Pergamon

Tetrahedron Letters, Vol. 36, No. 52, pp. 9437-9440, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)02099-3

(*E*)-(Hydroxyimino)(hydroxymethoxyphosphinyl)acetic Acid: Synthesis and pH-Dependent Fragmentation

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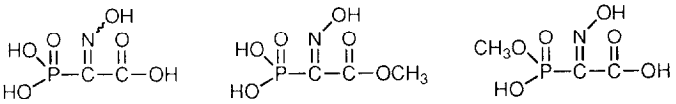
Abstract: In contrast to both its parent "troika" acid (*E*-**1**, a phosphorylating agent at pH 7 and 25 °C) and its C-methyl isomer (*E*-**2**, which is stable at both acidic and neutral pH), (*E*)-(hydroxyimino)(hydroxymethoxyphosphinyl)acetic acid *E*-**3** was unreactive at pH 7 and 25 °C but at pH 1.5 fragmented to methyl phosphate **10** (15%) and methyl phosphorocyanidate **11** (85%). The minor product is consistent with solvent phosphorylation, the reaction exclusively observed with *E*-**1**. The non-phosphorylating fragmentation pathway is proposed to involve a preliminary $E \rightarrow Z$ isomerization of **3** prior to $C\alpha$-$C\beta$ cleavage. Dual fragmentation pathways were also detected (^{31}P NMR) when the $DCHA^+$ salt of *E*-**3** (*E*-**9**) was heated in acetonitrile or EtOH; in addition to phosphorylation products (16-19%), **11** was formed (81-84%). Reaction of *E*-**9** in refluxing EtOH:*t*-BuOH (1:1) showed low stereoselectivity in product formation (~3:1 ethyl methyl phosphate:*t*-butyl methyl phosphate), supporting a dissociative phosphorylation process.

E/Z-Isomeric α-(hydroxyimino)phosphonoacetic acids, or "troika acids" (**1**) have a central carbon connecting phosphonic, carboxylic and oxime acid groups, and thus represent a trifunctional molecular system potentially rich in interesting chemical behavior modulated by the stereochemical status of the hydroxyimino moiety. Recently, the C-methyl ester of *E*-**1** (*E*-**2**, as a monoanionic salt) was shown to give phosphorylation products when heated in acetonitrile (AN) or alcohols.[1] Under neutral or moderately acidic conditions at room temperature, *E*-**2** (ionized in response to the pH) was stable in water at room temperature. Particularly intriguing was the observation that removal of the carboxy alkyl group of *E*-**2** (e.g., by alkaline hydrolysis) created a phosphorylating agent (*E*-**1**) active under mild aqueous conditions (pH 7, 25 °C). Fragmentation of **1** was stereospecific, the *E* isomer giving P-$C\alpha$ bond cleavage, and the *Z* isomer undergoing $C\alpha$-$C\beta$ bond cleavage to form phosphorocyanidate. To explore further the effect of structure on the chemical properties of troika acid derivatives, we have now synthesized the P-monomethyl isomer of *E*-**2**, *E*-**3**, and examined its fragmentation behavior in aqueous and non-aqueous solvents.



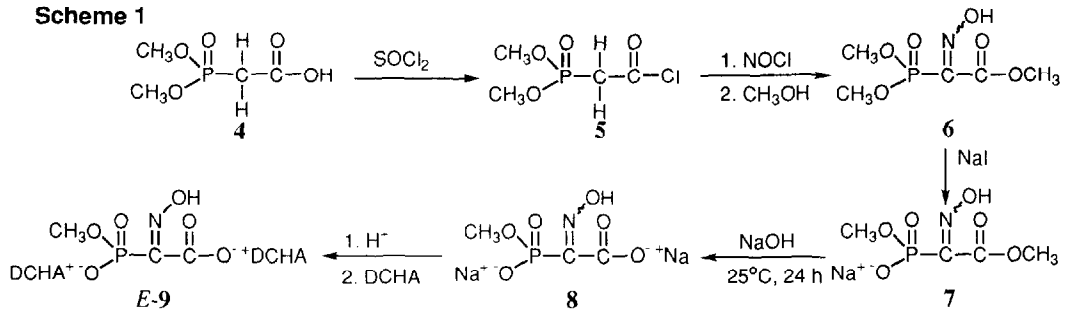
1 *E*-**2** *E*-**3**

RESULTS AND DISCUSSION

Synthesis of *E*-**3** (Scheme 1). Trimethyl α-(hydroxyimino)phosphonoacetate **6** was obtained (48%) as a 7 : 3 *E* : *Z* mixture[2] by nitrosation of the corresponding chlorocarbonyl compound **5**[5] followed by methanolysis. Monodealkylation of **6** with NaI gave **7** (88 : 12 *E* : *Z* mixture), which was hydrolyzed by NaOH to the P-monoester disodium salt **8**. The acid **3** was generated using an ion-exchange resin in H^+ form

and trapped as an *E/Z* mixture of dicyclohexylammonium ($DCHA^+$) salts, from which the pure bis-$DCHA^+$ salt of *E*-**3** (*E*-**9**) was obtained by recrystallization.

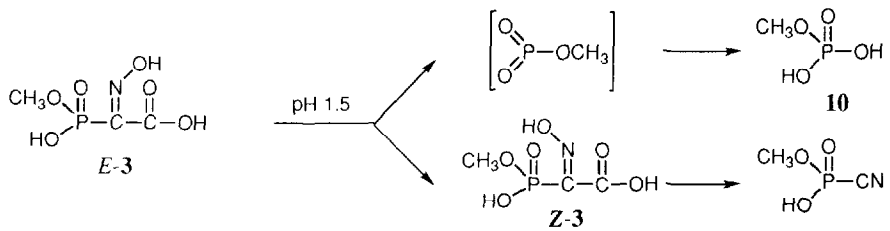
Scheme 1



4 5 6 7 8 *E*-9

Fragmentation of E-3. Like its C-methyl isomer *E*-**2**,[1] *E*-**3** (from the salt *E*-**9**) was stable in water at pH ~ 7 for 24 h (room temperature). However, in contrast to *E*-**2**, at pH 1.5 *E*-**3** (^{31}P NMR δ 2.4 ppm) quantitatively decomposed (Scheme 2) over 2.5 h. The minor product, methyl phosphate **10** (15%; ^{31}P NMR δ 2.1 ppm) was that expected from P-Cα bond cleavage by analogy with the behavior of *E*-**1**. The major product was methyl phosphorocyanidate **11** (85 %; ^{31}P NMR δ -17.4 ppm),[7] corresponding to Cα-Cβ cleavage. In the system **1**, this pathway was only observed with the *Z*-isomer,[1] suggesting that *E*-**3** undergoes acid-dependent isomerization to *Z*-**3**, which then decarboxylates to **11**. The predominantly *trans* elimination of α-hydroxyiminocarboxylic acids[9] is consistent with this idea. It is also supported by the observation of a small ^{31}P NMR peak at δ –0.2 ppm, assigned to *Z*-**3**, in reaction mixtures containing incompletely decomposed *E*-**3**. The product distribution observed in the system **3** indicates that the overall process: *E*-**3** → *Z*-**3** → **11** is about 6x faster than a dissociative fragmentation of *E*-**3**, whether to a putative methyl metaphosphate intermediate which should react rapidly with the solvent (Scheme 2), or via an analogous open transition state.[10]

Scheme 2



E-**3** **10** **Z**-**3** **11**

E-**2** (as a $DCHA^+$ salt) decomposed to polyphosphates after 1 da in refluxing AN,[1] whereas methyl α-(hydroxyimino)benzylphosphonate anion (**12**) is thermally stable under similar conditions.[11] *E*-**3** (as the $DCHA^+$ salt *E*-**9**) resembles **12** in having a monoanionic phosphonate group that might be expected to be less reactive to fragmentation via a dissociative pathway than a potentially dianionic phosphonate such as *E*-**1**. *E*-**9** in refluxing AN proved not to be stable, however, and the main P-Cα cleavage phosphorylation product (*sym*-dimethyl pyrophosphate, ^{31}P NMR; 16%) was dominated by an unexpected Cα-Cβ cleavage product, methyl phosphorocyanidate (84%). Similar product partitioning was seen in refluxing EtOH (19% ethyl methyl phosphate, 81% methyl phosphorocyanidate). Replacement of the EtOH by 1 : 1 EtOH-*t*-BuOH resulted in a 1 :

3.3 ratio of ethyl : *t*-butyl methyl phosphate products (total 24%). Formation of polyphosphates in AN and phosphorylation at comparable rates of *t*-BuOH *vs.* primary alcohols are considered to be characteristic of dissociative phosphate and phosphonate fragmentations.[10-13]

In conclusion, we note that the possibility of *trans* elimination in both *E* and *Z* oxime isomers of troika acids is an important feature of these compounds. In the system **3**, both pathways can be accessed from one stereoisomer (*E*-**3**) because $E \rightarrow Z$ isomerization competes favorably with direct fragmentation. The stability of *E*-**2** at low pH and fragmentation-isomerization of *E*-**3** under the same conditions indicates that these processes are facilitated in *E*-**3** by intramolecular protonation of the oxime OH by the carboxyl proton. The stability of *E*-**3**, and the fragmentation of *E*-**1** at pH 7 are consistent with a stereoelectronic control[14] effect (*E*-**1** *vs.* *E*-**3** has the higher number of antiperiplanar lone pairs). It is not surprising that dissociative fragmentation of a methyl phosphonate monoanion such as *E*-**3** at pH 7 would be more difficult than fragmentation of the dianion which should be available as an equilibrium species from **1** at this pH.

The stability of *E*-**2** and *E*-**3** under physiological aqueous conditions suggests that both types (P and C) of monoester could be precursors of *E*-**1** via mild esterolytic hydrolysis, with an appropriate choice of the ester group.

EXPERIMENTAL DETAILS

All reagents were AR grade from Aldrich, Inc. NMR (Bruker AM 360) spectra were referenced to tetramethylsilane (^{1}H, ^{13}C) or external 85% H_3PO_4 (^{31}P). Melting points were recorded on a Thomas Hoover apparatus. Elemental analysis were performed by Galbraith Laboratories, Inc.

Trimethyl α-(Hydroxyimino)phosphonoacetate **6**. Oxime **6** was prepared as previously described,[15] but the reaction conditions were 5 h at rt and **4**, obtained here by acidification of the corresponding potassium salt[16] using Dowex 50WX8 (H^+ form), was used as the starting material. The product was purified by column chromatography on silica gel (30-60 mesh) ($CHCl_3$/acetone, 5 : 1), yield 48%. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.7-3.9 (m, 9H, OCH_3), 12.4 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ (ppm) 143.5 (*E*), (d, $^1J_{CP}$ = 224 Hz, P-C=N), 143.1 (*Z*), (d, $^1J_{CP}$ = 164 Hz, P-C=N). ^{31}P NMR ($CDCl_3$): δ (ppm) 7.7 (*E*), 6.2 (*Z*). Calcd for $C_5H_{10}NO_6P$: C, 28.45; H, 4.77; N, 6.63. Found: C, 28.09; H, 4.79; N, 6.48.

Sodium Salt (7) of Methyl (Hydroxyimino)(hydroxymethoxyphosphinyl)acetate. A solution of **6** (420 mg, 1.99 mmole) in dry acetone (5 mL) was added to a solution of NaI (328 mg, 2.19 mmole) in dry acetone (5 mL) at room temperature. After 24 h, the precipitate was filtered and washed with dry acetone and Et_2O, yielding 320 mg (73.4%) **7** as a white solid, dec. 143 °C. ^{1}H NMR (D_2O): δ (ppm) 3.42 (*E*), (d, $^3J_{HP}$ = 11.5 Hz, OCH_3), 3.39 (*Z*), (d, $^3J_{HP}$ = 11.5 Hz, OCH_3), 3.71 (*E*), (s, OCH_3), 3.68 (*Z*), (s, OCH_3). ^{13}C NMR (D_2O): δ (ppm) 52.4 (d, $^2J_{CP}$ = 5.4 Hz, OCH_3), 52.7 (s, OCH_3), 150.0 (d, $^1J_{CP}$ = 193 Hz, P-C=N), 164.4 (d, $^2J_{CP}$ = 20 Hz, C=O). ^{31}P NMR (D_2O): δ (ppm) 2.14 (*E*), - 0.75 (*Z*).

Bis-DCHA$^+$ Salt (*E*-**9**) of *(E)-(Hydroxyimino)(hydroxymethoxyphosphinyl)acetic Acid E-3*. A solution of NaOH (100 mg, 2.5 mmole) in H_2O (25 mL) was added to a solution of **7** (273 mg, 1.25 mmole) in H_2O (2 mL) at 5 °C. After 24 h without cooling, the solvent was removed in vacuo. The residue was dissolved in 0.5 mL H_2O and 1 mL MeOH and the acid *E*-**3** was generated by filtration through Dowex 50WX8 (H^+ form). The filtrate was immediately treated with DCHA (3 eq.) in MeOH (5 mL). The mixture was evaporated in

vacuo and the residue recrystallized from *n*-propanol/acetone, giving 350 mg (51.3%) of *E*-**9** as white crystals: mp 141-142 °C. ^{1}H NMR (D_2O): δ (ppm) 1.0–2.1 (m, 40 H, CH_2), 3.19 (m, 4 H, CH), 3.54 (d, 3 H, OCH_3, $^3J_{HP}$ = 11 Hz). ^{13}C NMR (D_2O): δ (ppm) 23.8, 24.4, 28.9, 53.0 (cyclohexyl), 52.4 (d, OCH_3, $^2J_{CP}$ = 5.4 Hz), 156.4 (d, $^1J_{CP}$ = 185 Hz, P-C=N), 168.8 (d, $^2J_{CP}$ = 18 Hz, C=O). ^{31}P NMR (D_2O): δ (ppm) 4.2. Calcd for $C_{27}H_{52}N_3O_6P$: C, 59.43; H, 9.60; N, 7.70. Found: C, 59.17; H, 9.74; N, 7.65. Generation of the acid form, as described above but in MeOH provided it (major product) as a 1 : 1 mixture of *E* : *Z* isomers. ^{31}P NMR (D_2O): δ (ppm) 2.4 (*E*), -0.2 (*Z*). ^{13}C NMR ($CDCl_3$, C_2D_6O): δ (ppm) 146.8 (d, $^1J_{CP}$ = 212 Hz, P-C=N) (*E*), 144.4 (d, $^1J_{CP}$ = 157 Hz, P-C=N) (*Z*).

pH Dependence of the Stability of E-3. These experiments were carried out in 5 mm glass NMR tubes at 25 °C, concentration of *E*-**3** [prepared from *E*-**9** by treatment with Dowex 50X8 (H^+ form)] 0.1% in D_2O (w/v).

Stability of E-3 When Heated in Different Solvents. A solution of 40 mg *E*-**9** in 5 ml of solvent (AN, EtOH or EtOH-*t*-BuOH) was heated to reflux and reaction was monitored by ^{31}P NMR.

ACKNOWLEDGMENT

We thank the National Institutes of Health (Grant AI-25697) for financial support.

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(*Received in USA* 25 *August* 1995; *revised* 26 *October* 1995; *accepted* 28 *October* 1995)