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The formation of open-chain thioesters in the reaction of 2-lithio-2-methyl- and 2-lithio-2-phenyl-1,3-dithiane with chlorodiphenylphosphane followed by oxidation☆

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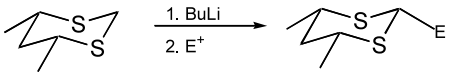
Abstract—The unexpected formation of open-chain thioesters (**3**) and (**6**) from the reaction of 2-lithio-*r*-2-*t*-4-*t*-6-trimethyl (**1**-Li) and 2-lithio-*r*-2-phenyl-*t*-4-*t*-6-dimethyl-1,3-dithiane (**4**-Li), respectively, with chlorodiphenylphosphane followed by oxidation was observed instead of the anticipated *gem*-derivatives. The X-ray diffraction analysis of (**6**) and the trapped intermediate (**10**) confirmed the structure and the proposed mechanism of formation of the open-chain products.

In 1971 Hartmann and Eliel[1] discovered that the 2-lithio derivative of conformationally fixed (anancomeric[2]) *cis*-4,6-dimethyl-1,3-dithiane reacts with electrophiles to afford, virtually as the exclusive product, the equatorially substituted 1,3-dithianes (Eq. (1)).

(1)



A systematic study of this reaction[3,4] led to the conclusion that the organolithium intermediate (contact or solvent separated ion pair) exhibits a robust (>6 kcal/mol,[4] or 14.2 kcal/mol as suggested by ab initio calculations[5]) preference for the equatorial orientation. Among several explanations to rationalize the stabilization of equatorial 2-lithio-1,3-dithiane,[5–7] sulfur polarizability was suggested by Bernasconi and Kittredge,[8] as to play a major role in the stabilization of sulfur carbanions. Meanwhile spectroscopic[9] studies discard interpretation in terms of classical bidented coordination of the lithium gegenion by the sulfur atoms, a crystallographic study of 2-lithio-2-methyl-1,3-dithiane[10] shows the coordination of sulfur with lithio in a dimeric structure (Fig. 1).

Reported in the present work is evidence of the interaction of the endocyclic sulfur of 1,3-dithianes with equatorial phosphorus-electrophiles attached to the C_2 carbon. The 2-phosphoryl substituted 1,3-dithianes have been used as Wittig–Horner precursors for the synthesis of ketene-dithioketals,[11–13] versatile intermediates in the homologation of umpolung carbonyl compounds.[14,15]

The reaction of 1,3-dithianes with chlorodiphenylphosphane followed by oxidation has been widely used by Juaristi et al.[16] and Mikolajczyk et al.[17] for the synthesis of a variety of 2-diphenylphosphinoyl-1,3-dithianes with noticeable conformational properties and reactivity. In a collaborative work with the group of Juaristi[18a] dealing with the synthesis and conformational analysis of 2,2-disubstituted 1,3-dithianes, we have found that

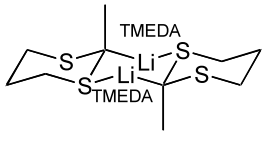


Figure 1.

Keywords: 1,3-dithianes; geminal substitution; phosphine oxidation; open-chain thioesters.

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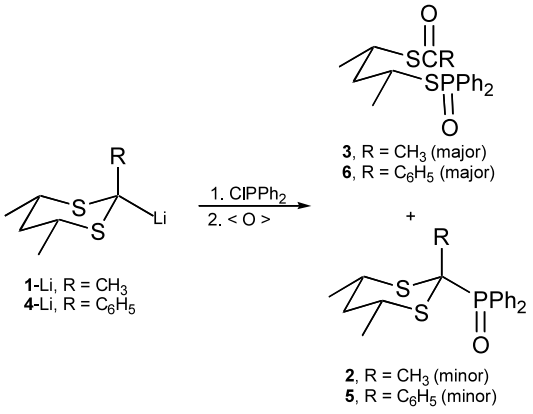
the reaction of anancomeric 2-lithio-*r*-2-*t*-4-*t*-6-trimethyl-1,3-dithiane (**1**-Li) and 2-lithio-*r*-2-phenyl-*t*-4-*t*-6-dimethyl-1,3-dithiane (**4**-Li) with chlorodiphenylphosphane followed by oxidation during work-up (Scheme 1), afforded open-chain thioesters (**3**) and (**6**), respectively, as main products, together with a minor amount of the *gem* substituted (**2**) and (**5**), respectively.[18b,19]

The structural identification of **3** and **6** was carried out by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy.[19] After recrystallization, compound **6** was obtained as crystals suitable for X-ray diffraction analysis. The ORTEP diagram confirms the open-chain nature of the structure of **6** (Fig. 2).

This assignment suggests that incorporation of the diphenylphosphino group in the open-chain product took place either via a nucleophilic attack of the endocyclic sulfur on chlorodiphenylphosphane with the concomitant formation of the ylide intermediate (path 1), or via the geminal precursor (path 2) as indicated in Scheme 2.



Scheme 1.

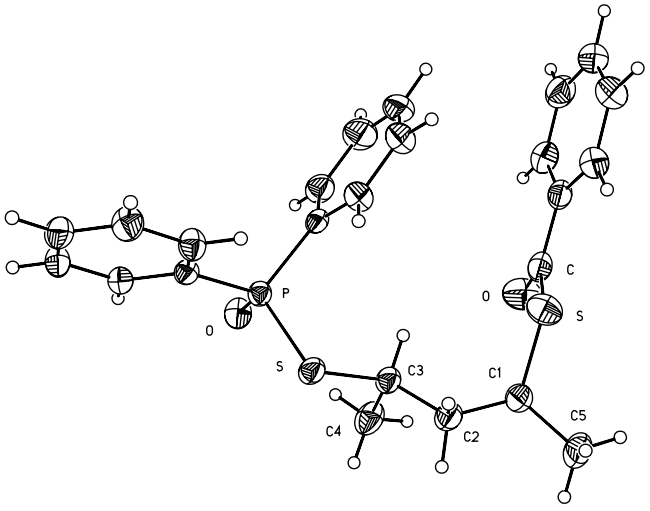
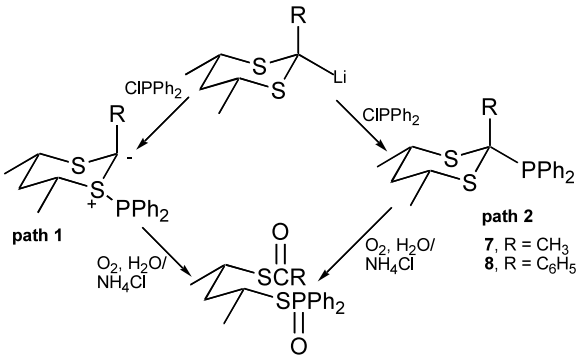


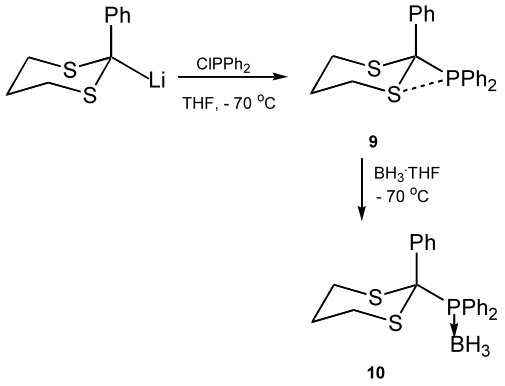
Figure 2. ORTEP structure of (1*S*,3*R*)-*S*-[3-(diphenylphosphinothioyl)-1-methylbutyl]thiobenzoate (**6**).



Scheme 2.

In order to throw light on the mechanism of formation of the open-chain products, reactions of carbanions (**1**-Li) and (**4**-Li) with chlorodiphenylphosphane were followed, separately, by ^{31}P NMR. Formation of a common specie at −14.4 ppm was observed within 10 min after the addition of chlorodiphenylphosphane to a flask containing **1**-Li or **4**-Li in dry THF under a nitrogen atmosphere at −20°C and transferred to NMR tubes via syringe. This species was less important than the one observed when the NMR tube was allowed to spin for 30 min at room temperature (22.7 or 30.6 ppm, for **1**-Li or **4**-Li, respectively). These two new species were stable under nitrogen. Formation of no other species was observed. After addition of 1–3 drops of aqueous saturated ammonium chloride solution, open-chain products **3** or **6** were formed predominantly, although a minor amount of the *gem* products **2** or **5** was also observed.[18b] Under these conditions, the formation of the products is slow (it can take 1 or 2 days to complete); however, oxidation of the intermediates and therefore formation of the open-chain products (^{31}P NMR: δ 42.81 for **3** and 42.92 for **6**)[19] was promoted by bubbling oxygen into the solutions.

The identification of the intermediate **7** (Scheme 2) was performed by ^{1}H and ^{13}C NMR of mixtures with different proportions of the specie at −14.4 and 22.7 ppm.[20] The species at −14.4 ppm turned out to be the butyldiphenylphosphane product of the reaction between unreacted BuLi with chlorodiphenylphosphane.[21] On the other hand, products at 22.7 and 30.6 ppm were characterized as the geminal phosphine precursors (Scheme 2).[22] In addition we were able to trap the intermediate by the addition of a solution of borane–THF to a flask containing 2-lithio-2-phenyl-1,3-dithiane and chlorodiphenylphosphane at −70°C (Scheme 3). The product was purified by column chromatography and the characterization of the phosphine–borane adduct **10** was performed by ^{1}H, ^{13}C, ^{11}B and ^{31}P NMR spectroscopy, elemental analysis and X-ray crystallography of the sample.[23] The ORTEP structure of the adduct (Fig. 3) clearly shows that the interatomic



Scheme 3.

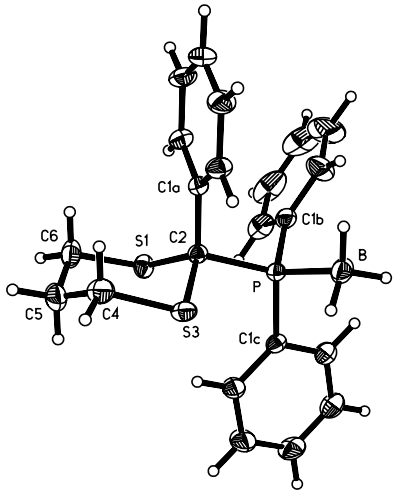


Figure 3. ORTEP structure of 2-boron, trihydro(diphenylphosphine)-2-phenyl-1,3-dithiane (**10**).

distance of the non-bonded phosphorus-sulfur atoms (2.97 Å average) is smaller than the sum of the van der Walls radii of them (3.65 Å) [1.85 Å (P) and 1.80 Å (S)].[24]

From these results it is evident that the formation of the open-chain products (**3**) and (**6**) took place during the oxidation step of the *gem*-phosphine precursors **7** or **8**, and not via the ylide intermediates, as postulated above (Scheme 2). The mechanism of oxidation of phosphines with molecular oxygen has been already reported,[25] so that based on those grounds we proposed the mechanism outlined in Scheme 4 to account for the formation of the open-chain products from the *gem*-precursors. Certainly we observed that the opening of the dithiane ring is taking place only if the diphenylphosphine group is constrained to occupy the equatorial orientation in the *gem*-precursors. To say it another way, the opening is not observed if the diphenylphosphine group in the geminal intermediate is axial, maybe due to the steric hindrance of the axial attack by molecular oxygen, therefore the final product in such a case, is the geminal 1,3-dithiane.[18]

Acknowledgements

We are grateful M. T. Cortez for the elemental analysis of compound **10** and to Professor E. Juaristi for useful comments. This work was financially supported by the project 32221-E granted by CONACyT.

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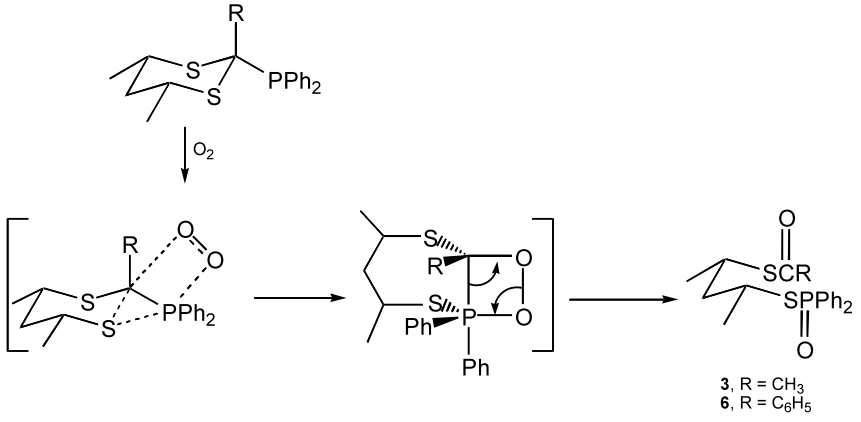

Scheme 4.

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19. For the experimental procedure to synthezise **3** and **6**, see footnotes ‡ and §, respectively.
20. Although attempts of purification of these intermediates by column chromatography failed, the interchange of THF by $CDCl_3$ was successfully performed by careful manipulation of the samples at room temperature, under a nitrogen atmosphere (see NMR data of intermediates in

‡ Preparation of (1*S*,3*R*)-*S*-[3-(diphenylphosphinothioyl)-1-methylbutyl]thioacetate **3**: to a solution of 2.0 g (0.0123 mol) of *trans*-**1** in dry THF under nitrogen at −20°C was added 5.4 mL (0.0135 mol) of BuLi (2.5 M in hexanes). The solution was stirred at −20°C for 2 h and transferred dropwise with a double-ended needle under nitrogen pressure to a solution of 2.4 mL (0.0135 mol) of chlorodiphenylphosphane in 10 mL of THF at −20°C. The mixture was stirred at −20°C for 1.5 h and 3 h at room temperature. The solution was poured into 120 mL of saturated ammonium chloride solution and extracted with methylene chloride. The extract was dried over sodium sulfate, filtered off and the solvent was removed with a rotary evaporator. Crude material analyzed by ^{31}P and ^{1}H NMR contained compounds **3**, **2**, $CH_3CH_2CH_2CH_2P(O)Ph_2$ (^{31}P NMR δ 33.4 ppm, from the reaction of BuLi and $ClPPh_2$ followed by oxidation), and unreacted *trans*-**1** in a ratio close to 3:1:1:2. The residue was chromatographed on silica gel using a mixture of solvents with a gradually polar increment, starting with 95% hexanes/ethyl acetate and ending with 60% hexanes/ethyl acetate. Compound **3** (isolated yield 1.78 g, 38.7%): ^{31}P NMR ($CDCl_3$) δ 42.81 ppm. ^{1}H NMR ($CDCl_3$) δ 1.21 (d, $J_{HH}=6.9$ Hz, 3H), 1.43 (d, $J_{HH}=6.9$ Hz, 3H), 1.77 (∼q, $J_{gem}=14.2$ Hz, 1H) 2.0 (∼q, $J_{gem}=14.2$ Hz, 1H), 2.30 (s, 3H), 3.36 (m, $^{3}J_{PH}=10.6$ Hz, $^{3}J_{HH}=7.9$ Hz, 1H), 3.70 (m, $^{3}J_{HH}=7.6$ Hz, $^{3}J_{HH}=6.9$ Hz, 1H), 7.57 (m, 6H), 7.97 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 21.17 (C_5), 23.97 (d, $^{3}J_{CP}=2.2$ Hz, C_4), 30.76 ($\underline{C}H_3$-C=O), 37.10 (C_1), 39.16 (d, $^{3}J_{CP}=2.2$ Hz, C_2), 45.30 (d, $^{2}J_{CP}=4.6$ Hz, C_3), 128.67 (d, $^{2}J_{CP}=13.0$ Hz, C_{ortho}), 131.60 (d, $^{1}J_{CP}=21.3$ Hz, C_{ipso}), 131.61 (s, C_{meta}), 132.27 (d, $^{4}J_{CP}=3.3$ Hz, C_{para}), 195.73 (C=O). Anal. calcd for $C_{19}H_{23}S_2PO_2$: C, 60.30; H, 6.13. Found: C, 60.09; H, 6.38.

§ Preparation of (1S, 3R)-S-[3-(diphenylphosphinothioyl)-1-methylbutyl]thiobenzoate **6**: to a solution of 3.6 g (0.0161 mol) of *trans*-**4** in dry THF under nitrogen at −20°C was added 7.1 mL (0.0178 mol) of BuLi (2.5 M in hexanes). The solution was stirred at −20°C for 2 h and transferred dropwise with a double-ended needle under nitrogen pressure to a solution of 3.2 mL (0.0178 mol) of chlorodiphenylphosphane in 10 mL of THF at −20°C. The mixture was stirred at −20°C for 1.5 h and 3 h at room temperature. The solution was poured into 120 mL of saturated ammonium chloride solution and extracted with methylene chloride. The extract was dried over sodium sulfate, filtered off and the solvent was removed with a rotary evaporator. Crude material analyzed by ^{31}P and ^{1}H NMR contained compounds **6**, **5**, and $CH_3CH_2CH_2CH_2P(O)Ph_2$ (^{31}P NMR δ 33.4 ppm, from the reaction of BuLi and $ClPPh_2$ followed by oxidation) in a ratio close to 8:2:1. The residue was a solid chromatographed on silica gel using a mixture of solvents with a gradually polar increment, starting with 95% hexanes/ethyl acetate and ending with 60% hexanes/ethyl acetate. Compound **6** (isolated yield 3.8 g, 54%): ^{31}P NMR ($CDCl_3$) δ 42.92 ppm. ^{1}H NMR ($CDCl_3$) δ 1.24 (d, $J_{HH}=6.7$ Hz, 3H), 1.40 (d, $J_{HH}=6.7$ Hz, 3H), 1.83 (∼q, $J_{gem}=14.1$ Hz, 1H), 2.12 (∼q, $J_{gem}=14.3$ Hz, 1H) 3.33 (m, $^{3}J_{PH}=10.1$ Hz, $^{3}J_{HH}=3.2$ Hz, $^{3}J_{HH}=6.9$ Hz, 1H), 3.85 (m, $^{3}J_{HH}=7.4$ Hz, $^{3}J_{HH}=7.2$ Hz, 1H), 7.46 (m, 9H), 7.88 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 21.22 (C_5), 24.08 (C_4), 37.18 (C_1), 39.33 (C_2), 45.58 (d, $^{2}J_{CP}=5.2$ Hz, C_3), 127.28 ($C_{ortho'}$), 128.58 (C_{meta}), 128.79 (d, $^{2}J_{CP}=3.0$ Hz, C_{ortho}), 131.61 (d, $^{1}J_{CP}=20.8$ Hz, C_{ipso}), 131.62 ($C_{meta'}$), 132.27 (C_{para}), 133.36 ($C_{para'}$), 137.15 ($C_{ipso'}$), 191.59 (C=O). Anal. Calcd for $C_{24}H_{25}S_2PO_2$: C, 65.44; H, 5.72. Found: C: 65.51; H, 5.92.

Refs. 21 and 22 below). The identity of $CH_3CH_2CH_2$-CH_2PPh_2 was also confirmed by reacting 1 equiv. of chlorodiphenylphosphane with 1 equiv. of BuLi in THF.

21. $CH_3CH_2CH_2CH_2PPh_2$: ^{31}P NMR ($CDCl_3$) δ −14.91 ppm. ^1H NMR ($CDCl_3$) δ 0.88 (t, $J_{HH}=7.0$ Hz, 3H), 1.42 (m, 4H), 2.01 (m, $^2J_{HP}=7.3$ Hz, 2H), 7.31 (m, 6H), 7.41 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 13.80 (CH_3), 24.31 (d, $^3J_{CP}=13.3$ Hz, C_3), 27.95 (d, $^1J_{CP}=41.3$ Hz, C_1), 28.01 (d, $^2J_{CP}=14.39$ Hz, C_2), 128.34 (d, $^2J_{CP}=9.4$ Hz, C_{ortho}), 128.38 (s, C_{meta}), 132.66 (d, $^3J_{CP}=18.31$ Hz, C_{para}), 139.01 (d, $^1J_{CP}=13.0$ Hz, C_{ipso}).
22. Intermediate **7**: ^{31}P NMR ($CDCl_3$) δ 21.27 ppm. ^1H NMR ($CDCl_3$) δ 1.21 (d, $^3J_{HH}=6.6$ Hz, 6H), 1.87 (d, $^3J_{HP}=12.1$ Hz, 3H), 2.04 (m, 1H), 2.07 (m, 1H), 3.14 (m, 2H), 7.37 (m, 6H), 7.78 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 21.29 (s, $\underline{C}H_3CH$), 29.22 (d, $^3J_{CP}=12.3$ Hz, $\underline{C}H_3C$), 35.84 (d, $^3J_{CP}=7.7$ Hz, $C_{4,6}$), 43.54 (s, C_5), 50.18 (d, $^1J_{CP}=32.3$ Hz, C_2), 127.92 (d, $^4J_{CP}=7.7$ Hz, C_{para}), 129.22 (s, C_{meta}), 135.43 (d, $^2J_{CP}=20.0$ Hz, C_{ortho}), 134.49 (d, $^1J_{CP}=17.7$ Hz, C_{ipso}).
23. Phosphine–borane adduct **10**: ^{31}P NMR ($CDCl_3$) δ 45.41 ppm. ^{11}B NMR ($CDCl_3$) δ −39.0 ppm. ^1H NMR ($CDCl_3$) δ 0.90–1.36 (br.s, BH_3, 3H), 1.95 (m, 2H), 2.68 (m, 4H), 7.36 (m, 9H), 7.69–7.89 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 24.14 (C_5), 27.68 (d, $^3J_{CP}=3.8$ Hz, $C_{4,6}$), 37.34 (d, $^1J_{CP}=33.8$ Hz, C_2), 126.87 (d, $^1J_{CP}=89.2$ Hz, C_{ipso}), 127.62 (d, $^4J_{CP}=3.1$ Hz, $C_{para'}$), 127.91 ($C_{meta'}$), 127.94 (d, $^3J_{CP}=10.0$ Hz, C_{meta}), 131.59 (d, $^3J_{CP}=3.0$, $C_{ortho'}$), 131.89 (d, $^4J_{CP}=3.8$ Hz, C_{para}), 133.35 (d, $^2J_{CP}=8.5$ Hz, $C_{ipso'}$), 135.09 (d, $^2J_{CP}=8.5$ Hz, C_{ortho}). Anal. calcd for $C_{22}H_{24}S_2PB$: C, 67.01; H, 6.13. Found: C, 66.60; H, 6.19.
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