Tetrahedron. Vol. 32, pp. 2417 to 2419. Pergamon Press 1976. Printed in Great Britain

THE ACTIVATION OF *N*-HYDROXY COMPOUNDS BY μ-OXO-BIS-[TRIS-(DIMETHYLAMINO)-PHOSPHONIUM] BIS-TETRAFLUOROBORATE

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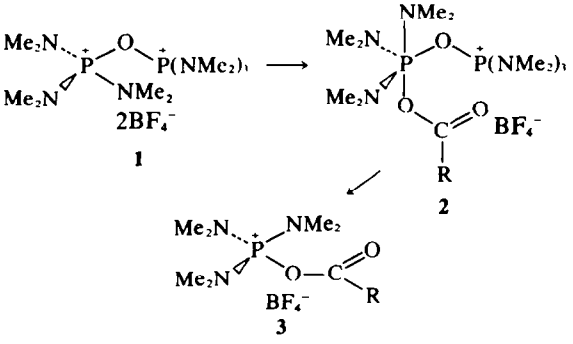
(*Received in the UK 22 January 1976; Accepted for publication 17 May 1976*)

Abstract—A study is made of the effect of 1-hydroxybenzotriazole on μ-oxo-bis-[tris(dimethylamino)-phosphonium]-bis-tetrafluoroborate **1** during amide bond formation. The reagent **1** is used to activate phenylhydroxamic acid towards a Lossen-type rearrangement and bring about Beckmann rearrangement of ketoximes under mild conditions. Both *syn*- and *anti*-benzaldoxime give benzonitrile by elimination.

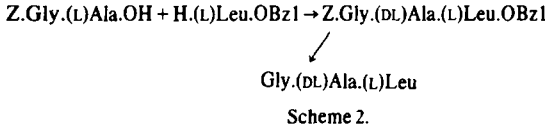
The reagent, μ-oxo-bis[tris-(dimethylamino)-phosphonium]-bis-tetrafluoroborate **1**, derived from hexamethylphosphoric triamide (HMPA), was developed[1] for activation of the carboxyl function and subsequent amide bond formation during peptide synthesis. Although the exact nature of the intermediate responsible for the activation is not certain, it is reasonable to postulate the intermediacy of **2** and **3**. Scheme 1 is lent support by



Scheme 1.

recent work[2] identifying ligand exchange, via phosphorane intermediates, in reactions of phosphonium salts derived from tris-(dimethylamino)-phosphine. Nucleophilic attack on either **2** or **3** by RNH_2 or $RCOO^-$ would result in amide or anhydride formation with the expulsion of HMPA.

In the course of this work it was found that addition of 1-hydroxybenzotriazole (HOBt) to coupling reactions involving **1** markedly reduced the degree of racemisation, as measured by the stringent Izumiya test[3] (Scheme 2), due



Scheme 2.

to the intermediacy of the active ester of Z.Gly.Ala.OH and HOBt. It was therefore thought desirable to investigate the reactivity of HOBt towards **1** in order to determine whether the salt **4** would have a beneficial or detrimental effect with respect to racemisation. Equimolar quantities of **1** and HOBt were reacted in MeCN solution in the presence of diethylaminoethylpolystyrene as base to give the stable, crystalline salt **4** (m.p. 129–131°) which proved to be soluble in MeCN and DMF. Recently other workers have described the hexafluorophosphate of **4**[4] and several *O*-sulphonyl derivatives of HOBt e.g. **6**.[5] From Table 1 it can be seen that reagents **4** and **6** cannot be used in racemisation-prone peptide couplings due to unacceptable degrees of racemisation (Izumiya test) under realistic experimental conditions for coupling of protected polypeptide fragments.

Reagents **4** and **6** gave results (Table 1) which are

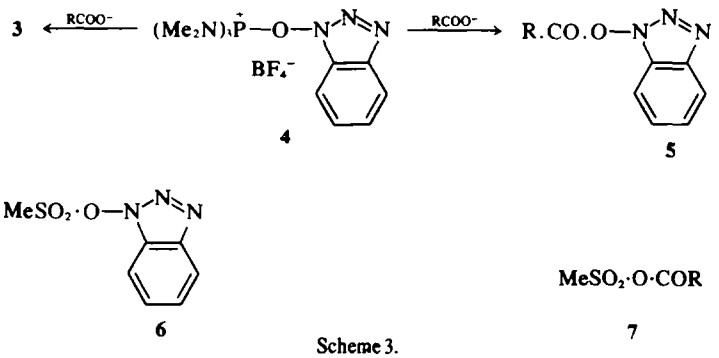
Table 1.

Reagent	% Racemisation $\frac{DL \times 100}{DL + LL}$
4	29.1
6	20.7
1 + HOBt	< 1[1]

typical of reactions which involve aminolysis of anhydride or oxazolone type intermediates and thus suggest that nucleophilic attack of $RCOO^-$ in the activating step takes place predominately at $P^{\oplus}$ in **4** and SO_2 in **6** to give **3** and **7** respectively. From this study it is now probable that the low racemisation (1%) process follows the sequence **1** → **3** → **5** → amide, i.e. initial attack by $RCOO^-$ in preference to HOBt, on **1**.

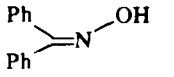
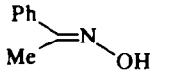
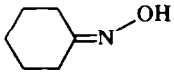
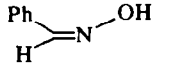
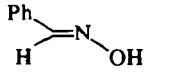
Due to the ready reaction of HOBt with **1** it was decided to investigate the possibility of activating other *N*-hydroxyl functional groups namely hydroxamic acids, oximes and aldoximes (Table 2). These would be expected to give intermediates of the type **9** and **15**, respectively, which should have the capability of undergoing Lossen and Beckmann-type rearrangements or nitrile formation in the case of aldoximes.

Rearrangement of phenylhydroxamic acid **8** via **9** should produce phenylisocyanate **10** or products derived therefrom. In the event, reaction of **8** and **1** in refluxing MeCN for 2 h in the presence of Et_3N or polymeric base, followed by addition of H_2O with further 10 min reflux gave diphenylurea **11** which is the usual product of hydrolysis of **10**. Although no IR evidence could be obtained for the presence of **10** in the initial MeCN reaction mixture, an unstable intermediate could be isolated which gave **11** on treatment with H_2O. This intermediate was also isolated from the same reaction performed in MeOH making the isocyanate an unlikely intermediate since under these conditions the correspond-



Scheme 3.

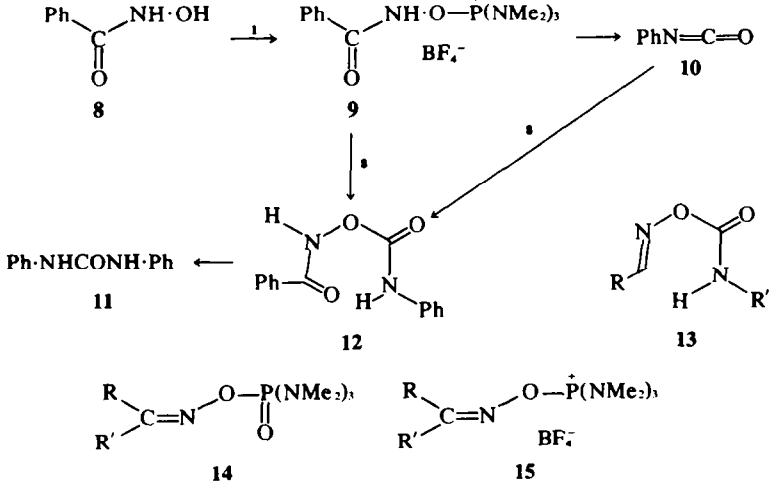
Table 2.

Oxide		Beckmann rearrangement product 1	Beckmann rearrangement product HMPA[7]	Dehydration product 1	Dehydration product HMPA[7]
	16	86	27		
	17	75	17		
	18	20	—		
	19			89	92
	20			92	99

ing methyl urethane would be the expected major product. Structure **12** may tentatively be assigned to this intermediate which could be formed by nucleophilic attack by another molecule of **8**, either on **9** with concomitant phenyl migration, or **10** as shown in Scheme 4. Although this latter route has analogy in the dehydration of aldoximes by isocyanates via **13**,[6] the lack of evidence for **10** in the reaction mixture makes this alternative less attractive. In the normal Lossen rearrangement the type of bimolecular reaction outlined in Scheme 4 is precluded due to prior esterification of the *N*-hydroxyl function.

In recent years HMPA has been shown[7] to activate ketoximes and aldoximes through probable formation of **14** to produce amides and nitriles respectively, however the high temperatures required to achieve these processes might be expected to lessen the utility of the method. It was thought that activation of oximes by **1** would be more facile than by HMPA alone and give an intermediate **15** susceptible to rearrangement or elimination under overall more mild conditions. Reaction of the ketoximes **16**, **17** and **18** with **1** in refluxing MeCN and subsequent addition of H_2O gave the expected products (Table 2). Thus under these relatively mild conditions these ketoximes rearrange more efficiently than by using HMPA at high temperature (>200°C). The effective dehydration of both *syn* and *anti* isomers **19** and **20** proceeded smoothly in refluxing DMF to afford benzonitrile in accord with the results obtained using HMPA/220°C which suggests either ionisation of the N–O bond prior to deprotonation or thermal interconversion of the *syn* and *anti* forms.

These results show that μ-oxo-bis-[tris (dimethylamino)-phosphonium]-bis-tetrafluoroborate **1** is capable of activating *N*-hydroxy compounds under relatively mild neutral conditions. It is intended to study



Scheme 4.

the reactivity of this reagent towards other hydroxyl functions.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were determined using Unicam SP1000 or Unicam SP200 spectrometers. Mass spectra were obtained from A.E.I. MS 12 and MS 902 instruments (the latter with on-line computer). Separation of diastereoisomeric Gly.Ala.Leu was achieved using a Jeol JLC-5AH automatic analyser with digital integrator unit.

Starting materials. Phenylhydroxamic acid, acetophenone oxime, benzophenone oxime, *syn* and *anti* benzaldoximes and their respective rearrangement products were either commercially available or prepared by standard literature procedures. All reagents were purified before use by crystallisation or drying followed by distillation. Diethylaminomethylpolystyrene was purchased from Fluka.

Benzotriazoyl - N - oxy[tris - (dimethylamino) - phosphonium] fluoroborate (**4**)

μ - Oxo - bis - [tris - (dimethylamino) - phosphonium] - bis - tetrafluoroborate **1** (1.54 g, 3.0 mmole) was dissolved in anhydrous MeCN (15 ml). Diethylaminomethylpolystyrene (2.00 g, 6.00 mmole) and 1-hydroxybenzotriazole (0.41 g, 3.0 mmole) were added and the mixture was stirred at room temperature for 48 h. After filtering the reaction mixture the MeCN was removed *in vacuo* and anhydrous ether was added to the residue. The solid obtained was filtered, dried and crystallised from MeCN-petroleum ether to give **4** (0.82 g, 71%), m.p. 129–131°. Mass spectrum *m/e* 297 (M^+–HBF_4 requires 297). (Found: C, 38.00; H, 5.94; N, 21.73. $C_{12}H_{22}N_6OPBF_4$ requires: C, 37.53; H, 5.77; N, 21.88%).

Izumiya test using **4** *and* **6**. Z.Gly.Ala.OH (155 mg, 0.55 mmole) and **4** (120 mg, 0.56 mmole) were dissolved in DMF (1 ml) containing *N*-methylmorpholine (NMM) (0.06 ml, 0.56 mmole) and the solution stirred for 0.5 h at 0–5°. $Tos^-H_2^+$ LeuOBzl (198 mg, 0.5 mmole) in DMF (2 ml) containing NMM (0.06 ml, 0.5 mmole) was added to the above solution. After 16 h at room temperature the solvent was removed *in vacuo* and the residue was partitioned between EtOAc and H_2O. The EtOAc layer was washed with 10% citric acid solution (×3), 3% $NaHCO_3$ solution (×3), H_2O (×3), brine (×1) followed by drying (Na_2SO_4). Removal of EtOAc *in vacuo* afforded a white solid (255 mg). A portion of this Z.Gly.Ala.Leu.OBzl (50 mg) in HOAc (4.5 ml) was treated with 10% Pd/C (100 mg) and hydrogenated for 16 h. After filtering the solvent was removed *in vacuo* and the residue dissolved in citrate buffer (pH 2.2, 10 ml). An aliquot (1 ml) of this solution was diluted to 3 ml and applied to the Jeol JLC-5AH automatic analyser—short column, pH 3.28, flow rate 50 ml/h at 57°. Racemisation found for amide bond formation using **4** was 29.1%. This experiment was repeated for reagent **6** and the racemisation was 20.7%.

†An aliquot (0.4 ml) was removed and evaporated *in vacuo*. The residue was triturated with ether then the ether removed *in vacuo* to give an oil. Neither this oil nor the original MeCN solution contained phenylisocyanate from the IR spectra. Addition of H_2O to this intermediate gave **11**.

Reaction of phenylhydroxamic acid **8** *with* **1**. A solution of **8** (100 mg, 0.73 mmole), **1** (413 mg, 0.8 mmole) in anhydrous MeCN (5 ml) containing Et_3N (0.22 ml, 2.2 mmole) was refluxed for 2.25 h† then H_2O (0.5 ml) added and the solution refluxed for 7 min. After concentrating the reaction mixture *in vacuo* the residue was partitioned between Et_2O and H_2O. The Et_2O layer was washed with H_2O dried ($MgSO_4$) and evaporated to yield diphenylurea **11** (54 mg, 70%) m.p. 238–240° which was identical with authentic material by IR and mixed m.p.

Rearrangement of **16** *and* **17**. A soln of **16** (0.5 g, 2.5 mmole) and **1** (2.2 g, 4.25 mmole) in anhydrous MeCN (15 ml) was refluxed for 4.5 h then H_2O (10 ml) was added. The mixture was concentrated to *ca.* 5 ml and H_2O (5 ml) was added followed by 20 min reflux. The solid was filtered and recrystallised from EtOH–H_2O to give benzanilide (0.43 g, 86%) m.p. 162–163°, identical to authentic material by IR, mass spectra and mixed m.p.

Rearrangement of **17** was carried out under identical conditions to give acetanilide (0.19 g, 75%) m.p. 114–116°, identical with authentic material.

Rearrangement of **18**. A soln of **18** (0.5 g, 4.1 mmole) and **1** (4.0 g, 7.7 mmole) in anhydrous MeCN (20 ml) was refluxed for 20 h, after which H_2O (10 ml) was added and the mixture was warmed at 60° for 10 min. The solvent was concentrated *in vacuo* and the residue extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and the $CHCl_3$ removed *in vacuo* to give a crude product which was purified by preparative TLC silica gel PF_{254} (Merck) (EtOAc–Et_2O, 4:1). ϵ-Caprolactam (0.1 g, 20%) m.p. 70° was isolated, crystallised from petroleum ether and shown to be identical with authentic material.

Rearrangement of **17** *and* **18**. A soln of *syn* benzaldoxime **9** (0.3 g, 2.5 mmole) and **1** (2.1 g, 4.1 mmole) in DMF (7 ml) was refluxed for 4.5 h. The mixture was fractionated to give benzonitrile (229 mg, 89%) b.p. 67–72°/10 mm identical with authentic material by IR and mass spectra. The *anti* benzaldoxime **20** gave benzonitrile (232 mg, 92%) under these conditions.

Acknowledgements—We thank the University of Liverpool for support (I.J.G., W.D.T.) and Liverpool Education Authority for a maintenance award (P.F.G.).

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