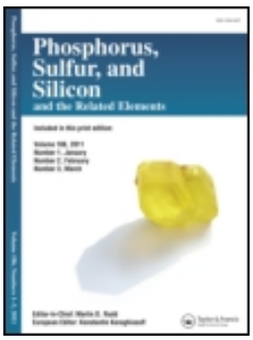


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: http://www.tandfonline.com/loi/gpss20

Study of the Stability of O,O-Dialkyl-O-Arylthiophosphate: Evidence of the Formation of O,S-Dialkyl-O-Arylphosphate

Stéphanie S. Le Corre, Aurore Fraix, Mathieu Berchel & Paul-Alain Jaffrès

To cite this article: Stéphanie S. Le Corre, Aurore Fraix, Mathieu Berchel & Paul-Alain Jaffrès (2015) Study of the Stability of O,O-Dialkyl-O-Arylthiophosphate: Evidence of the Formation of O,S-Dialkyl-O-Arylphosphate, Phosphorus, Sulfur, and Silicon and the Related Elements, 190:5-6, 747-750, DOI: 10.1080/10426507.2014.974751

To link to this article: http://dx.doi.org/10.1080/10426507.2014.974751

Accepted author version posted online: 03 Nov 2014.

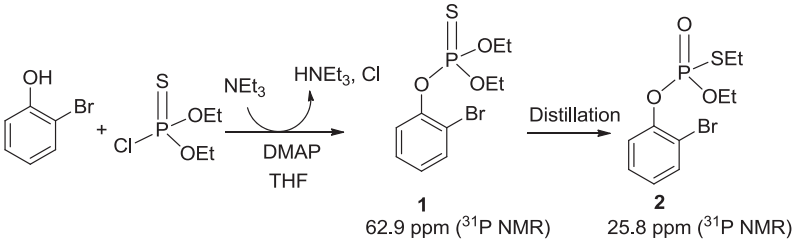
Phosphorus, Sulfur, and Silicon, 190:747–750, 2015

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2014.974751

STUDY OF THE STABILITY OF *O,O*-DIALKYL-*O*-ARYLTHIOPHOSPHATE: EVIDENCE OF THE FORMATION OF *O,S*-DIALKYL-*O*-ARYLPHOSPHATE

Stéphanie S. Le Corre, Aurore Fraix, Mathieu Berchel, and Paul-Alain Jaffrès
Université de Brest, UEB, CEMCA, Brest, France

GRAPHICAL ABSTRACT



Abstract *During the synthesis of cationic lipids that included thiophosphoramidate moiety or pincer ligands based on O,O-diethyl-thiophosphonate as coordination group, the rearrangement of O,O-diethyl-thiophosphoryl in O,S-diethylthiophosphoryl group was observed. This rearrangement, which does not occur by a simple heating at 130°C, is catalyzed by nucleophilic amine like N,N-dimethylaminopyridine. However, at some occasion, dealkylation of the O,S-diethylthiophosphoryl compound is observed.*

Keywords Rearrangement; thiophosphonate; organocatalysis

In previous works, we have shown that *O,O*-diethylthiophosphoryl moiety was adapted to produce *N,S*-monoanionic bidentate ligand or[1] *S,N,S*-monoanionic pincer ligand.[2] This functional group was used as coordination site to produce stable palladium and silver complexes. It is worth noting that *O,O*-dialkylthiophosphoryl moiety is not altered in presence of water or oxygen, thus, greatly facilitating the handling of such compounds. In other works, we have incorporated the *O,O*-dialkylthiophosphoryl moiety[3] in place of the of phosphoramidate moiety[4,5] in the structure of cationic lipids to produce vectors for gene delivery. Recently, we have reported an original method to prepare *O,O*-diethylthiophosphonate by making use of a [1,3][6] or [1,4][7] base-assisted rearrangement also identified as phospho-Fries rearrangement. This original method uses only air nonsensitive precursors constituting an advantage when compared to the methods previously reported. With the aim to prepare

Received 21 July 2014; accepted 5 October 2014.
Address correspondence to Paul-Alain Jaffrès, Université de Brest, UEB, CEMCA, UMR CNRS 6521, 6 Avenue Le Gorgeu, 29238 Brest, France. E-mail: pjaffres@univ-brest.fr; http://www-tmp.univ-brest.fr/phosvec/home

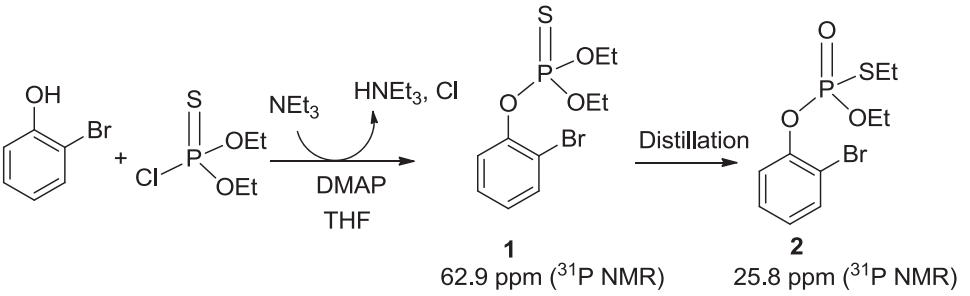


Figure 1 Preliminary results that unexpectedly produced compound **2**.

O-aryl-*O,O*-diethylthiophosphonate at a multigram scale, we have investigated the purification of its direct synthetic precursor *O*-(2-bromophenyl)-*O,O*-diethyl-thiophosphate **1** (scheme 1) by distillation under vacuum (Kugelroch). In this experiment, compound **1** was synthesized in tetrahydrofuran by reaction of diethylchlorothiophosphate with 2-bromophenol in presence of triethylamine and 4-dimethylaminopyridine (DMAP) as previously reported.[6] At the end of the reaction, most of the amine hydrochloride salts formed were removed by filtration before Kugelroch distillation (140°C, 2.10^{-2} mbar). In the course of this distillation, we observed by ^{31}P NMR the presence of a new compound (10%) that was actually the most abundant product. After separation and characterization, compound **2** was unambiguously identified as *O*-(2-bromophenyl)-*O,S*-diethyl thiophosphate **2**. One CH_2-O at 4.02 ppm and one CH_2-S at 3.05 ppm were observed by ^{1}H NMR analyses. ^{31}P NMR resonance at 25.8 ppm for **2** was in agreement with the presence of a P=O double bond and ^{13}C NMR and 2D experiments (HMBC, HMQC) were consistent with the structure of compound **2**. This result indicates that a rearrangement, characterized by the migration of an alkyl group from one oxygen atom to the sulfur atom, occurred. This type of rearrangement has some common features with the Pistschimuka reaction[8] (reaction of thiophosphoryl-based compounds with iodomethane) and it was also reported by Zhankai et al.[9] but in that case the author exclusively used *O,O*-diallylthiophosphate as substrate. From their studies they concluded that the allylic system was needed to allow a [3,3]-sigmatropic type rearrangement. On the contrary, our initial finding reported above indicates that even alkyl derivatives can produce the same type of rearrangement. This preliminary result encouraged us to study further this type of rearrangement which represent an easy access to *O,S*-dialkylphosphono derivatives present in some pesticides (e.g., Methamidophos), but also to identify the parameters that influence this type of rearrangement that can explain the formation of *O,S*-dialkylphosphono side products when this rearrangement is not desired.

First of all, compound **1** was synthesized and purified by column chromatography on silica gel to study the rearrangement on a pure substrate. After heating this compound at 138°C for 15 h in *p*-xylene, only the ^{31}P signal of the substrate **1** was detected thus attesting of the absence of rearrangement in such a condition. Then different nucleophilic bases (*N*-methylimidazole, *N,N*-dimethylaminopyridine, triethylamine, and spermine) were added (20 mol%) to the reaction media and the mixture was heated for the same period of time at 138°C. In all these experiments, the rearranged product **2** was detected. The best results were obtained with DMAP. However, even with DMAP only a partial conversion was obtained (65%). Accordingly, the quantities of DMAP were increased to 40 and 60 mol%.

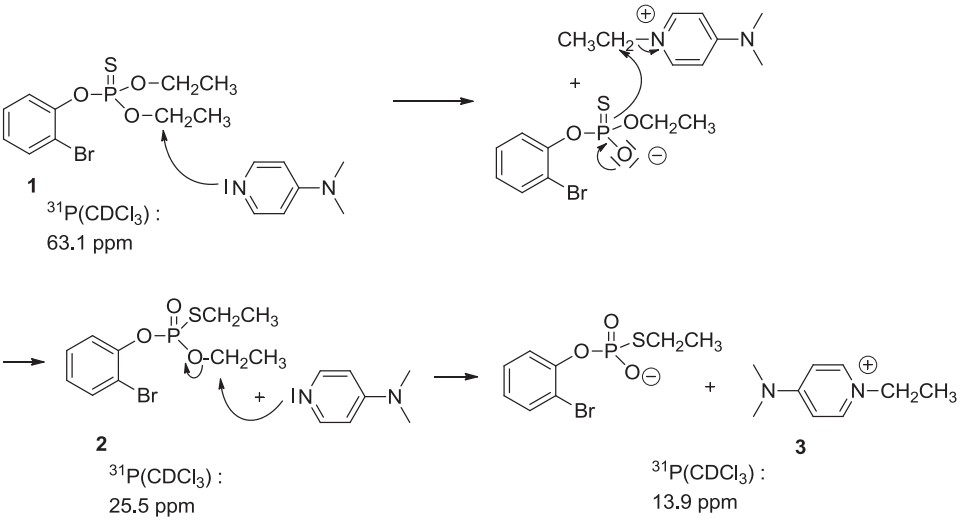


Figure 2 Suggested mechanism for the P=S to P=O rearrangement of compound **1** and the subsequent dealkylation to produce the salt **3**.

In the last condition, a full conversion was obtained but even at 40 mol% of DMAP another product that exhibited a ^{31}P NMR signal at 13.9 ppm was detected. This side product was present in large quantities (73%) when 60 mol% of DMAP was employed. MALDI TOF spectrometry indicate the presence of *N,N*-dimethyl-*N*'-ethylpyridinium salt and the ^{1}H NMR spectrum was consistent with the presence of a salt that would likely result from the dealkylation of the rearranged product **2** by *N,N*-dimethylaminopyridine at the CH_2 group bonded to the oxygen atom. This dealkylation at this position of the *O,S*-diethylphosphoryl moiety is confirmed by ^{1}H that exhibit the P-S-CH_2-R moiety at 2.8 ppm. On the basis of these results, the suggested mechanism that would explain the formation of the salt **3** is shown on Figure 2.

EXPERIMENTAL

To a solution of *O*-(2-bromophenyl)-*O,O*-diethylthiophosphate (1.22 mmol; 400 mg) in xylene (para isomer; 10 mL) was added *N,N*-dimethylaminopyridine DMAP (0.24 mmol; 20 mol%:30 mg). The reaction mixture was stirred at room temperature for 10 min. Then, the mixture was stirred and heated at 138°C (reflux of *p*-xylene) for 15 h. After cooling to room temperature, diethyl ether was added and the mixture was washed with water and dried over $MgSO_4$. Filtration and evaporation of the solvents produced an oil which was purified by chromatography on silica gel (petroleum ether/ethyl acetate 9/1; $r_f = 0.12$) to give *O*-(2-bromophenyl)-*O,S*-diethyl thiophosphate **2** in 21% yield (83 mg).

^{1}H-NMR (400.08 MHz, $CDCl_3$): 1.32 (t, $^{3}J_{HH}$ = 8 Hz, 3H, S-CH_2-C**H**$_3$); 1.40 (t, $^{3}J_{HH}$ = 8 Hz, 3H, O-CH_2-C**H**$_3$); 2.93 (m, 2H, S-C**H**$_2$-CH_3); 4.32 (m, 2H, O-C**H**$_2$-CH_3); 7.03 (t, $^{3}J_{HH}$ = 8 Hz, 1H, C_4-**H**); 7.24 (t, $^{3}J_{HH}$ = 8 Hz, 1H, C_5-**H**); 7.54 (m, 2H, C_3-**H**, C_6-**H**).

^{31}P-NMR (161.97 MHz, $CDCl_3$): 25.8

^{13}C-NMR (125.80 MHz, $CDCl_3$): 15.92 (S-CH_2-$\underline{C}H_3$); 16.20 (O-CH_2-$\underline{C}H_3$); 25.86 (S-$\underline{C}H_2$-CH_3); 64.61 (O-$\underline{C}H_2$-CH_3); 114.57 (C_2); 121.68 (C_3); 126.23 (C_4); 128.46 (C_5); 133.56 (C_6); 147.50 (C_1).

ACKNOWLEDGMENT

The authors are thankful to Prof. D. Villemin for fruitful discussions.

FUNDING

This work was supported by CNRS.

REFERENCES

1. Marie, S.; Lutz, M.; Spek, A. L.; Klein Gebbink, R. J. M.; van Koten, G.; Kervarec, N.; Michaud, F.; Salaün, J. Y.; Jaffrès, P. A. *J. Organomet. Chem.* **2009,** 694, 4001-4007.
2. Fraix, A.; Lutz, M.; Spek, A. L.; Klein Gebbink, R. J. M.; van Koten, G.; Salaün, J. Y.; Jaffrès, P. A. *Dalton Trans*. **2010,** 39, 2942-2946.
3. (a) Fraix, A.; Montier, T.; Carmoy, N.; Loizeau, D.; Burel-Deschamps, L.; Le Gall, T.; Giamarchi, P.; Couthon-Gourvès, H.; Haelters, J. P.; Lehn, P.; Jaffrès, P. A. *Org. Biomol. Chem.* **2011,** 9, 2422-2432. (b) Fraix, A.; Montier, T.; Le Gall, T.; Sevrain, C. M.; Carmoy, N.; Lindberg, M. F.; Lehn, P.; Jaffrès, P. A. *Org. Biomol. Chem.* **2012,** 10, 2051-2058.
4. (a) Berchel, M.; Le Gall, T.; Couthon-Gourvès, H.; Haelters, J. P.; Montier, T.; Midoux, P.; Lehn, P.; Jaffrès, P. A. *Biochimie*. **2012,** 94, 33-41. (b) Le Corre, S. S.; Berchel, M.; Couthon-Gourvès, H.; Haelters, J. P.; Jaffrès, P. A. *Beilstein J. Org. Chem.* **2014,** 10, 1166-1196. (c) (c) Perche, F.; Benvegnu, T.; Berchel, M.; Lebegue, L.; Pichon, C.; Jaffrès, P. A.; Midoux, P. *Nanomedicine.* **2011,** 7, 445-453.
5. (a) Le Gall, T.; Berchel, M.; Le Hir, S.; Fraix, A.; Salaün, J. Y.; Férec, C.; Lehn, P.; Jaffrès, P. A.; Montier, T. *Adv. Healthcare Mater.* **2013,** 2, 1513-1524. (b) Fraix, A.; Le Gall, T.; Berchel, M.; Denis, C.; Lehn, P.; Montier, T.; Jaffrès, P. A. *Org. Biomol. Chem.* **2013,** 11, 1650-1658. (c) Le Corre, S. S.; Berchel, M.; Belmadi, N.; Denis, C.; Haelters, J. P.; Le Gall, T.; Lehn, P.; Montier, T.; Jaffrès, P. A. *Org. Biomol. Chem.* **2014,** 12, 1463-1474.
6. Dieng, T.; Fraix, A.; Salaün, J. Y.; Dez, I.; Klein Gebbink, R. J. M.; van Koten, G.; Jaffrès, P. A. *Synlett*. **2008,** 3121-3124.
7. Berchel, M.; Salaün, J. Y.; Couthon-Gourvès, H.; Haelters, J. P.; Jaffrès, P. A. *Dalton Trans*. **2010,** 39, 11314-11316.
8. Pistchimuka, P. *Ber*. **1908,** 41, 3854.
9. Zhankai, Y.; Zhaojie, L.; Weibing, C. *Chem. Mag. CJI* **2005,** 7, P29.