow oil. The material was purified by silica gel column chromatography (5:95 ethyl acetate:hexane) to yield a light yellow oil (239 mg, 60 %). ^{1}H NMR ($CDCl_3$) : δ 7.98 (d, 1H), 7.27 (m, 2H), 7.11 (m,1H), 4.72 (s, 1H), 3.88 (s, 3H);^{13}C NMR ($CDCl_3$): δ 167.0, 138.2, 132.4, 131.6, 130.8, 125.7, 124.6, 52.1 (corresponds with literature NMR data[5]). Production of methyl 2-mercaptobenzoate (**7**) from 3H-1,2-benzodithiol-3-one 1-oxide (**3**) was performed under the same conditions as described above, with the exception that two equivalents of triphenylphosphine (based on moles of **3**) was used. The reaction was stirred for 15 minutes and the yield of the methyl ester **7** was 35 %.

(*Received in USA* 28 *November* 1994; *revised* 21 *December* 1994; *accepted* 22 *December* 1994)