Unusual solvent-dependent behaviour of hydroxyiminophosphonamidates in the Beckmann reactions: choice between rearrangement or fragmentation to metaphosphonamidate species

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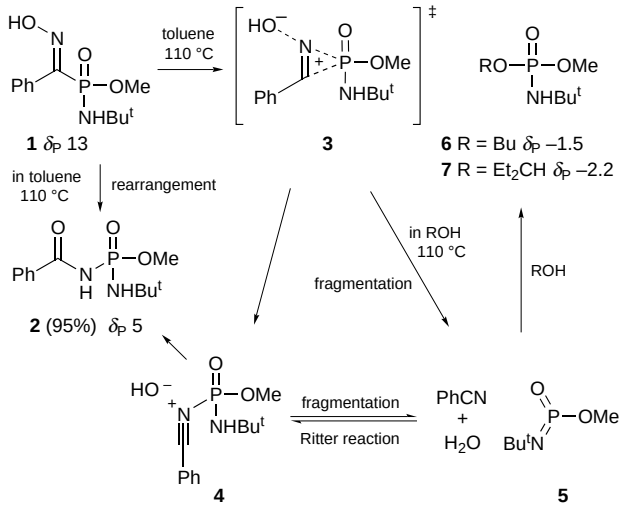
Methyl α-hydroxyiminobenzyl-*N*-*tert*-butylphosphonamidate undergoes Beckmann rearrangement (BR) when heated in toluene, but fragmentation (*via* metaphosphonamidate) to a phosphoramidate and PhCN when heated in BuOH, supporting the assumption of a common intermediate for the BR and the Beckmann fragmentation; polar solvents retard the rearrangement.

Recently it was reported from our laboratory that α-hydroxyiminobenzylphosphonamidates (*e.g.* **1**) rearrange easily ($t_{1/2}$ 92 min) in boiling toluene to *N*-benzoylphosphorodiamidates (*e.g.* **2**, Scheme 1).[1] Here we report that the behaviour of methyl *N*-*tert*-butyl α-hydroxyiminobenzylphosphonamidate **1** changes dramatically with a change in the solvent. While in aprotic solvents it undergoes cleanly Beckmann rearrangement (BR) to methyl *N*-benzoyl-*N*′-*tert*-butylphosphorodiamidate **2**, in alcohols it undergoes fragmentation to PhCN and a (mixed) dialkyl *N*-substituted phosphoramidate (*e.g.* **6** or **7**).

Although the mechanism of the Beckmann reactions is still not completely understood, according to the generally accepted view,[2] the BR and the Beckmann fragmentation reactions both involve the intermediacy of a nitrilium species (analogous to **4a**) formed by the concerted migration of the group *anti* to the departing hydroxy *via* a transition state such as **3**. Very recently it was calculated[3] that the first event in the classical BR is most likely protonation of the nitrogen, followed by a rate-determining 1,2 proton migration to the oxygen. Another result in this recent paper was the prediction of catalysis by solvents such as water, formaldehyde or formic acid, which were shown to play an important role in the transition state of the rate determining step. Once formed, the nitrilium species can undergo water addition to form the BR product or it can fragment in what is called the abnormal BR (considered a side reaction) to a nitrile and a carbocation or, as in our case, a metaphosphate species such as **5**. In the classical BR it has not been possible to control the ratio of rearrangement to fragmentation, however, it was found that the electronic properties of the migrating group played a crucial role. Thus, it was found that migrating groups capable of forming stable carbocations favour fragmentation.‡ The overall mechanistic picture is complicated by the fact that the nitrile and the electrophilic species can recombine in a Ritter reaction, reforming the nitrilium ion. Application of these mechanistic considerations to the Beckmann reaction of an α-hydroxyiminobenzylphosphonamidate is shown in Scheme 1.



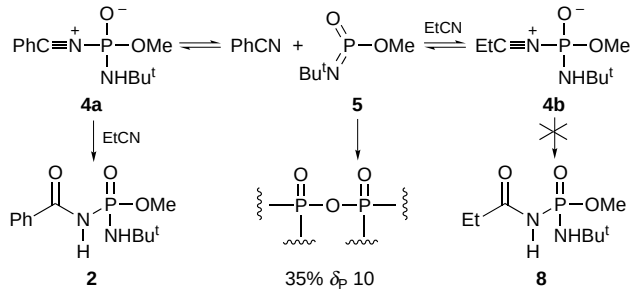
Scheme 1

Nitrilium species such as **4a** have been postulated as reversibly forming intermediates when metaphosphates were generated in MeCN.[4] Therefore, **4a** is conceivably a metaphosphonamidate (**5**) precursor. One of the commonly accepted diagnostic tests for metaphosphate-like species as reactive intermediates is the absence of any steric effect in the phosphorylation of hindered alcohols as compared to primary ones.[5] Consequently, in order to further investigate the present Beckmann fragmentation, we studied the thermal behaviour of methyl *N*-*tert*-butyl-α-hydroxyiminobenzylphosphonamidate **1** as a representative of this type of compounds in alcohols (butan-1-ol and pentan-3-ol) capable of trapping metaphosphates. The two alcohols were chosen as media for the thermal reactions of **1** for two reasons: (i) the closeness of their boiling points to that of toluene§ should allow easy comparison of reaction rates and (ii) their differing steric effects should shed light as to the nature of the reaction intermediates.[6] Monitoring by ^{31}P NMR spectroscopy of a 0.18 M butan-1-ol solution of **1** kept at 110 °C revealed the relatively slow ($t_{1/2}$ 1829 min; first order kinetics) development of one new product (δ_P −1.5), along with concurrent consumption of the starting material (δ_P 13), in a clean reaction. The product was isolated and identified as butyl methyl *N*-*tert*-butylphosphoramidate **6**.¶ Similarly, heating a solution of **1** in pentan-3-ol at 110 °C gave methyl 1-ethylpropyl *N*-*tert*-butylphosphoramidate **7** (δ_P −2.5).‖ In addition, the presence of PhCN in both reaction mixtures was demonstrated by GC–MS and HPLC. Carrying out the reaction in a 1 : 1 (v/v) mixture of butan-1-ol and toluene gave the same result. When **1** was heated in a 1 : 1 (mol/mol) mixture of butan-1-ol and pentan-3-ol the formation of the two products **6** and **7** in 65 : 35 ratio was observed by ^{31}P NMR spectroscopy.

The formation of the two phosphorodiamidates **6** and **7** in a 65 : 35 ratio in the thermolysis in the butan-1-ol–pentan-3-ol mixture is consistent with the formation of a reactive metaphosphonamidate intermediate **5** which is trapped by two alcohols with different steric requirements in an almost non-selective manner. If the alcohols were involved in the rate determining step of the reaction the ratio between the rates of formation of products should reflect the steric effects of the two alcohols[6] and therefore, the ratio of yields for **6** and **7** should be about 40 : 1.

Further considering the possible intermediacy of metaphosphate–nitrile addition species in the thermolytic reactions

of **1**, we reasoned that if species **4a** were involved, then carrying out the reaction in the presence of a large excess of another nitrile (*e.g.* EtCN) would cause the two nitriles to compete and lead to **4b** (Scheme 2), which in turn would give methyl *N*-propionyl-*N′*-*tert*-butylphosphorodiamidate. However, when **1** was heated in EtCN at 110 °C, it reacted ($t_{1/2}$ 225 min) to give two types of product only: (i) **2** (65%) by BR, and (ii) products (35%) having a group of signals at around δ_P −10,[7] consistent with oligomeric P–O–P type species; no methyl *N*-*tert*-butyl-*N′*-propionylposphorodiamidate was formed. In contrast, heating **1** in DMF at 100 °C, gave **2** cleanly in a slow ($t_{1/2}$ 5500 min) BR.



Scheme 2

Our system is unique in a number of ways. (i) In contrast to the normal BR, both the rearrangement and the fragmentation occur without acid catalysis. This makes it possible to isolate and to study the influence of further environmental and structural variations on the reactions and on the choice between them. (ii) In contrast to the predictions in ref. 3, in our case the BR is *retarded* by polar, basic solvents (DMF or EtCN) in comparison to toluene. This can be rationalized by assuming ground state stabilization of **1** by strong hydrogen bonding. In fact, **1** has a significantly lower solubility in toluene. Along with suppressing the rearrangement, the polar solvents DMF and alcohol (and to some extent EtCN) promote dissociation of intermediate **4a** by solvating the incipient metaphosphonamidate **5**, which can subsequently be trapped by the alcohols. The absence of steric effects observed in the reactions in alcohols is consistent with the formation of a reactive intermediate trapped nonselectively by alcohols of differing steric requirements. In EtCN the solvent forms an addition compound, thus stabilizing the metaphosphonamidate intermediate which polymerizes in the absence of an efficient trap, in addition to considerable proportion of the normal rearrangement product. (iii) The reactions described here proceed without acid catalysis, presumably because of the high migratory aptitude of the phosporus moiety. This seems to be a new manifestation of the 'β-effect' namely the ability of phosphorus functionalities to stabilize an electron deficient centre situated in β-relationship.[8]

In conclusion, our results show a new aspect of acylphosphonate and oxyiminophosphonate chemistry.[9] The versatility of this class of molecules, the countless ways they can be modified and the different types of reactions they can undergo so readily make them a focus of continuing interest and a source of models uniquely suitable for mechanistic studies.

Finally, our results seem to support the assumption that both the BR and the fragmentation proceed *via* a common intermediate. To the best of our knowledge, such a dramatic change in the reactions' course resulting from changing the solvent is unprecedented in this area.

Footnotes and References

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† On leave from the Department of Organic Chemistry, University of Copenhagen.
‡ It should be noted that metaphosphates have certain features in common with carbocations: they are both frequently formed in dissociative-type reactions, they are both electrophilic and planar, and they both are intermediates leading to racemization.
§ Toluene: bp 111 °C; butan-1-ol: bp 118 °C; pentan-3-ol: bp 115 °C.
¶ *Selected data* for **6**: mp 87–88 °C; δ_P ($CDCl_3$) −1.5 (m); δ_H ($CDCl_3$) 8.40 (br s, 1 H, NH), 3.80 (dt, 2 H, CH_2OP), 3.50 (d, 3 H, *J* 10.5, CH_3OP), 1.60 (dt, 2 H, CH_2), 1.38 (s, 9 H, Bu^t), 1.38 (m, 2 H, CH_2), 0.89 (t, 3 H, *J* 7.2 Me); δ_C ($CDCl_3$) 63 (d, J_{POC} 5.5, CH_2OP), 51 (d, J_{POC} 5.5, CH_3OP), 49, 31 (d, J_{PNC} 7.5, CNP), 26, 18, 12; *m/z* 223. Calc. ($C_9H_{22}NO_3P·H_2O$): C, 44.80; H, 10.03; N, 5.81. Found: C, 45.18; H, 10.03; N, 5.52%.
‖ *Selected data* for **7**: mp 134–136 °C; δ_P ($CDCl_3$) −2.2 (dquintet); δ_H ($CDCl_3$) 4.05 (m, 1 H, CHOP), 3.56 (d, 3 H, *J* 10.8, CH_3OP), 2.60 (br s, 1 H, NH), 1.60 (dq, 4 H, 2 × CH_2), 1.40 (s, 9 H, Bu^t), 0.39 (t, 6 H, *J* 7.5, 2 × CH_3); δC ($CDCl_3$) 78 (d, J_{POC} 5.5, CHOP), 52 (d, J_{POC} 5.5, CH_3OP), 51, 28, 27 (d, J_{PNC} 7.5, CNP), 9; *m/z* 238. Calc. ($C_{10}H_{25}NO_3P·H_2O$): C, 46.67; H, 10.33; N, 5.46. Found: C, 46.60; H, 10.33; N, 5.46%.

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