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Phosphorochloridates from phosphorohydrazides with Bu^{t}OCl: stereospecificity, selectivity and phosphorylium ion intermediates

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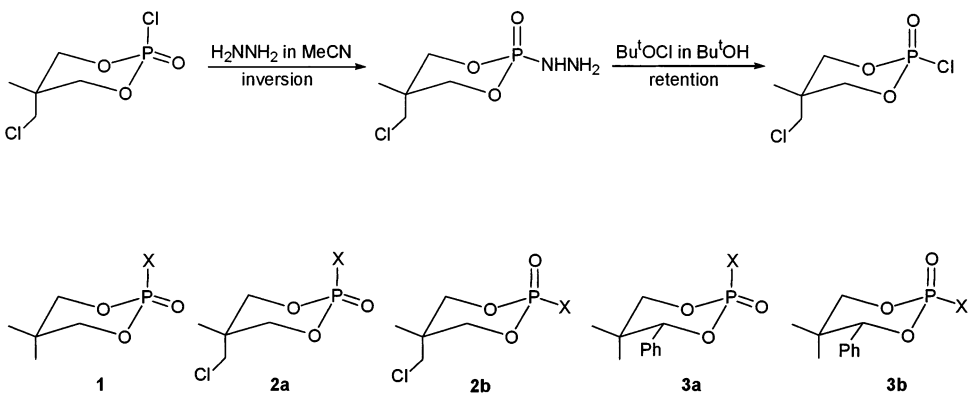
Abstract—The efficiency with which a six-membered cyclic phosphorochloridate can be obtained from the corresponding hydrazide with retention of configuration at phosphorus, using *tert*-butyl hypochlorite in *tert*-butyl alcohol, depends on how stereoelectronic factors influence the fate of an intermediate chloride–phosphorylium ion pair.

Phosphoryl transfer reactions play a vital part in biological chemistry,[1] and phosphorylating agents having a defined configuration are important in synthesis[2,3] and in mechanistic studies.[3,4] Phosphoryl halides are the most widely used laboratory phosphorylating agents and a method for changing the configuration at phosphorus in a controlled and reliable way is of great potential value.

Thenappen and Wadsworth[5] have reported the successful (and apparently efficient) conversion of a phosphorochloridate into its stereoisomer by a two-stage sequence (Scheme 1) involving the phosphorohydrazide. The generality of their strategy has never been examined, however, and nothing is known about the mechanism of the crucial retention-of-configuration reaction of the hydrazide in the second stage.

The phosphorochloridates **2a** and **2b** (X = Cl) are conformationally mobile (chair–chair inversion) so it is easy for the P–Cl bond to assume its preferred orientation (axial).[6] For the related chloridates **3a** and **3b** (X = Cl), however, the C-4 phenyl substituent anchors the chair, with the phenyl group equatorial,[7,8] so one of the isomers cannot have the favoured orientation of the P–Cl bond. By comparing the behaviour of these conformationally mobile and anchored systems we hoped to gain some indication of the likely generality of the Thenappen–Wadsworth approach, and some clues as to mechanism of the hydrazide-to-chloridate conversion.



Scheme 1. Conversion of a phosphorochloridate into its stereoisomer.

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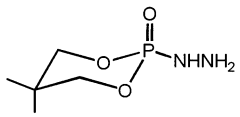
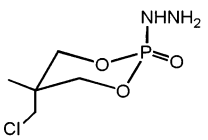
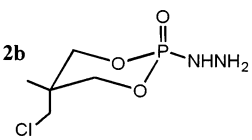
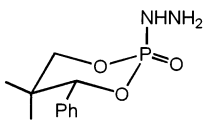
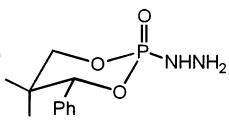
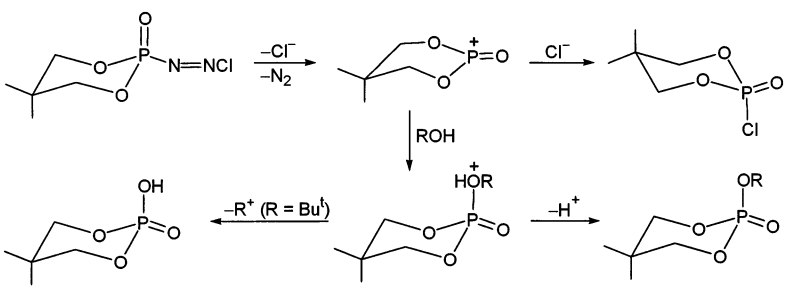
The phosphorohydrazides **2b**[5] and **3b** (X = $NHNH_2$) were prepared directly from the available chloridates **2a**[9] and **3a** (X = Cl).[8,10,11] (**CAUTION** anhydrous hydrazine is extremely reactive with oxidising agents including air.) They were treated with Bu^{t}OCl and then H_2NNH_2 to give (after chromatography) the stereoisomeric hydrazides **2a**[5] and **3a** (X = $NHNH_2$). The symmetrical hydrazide **1** (X = $NHNH_2$) (no stereoisomers) was also prepared as a standard for comparison.[12]

The hydrazides **1**–**3** all reacted readily with Bu^{t}OCl in Bu^{t}OH (N_2 evolution) at room temperature.[13] The reaction mixtures were analysed by ^{31}P and ^1H NMR spectroscopy (Table 1) with reference to the spectra of authentic samples.[14–16] In no case was the phosphorochloridate (X = Cl) the only product, nor was it formed with complete retention of configuration, but with one exception (**3b** in Table 1) the yield was at least 70% and the stereospecificity (de) ≥ 88%. In all cases the other products were the *tert*-butyl phosphate ester (X = OBu^t) (both stereoisomers) and the phosphoric acid (X = OH). Important stereochemical information is lost in the dealkylation that produces the acid (Scheme 2)[17] so the reactions were also carried out with MeOH as solvent. The yield of the chloridate was inevitably reduced but dealkylation was no longer a problem, so the stereoisomer composition of the methyl ester (X = OMe) is a true reflection of how the alcohol attacks.

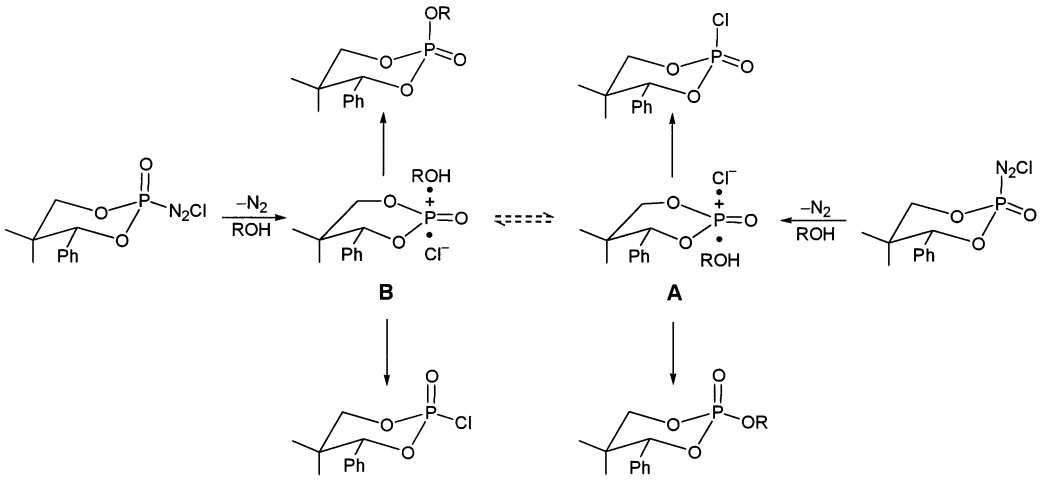
We suppose that Bu^{t}OCl converts the hydrazide into the diazo chloride and that the products are derived from this.[18] If, as the original report seems to imply,[5] the chloridate were the *only* product and its formation was *completely* stereospecific a concerted mechanism might be indicated. As it is, we think a phosphorylium cation is the product-forming species (Scheme 2), being

Table 1. Reactions of phosphorohydrazides with Bu^{t}OCl. Yields of products and stereochemistry of formation

Substrate	Solvent (ROH)	Product (%)		
		X = Cl (ret + inv)	X = OR (inv + ret)	X = OH
1 	Bu^{t}OH	76	15	9
	MeOH	35	65	
2a 	Bu^{t}OH	70 (66 + 4)	16 (11 + 5)	14
	MeOH	28 (26.5 + 1.5)	72 (63 + 9)	
2b 	Bu^{t}OH	75 (71.5 + 3.5)	17 (14 + 3)	8
	MeOH	36 (34.5 + 1.5)	64 (55 + 9)	
3a 	Bu^{t}OH	83 (81.5 + 1.5)	11 (6.5 + 4.5)	6
	MeOH	38 (38 + < 1)	62 (49 + 13)	
3b 	Bu^{t}OH	41 (32 + 9)	45 (43 + 2)	14
	MeOH	15 (13.5 + 1.5)	85 (83 + 2)	



Scheme 2. Formation and reactions of a phosphorylium cation.



Scheme 3. Fates of chloride–phosphorylium ion pairs.

trapped competitively by chloride ion and the alcohol solvent (ROH).[19] The competition depends on the bulk of the alcohol (Table 1), but not as much as it would for a normal associative substitution reaction [S_N2(P)] at a four-coordinate phosphoryl centre.[20] This itself may be seen as evidence for a reactive and sterically accessible three-coordinate phosphoryl intermediate.[21]

A free and symmetrically solvated phosphorylium ion cannot be the principal product-forming species however, as there is little stereochemical congruence of the products from stereoisomeric hydrazides. Also, the competing chloride and alcohol nucleophiles form products with contrasting stereochemistries (retention and predominant inversion, respectively). The phosphorylium ion will, in fact, be generated alongside a chloride ion and it is the behaviour of this ion pair that determines the outcome of the reaction. Stereoelectronic factors seem to be of major importance, influencing the composition of the product (chloridate versus ester) as well as the stereochemistry of its formation (retention versus inversion).

The P–X bond of the product (X = Cl or OR) prefers to be axial, especially when X = Cl (anomeric effect).[6,8] With the conformationally mobile system **2**, it makes little difference whether the $ClCH_2$ or CH_3 group at C-5 is axial, so whatever the geometry of the product (*cis* or *trans*) the P–X bond can easily be placed axial. The isomeric hydrazides **2a** and **2b** ($X = NHNH_2$), therefore, behave in much the same way as one another and as the symmetrical substrate **1**. But with the conformationally anchored system **3** the P–X bond can be axial only when X is *trans* to the equatorial C-4 phenyl group. In the case of the ion pair **B** (Scheme 3) from the equatorial hydrazide formation of the less stable equatorial chloridate (retention) is relatively unfavourable (slow), so competition from ester formation (inversion; ax-OR) is severe. Also, there is considerable leakage to the alternative ion pair **A** and to the symmetrically-solvated phosphorylium ion (ROH in place of Cl^- in **B**); the former collapses mainly to the other (axial) chloridate while the latter stereoselectively forms more of the same (axial) ester. Both the yield and the stereochemical integrity are, therefore, low for the chloridate but high for the ester (**3b** in Table 1). In the case of the ion pair **A** from the axial hydrazide, formation of the chloridate (retention; ax-Cl) is more favourable (faster) and competition from ester formation (inversion; eq-OR) less severe. There is also less leakage, and that which does occur results in axial ester rather than the unstable equatorial chloridate. So now the yield and the stereochemical integrity are high for the chloridate but low for the ester (**3a** in Table 1).

As a method for reversing the configuration of a phosphorochloridate the hydrazine–hypochlorite protocol may not be as efficient as was thought,[5] but that is hardly surprising given the (apparent) intermediacy of a high energy phosphorylium ion in the second stage. It should still prove very useful for systems in which the stereoelectronic requirements of the reaction are not opposed by powerful conformational constraints.[22]

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10. Cullis, P. M.; Fawcett, J.; Griffith, G. A.; Harger, M. J. P.; Lee, M. *J. Am. Chem. Soc.* **2001**, *123*, 4147–4154.
11. The chloridate was added in portions to anhydrous H_2NNH_2 (2.5 equiv.) in MeCN (N_2 atmosphere; safety screen). Hydrazine hydrochloride was removed by filtration or washing with water and the hydrazide product was purified by crystallisation. [Anhydrous hydrazine is commercially available (Aldrich) but we preferred to prepare it in small amounts (1–2 g) as required from the hydrate: Day, A. C.; Whiting, M. C. *Org. Synth. Coll.* **1988**, *6*, 10–12.]
12. Phosphorohydrazides (X = $NHNH_2$): **1**, mp 148–150°C, δ_P ($CDCl_3$) 3.05; **2a**, mp 159–161°C (lit. 177–178°C), δ_P 1.4; **2b**, mp 156–158°C (lit. 156°C), δ_P 4.15; **3a**, mp 211–214°C, δ_P 0.35; **3b**, mp 208–210°C, δ_P 5.35. In the ^1H NMR spectra ($CDCl_3$) the NH group gave a doublet (J_{PH} 25–35 Hz) at δ_H 4.3–4.8. The new compounds **1**, **3a** and **3b** gave satisfactory results in elemental analysis and/or accurate mass measurement.
13. Bu^{t}OCl (2.5 equiv.) was added to a suspension or solution of the phosphorohydrazide (22.5 μmol) in Bu^{t}OH or MeOH (0.45 ml). Reaction mixtures were examined directly by ^{31}P NMR spectroscopy (relative amounts of products) and after replacement of the alcohol solvent with $CDCl_3$, by ^1H and ^{31}P NMR (identities of products).
14. The phosphorochloridates (X = Cl) **2b** (Ref. 9) and **3b** (Ref. 10) were only available as mixtures with their stereoisomers. The phosphoric acids (X = OH) were prepared by hydrolysis of the chloridates, and the phosphate esters (X = OMe or OBu^t) (mixtures of stereoisomers) by treatment of the acids with diazomethane or the chloridates with KOBu^t.
15. (a) For 2-X-1,3,2-dioxaphosphorinane 2-oxides the ^{31}P NMR chemical shift δ_P is smaller (higher field) when X is axial (P=O equatorial). Gallagher, M. J. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G.; Quin, L. D., Eds.; VCH Publishers: Deerfield Beach, 1987; Chapter 9; (b) For X = Cl, δ_P ($CDCl_3$): **1**, −2.9; **2a**, −2.9; **2b**, −2.8; **3a**, −2.25; **3b**, 4.0. For X = OBu^t, δ_P ($CDCl_3$): **1**, −12.6; **2a**, −13.3; **2b**, −10.8; **3a**, −12.3; **3b**, −6.3. For X = OMe, δ_P ($CDCl_3$): **1**, −6.6; **2a**, −7.1; **2b**, −5.5; **3a**, −6.2; **3b**, −2.4. For X = OH, δ_P ($CDCl_3$): **1**, −4.25; **2**, −4.45; **3**, −3.2.
16. For the compounds **2** the ^1H NMR chemical shifts δ_H of the $ClCH_2$ and CH_3 groups on C-5 are larger (lower field) when they are axial: Wadsworth, W. S. *J. Org. Chem.* **1987**, *52*, 1748–1753.
17. *tert*-Butyl phosphate esters are very easily dealkylated with acid: Perich, J. W.; Johns, R. B. *Synthesis* **1988**, 142–144 and references cited therein.
18. For a similar supposition, see: Carpino, L. A. *J. Am. Chem. Soc.* **1957**, *79*, 96–98 (reaction of $RCONHNH_2$ with Cl_2 leading to RCOCl).
19. Phosphorylium ions probably play no part in normal nucleophilic substitution reactions of phosphoryl compounds. Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley–Interscience: New York, 2000; p. 28. In the present reactions the liberation of N_2 could provide the driving force for their formation.
20. Treatment of the hydrazide **1** (X = $NHNH_2$) with Bu^{t}OCl in a 1:1 mixture of MeOH and Bu^{t}OH gave products derived from the two alcohols in a 2.2:1 ratio. By contrast Ag^+-catalysed solvolysis of the chloridate **1** (X = Cl) [S_N2(P)] gave ≥ 96.5% of the methyl ester.
21. Cf.: Ramirez, F.; Marecek, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 1460–1465.
22. (a) Most potential alternatives can be discounted because the chloridate product would be generated under conditions in which it is configurationally unstable; (b) In extreme cases even the first stage (hydrazide formation) may not be completely stereospecific (inversion); thus **3b** (X = Cl) reacts with H_2NNH_2 with partial retention of configuration.