Synthesis of *O,O*-Diethyl Arylthiophosphonate from *O*-Aryl-*O,O*-diethylthiophosphate

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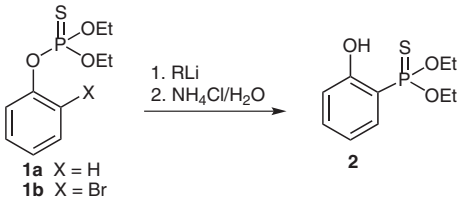
Abstract: The synthesis of *O*,*O*-diethyl 2-hydroxyarylthiophosphonate is reported by using a [1,3]-rearrangement. This method is achieved in high yield from *ortho*-bromophenols derivatives by a two-step process

Key words: phosphorylation, metallation, phenols, rearrangement

O,*O*-Dialkyl arylthiophosphonates which are the sulfur analogues of *O*,*O*-dialkyl arylphosphonate have been proved useful to design coordination complexes[1] or supramolecular assemblies.[2] The synthesis of arylthiophosphonates is usually achieved by the thiooxidation of phosphorus(III) species.[3] The direct phosphorylation of aryllithium intermediates with *O*,*O*-dialkylchlorothiophosphate has also been reported.[4] With the aim to synthesize 2-hydroxyarylthiophosphonates as precursors of coordination complexes we have investigated a base-induced rearrangement of *O*-aryl-*O*,*O*-diethylthiophosphate to form thiophosphonate as reported in Scheme 1. This type of rearrangement, also identified as phospho-Fries rearrangement,[5] is well documented for the synthesis of 2-hydroxyarylphosphonates,[6] 2-hydroxyarylphosphonodiamidates,[7] 2-hydroxyarylphosphinoxides,[8] 2-mercaptoarylphosphonates[9] or 2-mercaptoarylphosphonodiamidates.[10] On the contrary, this type of rearrangement to produce 2-hydroxyarylthiophosphonate has been exemplified only once. In this reported example, LDA was used as base but both the yield (30%) and the regioselectivity (3:1 mixture) of the reaction were low.[11] It is postulated that all these phospho-Fries rearrangements are achieved according to a two-step process initiated by an orthometallation of the aromatic ring performed by a base and followed by the [1,3]-migration of the phosphono group leading to the formation of the P–C bond. After hydrolysis of the phenolate or thiophenolate intermediates the reaction product is formed.

To achieve a base-induced [1,3]-rearrangement of thiophosphate to thiophosphonate (Scheme 1), butyllithium was used as a base instead of LDA which is the base commonly employed to achieve phospho-Fries rearrangement. As reported in Table 1 (entries 1–3), the choice of the solvent had a crucial influence on the conversion ratio, the best yield being obtained in THF (entry 3). It is noteworthy that the starting compound was recovered in large quantities in all these reactions (entries 1–3) suggesting a poor efficiency of the orthometallation in these experimental conditions and a weak reactivity of the thiophosphate or thiophosphonate functional groups towards butyllithium at low temperature. This behavior can be rationalized by a weak polarity of the P=S bond affording a weak electrophilic character to the phosphorus atom. It is interesting to notice that this observation is in contrast to the reactivity of phosphono functional group possessing a P=O bond. For instance, the phospho-Fries rearrangement starting from *S*-aryl-*O*,*O*-dialkylthiophosphate (compound possessing a P=O bond) is highly sensitive to nucleophilic attack.[12] Indeed the rearrangement is only



Scheme 1 Base-induced [1,3]-sigmatropic rearrangement affording thiophosphonate **2** from *O*-aryl-*O*,*O*-diethylthiophosphates **1a**,**b**

Table 1 Results of the Rearrangements Performed on Compounds **1a** or **1b**

Entry	RLi	Solvent	X	Conversion[c] (%)	Isolated yield (%)[d]
1	*n*-BuLi[a]	hexane	H	5	–
2	*n*-BuLi[a]	Et_2O	H	30	10
3	*n*-BuLi[a]	THF	H	40	15
4	*t*-BuLi[b]	THF	H	85	48
5	*n*-BuLi[a]	THF	Br	100	95

[a] Amount of reagent: 1.1 equiv.
[b] Amount of reagent: 2.2 equiv.
[c] Determined by ^{31}P NMR.
[d] Yield after purification by column chromatography over silica gel.

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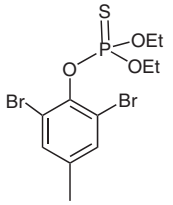
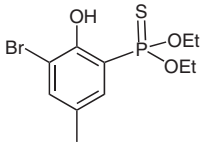
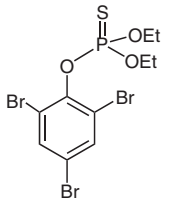
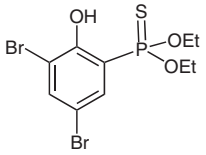
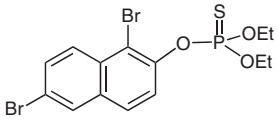
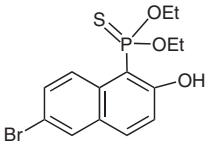
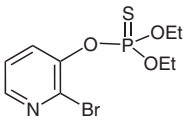
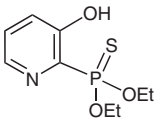
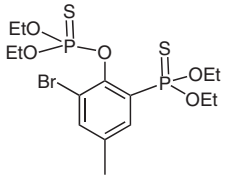
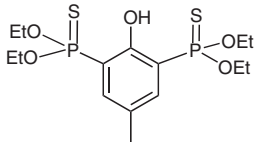
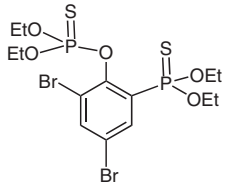
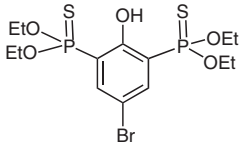
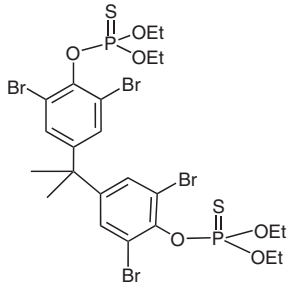
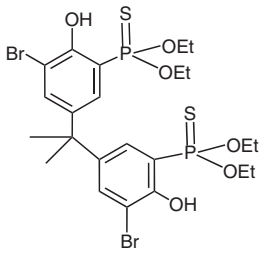
Table 2 Metal-Halogen Exchange Giving Rise to a [1,3]-Phospho-Fries Rearrangement of *O*-Aryl-*O*,*O*-diethylthiophosphate **1c–i** into *O*,*O*-Diethyl Arylthiophosphonate **2c–i**

Entry	Substrate	^{31}P NMR ($CDCl_3$): δ	Isolated yield (%)	Product	^{31}P NMR ($CDCl_3$): δ	Isolated yield (%)
1	 **1c**	63.6	99	 **2c**	78.8	94
2	 **1d**	62.9	92	 **2d**	75.8	88
3	 **1e**	62.8	98	 **2e**	80.0	87
4	 **1f**	62.9	95	 **2f**	69.7	85
5	 **1g**	62.2 and 83.5	87	 **2g**	81.1	97
6	 **1h**	61.7 and 80.3	76	 **2h**	77.3	77
7	 **1i**	62.6	96	 **2i**	77.7	92

successful if the hindrance around the phosphorus atom is increased by the presence of two isopropyloxy chains.[9a]

With the aim to improve the efficiency of the orthometallation of substrate **1a**, *t*-BuLi was used to perform the re-

action (Table 1, entry 4). The conversion was indeed increased but the yield stayed quite modest (48%). Finally, a metal-halogen exchange performed by reaction of *n*-BuLi with **1b** (Table 1 entry 5) allowed us to observe a full conversion of the substrate affording the pure arylthiophosphonate **2** in good yield (95%). A ^{31}P NMR monitoring of this reaction performed at –80 °C showed the presence of a single signal at δ = 96.01 ppm. This resonance was proved to correspond to that of the lithium phenolate compound (also characterized by ^{1}H and ^{13}C NMR) resulting from a halogen-metal exchange on **1b** followed by a [1,3]-migration of the thiophosphono group. Hydrolysis of this compound was found to afford quantitatively **2**. This experiment demonstrates that, at –80 °C, both the metal-halogen exchange and the [1,3]-rearrangement are extremely fast. This rearrangement has been extended to other phenols displaying one or two bromides in *ortho* positions. First, the thiophosphates **1c–i** (Table 2) were prepared from their corresponding phenol by reaction with the commercially available diethylchlorothiophosphate.[13] Then the [1,3]-rearrangement was achieved on these compounds by reaction with *n*-butyllithium in THF at –78 °C.[14] This reaction was easily followed by ^{31}P NMR since the thiophosphates are characterized by a ^{31}P chemical shift at δ = 61.7–63.6 ppm while the resonances of the formed thiophosphonates are observed at δ = 69.7–80.0 ppm (see Table 2). The [1,3]-rearrangements were accomplished in good yields (77– 97%, see Table 2). This rearrangement has been applied on polybromide substrates (Table 2, entries 1–3, 6 and 7) to produce the expected thiophosphonates in good yields. For the heteroaromatic substrate **1f**, a regiospecific reaction was observed giving rise to **2f** in 85% yield (entry 4). The efficiency of this reaction is in contrast to that observed for the method previously reported for the synthesis of compound **2f** which was isolated in 30% yield and as a 3:1 mixture of regioisomers.[11] The presence of a second bromide atom in the *ortho* position of the phenol group of compounds **2c** and **2d**, has allowed us to introduce, via a subsequent two-step sequence, a second thiophosphono group giving rise in good yields to **2g** and **2h** (entries 5 and 6). The synthesis of compound **2i**, resulting from a simultaneous double [1,3]-rearrangement, has also been achieved in good yield (92%) starting from the bisthiophosphate **1i** (entry 7). In that case, 2.2 equivalents of BuLi were used.

In the present communication, a [1,3]-phospho-Fries rearrangement has been applied to the synthesis of *O*,*O*-diethyl 2-hydroxyarylthiophosphonate. This simple method has allowed the formation of a P–C bond via a two-step process: (1) an orthometallation achieved by a metal-halogen exchange reaction, and (2) the rearrangement itself. This methodology has also allowed the introduction of thiophosphono groups on both *ortho* positions of a α,α′-dibromophenol. A double rearrangement, starting from a bi-phenol derivative, is also illustrated.

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(12) Garbers, H. V.; Modro, T. A. *Heteroat. Chem.* **1990**, *1*, 241.
(13) **Preparation of Thiophosphates 1a–i Represented by the Preparation of *O*,*O*-Diethyl 6-Bromo-2-(diethoxythiophosphinyl)-4-methylphenylthiophosphonate (1g)**: A solution of the phenolic derivative **2c** (3.70 g, 8.85 mmol), triethylamine (1.48 mL, 10.6 mmol, 1.2 equiv) and DMAP (0.108 g, 0.88 mmol, 0.1 equiv) in THF (36 mL) was slowly added (15 min) to a solution of *O*,*O*-diethylchlorothiophosphate (1.67 g, 8.85 mmol) in THF (10 mL). The solution was then stirred overnight. The obtained suspension was filtered on celite and washed with Et_2O. The filtrate was concentrated and redissolved in Et_2O (80 mL). The organic phase was washed with H_2O (2 × 20 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The obtained crude product was purified by column chromatography over silica gel (70–230 mesh; pentane–EtOAc, 100:5) to produce **1g** (87% yield) as a colorless solid; mp 81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33, 1.40 (2 × t, $^{3}J_{HH}$ = 7.0 Hz, 12 H, CH_3CH_2O), 2.34 (s, 3 H, Me), 4.14, 4.31 (2 × m, 8 H, CH_3CH_2O), 7.57 (d, $^{5}J_{HP}$ = 1.8 Hz, 1 H, H5), 7.92 (d, $^{3}J_{HP}$ = 19.0 Hz, 1 H, H3). ^{31}P (81.03 MHz, $CDCl_3$): δ = 62.2 (d, $^{4}J_{PP}$ = 2.7 Hz), 83.5 (d, $^{4}J_{PP}$ = 2.7 Hz). ^{13}C (75.48 MHz, $CDCl_3$): δ = 16.0 (m, CH_2CH_3), 20.7 (s, Me), 63.3 (d, $^{3}J_{HP}$ = 5 Hz, OCH_2CH_3), 65.2 (m, OCH_2CH_3), 117.6 (dd, $^{3}J_{CP}$ = 12 Hz, $^{3}J_{CP}$ = 5 Hz, CBr), 127.6 (dd, $^{1}J_{CP}$ = 143 Hz, $^{3}J_{CP}$ = 5 Hz, $C_{Ar}P$), 136.0–136.42 (m, 2 × C_{Ar}), 139.0 (s, $C_{Ar}H$), 147.3 (m, $C_{Ar}O$). IR (neat): 709, 735, 790, 889, 927, 966, 1018, 1245,

1432, 2979 cm^{-1}. Anal. Calcd for $C_{15}H_{25}BrO_5P_2S_2$: C, 36.67; H, 5.13; S, 13.05. Found: C, 36.74; H, 5.10; S, 13.02.

(14) **Synthesis of Thiophosphonate 2–2i from Thiophosphate Represented by the Preparation of *O*,*O*-Diethyl 6-Hydroxy-2-pyridinylthiophosphonate (2f)**:
n-Butyllithium (1.5 M in *n*-hexane, 2.25 mL, 3.38 mmol, 1.1 equiv) was added dropwise to a solution of **1f** (1 g, 3.07 mmol) in THF (10 mL) previously cooled to –78 °C. At the end of the addition, the solution was left to warm slowly. Then an aqueous solution of ammonium chloride was added (10 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with H_2O and dried over $MgSO_4$. After filtration and concentration the crude product was purified by column chromatography over silica gel (PE–EtOAc, 5:1) to produce the pure compound **2f** as a white solid in 85% yield; mp 70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, $^3J_{HH}$ = 7.0 Hz, 6 H, OCH_2CH_3), 4.26 (m, 4 H, OCH_2CH_3), 7.31 (dd, $^3J_{HH}$ = 7.0 Hz, $^3J_{HP}$ = 1.0 Hz, 1 H, C4-H), 7.36 (m, 1 H, C5-H), 8.34 (dt, $^3J_{HH}$ = 5.0 Hz, $^4J_{HP}$ = 1.0 Hz, 1 H, C6-H), 9.65 (s, 1 H, OH). ^{31}P NMR (81.03 MHz, $CDCl_3$): δ = 69.7. ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 16.0 (d, $^3J_{CP}$ = 7 Hz, OCH_2CH_3), 63.6 (d, $^2J_{CP}$ = 6 Hz, OCH_2CH_3), 126.4 (d, $^3J_{CP}$ = 10 Hz, C4), 128.4 (d, $^4J_{CP}$ = 4 Hz, C5), 135.4 (d, $^1J_{CP}$ = 188 Hz, C2), 141.9 (d, $^3J_{CP}$ = 20 Hz, C6), 158.3 (d, $^2J_{CP}$ = 27 Hz, C3). Anal. Calcd for $C_9H_{14}NO_3PS$: C, 43.72; H, 5.71; N, 5.66; S, 12.87. Found: C, 44.19; H, 5.90; N, 5.30; S, 12.66. HRMS (ES–TOF): *m*/*z* [M + H] calcd for $C_9H_{15}NO_3PS$: 248.0505; found: 248.0510. IR (neat): 953, 1009, 1306, 1455, 1570, 2733, 2927 cm^{-1}.