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SYNTHESIS OF S-ALKYL PHOSPHORODICHLORIDOTHIOATES *VIA* MICHAELIS-ARBUZOV REARRANGEMENT

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Abstract. S-alkyl phosphorodichloridothioates, phosphorylating agents of potential use in the synthesis of *antisense* oligonucleotides, have been obtained from O-methyl phosphorodichloridite *via* Michaelis-Arbuzov rearrangement.

Introduction

Phosphorodichloridothioates have proved to be valuable reagents in the synthesis of dinucleoside phosphorothioates.[1,4] A general entry into this class of phosphorylating agents is represented by the reaction of appropriate O-aryl, or O-alkyl, phosphorodichloridite with sulfenyl

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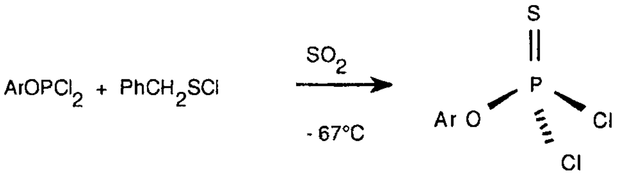
chlorides, in liquid sulfur dioxide.[5,6] It has been , recently, evaluated that in the sulfenylation of O-aryl phosphorodichloridite the nature of the akyl group of the sulfenyl chloride plays a fundamental role in driving the observed transformations.[7] In this case, in fact, the S-alkyl moiety is released and phosphorodichloridothioates, bearing a P=S function, are formed by a novel Michaelis-Arbuzov rearrangement (scheme 1). The results discussed below show that in the case of O-alkyl phosphorodichloridites the sulfenylation with alkyl sulfenyl chlorides leads to the formation of phosphorodichloridothioates were the S-alkyl moiety is retained.



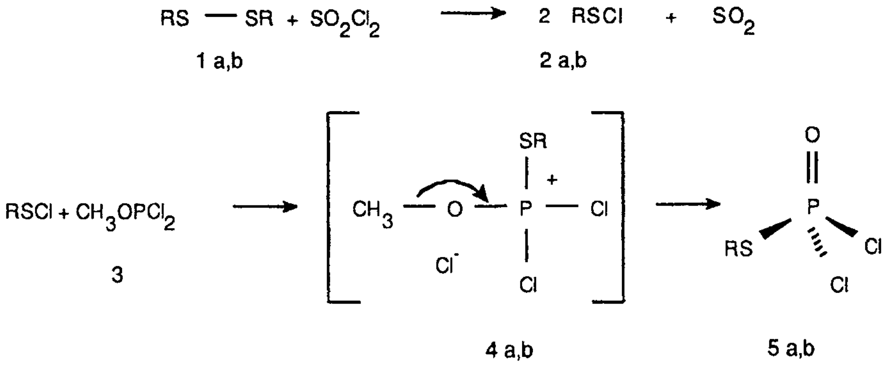
Scheme 1

Results and Discussion

When O-methyl phosphorodichloridite (3) reacts, in liquid sulfur dioxide, with the sulfenyl chlorides **2a,b**, generated *in situ* from the correspondent disulfides by means of sulfuryl chloride, high yields of the phosphorodichloridothioates **5a,b** are obtained. A characterization of the phosphorilating agents has been achieved by mass spectrometry (MS) and ^{1}H and ^{31}P nmr (scheme 2)

The formation of the products likely occurs through the Arbuzov rearrangement of the putative tetracoordinated phosphorous intermediates **4a,b**[8].The mechanism of the second stage of the Arbuzov rearrangement, i.e. the transformation of intermediates **4** (chart), shifts from S_N2 to S_N1 as a function of the solvent polarity[9] and of the substituents present on the reaction intermediates.[9,10]

The dielectric constant of the solvent employed in the experiment discussed so far (ε=17.6) and the presence of two strong electron withdrawing chlorine atoms on **4** should favor the SN_1 mechanism, particularly when theS-benzyl moiety is present.

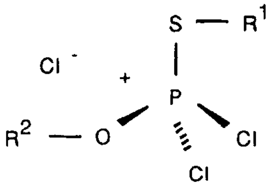


a; $R = CH_3$. b; $R = PhCH_2$.

Scheme 2

From previous[5-7] and present experiments it can be envisaged that the formation of products in the reaction of phosphorodichloridite with sulfenyl chlorides depends on (i) the stability of **4**, (ii) the relative strenght of the carbon-oxygen and carbon-sulfur bonds and (iii) the preferred formation, when possible, of the energy rich P=O bond instead of the weaker P=S function.[11] The obtainment of S-alky O Aryl phosphorochloridothioates[3,5] from **4c** can be correlated with the lifetime of the latter which further reacts with an SO_2 solvent molecule; the replacement of the S-methyl group with a S-benzyl function (4d), favors the SN_1 mechanism thus inducing the formation of the P=S funcionality *via* Arbuzov rearrangement[7].

Finally, in the experiments reported here, the driving force of the process is represented by the lability of the C-O bond of intermediates **4a,b** which induces the selective development of the P=O functionality groups according to the criterion (iii), and leads to phosphorodichloridothioates were the S-alkyl moiety is retained.



4

a; R^1 = Me; R^2 = Me
b; R^1 = $PhCH_2$; R^2 = Me
c; R^1 = Me; R^2 = Aryl
d; R^1 = $PhCH_2$; R^2 = Aryl

Chart

Experimental

All reagents were commercially available. Phosphorus trichloride and sulfuryl chloride were distilled before use. O-methyl phosphorodichloridite (3) was prepared following literature procedures.[11] Mass spectra have been recorded with a Varian-Mat CH-5 DF mass spectrometer; ^{1}H and ^{31}Pnmr have been obtained from AM 80 Bruker and WM 300 Bruker spectrometers, respectively.

S-alkyl phosphorodichloridothioates 5a,b: general procedure. Freshly distilled sulfuryl chloride (4.05g, 50 mmol) is added dropwise to dimethyl (1a) ore dibenzyl (1b) disulfide (50 mmol) at - 68°C (acetone, dry ice bath). The orange mixture thus obtained, dissolved in liquid SO_2 (15 ml) in the case of **1b**, is transferred at once into a reaction flask containing the chlorophosphine **3** in liquid SO_2 (20 ml), at -68°C. The yellow mixture is stirred fro 30 min. and then left at room temperature until complete evaporation of the solvent. Pure **5a,b** have been obtained after vacuum distillation.

S-methyl phosphorodichloridothioate (5a). Yield, 75% ; b.p.$_{3\ torr}$ 56-58 °C. ^{1}H nmr δ_{ppm} ($CDCl_3$/TMS): 2.65 (3H, d, J=23 Hz); ^{31}Pnmr δ_{ppm} ($CHCl_3/H_3PO_4$) : 39. EIMS (70 eV) : m/z 164 (M^+, 10%), m/z 47 (100%, b. peak).

S-benzyl phosphorodichloridothioate (5b). Yield, 70%; b.p.$_{3torr}$ 118-23 °C. ^{1}H nmr δ_{ppm}: 7.20-7.40 (5H, m), 4.35 (2H, d, J=18 Hz); ^{31}Pnmr δ_{ppm} : 34. EIMS: m/z 240 (M^+, 10%), m/z 122 (100%, b. peak).

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