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Ozonization and reduction of α-methylene *N*-(ethoxycarbonyl)-β-amino phosphonic esters

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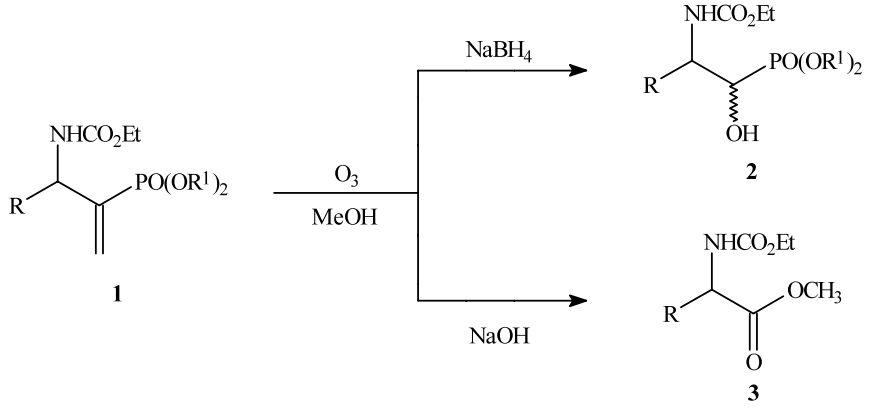
Abstract—*N*-(Ethoxycarbonyl)-β-amino-α-methylene phosphonic esters give *N*-(ethoxycarbonyl)-β-amino-α-hydroxy phosphonic esters by ozonization and subsequent reduction with a large excess of $NaBH_4$. If there is a small excess of $NaBH_4$ or if the intermediate is treated with methanolic NaOH–CH_2Cl_2 an anomalous ozonolysis occurs, affording *N*-(ethoxycarbonyl)-α-amino methyl carboxylic esters due to the cleavage of both the C=C double bond and the adjacent C–P single bond.

β-Amino-α-hydroxy phosphonic acid derivatives have achieved a growing interest due to their potent and selective activities in many biological fields.[1] They are also versatile substrates for the synthesis of a variety of organophosphorus compounds[2,3] and short peptide derivatives. A number of protease inhibitors, like phosphonamides and amino phosphonic ester derivatives, act as transition state mimics of peptide hydrolysis not only in medicinal field[1] but also in the agricultural one.[4] Therefore several routes to their synthesis have been reported.[5]

Our approach in order to obtain β-amino-α-hydroxy phosphonic esters is based on the ozonolysis and subsequent reduction of α-methylene *N*-(ethoxycarbonyl)-β-amino phosphonic esters **1**, prepared in turn by the amination of (1-trimethylsilanylmethyl-vinyl)-phosphonic esters, as reported in a previous study.[6]



Scheme 1. Ozonization of **1** and subsequent cleavages.

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In this communication we describe the results of the ozonolysis of compounds **1a–f** followed by cleavage with $NaBH_4$ or NaOH using various experimental conditions (Scheme 1 and Table 1). Substrates **1d** and **1e** were prepared by the described amination procedure[6] in a 1:1 mixture of *syn* and *anti* diastereomers.

When the α-methylene β-amino phosphonic esters **1a–e** were added to a saturated solution of ozone in MeOH at −78°C and the resulting ozonides were reduced by a large excess of $NaBH_4$ (molar ratio: 10/1) we obtained a quantitative conversion of substrates into the corresponding β-amino α-hydroxy phosphonic esters **2a–e**.[7] Because of the insolubility of compound **1f** in MeOH the reaction was performed in a solution of CH_2Cl_2/MeOH (1:1). In this case, after the usual workup, the expected product **2f** was present only in traces in the crude mixture, while the main product was the *N*-(ethoxycarbonyl)-α-amino methyl carboxylate **3f**.

In the presence of a small excess of $NaBH_4$ (molar ratio: 2.5/1) with compounds **1a–e**, we have always observed the formation of both α-hydroxy derivatives **2a–e** and *N*-(ethoxycarbonyl)-α-amino methyl carboxylic esters **3a–c**.

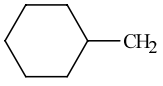
This anomalous ozonolysis of α-methylene *N*-(ethoxycarbonyl)-β-amino phosphonic esters involves the cleavage of the single bond C–P, with the loss of $PO(OR^1)_2$.[8] To the best of our knowledge this is the first example of this kind of ozonolysis of α,β-unsaturated phosphonic esters.

These results are in agreement with the reaction pathway suggested by Marshall and Garofalo regarding the ozonolysis[9] of certain allylic amine derivatives in methanolic NaOH–CH_2Cl_2 at −78°C, in which both the double bond and an adjacent single bond are cleaved with formation of protected α-amino methyl esters.

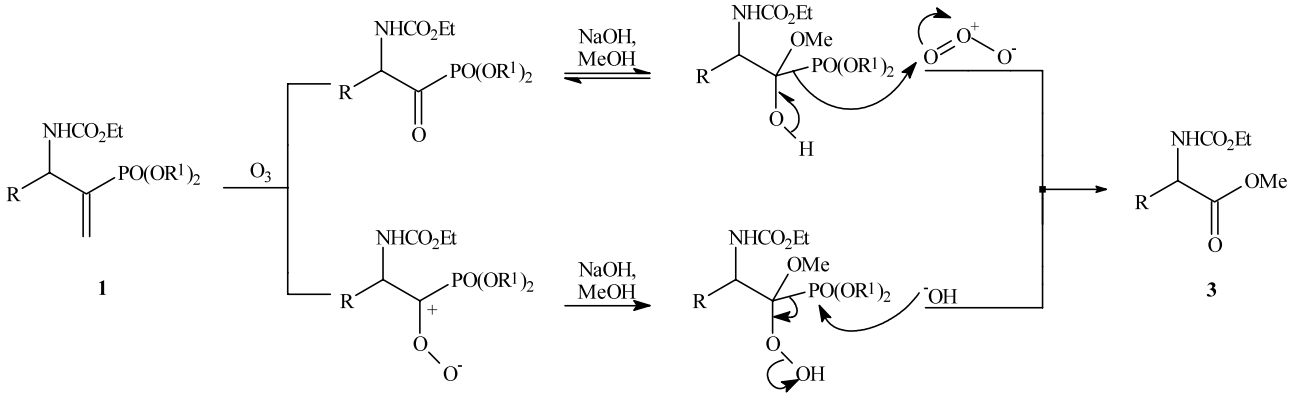
In order to confirm this hypothesis, we carried out the ozonolysis of the substrates **1a–d** in methanolic NaOH–CH_2Cl_2 and the only isolated products were the *N*-(ethoxycarbonyl)-α-amino methyl carboxylic esters **3a–c** (Scheme 2).

Higher yields of **3a–c** were obtained adding the NaOH methanolic solution (2.5 M) only after the saturation of the reaction mixture by ozone (yields reported in Table 1).

Table 1. Ozonization of **1** and subsequent cleavages: conditions and yields

Entry	R	R^1	Solvent	Conditions	Products **2**[7] yield (%)	Products **3**[10] yield (%)
a	H	C_2H_5	CH_3OH	$NaBH_4$	96	–
				NaOH	–	55
b	CH_3	C_2H_5	CH_3OH	$NaBH_4$	91	–
				NaOH	–	64
c	C_4H_9	C_2H_5	CH_3OH	$NaBH_4$	98	–
				NaOH	–	73
d	CH_3	(*S*)-$CH(CH_3)C_2H_5$	CH_3OH	$NaBH_4$	98	–
				NaOH	–	57[a]
e	C_4H_9	(*S*)-$CH(CH_3)C_2H_5$	CH_3OH	$NaBH_4$	93	–
f		C_2H_5	CH_3OH/CH_2Cl_2 (1:1)	$NaBH_4$	Traces	44

[a] **1d** gives the methyl ester **3b**.



Scheme 2. Suggested reaction pathways for ozonolysis of **1** in methanolic NaOH–CH_2Cl_2.

The structures of the *N*-(ethoxycarbonyl)-α-amino methyl carboxylic esters **3a**–**c** and **3f** were confirmed by comparison with samples prepared from the corresponding commercial α-amino acids. These were previously protected as *N*-(ethoxycarbonyl)amino acids, then esterified with CH_2N_2.[11]

In conclusion, it is possible to obtain the interesting α-hydroxy β-amino phosphonic acid derivatives by the ozonization and $NaBH_4$ reduction of α-methylene *N*-(ethoxycarbonyl)-β-amino phosphonic esters, in turn obtained from simple α,β-unsaturated phosphonic esters.[6] In the presence of inadequate quantities of $NaBH_4$ or in the presence of NaOH an anomalous ozonolysis occurs with formation of *N*-(ethoxycarbonyl)-α-amino methyl carboxylic esters.

This last procedure can be used to confirm the configuration of new chiral α-methylene β-amino phosphonic esters by transformation into known α-amino carboxylic methyl esters.

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References

1. (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett*. **1990**, *31*, 5587–5590; (b) Stowasser, B.; Budt, M.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett*. **1992**, *33*, 6625–6628; (c) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1779–1782; (d) Wester, R. T.; Chambers, R. J.; Green, M. D.; Murphy, W. R. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2005–2010.
2. Hirschmann, R.; Smith, A. B., II; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234–237.
3. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 2931–2932.
4. Hamada, Y.; Shiori, T. *Tetrahedron Lett*. **1982**, *23*, 235–236.
5. (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, O. A.; Lynn Rogers, W.; Smith, S. A.; De Forrest, J. M.; Oehl, R. S.; Petrillo, E. W., Jr. *J. Med. Chem*. **1995**, *38*, 4557–4569; (b) Zygmunt, J.; Gancarz, R.; Lejeczak, B.; Wieczorek, P.; Kafarski, P. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 2989–2992 and references cited therein.
6. Loreto, M. A.; Pompili, C.; Tardella, P. A. *Tetrahedron* **2001**, *57*, 4423–4427.
7. *Experimental procedure*. The *N*-(ethoxycarbonyl)-β-amino phosphonic esters **1** (0.4 mmol) in 2.0 mL of anhydrous CH_2Cl_2 was added to a saturated solution of ozone in 3.5 mL of anhydrous MeOH at −78°C. More ozone was added until the blue color persisted. Ozone bubbling was then terminated and the excess of ozone was displaced by passing a stream of oxygen through the solution. An excess of $NaBH_4$ (4.0 mmol) was added and the solution was stirred at −78°C for 2.5 h and additional 3 h at room temperature. The reaction was then quenched with 7.5 mL of saturated solution of NH_4Cl. After the work up the solvent was evaporated in vacuo giving the product **2**. Spectral data: **2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, 3H, CH_3CH$_2$OC), 1.31 (t, 6H, CH_3CH$_2$OP), 3.26–3.40 (dt, 1H, C*H*OH, J_{HP} = 14.3 Hz), 3.53–3.74 (m, 1H, C*H*HNH), 3.92–4.23 (m, 7H, CH$_3$CH_2OP, CH$_3$CH_2OC, CH*H*NH), 4.72 (br s, 1H, OH), 5.62 (br s, 1H, NH); ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$): 23.20; IR: 3456, 3302, 1722, 1241 cm^{-1}; **2b** (mixture *syn*/*anti*): ^{1}H NMR: 1.12–1.38 (m, 24H, CH_3CH, CH_3CH$_2$OC, CH_3CH$_3$OP), 3.61–3.93, 3.96–4.26 (2m, 16H, C*H*OH, C*H*NH, CH$_3$CH_2OC, CH$_3$CH_2OP), 4.65 (br s, 1H, OH), 5.06 (br s, 1H, OH), 5.40 (br d, 1H, NH), 5.83 (br d, 1H, NH); ^{31}P{^{1}H} NMR δ: 23.09; 22.80; IR: 3445, 3346, 1721, 1219 cm^{-1}; **2c** (mixture *syn*/*anti*): ^{1}H NMR: 0.75–0.94 (br t, 6H, CH$_3$chain); 1.09–1.44, 1.47–1.78 (2m, 30H, CH_3CH$_2$OP, CH_3CH$_2$OC, CH$_2$chain), 3.75–4.27 (m, 16H, CH$_3$CH_2OP, CH$_3$CH_2OC, C*H*OH, CH$_2$C*H*NH), 4.45 (br s, 1H, OH), 5.12 (br s, 1H, OH), 5.37 (br d, 1H NH), 5.81 (br d, 1H, NH); ^{31}P{^{1}H} NMR δ: 23.46; 23.11; IR: 3445, 3345, 1722, 1239 cm^{-1}; **2d** (mixture *syn*/*anti*): ^{1}H NMR δ: 0.85–0.95 (br t, 12H, CH_3CH$_2$CH), 1.14–1.34 (m, 24H, CH_3CH, CH_3CHNH, CH_3CH$_2$OC), 1.46–1.76 (m, 8H, CH_2CH), 3.67–3.86, 3.89–4.28, 4.35–4.88 (3m, 13H, OH, C*H*NH, C*H*OH, CH$_3$CH_2O, CHOP), 5.18 (br s, 1H, OH), 5.39 (br s, 1H, NH), 5.92 (br d, 1H, NH); ^{31}P{^{1}H} NMR δ: 21.38, 21.44. IR: 3446, 3339, 1721, 1216 cm^{-1}; **2e** (mixture *syn*/*anti*) ^{1}H NMR δ: 0.81–0.95 (m, 18H, CH_3CH$_2$CH, CH$_3$ chain), 1.15–1.33 (m, 26H, CH_3CH, CH_3CH$_2$OC, CH$_2$ chain), 1.43–1.84 (m 12H, CH_2CHOP, CH_2CHNH), 3.78–4.35, 4.37–4.67 (2m, 13H, C*H*OH, C*H*NH, CH$_2$OC, C*H*OP, OH), 5.12 (br s, 1H, OH), 5.28 (br d, 1H, NH), 5.83 (br d, 1H, NH); ^{31}P{^{1}H} NMR δ: 21.74, 21.86; IR: 3444, 3335, 1721, 1251 cm^{-1}.
8. The GC–MS of the reaction mixture shows one peak having a pattern of fragmentation like that reported for HPO(OEt)$_2$: Pritchard, J. G. *Org. Mass Spectrom*. **1970**, *3*, 163–169.
9. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem*. **1993**, *58*, 3675–3680.
10. *Experimental procedure*. The *N*-(ethoxycarbonyl)-β-amino phosphonic esters **1** (0.4 mmol) in 2.0 mL of anhydrous MeOH was added to a saturated solution of ozone in 3.5 mL of anhydrous MeOH at −78°C. More ozone was added until the blue characteristic color persisted. Then a solution of methanolic NaOH (2.5 M) was added and ozone was admitted again until a blue color was discernible. The reaction mixture was allowed to warm to room temperature, then diluted with ether and water. After the workup the solvent was evaporated in vacuo giving the product **3**. Spectral data: **3a**[12] ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, CH_3CH$_2$O), 3.75 (s, 3H, CH$_3$OC), 3.96 (br d, 2H, CH_2NH), 4.13 (q, 2H, CH$_3$CH_2O), 5.15 (br s, NH); **3b**[13] ^{1}H NMR δ 1.21 (t, 3H, CH_3CH$_2$O), 1.37 (d, 3H, CH_3CH), 3.72 (s, 3H, CH$_3$O), 4.09 (q, 2H, CH$_2$O), 4.32 (m, 1H, C*H*NH), 5.20 (br s,

1H, NH); **3c**[14] ^{1}H NMR δ: 0.83 (t, 3H, CH_3CH$_2$), 1.18 (t, 3H, CH_3CH$_2$O), 1.22–1.28 (m, 4H, 2 CH$_2$), 1.74 (m, 1H, CHCHNH), 3.67 (s, 3H, CH$_3$O), 4.05 (q, 2H, CH$_2$O), 4.27 (m, 1H, CHNH), 5.22 (br s, 1H, NH); **3f** ^{1}H NMR δ 0.76–1.05 (m, 2H, CH$_2$cyclohex.), 1.08–1.30 (m, 5H, CH_3CH$_2$, CH$_2$cyclohex.), 1.30–1.89 (m, 9H, CH_2CHNH, CHcyclohex., CH$_2$cyclohex.), 3.73 (s, 3H, CH$_3$O), 4.12 (q, 2H, CH$_2$O), 4.30–4.46 (m, 1H, CHNH).

11. Tofani, D. PhD Thesis, University of Rome 'La Sapienza', 1996.
12. Kanth, J. V. B.; Periasamy, M. *Synth. Commun.* **1995**, *25*, 1523–1530.
13. Graziano, M. L.; Scarpati, R. *J. Heterocycl. Chem.* **1976**, *13*, 205–210.
14. Effenberger, F.; Drauz, K.; Foerster, S.; Mueller, W. *Chem. Ber.* **1981**, *114*, 173–189.