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

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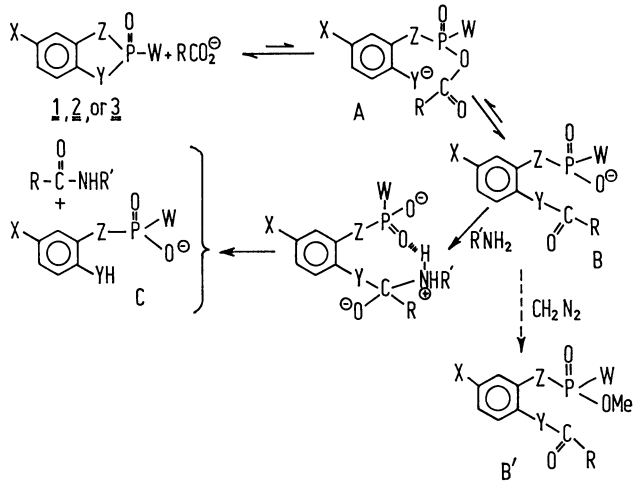
(Received March 8, 1982)

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 sulfur[3] 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; δ ^{31}P: 58.4 ($CDCl_3$); *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. δ($CDCl_3$) 8.0 (m, 2H, ArH), 6.90 (d, J=10, 1H, ArH), 4.05 (m, 2H, $POCH_2$), 3.25 (m, 2H, PCH_2), 1.45 (m, 6H, PCH_3+ $POCH_2C\underline{H}_3$), *m/e*: 260 (14), 259 (46), 213 (100).

4b: Mp (decomp) 186 °C; 88% yield. δ($CDCl_3$) 8.1—7.5 (m, 7H, ArH), 6.95 (d, J=10, 1H, ArH), 4.0 (m, 2H, $POCH_2$), 3.40 (m, 2H, PCH_2), 1.30 (t, 3H, $POCH_2C\underline{H}_3$), *m/e*: 322 (16), 321 (63), 275 (23), 229 (15).

5: Mp 162 °C; 90% yield. δ($CDCl_3$) 10.1 (1H, OH), 7.90 (m, 2H, ArH), 6.80 (d, J=10, 1H, ArH), 3.70 (d, J=11, 6H, $POCH_3$), 3.20 (d, J=22, 2H, PCH_2). Found: C, 41.34; H, 4.62%. Calcd for $C_{19}H_{12}NO_6P$: C, 41.39; H, 4.63%. Cyclization occurs by heating to 190 °C under 0.2 mmHg (1 mmHg≈133.322 Pa).

2b: $Bp_{0.5}$ 250 °C (8); 75% yield. δ($CDCl_3$) 8.10 (m, 2H, ArH), 7.05 (d, J=10, 1H, ArH), 3.90 (d, J=10, 3H, $POCH_3$), 3.25 (d, J=16, 2H, PCH_2), *m/e*: 229 (100), 215 (32).

3a: $Bp_{0.5}$ 220 °C (8); 85% yield. δ($CDCl_3$) 7.0 (m, 4H, ArH), 3.15 (m, 2H, PCH_2), 1.80 (d, J=13, 3H, PCH_3), δ ^{31}P: 70.4, *m/e*: 169 (22), 168 (100), 153 (100).

3b: Mp 173 °C; 80% yield. δ($CDCl_3$) 8.05 (m, 2H, ArH), 7.0 (d, J=11, 1H, ArH), 3.25 (m, 2H, PCH_2), 1.85 (d, J=15, 3H, PCH_3), *m/e*: 213 (100), 198 (14), 183 (13), 167 (65).

3c: Mp 175 °C; 90% yield. δ($CDCl_3$) 8.2—7.5 (m, 7H, ArH), 7.10 (d, J=10, 1H, ArH), 3.50 (m, 2H, PCH_2), *m/e*: 275 (69), 229 (33), 158 (100), 141 (19). **B'** (X=NO_2, Y=O, W=Me, Z=CH_2) was obtained after methylation by preparative thin layer chromatography (SiO_2; MeOH–EtOAc: 25—75) in 15% yield. δ($CDCl_3$) 8.30 (m, 2H, ArH) 7.40 (d, 1H, ArH) 3.75 (d, J=11, 3H, $POCH_3$) 3.30 (d, J=19, 2H, PCH_2) 2.40 (s, 3H, $COCH_3$) 1.50 (d, J=14, 3H, PCH_3), IR(CH_2Cl_2): 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=CH_3, Z=CH_2), mp 124 °C. δ(CD_3COCD_3) 9.5 (s, 2H, OH), 6.85 (m, 4H, ArH), 3.25 (d, J=18, 2H, PCH_2), 1.4 (d, J=13, 3H, PCH_3), *m/e*: 186 (46), 168 (91), 153 (63), δ ^{31}P: 53.8.

From ***3b***: C(X=NO_2, Y=O, W=CH_3, Z=CH_2), mp 215—217 °C. δ(CD_3COCD_3) 8.0 (m, 2H, ArH), 6.85 (d, J=10, 1H, ArH), 3.20 (d, J=18, 2H, PCH_2), 1.40 (d, J=13, 3H, PCH_3), *m/e*: 231 (35), 213 (>100), 198 (25), 183 (14), 167 (100).

From ***3c***: C(X=NO_2, Y=O, W=C_6H_5, Z=CH_2), mp 220 °C. δ(CD_3COCD_3) 8.0—7.5 (m, 7H, ArH), 6.75 (d, J=10, 1H, ArH), 3.40 (d, J=13, 2H, PCH_2), *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 procedure[5] 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.

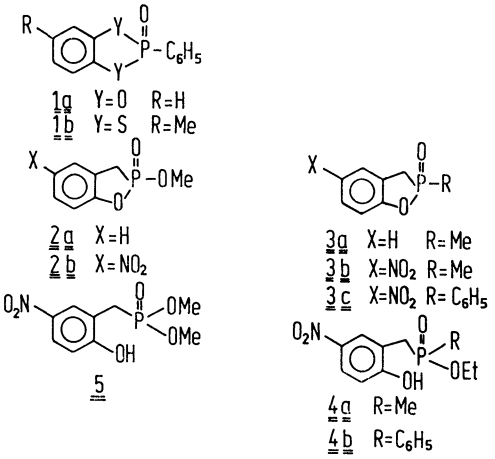


Fig. 1.

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 hypothesis, 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 $\overset{O}{\overset{\|}{P}}$–W[3]).

In conclusion the hygroscopic cyclic phosphonates and phosphinates are not better reagents for coupling than the very efficient alicyclic phosphonates[2] and sultone.[3] Nevertheless the formation of ester **B** corroborates the mechanism of the first steps in the previous method of peptide synthesis.[1]

We thank Dr P. Savignac for his help in the preparation of the diethyl methylphosphonite.

References

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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.