An unexpected base-induced [1,4]-phospho-Fries rearrangement

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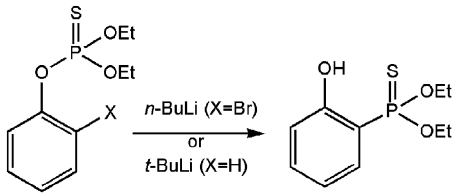
An unexpected [1,4]-phospho-Fries rearrangement that gives rise to the formation of a *O*,*O*,*O*,*O*-tetraethyl methylenebis(thiophosphonate) derivative is reported. The regioselectivity of the metallation with *n*-BuLi or *t*-BuLi is the key factor that explains either the [1,4] or [1,3] rearrangement observed.

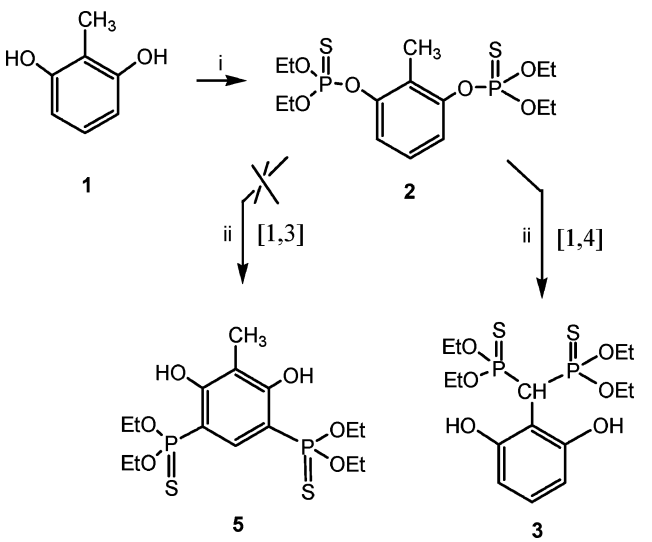
The phospho-Fries rearrangement, which was first reported by Melvin,[1] consists in the transposition of an aryl phosphate into an aryl phosphonate. This reaction requires as an initial step: the formation of an *ortho*-metallated intermediate that, *via* a [1,3]-rearrangement, produces an aryl phosphonate. The *ortho*-metallation can be achieved by either deprotonation with LDA or *n*-BuLi or by halogen–metal exchange. The good to excellent yields associated with this phospho-Fries rearrangement explained its use for the synthesis of *o*-hydroxyarylphosphonates.[2] This rearrangement has been extended to the synthesis of other aryl-phosphorylated compounds including 2-hydroxyarylphosphonodiamidates,[3] 2-hydroxyarylphosphinoxides,[4] 2-mercaptoarylphosphonates[5] and 2-mercaptoarylphosphonodiamidates[6] For the five-membered pyrrole ring, the introduction of phosphorylated species in the α-position to the nitrogen atom has been also reported.[4] The [1,4]-phospho-Fries rearrangement has been attempted by Buono and coworkers.[7] who synthesized an *O*-(2,6-dimethyphenyl)phosphoramide derivative. This compound in the presence of an alkyllithium did not produce the [1,4]-rearrangement that would have placed the phosphorus moiety on one of the methyl groups localized in position 2 and 6 of the phenyl ring. In that case only by-products resulting from nucleophilic attack of the base at the phosphorus atom were observed.[7] Recently we explored [1,2]- and [1,3]-rearrangement for the synthesis of *O*,*O*-dialkylarylthiophosphonates. When pyrrole is used as a substrate, *O*,*O*-dialkyl-2-pyrrolthiophosphonates can be obtained in good yields by a two-step process that makes use of the [1,2]-phospho-Fries rearrangement.[8] This procedure can be repeated to yield pyrrol-*bis*-thiophosphonate, which is a pincer ligand that has been engaged for the synthesis of palladium and silver coordination complexes.[9] Aryl-thiophosphonates can be also obtained *via* a [1,3]-phospho-Fries rearrangement that makes use of phenol derivatives as initial substrates (Scheme 1).[10] In that case the efficiency of the rearrangement is strongly dependent on the nature of the precursor and of the base used. Indeed, with an *ortho*-bromo derivative as a substrate (Scheme 1, X = Br), the metallation is efficiently achieved by using *n*-BuLi and the rearranged product is isolated in high yield. Interestingly even a



Scheme 1 Synthesis of an arylthiophosphonate *via* a [1,3]-phospho-Fries rearrangement.

simultaneous double rearrangement can be achieved in high yield (92%) on dibromophenol derivatives.[10] On the other hand, when a non-halogenated substrate is employed (Scheme 1, X = H), the reaction requires a stronger base (*t*-BuLi). However a complete conversion is usually not observed and thiophosphonates are obtained in modest yields (around 50%).[10]

With the aim of synthesizing compound **5** *via* a double [1,3]-phospho-Fries rearrangement on substrate **2** (Scheme 2), we first synthesized the bis-thiophosphate **2** by reaction of 2-methylresorcinol **1** with *O*,*O*-diethylchlorothiophosphate and triethylamine following a reported procedure[10] (yield 40%)†. Then, *t*-BuLi (3 equivalents), which is the base required when non-halogenated substrates are used, was added to a solution of **2** in THF at –78 °C; after warming up the reaction media to 20 °C and a hydrolysis step, the crude product was purified on silica gel to produce compound **3**‡ in 29% yield instead of the expected compound **5**. Neither in the crude product nor in a fraction of chromatography, was compound **5** detected by



Scheme 2 Synthesis of *O*,*O*,*O*,*O*-tetraethyl(2,6-dihydroxyphenyl)-methylene-dithiophosphoante **3**: (i) Cl-P(S)(OEt)$_2$ (2.2 equivalents), NEt$_3$ (2.4 equivalents), DMAP (10 mol%), THF, 20 °C; (ii) *t*-BuLi, THF, –78 °C then water.

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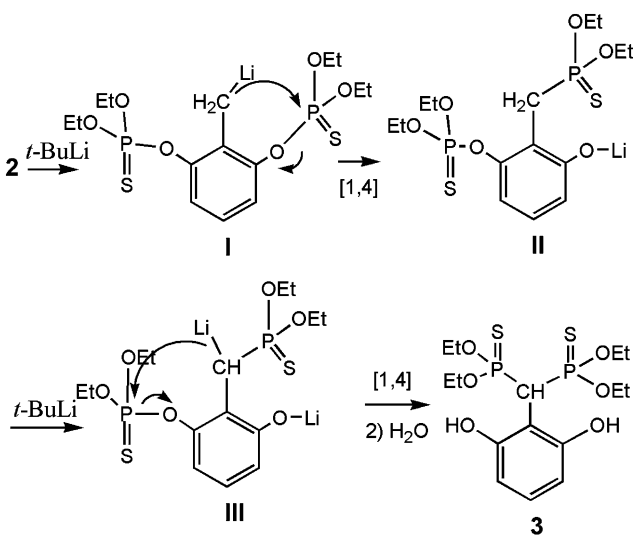
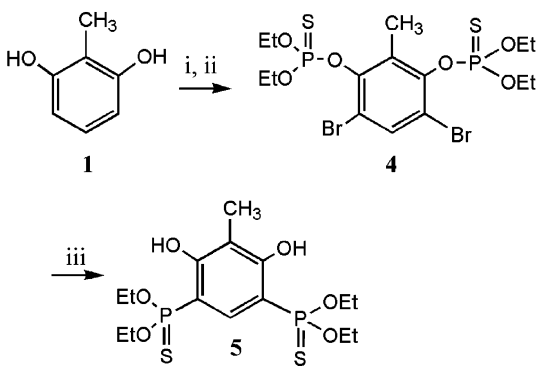
NMR. Spectroscopic data attest to the formation of compound **3**. According to ^{1}H NMR, a characteristic triplet, observed at 5.10 ppm with $^{3}J_{HP}$ = 26 Hz, is ascribed to the CH of the P–CH–P moiety. 3 protons are observed in the aromatic resonance area (6.45, 6.60 and 7.07 ppm). The ^{31}P chemical shift for compound **3** is 84.8 ppm while the signal of the starting compound **2** is observed at 62.9 ppm. ^{13}C NMR spectroscopy corroborates the previous characterizations, since a characteristic triplet attributed to the C–H pattern ($^{1}J_{CP}$ = 102.8 Hz) is observed at 49.5 ppm. Interestingly the carbon atoms of the aromatic ring generate 6 peaks. The presence of these 6 signals is explained by the absence of a plane of symmetry due to the presence of the two thiophosphonate functional groups on a pro-chiral carbon atom. Moreover the peak observed at *m*/*z* 429.072 by MALDI-TOF spectrometry is in agreement with the formula $C_{15}H_{27}O_6P_2S_2$ (M + 1).†

With the aim of improving the yield of formation of compound **3**, a screening of the required quantities of *t*-BuLi was achieved. The best result was obtained by using 6.2 equivalents of *t*-BuLi. In that case a conversion of 58% was observed and compound **3** was isolated after chromatography in 40% yield. The generalization of this rearrangement was investigated by using *O*-(2-methylphenyl)-*O*,*O*-diethylthiophosphate as substrate. Surprisingly in that case the addition of 2.2 equivalents of *t*-BuLi on this substrate was unsuccessful and 90% of the starting compound was recovered. This result indicates that the [1,4]-phospho-Fries rearrangement can not be generalized by the application of this experimental procedure. The formation of compound **3** is explained by a double [1,4]-phospho-Fries rearrangement which is only observed when the two thiophosphate groups are present in *o*-positions of the methyl group. These groups might favour the proximity of *t*-BuLi since the two thiophosphophosphate moieties can act as a pincer towards *t*-BuLi *via* Li···O interactions. Consequently the deprotonation on the methyl group might be favoured due to this pre-organization. As soon as the metallation takes place, the [1,4]-rearrangement can occur leading to the formation of the likely intermediate **II** (Scheme 3). The fact that the protonated form of this intermediate was never observed either in the crude media or in the fractions of chromatography indicates that this intermediate is more reactive than compound **2** itself in the presence of *t*-BuLi. After the first [1,4]-rearrangement affording **II**, the mesomeric effects favour the deprotonation on the benzylic position of this intermediate to induce the formation of **III** which then evolves into **3** after hydrolysis. This reaction constitutes an interesting alternative way to the synthesis and the study of methylenebis(thiophosphonate), which has been much less studied than its diphosphonate analogue methylenediphosphonate. [11]



Scheme 3 Proposed mechanism for the formation of compound **3**.

With the aim of achieving a double [1,3]-phospho-Fries rearrangement in place of the [1,4] previously observed, we used the dibromobis-thiophosphate **4** (Scheme 4) as substrate with the objective of changing the regioselectivity of the metallation and consequently the type of phospho-Fries rearrangement. Dibromo-bisthiophosphate **4**§ was synthesized following a two-step sequence that starts by the bromination of 2-methylresorcinol **1**,[12] followed by the introduction of the two thiophosphate functional groups according to a reported procedure.[10] The reaction of this compound with *n*-BuLi gives rise to the double [1,3]-rearrangement indicating that a full regiocontrol of the metallation governs the regioselectivity of the phospho-Fries rearrangement. After purification compound **5** was isolated in 97% yield.¶ Spectroscopic data confirm the formation of compound **5**. Its ^{31}P NMR shows a peak at 78.1 ppm that contrasts with the ^{31}P NMR resonance for compound **4** (62.5 ppm). According to its ^{1}H NMR spectrum, the methyl group linked to the aromatic ring is observed at 2.10 ppm. At 7.70 ppm the signal of the aromatic proton exhibits a characteristic triplet which is ascribed to its coupling with two phosphorus atoms ($^{3}J_{HP}$ = 14.9 Hz). In ^{13}C NMR **5** also exhibits a characteristic doublet of doublet at 107.2 ppm ($^{1}J_{CP}$ = 156.0 Hz, $^{3}J_{CP}$ = 13.0 Hz) that can be attributed to the sp^2 carbon atoms bound to a phosphorus atom. Two triplets are observed at 114.7 ($^{2}J_{CP}$ = 9.5 Hz) and 132.5 ppm ($^{3}J_{CP}$ = 8 Hz) which are attributed respectively to the sp^2 carbon atom linked to the methyl group and to the C_{sp2}–H. Finally the signal at 162.4 is ascribed to the aromatic carbon atoms bearing hydroxyl groups.



Scheme 4 Synthesis of the aryl bis(thiophosphonate) **5** following a double [1,3]-phospho-Fries rearrangement. (i) Br_2, CH_3COOH; (ii) Cl-P(S)$(OEt)_2$ (2.2 equivalents), NEt_3 (2.4 equivalents), DMAP (10 mol%), THF, 20 °C; (iii) *n*-BuLi (2.4 equivalents), THF, −78 °C then water.

To the best of our knowledge, we report herein the first example of a [1,4]-phospho-Fries rearrangement which is observed when the bisthiophosphate **2**, synthesized from 2-methylresorcinol, is treated with *t*-BuLi. It is suggested that this [1,4]-rearrangement is due to the presence of the two thiophosphate groups that might localize *t*-BuLi in the proximity of the methyl group thus helping the first metallation. This original reaction

offers a straightforward way to synthesize an *O*,*O*,*O*,*O*-tetraalkylmethylenebis(thiophosphonate) derivative. On the other hand, when the metallation is imposed on the aromatic ring, by using a metal–halogen exchange procedure, a more classic [1,3]-phospho-Fries rearrangement is observed leading to the formation of the arylbis(thiophosphonate) **5**. The coordination behaviour of compounds **3** and **5** will be investigated in our next study.

Acknowledgements

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Notes and references

† Spectroscopic data for compound **2**: ^{1}H-NMR (400 MHz, $CDCl_3$): 1.36 (t, $^{3}J_{HH}$ = 7 Hz, 12H, 4 × O–CH_2–CH_3); 2.25 (s, 3H, C_2–CH_3); 4.24 (m, 8H, 4 × O–CH_2–CH_3); 7.12 (s, 2H, C_4–*H* et C_6–*H*); 7.26 (s, 1H, C_5–*H*); ^{31}P-NMR (161.9 MHz, $CDCl_3$): 62.9; ^{13}C-NMR (75.5 MHz, $CDCl_3$): 10.83 (s, C_2–CH_3); 16.16 (d, $^{3}J_{CP}$ = 8 Hz, O–CH_2–CH_3); 65.30 (d, $^{2}J_{CP}$ = 6 Hz, O–CH_2–CH_3); 117.55 and 117.58 (2d, $^{3}J_{CP}$ = 2 Hz, C_4 and C_6); 123.44 (t, $^{3}J_{CP}$ = 6 Hz, C_2); 126.28 (t, $^{4}J_{CP}$ = 2 Hz, C_5); 150.07 (d, $^{2}J_{CP}$ = 7 Hz, C_1 and C_3); IR: 950 (C–O); 1015 (P–O); 1464; 1583 (C═C); 2982 (C–H).

‡ Spectroscopic data for compound **3**: ^{1}H-NMR (400 MHz, $CDCl_3$): 1.24 et 1.31 (2t, $^{3}J_{HH}$ = 7 Hz, 12H, 4 × O–CH_2–CH_3); 4.16 (m, 8H, 4 × O–CH_2–CH_3); 5.10 (t, $^{2}J_{HP}$ = 26 Hz, 1H, C*H*–P); 6.45 et 6.60 (2d, $^{3}J_{HH}$ = 8 Hz, 2H, 2 × CH); 7.07 (t, $^{3}J_{HH}$ = 8 Hz, 1H, CH); 7.42 (s, 1H, OH); ^{31}P-NMR (161.9 MHz, $CDCl_3$): 84.8; ^{13}C-NMR (75.5 MHz, $CDCl_3$): 15.98 (m, O–CH_2–CH_3); 49.46 (t, $^{1}J_{CP}$ = 102.8 Hz, *C*H–P); 63.80, 63.82, 64.12 and 64.15 (4d, $^{2}J_{CP}$ = 3.4 Hz, O–CH_2–CH_3); 106.28 (t, J_{CP} = 5.6 Hz, C_{ar}); 107.94 (s, C_{ar}); 111.40 (t, J_{CP} = 2.4 Hz, C_{ar}); 129.63 (t, J_{CP} = 2.5 Hz, C_{ar}); 154.70 (t, J_{CP} = 6.9 Hz, C_{ar}); 157.02 (t, J_{CP} = 4.5 Hz, C_{ar}). MALDI-TOF: *m*/*z* calc. for $C_{15}H_{27}O_6P_2S_2$ [M + 1]: 429.0724, Found: 429.072.

§ Spectroscopic data for compound **4**: ^{1}H-NMR (400 MHz, $CDCl_3$): 1.36 (t, $^{3}J_{HH}$ = 7.1 Hz, 12 H, C*H*$_3$–CH_2–O), 2.41 (s, 3H, C*H*$_3$–), 4.27 (m, 8H, CH_3–C*H*$_2$–O), 7.68 (s, 1H, C–*H*); ^{31}P-NMR: (161.9 MHz, $CDCl_3$): 62.5; ^{13}C (75.5 MHz, $CDCl_3$): 14.16 (s, Ar–CH_3), 15.95 (d, $^{3}J_{CP}$ = 8.0 Hz; O–CH_2–CH_3), 65.44 (m,; O–CH_2–CH_3), 113.39 and 113.46 (2d, $^{3}J_{CP}$ = 4.0 Hz, *C*–Br); 129.15 (t, $^{3}J_{CP}$ = 3.7 Hz, *C*–CH_3); 133.42 (s, C–H); 147.68 (m, C_{ar}–O–P)

¶ Spectroscopic data for compound **5**: ^{1}H-NMR (400 MHz, $CDCl_3$): 1.33 (t, $^{3}J_{HH}$ = 7.1 Hz, 12 H, C*H*$_3$–CH_2–O), 2.10 (s, 3H, C*H*$_3$–), 4.13 (m, 8H, CH_3–C*H*$_2$–O), 7.70 (t, $^{3}J_{HP}$ = 14.9 Hz, 1H, C–*H*), 9.67 (s, 2H, O–*H*); ^{31}P: (161.9 MHz, $CDCl_3$): 78.1; ^{13}C NMR (75.5 MHz, $CDCl_3$): 8.12 (t, $^{4}J_{CP}$ = 1.5 Hz, Ar–CH_3), 15.94 and 16.00 (2d, $^{3}J_{CP}$ = 4.0 Hz; O–CH_2–CH_3), 63.11 and 63.15 (2d, $^{2}J_{CP}$ = 2.7 Hz; O–CH_2–CH_3), 107.22 (dd, $^{1}J_{CP}$ = 156.0 Hz, $^{3}J_{CP}$ = 13.0 Hz, *C*–P); 114.70 (t, $^{2}J_{CP}$ = 9.5 Hz, *C*–H); 132.48 (t, $^{3}J_{CP}$ = 8 Hz, *C*–CH_3); 162.36 (~dd, $^{2}J_{CP}$ = 11 Hz, $^{4}J_{CP}$ = 3.5 Hz, *C*–OH); Anal, Calcd for $C_{15}H_{26}O_6P_2S_2$: C,42.05; H,6.12; S,14.97, Found: C, 41.70; H,6.32; S, 14.84; IR (ATR): 777 (52); 795 (53); 959 (O–C, 46); 1011 (P–O, 48); 1108 (67); 1388 (79); 1586 (74); 1599 (73); 2981 (86); 3131 (O–H . . . S; 79); Exact Mass, Calcd for $C_{15}H_{27}O_6P_2S_2$ (M+1): 429.0724; found: 429.0711; *m*/*z* (MSMS *m*/*z* = 429; ESI): 429 (M + 1, 63%); 401 (M + 1 – CH_2═CH_2; 100%); 383 (31%); 373 (M + 1 – 2 × CH_2═CH_2; 10%); 355 (34%).

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