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A Convenient Synthesis of 2-(Diethoxyphosphonyl)Glycine and its derivatives

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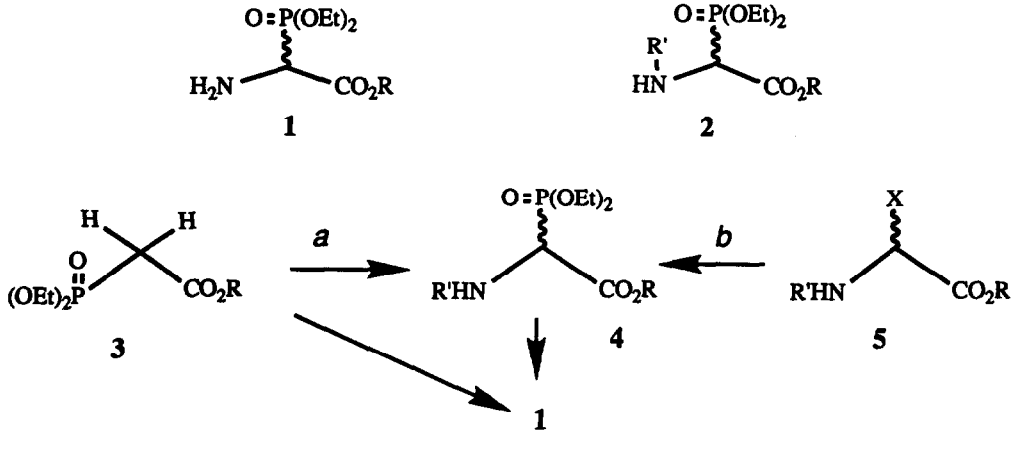
Abstract: A simple and very efficient method for the preparation of 2-(diethoxyphosphonyl)-glycine and its N-methyl analog *as the free acids* is described and their conversion to the corresponding t-butyl esters demonstrated.

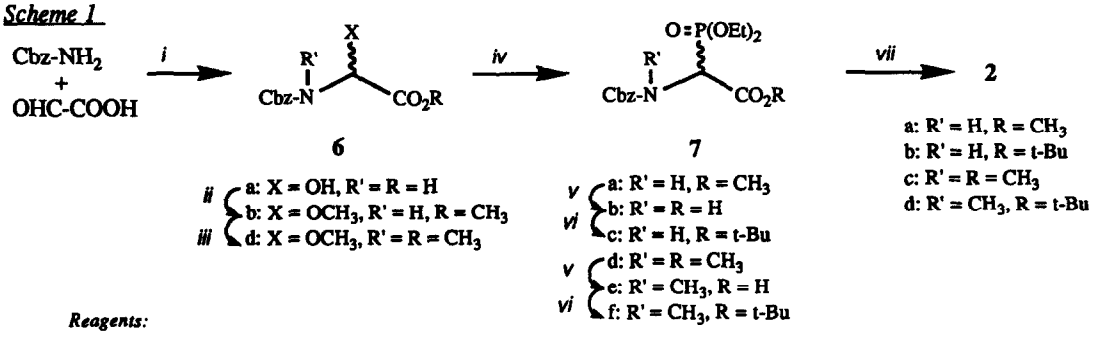
During the course of developing novel class of heterocycle-peptide conjugates and unique functionalized peptides as protease inhibitors[1], we required an efficient scheme for differential and selective protection of the carboxyl in 2-(diethoxyphosphonyl)glycine (**1**, R = Protecting group) and its N-alkyl derivatives (as **2**). Originally introduced by Ratcliffe and Christensen[2] as the critical building block in the synthesis of (±) cephalothin, derivatives of **1** have been extensively employed in the construction of a large variety of β-lactam derivatives[3-5], α-dehydro-α-amino acids and their oligopeptides[6] and also are the subject of numerous patents.[7]



The preparation of **1** has been accomplished by direct amination of 2-(diethoxyphosphonyl) acetates[8] (**3**, R = Me, Et or t-Bu; route a) or by Michaelis - Arbuzov reaction of N-protected α-halo glycine esters[9] (**5**, X = Cl, Br; R = Me or Et, route b). However, in both

methods, the choice of carboxyl protection is restricted to the starting esters employed (route a) or limited to the stability of the protecting group to the preparative procedure (route b). The t-butyl group offers the best differential and orthogonal protection of the carboxyl functionality in peptide synthesis but, the only reported method[10] for the preparation of such esters (**1**, R = t-Bu) is unsuitable on large scale due to the use of unstable and hazardous reagents coupled with low yields. The free acid **4** (R = H) should make the ideal starting material for the preparation of any desired ester of **1**. Although selective hydrolysis of the esters (as **4** prepared through either method) should furnish the free acid, no such preparations have been reported so far. Herein, we report a simple method for the preparation of **4** (R = H) and, for the first time, the N-methyl derivatives, **2** (R' = CH_3, R = H, CH_3 or t-Bu).

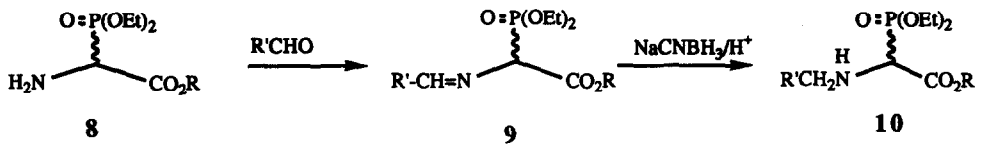
Scheme 1



Reagents:

i; ether, 16 h (95%); *ii:* MeOH/H_2SO_4, 48 h (98%); *iii:* MeI/NaH/DME/0→20°C, 16 h (98%); *iv:* $PCl_5/CHCl_3$/rt, 16 h; $P(OEt)_3$/70°C, 3 h (95%); *v:* 2M piperidine/rt, 6 h (100%); *vi:* *i*-butylene/H_2SO_4/CH_2Cl_2 (95%); *vii:* Pd/C/H_2 (42psi)/EtOH/HCl, 4 h (98%)

Scheme 2



N-Benzyloxycarbonyl-α-hydroxy glycine (**6a**) prepared from benzyl carbamate and glyoxylic acid was converted to methyl N-benzyloxycarbonyl-2-(diethoxyphosphonyl)glycinate (**7a**) by modification of the published procedure[11] in over 88% yield (*Scheme 1*). All attempts to selectively deprotect the carboxyl group in **7a** under a variety of basic and neutral conditions (LiOH/THF[12], K_2CO_3/MeOH[13], EtSH/$AlBr_3$, LiI/Py[14] etc.) resulted in inseparable reaction mixtures. Stronger acidic conditions also resulted in total decomposition of the ester. However, 2M piperidine in degassed water (5-7 eq.) effected quantitative hydrolysis of the methyl ester **7a**[15] in 6 h at room temperature. The free acid **7b**[16] was a stable solid with low solubility in most organic solvents at room temperature and could be converted to any desired carboxyl

derivative as demanded by the synthetic strategy employed. Thus, **7b** was converted to the t-butyl ester **7c**[16] in over 95% isolated yield.

N-Alkylation of base-sensitive amines is often accomplished through the reduction of the corresponding Schiff's bases[17] but, reduction of **9** (R' = Ph, R = CH_3) prepared from **8** (R = CH_3) and benzaldehyde (*Scheme 2*) gave an intractable mixture and was not investigated further. However, methyl N-benzyloxycarbonyl α-methoxy glycinate (**6b**) could be methylated directly with CH_3I/NaH[18] to furnish **6d** in quantitative yield. Under these conditions, **6a** decomposed to benzyl carbamate and other unidentified products while **7a** underwent further methylation on the α-carbon. The methyl ester **7d**[16] (prepared from **6d**) was saponified with 2M piperidine to **7e**[16] and further transformed to the t-butyl ester **7f**[16] (as before) in quantitative yield. Hydrogenolysis of the esters **7a, 7c, 7d** and **7f** gave the corresponding free amines **2a-d**[16] in quantitative yield. This simple yet very efficient preparation of the free acids **7b** and **7e** offers ready access to any desired carboxyl derivative of this important building block in the synthesis of β-lactams, novel heterocycles, α-dehydro-α-amino acids and their oligopeptides.

A coment on the NMR spectra: ^1H and ^{13}C spectra of the diethoxyphosphonates **7a-f** indicate that the two ethyl groups in the diethoxyphosphonyl moiety are non-equivalent, a fact further confirmed by molecular modelling studies. ^{31}P-^1H and ^{31}P-^{13}C spin-coupling further contributes to the complexity of the NMR spectra of these compounds. Additionally, the N-methyl derivatives **6d** and **7d -f** exist as 3:1 mixtures of torsional isomers.

References and Notes

1. To be reported elsewhere.
2. Ratcliffe, C. W.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 4645-4648
3. Ogasa, T.; Saito, H.; Hashimoto, Y.; Sato, K.; Hirata, T. *Chem. Pharm. Bull.* **1989**, *37*, 315-321
4. Hegedus, L. S.; Schultze, L. M.; Toro, J.; Yijun, C. *Tetrahedron* **1985**, *41*, 5833-5838
5. Hedewijn, P.; Claes, P. J.; Vanderhaeghe, H. *J. Med. Chem.* **1986**, *29*, 661-664
6. e.g.; a) Shin, C.G.; Takahashi, N; Yonezawa, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2020-2023; b) Schmidt, U.; Liberknecht, A.; Wild, J. *Synthesis* **1984**, 53-60
7. e.g.; a) Japan Patent JP 57200396 Dec 8, 1982; *Chem. Abstr. 99*, 38636u; b) Japan Patent JP 5801595 Jan 21, 1983; *Chem. Abstr. 99*, 38633r; c) Japan Patent JP 56034693 Apr 6, 1981; *Chem. Abstr. 95*, 169435t
8. Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, *23*, 3835-3836
9. Ku, B.; Oh, D. Y. *Tetrahedron Lett.* **1988**, *29* ,4465-4466
10. Shiraki, C.; Saito, H.; Takahashi, K.; Urakawa, C.; Hirata, T. *Synthesis* **1988**, 399-401
11. Schmidt, U.; Lieberknecht, A.; Schanbacher, U.; Beuttler, T. *Angew. Chem. Intl. Ed. Engl.* **1982**, *21*, 797-798
12. McNamara, J. M.; Leazer, J. L.; Bhupathy, M.; Amato, J. S.; Reamer, R. A.; Reider, P. J.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3718-3727

13. Yim, N. C. F.; Bryan, H.; Huffmann, W. F.; Moore, M. L. *J. Org. Chem.* **1988**, *53*, 4605-4607

14. Haslam, E. *Tetrahedron* **1980**, *36*, 2409-2433

15. Saponification of the corresponding ethyl ester was incomplete even after 48 h.

16. All the compounds were fully characterized (^1H and ^{13}C NMR, IR and MS). Data shown for selected products and only for the major isomer for compounds **7e-f**.
2b: ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 and 1.29 (each t, J = 7 Hz, 3H), 1.43 (s, 9H), 1.79 (bs, 2H), 3.75 (d, J = 19.8 Hz, 1H), 4.15 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.79, 27.21, 53.5 (d, J = 138 Hz), 62.29, 81.67 and 167.74: IR (film) 3400, 1735 and 1250 cm^{-1}; M^+ (m/z): 267.
2c: ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 and 1.28 (each t, J = 7 Hz, 6H), 2.28 (bs, 1H), 2.36 (s, 3H), 3.61 (d, J = 23 Hz, 1H), 3.75 (s, 3H) and 4.12 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.86, 35.68, 52.1, 61.9 (d, J = 147 Hz), 63.04 (d, J = 6 Hz) and 169.27; M+ (m/z): 239
2d: ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 and 1.31 (each t, J = 7 Hz, 3H), 1.47 (s, 9H), 1.97 (bs, 1H), 2.4 (s, 3H), 3.47 (d, J = 22 Hz, 1H) and 4.15 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.14, 27.67, 35.84, 62.66 (d, J = 147.5 Hz), 62.92 (d, J = 6 Hz), 82.23 and 168.0; IR (film) 3325, 1730 and 1255 cm^{-1}; M+ (m/z): 281
7b: ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 and 1.20 (each t , J = 6.8 Hz, 3H), 4.09 and 4.15 (each m, 2H), 4.94 (dd, J = 9.4, 22.9 Hz, 1H), 5.12 (ABd, J = 12.4 Hz, 2H), 6.13 (d, J = 9.4 Hz, 1H) and 7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9 and 15.93, 52.25 (d, J = 150 Hz), 64.14 and 64.38 (each d, J = 6.3Hz), 67.16, 127.80-128.22, 135.8, 155.6 and 167.54; ^1H NMR (500 MHz, CD_3COCD_3) δ 1.25 (m, 6H), 4.14 (m, 4H), 4.85 (dd, J = 9.4, 23.5 Hz, 1H), 5.11 (ABd, J = 12.4 Hz, 2H), 6.9 (d, J = 9.4 Hz, 1H), 7.36 (m, 5H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 16.54, 53.5 (d, J = 147 Hz), 64.18, 67.29, 128.69-129.16, 137.26, 156.67 and 168.29; IR (KBr disk) 1740, 1695 and 1240 cm^{-1}; M^+ (m/z): 345.
7c: m.p. 69° C (ether : hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 and 1.21 (each t, J = 6.8 Hz, 3H), 1.37 (s, 9H), 4.02 (m, 4H), 4.68 (dd, J = 9.16, 22.1 Hz, 1H), 5.01 (ABd, J = 12.2 Hz, 2H), 5.74 (d, J = 9.16 Hz, 1H) and 7.22 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 27.47, 53.39 (d, J = 146 Hz), 63.12 (d, J = 6.5 Hz), 66.9, 83, 127.83- 128.17, 135.79, 155.45 and165.4; IR (KBr disk) 3240, 1750, 1720, 1235 cm^{-1}; M^+ (m/z): 401.
7e: ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (m, 6H), 3.07 (s, 3H), 4.08 (m, 4H), 5.13 (ABd, J = 12.2 Hz, 2H), 5.54 (d, J = 25.9 Hz, 1H) and 7.3 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 20.6, 33.0, 57.0 (d, J = 145 Hz), 63.85 (d, J = 6.5 Hz), 67.8, 127-128.5, 135, 156.8 and 166.8; IR (film) 1740, 1705 and 1240 cm^{-1}; M+ (m/z): 359
7f: ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (m, 6H), 1.42 (s, 9H), 3.05 (s, 3H), 4.04 (m, 4H), 5.09 (ABd, J = 12.2 Hz, 2H), 5.36 (d, J = 25.9 Hz, 1H) and 7.25 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.02, 27.64, 32.7, 57.6 (d, J = 151 Hz), 62.53 (d, J = 6 Hz), 67.54, 83.15, 127.5-128.21, 136.1, 156.6 and 165.09.

17. a) Chaykovsky, M.; Modest, E. J.; Sengupta, S. *J. Heterocyclic Chem.* **1977**, *14*, 661-664; b) Zydowsky, M. T.; Dellaria, J. F.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607-5616

18. Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487-499

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