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New Route to *O,O*-Diethyl Phosphorocyanidate

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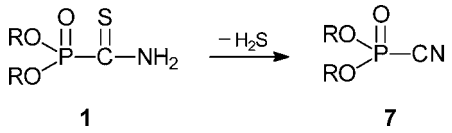
ABSTRACT: *A new and efficient route for synthesis of diethyl phosphorocyanidate* **7a** *by decomposition of diethyl phosphoryl-1,2,4,-dithiazolin-5-one is described.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:395–397, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20027

INTRODUCTION

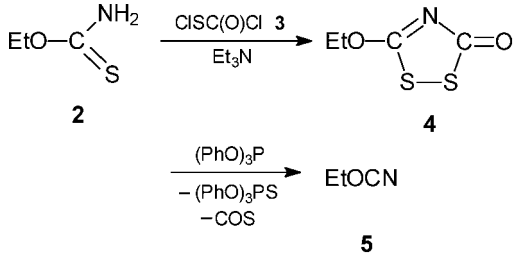
During the course of our studies on the search for new phosphorylating agents, we turned our attention to *O,O*-dialkyl phosphorocyanidates. These compounds have been known for more than fifty years [1–4], and their phosphorylating ability was studied by Horner [5]. The use of phosphorocyanidates as coupling reagents in peptide chemistry [4–6] and other applications of these compounds in organic synthesis have also been demonstrated [7].

However, these compounds appeared to be relatively unstable [1] and decompose easily, especially in the presence of water [4] with the formation of hydrogen cyanide. The synthesis of phosphorocyanidates according to the existing procedures provides products usually contaminated by isomeric phosphoroisocyanidates [4], and therefore the use of an additional procedure for their isomerization [3,4] into phosphorocyanidates is necessary. This prompted us to search for synthons, which after a one-step reaction could be converted in situ into the required phosphorocyanidates. The most promising candidates seem to be *O,O*-dialkyl (thiocarbamoyl) phosphonates (**1**), which, formally, could be transformed into *O,O*-dialkyl phosphorocyanidates (DEPC) (**7**) [Eq. (1)] after elimination of hydrogen sulfide. However, such a transformation would require the use of rather harsh conditions.



1 **7** (1)

Recently, Barany et al. published the observation that the condensation of *O*-ethyl thiocarbamate (**2**) with chlorocarbonylsulfenyl chloride (**3**) in the presence of triethylamine resulted in the formation of stable 3-ethoxy-1,2,4-dithiazolin-5-one (**4**) [8]. The latter undergoes rapid desulfurization by triphenyl phosphite and provides a novel entry to *O*-ethyl cyanate (**5**) [Eq. (2)].



2 **4** **5** (2)

On the basis of this information it was tempting to study the reaction of *O,O*-diethyl (thiocarbamoyl)

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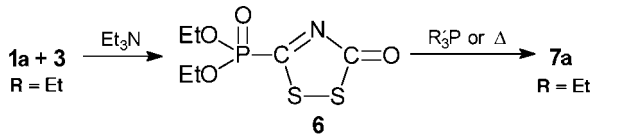
phosphonate (**1a**) with sulfenyl chloride **3** with the hope of obtaining 3-(*O*,*O*-diethylphosphoryl)-1,2,4-dithiazolin-5-one (**6**) as a stable compound. **6** should undergo an easy desulfurization with the formation of the desired phosphorocyanidate **7a** [Eq. (3)].



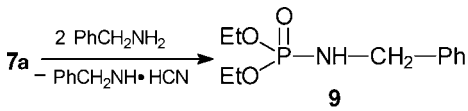
(3)

Having this in mind, we performed the following experiments. An equimolar mixture of triethylamine and **1a** was added to **3** (1 equiv), in diethyl ether at 0–5°C. This resulted in the formation of several organophosphorus products. The ^{31}P NMR spectrum of the reaction mixture showed signals at δ (ppm) 57.0, 42.0, 1.5–2.0 (total intensity 10%), −12.59 (17%), and −20.44 (73%). The signal of the most abundant product is characteristic for **7a**. The addition to this mixture of the excess of triethyl phosphite resulted in the formation of two new products at δ 68.07 ppm and δ 7.64 ppm, which correspond to *O*,*O*,*O*-triethyl phosphorothioate and *O*,*O*-diethyl phosphite, respectively. The latter results from the dealkylation of triethyl phosphite by hydrogen chloride present in the reaction solution. Simultaneously, the signal at δ −12.59 ppm in the ^{31}P spectrum of the reaction mixture decreased significantly.

In a similar reaction between **1** and **3** in the presence of 2 equiv triethylamine in toluene at −3 to +2°C, the formation of three products with δ (ppm) 1.41, −12.54, and −20.66 (ratio 18:27:55) was observed by ^{31}P NMR. The addition of cyclohexylamine to the crude reaction mixture caused the appearance of a new product at δ 8.89 ppm, accompanied by complete disappearance of the compound at δ −20.6 ppm. This product was isolated as a crystalline compound by fractional crystallisation from petroleum ether, mp. 71–73°C, and identified as a diethyl cyclohexylphosphoramidate (**8**). Its formation is most probably due to the phosphorylation of cyclohexylamine by **7a**, formed in situ. Treating the same crude reaction mixture with the excess of triethyl phosphite resulted in the formation of *O*,*O*,*O*-triethyl phosphorothioate (δ 68.17 ppm). During this operation an increase in the intensity of a signal at −20.6 ppm in the ^{31}P NMR spectrum of the reaction solution was observed.

The results obtained suggested that the reaction of **3** with **1** in the presence of triethylamine took place probably with the transient formation of phosphorylated 1,2,4-dithiazolin-5-one **6**, which decomposes spontaneously with the formation of **7a**. The attempted isolation of this intermediate or further spectroscopic confirmation of its structure failed.

The reaction of **1** with **3** repeated on a preparative scale gave **7a**, which was isolated from the reaction mixture by distillation in 68% yield. The product was identical with that prepared according to the known reaction of cyanogen bromide with triethyl phosphite [4]. **7a** reacts with benzylamine in toluene at 5–15°C giving *O*,*O*-diethyl benzylphosphoramidate (**9**) in 85% yield [Eq. (4)].



(4)

The present results offer a new efficient route to *O*,*O*-dialkyl phosphorocyanidates, which are not contaminated by isomeric isocyanidates and may be used as the substrates for further synthetic purposes.

EXPERIMENTAL

The solvents and reagent were dried and purified by standard method before use. Triethylamine and cyclohexylamine were refluxed and then distilled over sodium. Melting points were determined with a Boetius apparatus and are uncorrected. IR spectra were measured as a thin film using an ATT Mattson FT IRapparatus. ^{1}H NMR spectra were determined at 200.13 MHz with a Bruker AC 200 spectrometer. ^{31}P NMR spectra were taken on the same spectrometer at 81 MHz. Positive chemical shifts are downfield from 85% H_3PO_4 used as an external reference.

CI/MS spectra were recorded on a Finnigan MAT 95 spectrometer using isobutane as a reagent gas. The following substrates were synthesized according to the described procedures [10]: diethyl-(thiocarbamoyl)phosphonate (**1a**), mp 99–100°C (ether–hexane), yield 87%, CI/MS *m*/*z* 198 [M + 1], ^{31}P NMR δ −1.39 ($CDCl_3$), lit.[9] mp 91–92°C; chlorocarbonylsulfenyl chloride (**3**), bp 97–98°C, yield 85%.

Reaction of **1** *with* **3** *in the Presence of Two Equivalents of Triethylamine*

The solution of **1** (0.9 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in 80 mL dry toluene was added, with stirring at −3 to 2°C, to a solution of **3** (0.65 g, 0.005 mol) in 125 mL of toluene. The cooling bath was removed, and stirring was continued at room

temperature for 6 h. Amine hydrochloride was filtered off in the closed system and 150 mL of toluene was distilled off from the reaction solution under reduced pressure of 15 mmHg at 30°C. Ten milliliter of the above solution was treated at 0°C with 0.8 g of cyclohexylamine in 5 mL of toluene and stirred for 1 h at room temperature. The reaction mixture was concentrated and the residue was crystallized from petroleum ether; 0.2 g of **8**, mp 71–73°C, ^{31}P NMR ($CDCl_3$) 8.89, CI/MS *m/z* 236.3 [M + 1], was isolated (lit. [11] mp 72–74°C , ^{31}P δ 8.8).

*Synthesis of O,O-Diethyl Phosphorocyanidate (**7a**)*

Into the stirred solution of 2.9 g (0.022 mol) of **3** in 80 mL of toluene was added, dropwise at −10 to 0°C, 4.37 g (0.022 mol) of **1**, and 4.45 g (0.044 mol) of triethylamine in 125 mL of toluene. The reaction solution was stirred for 1.5 h at room temperature, the amine hydrochloride was filtered off, the solvent was evaporated, and from the residual oily yellow liquid containing elemental sulfur, **7a** was isolated by distillation: bp 38–40°C/1 mmHg, ^{31}P NMR ($CDCl_3$) −20.60 ppm (quintet), 2.46 g, yield 68%.

*Reaction of **7a** with Benzylamine*

To a stirred solution of dry benzylamine (2.35 g, 0.021 mol) in 25 mL dry toluene was added dropwise freshly distilled **7a** (3.26 g, 0.02 mol) at 0–5°C. The cooling bath was removed, and the reaction mixture was stirred for 3 h at room temperature. The reaction solution was diluted with 20 mL toluene, washed with water (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and filtered. Fractional distillation of this solution gave 3.3 g (yield 85%) of oily liquid, with bp 118–119°C/0.01 mmHg; ^{31}P NMR ($CDCl_3$) 8.99, CI/MS, *m/z* 244 [M + 1], identified as **9** (lit. [12], ^{31}P NMR 9.75).

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