

Aminolysis of Activated Esters Formed by Reaction of Carboxylate Salts with Strained Phosphonates and Phosphinates

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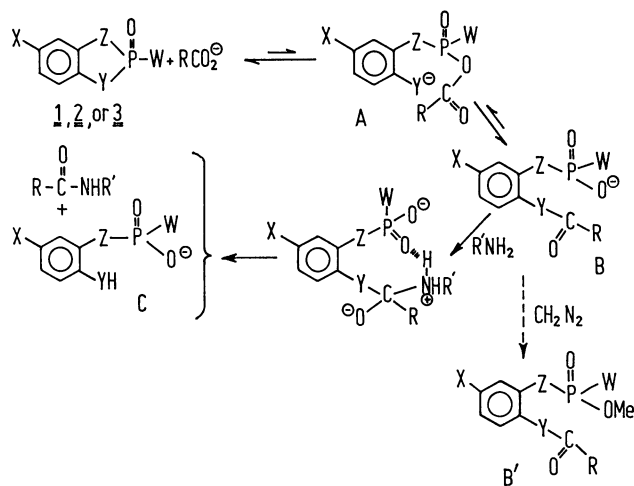
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Synopsis. Nucleophilic attack of a carboxylate salt on a five-membered phosphonic or phosphinic ester followed by an intramolecular acyl transfer reaction gives a substituted aryl ester. Due to the intramolecular base catalysis of a neighbouring P=O group the bimolecular aminolysis of this ester is a fast process.

The study of the reactions of carboxylate salts with strained five-membered phosphonates or phosphinates and the aminolysis of the resulting aryl esters was undertaken for two purposes: on the one hand to serve as a model of the first steps in a scheme for peptide synthesis by means of the "prior amine capture" principle;¹⁾ on the other hand, to compare the reactivities of tetracoordinated alicyclic,²⁾ cyclic phosphorus (this study) and sulfur³⁾ esters, all of which also lead to peptides but by different means (bimolecular aminolysis).

Five-membered cyclic phosphonate and phosphinate esters **1**, **2**, and **3** were prepared (*vide infra*). The probable mechanism of their reaction with a carboxylate anion is shown on the scheme. Relief of the strain facilitates the formation of a pentacoordinated intermediate (not shown) which in turn yields a mixed anhydride A. Then an intramolecular acyl transfer reaction gives a substituted aryl ester B. The aminolysis of B can be assisted by the neighbouring phosphoryl group.



Scheme 1.

Experimental

Phosphonothioate **1b** was prepared by adding a mixture of 3,4-toluenedithiol and triethylamine (2 equiv.) to a cooled solution of phenylphosphonic dichloride in benzene. Mp 98 °C; 65% yield; $\delta^{31}\text{P}$: 58.4 (CDCl₃); m/e : 278 (100) 156 (32) 154 (37.5).

The phosphinates **4a** and **4b** and the phosphonate **5** were obtained by the addition of a solution of 2-hydroxy-5-nitrobenzyl bromide (5 mmol) in 5 ml of dry acetone to a solution

of a diethyl phosphonite or trimethyl phosphite (5 mmol) in 1 ml of acetone under dry nitrogen. After 15 min the precipitate was collected.

4a: Mp (decomp) 173 °C; 65% yield. $\delta(\text{CDCl}_3)$ 8.0 (m, 2H, ArH), 6.90 (d, $J=10$, 1H, ArH), 4.05 (m, 2H, POCH₂), 3.25 (m, 2H, PCH₂), 1.45 (m, 6H, PCH₃+POCH₂CH₃), m/e : 260 (14), 259 (46), 213 (100).

4b: Mp (decomp) 186 °C; 88% yield. $\delta(\text{CDCl}_3)$ 8.1—7.5 (m, 7H, ArH), 6.95 (d, $J=10$, 1H, ArH), 4.0 (m, 2H, POCH₂), 3.40 (m, 2H, PCH₂), 1.30 (t, 3H, POCH₂CH₃), m/e : 322 (16), 321 (63), 275 (23), 229 (15).

5: Mp 162 °C; 90% yield. $\delta(\text{CDCl}_3)$ 10.1 (1H, OH), 7.90 (m, 2H, ArH), 6.80 (d, $J=10$, 1H, ArH), 3.70 (d, $J=11$, 6H, POCH₃), 3.20 (d, $J=22$, 2H, PCH₂). Found: C, 41.34; H, 4.62%. Calcd for C₁₉H₁₂NO₆P: C, 41.39; H, 4.63%. Cyclization occurs by heating to 190 °C under 0.2 mmHg (1 mmHg $\approx$ 133.322 Pa).

2b: Bp_{0.5} 250 °C (8); 75% yield. $\delta(\text{CDCl}_3)$ 8.10 (m, 2H, ArH), 7.05 (d, $J=10$, 1H, ArH), 3.90 (d, $J=10$, 3H, POCH₃), 3.25 (d, $J=16$, 2H, PCH₂), m/e : 229 (100), 215 (32).

3a: Bp_{0.5} 220 °C (8); 85% yield. $\delta(\text{CDCl}_3)$ 7.0 (m, 4H, ArH), 3.15 (m, 2H, PCH₂), 1.80 (d, $J=13$, 3H, PCH₃), $\delta^{31}\text{P}$: 70.4, m/e : 169 (22), 168 (100), 153 (100).

3b: Mp 173 °C; 80% yield. $\delta(\text{CDCl}_3)$ 8.05 (m, 2H, ArH), 7.0 (d, $J=11$, 1H, ArH), 3.25 (m, 2H, PCH₂), 1.85 (d, $J=15$, 3H, PCH₃), m/e : 213 (100), 198 (14), 183 (13), 167 (65).

3c: Mp 175 °C; 90% yield. $\delta(\text{CDCl}_3)$ 8.2—7.5 (m, 7H, ArH), 7.10 (d, $J=10$, 1H, ArH), 3.50 (m, 2H, PCH₂), m/e : 275 (69), 229 (33), 158 (100), 141 (19). **B'** (X=NO₂, Y=O, W=Me, Z=CH₂) was obtained after methylation by preparative thin layer chromatography (SiO₂; MeOH-EtOAc: 25—75) in 15% yield. $\delta(\text{CDCl}_3)$ 8.30 (m, 2H, ArH) 7.40 (d, 1H, ArH) 3.75 (d, $J=11$, 3H, POCH₃) 3.30 (d, $J=19$, 2H, PCH₂) 2.40 (s, 3H, COCH₃) 1.50 (d, $J=14$, 3H, PCH₃), IR(CH₂Cl₂): 1770 cm⁻¹, m/e : 273 (9), 245 (100), 213 (50).

Some acids C have been characterized.

From **3a**: C(X=H, Y=O, W=CH₃, Z=CH₂), mp 124 °C. $\delta(\text{CD}_3\text{COCD}_3)$ 9.5 (s, 2H, OH), 6.85 (m, 4H, ArH), 3.25 (d, $J=18$, 2H, PCH₂), 1.4 (d, $J=13$, 3H, PCH₃), m/e : 186 (46), 168 (91), 153 (63), $\delta^{31}\text{P}$: 53.8.

From **3b**: C(X=NO₂, Y=O, W=CH₃, Z=CH₂), mp 215—217 °C. $\delta(\text{CD}_3\text{COCD}_3)$ 8.0 (m, 2H, ArH), 6.85 (d, $J=10$, 1H, ArH), 3.20 (d, $J=18$, 2H, PCH₂), 1.40 (d, $J=13$, 3H, PCH₃), m/e : 231 (35), 213 (>100), 198 (25), 183 (14), 167 (100).

From **3c**: C(X=NO₂, Y=O, W=C₆H₅, Z=CH₂), mp 220 °C. $\delta(\text{CD}_3\text{COCD}_3)$ 8.0—7.5 (m, 7H, ArH), 6.75 (d, $J=10$, 1H, ArH), 3.40 (d, $J=13$, 2H, PCH₂), m/e : 293 (5.6), 275 (100), 245 (15), 229 (56).

Results and Discussion

We were unable to isolate the *o*-phenylene phenylphosphonate **1a** using the described method,⁴⁾ even when the rather unexpected aqueous treatments were omitted. A hygroscopic compound was formed following the preparation procedure⁵⁾ for a di-*t*-butyl de-

rivative.⁶⁾ However, a thioanalog **1b** was obtained from 3,4-toluenedithiol.

Cyclic phosphonate **2a** was prepared from saligenol and a phosphite.⁷⁾ The use of diethyl methylphosphonite instead of trimethyl phosphite led to a cyclic phosphinate **3a**.

The reaction of 2-hydroxy-5-nitrobenzyl bromide with diethyl methylphosphonite rapidly gave **4a** which in turn produced **3b** by vacuum heating. Under the same conditions **4b** and **3c** were obtained from diethyl phenylphosphonite. By an analogous Arbuzov reaction and cyclization, **5** and **2b** were formed from trimethyl phosphite.

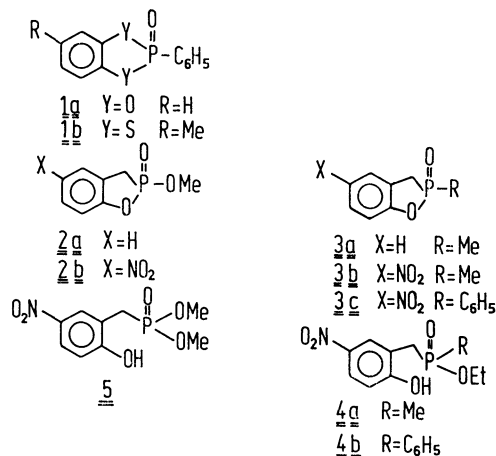


Fig. 1.

1b slowly reacts (2 h) with a mixture of acetic acid (1 mmol) and triethylamine (1 mmol) in 1 ml of $CHCl_3$ to give thioester **B** ($Y = Z = S$, $X = Me$, $W = C_6H_5$; $\nu_{C=O}$ 1700 cm^{-1}). The reaction of triethyl or tetrabutylammonium acetate with the unsubstituted phosphonate or phosphinate **2a** and **3a** leading to esters **B** ($Y = O$, $Z = CH_2$, $X = H$, $W = Me$, or OMe ; $\nu_{C=O}$ 1760 cm^{-1} (CH_2Cl_2)), occurs by heating the substances to 40 °C in CH_2Cl_2 . The activated nitro derivatives **2b**, **3b**, and **3c** react at room temperature in 2 h, giving **B** ($X = NO_2$; $\nu_{C=O}$ 1765 cm^{-1}) in about 80% yield.

In one case, the methylated derivative **B'** ($X = NO_2$, $Y = O$, $W = Me$, $Z = CH_2$) was isolated by treating **B** with diazomethane and HBf_4 .

We did not observe an IR frequency in relationship with mixed anhydride **A**, which did not accumulate in the reaction.

In each case, the rate of aminolysis of **B** is much faster than that of the corresponding unsubstituted aryl ester or thioester. *E.g.*, the reaction of 1 mmol of **B** ($Y = O$, $Z = CH_2$, $W = CH_3$, $X = NO_2$) with 1 equiv. of benzylamine in 3 ml of CH_2Cl_2 yielding *N*-benzylacetamide (mp 61 °C) is complete in less than five minutes at 20 °C. Under the same conditions the reaction with *p*-nitrophenyl acetate takes about 90 min.

We believe that the observed increase in the reaction rate is mainly due to an anchimeric assistance by the neighbouring P=O group.⁹⁾ With this hypo-

thesis, aminolysis of **B** ($X = NO_2$) is doubly accelerated, first, by the electronwithdrawing effect of the nitro substituent and second, by intramolecular general base catalysis.

Addition of the highly reactive cyclic phosphinate **3b** or **3c** to an equimolar mixture of acetic acid, triethylamine, and benzylamine in CH_2Cl_2 gives *N*-benzylacetamide with a 67% yield.¹⁰⁾ However, the main drawback in using cyclic phosphonic or phosphinic ester as coupling reagents is their sensitivity to moisture.¹¹⁾

We have recently shown that the analogous 5-nitrotoluene- α , 2-sultone is stable and yields peptides by

a similar mechanism (Scheme 1: SO_2 instead of $P(=O)(W^3)$).

In conclusion the hygroscopic cyclic phosphonates and phosphinates are not better reagents for coupling than the very efficient alicyclic phosphonates²⁾ and sultone.³⁾ Nevertheless the formation of ester **B** corroborates the mechanism of the first steps in the previous method of peptide synthesis.¹⁾

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References

- 1) M. Wakselman and F. Acher, *Tetrahedron Lett.*, **1980**, 2705.
- 2) T. Mukaiyama, N. Morito, and Y. Watanabe, *Chem. Lett.*, **1979**, 1305; Y. Watanabe, N. Morito, K. Kamekawa, and T. Mukaiyama, *ibid.*, **1981**, 65.
- 3) M. Wakselman and F. Acher, *J. Chem. Soc., Chem. Commun.*, **1981**, 632.
- 4) H. Ohkawa, S. Maruo, and M. Eto, *J. Fac. Agr. Kyushu Univ.*, **17**, 13 (1972).
- 5) I. S. Belostotskaya, N. L. Komissarova, T. I. Prokof'eva, V. R. Vol'eva, and V. V. Ershov, *Iz. Akad. Nauk SSSR Ser. Khim.*, **1978**, 2385.
- 6) In the same reaction, under different experimental conditions, tris(*o*-phenylene)phosphate has been isolated. (T. Koizumi, Y. Watanabe, Y. Yoshida, and E. Yoshii, *Tetrahedron Lett.*, **1974**, 1075).
- 7) B. E. Ivanov and H. B. Ageeva, *Izv. Akad. Nauk SSSR Ser. Khim.*, **1967**, 226; A. B. Ageeva and B. E. Ivanov, *ibid.*, **1967**, 1494; W. Vogt, *Phosphorus and Sulfur*, **5**, 123 (1978).
- 8) Temperature of the oven of a Büchi GKR (Bulb to bulb) apparatus.
- 9) The slightly basic ϕ_3PO is an efficient catalyst of the aminolysis of *p*-nitrophenyl acetate in chlorobenzene. Acceptance of the ammonium proton probably facilitates the decomposition of the tetrahedral intermediate (C. W. Su and J. W. Watson, *J. Am. Chem. Soc.*, **96**, 1854 (1974)). General base catalysis by a neighbouring anion is probably excluded because the aminolysis of the methyl ester of **B** is fast too.
- 10) We have not observed the formation of a phosphinic amide by the competitive aminolysis of **3b**. Base-catalyzed hydrolysis by contaminant water (M. Mulliez and M. Wakselman, *Phosphorus and Sulfur*, **8**, 41 (1980)) occurs by mixing **3b** or **3c** with a primary amine.
- 11) However the *o*-hydroxybenzylphosphinic acids may be cyclized by simply vacuum heating them to their melting.