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A Practical Preparation of Ethyl *N*-Acyl-2-(dimethoxyphosphoryl)glycinate

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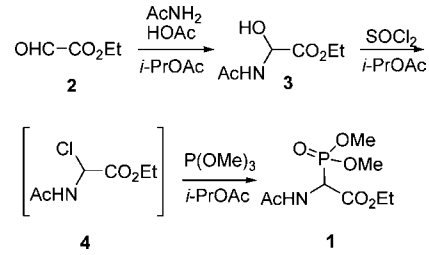
Abstract:

A practical, cost-effective preparation of ethyl *N*-acyl-2-(dimethoxyphosphoryl)glycinate has been developed. The two-step process achieved an 80% overall isolated yield.

Introduced by Ratcliffe and Christensen in 1973,[1] ethyl *N*-acyl-2-(dimethoxyphosphoryl)glycinate (**1**) as well as its derivatives are useful synthetic building blocks with wide applications in organic synthesis. For example, α,*β*-unsaturated α-amino acid derivatives, which are also common moieties of natural dehydropeptides, can be prepared easily via a Horner−Wadsworth−Emmons reaction by coupling **1** with an aldehyde or ketone.[2] Furthermore, subsequent asymmetric hydrogenation of α,*β*-unsaturated α-amine acid derivatives provides one of the most desirable ways to access natural and unnatural amino acids.[2,3] In addition, **1** and its derivatives have also been applied to prepare various important *β*-lactam antibiotics.[1,4]

Although analogues of **1** are commercially available, the use of these reagents in large-scale synthesis is limited due to cost.[5] Various methods have been developed to prepare **1** as well as its derivatives in the past decades.[1,6] Most of the reported methods either offered poor to moderate yield or were not atom-economically efficient. However, the approach[7] to install a phosphoryl group by applying a Michaelis−Arbuzov reaction on α-halo glycine esters is scientifically sound and attractive. After further study/modification of this strategy, we herein report a practical two-step process, which is suitable for large-scale preparation, to afford **1** in 80% overall isolated yield (Scheme 1).

Scheme 1. **Two-step preparation of 1**



Readily available ethyl glyoxalate (**2**) became our inexpensive starting material of choice.[8] Efficient condensation of the derivative of **2**, hemiacetal $MeOCH(OH)CO_2Me$, with acetamide has been reported.[9] However, attempts to follow the similar procedure to condense **2** with acetamide in refluxing toluene did not give satisfactory conversion and yield.[10] After several experiments, we found that introducing HOAc to the reaction solution improved the reaction rate as well as the conversion significantly. The HOAc charge could be varied from 0.05 to 2 equiv with 0.4−0.6 equiv being optimal (Table 1). In order to directly isolate the product **3** from the reaction mixture, a combination of *i*-PrOAc and heptane became solvents of choice. In practice, after aging the mixture of **2** (1.05 equiv, 50 wt % solution in toluene) and acetamide in the presence of 40 mol % of HOAc at 55−60 °C for about 1 h (∼30% conversion), the reaction solution was then seeded to relieve

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(1) (a) Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 4645. (b) Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 4649.

(2) For recent examples, see: (a) Okuma, K.; Ono, A. M.; Tsuchiya, S.; Oba, M.; Nishiyama, K.; Kainosho, M.; Terauchi, T. *Tetrahedron Lett.* **2009**, *50*, 1482. (b) Elaridi, J.; Patel, J.; Jackson, W. R.; Robinson, A. J. *J. Org. Chem.* **2006**, *71*, 7538. (c) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10488. (d) Aguado, G. P.; Moglioni, A. G.; Garcia-Exposito, E.; Branchadell, V.; Ortuno, R. M. *J. Org. Chem.* **2004**, *69*, 7971. (e) Aguado, G. P.; Moglioni, A. G.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2003**, *14*, 217. (f) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. (g) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. (h) Lorenz, J. C.; Busacca, C. A.; Feng, X.; Ginberg, N.; Haddad, N.; Johnson, J.; Kapadia, S.; Lee, H.; Saha, A.; Sarvestani, M.; Spinelli, E. M.; Varsolona, R.; Wei, X.; Zeng, X.; Senanayake, C. H. *J. Org. Chem.* **2010**, *75*, 1155.

(3) For recent reviews, see: (a) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267. (b) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (d) Brown, J. M. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol I, p 121.

(4) For recent examples, see: (a) Norris, T.; Nagakura, I.; Morita, H.; McLachlan, G.; Desneves, J. *Org. Process Res. Dev.* **2007**, *11*, 742. (b) Hakimelahi, G. H.; Moosavi-Movahedi, A. A.; Saboury, A. A.; Osetrov, V.; Khodarahmi, G. A.; Shia, K.-S. *Int. J. Sci. Res.* **2005**, *14*, 59. (c) Seki, M.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Perkin Trans. I* **1996**, *1*, 3. (d) Narukawa, Y.; Juneau, K. N.; Snustad, D.; Miller, D. B.; Hegedus, L. S. *J. Org. Chem.* **1992**, *57*, 5453, and references cited therein.

(5) For example, methyl 2-acetamido-2-(dimethoxyphosphoryl)acetate: ∼$3780/kg at 100 kg scale Digital Specialty Chemicals Ltd. (Canada); methyl *tert*-butoxycarbonylamino(dimethoxyphosphoryl)acetate: ∼$2370/kg at 500 kg scale from Sigma-Aldrich (USA).

(6) For lead references, see: (a) Mazurkiewicz, R.; Kuznik, A. *Tetrahedron Lett.* **2006**, *47*, 3439. (b) Mauldin, S. C.; Hornback, W. J.; Munroe, J. E. *J. Chem. Soc., Perkin Trans. I* **2001**, 1554. (c) Ferries, L.; Haigh, D.; Moody, C. J. *J. Chem. Soc., Perkin Trans. I* **1996**, 2885. (d) Shankar, R.; Scott, A. I. *Tetrahedron Lett.* **1993**, *34*, 231. (e) Narukawa, Y.; Juneau, K. N.; Snustad, D.; Miller, D. B.; Hegedus, L. S. *J. Org. Chem.* **1992**, *57*, 5453. (f) Daumas, M.; Vo-Quang, L.; Goffic, F. L. *Synth. Commun.* **1990**, *22*, 3395. (g) Shiraki, C.; Saito, H.; Takahashi, K.; Urakawa, C.; Hirata, T. *Synthesis* **1988**, 399. (h) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53, and references cited therein.

(7) For lead references and examples, see: refs 6d,e,g,h.

(8) Ethyl glyoxalate (∼50% in toluene): ∼$34/kg at 1000 kg scale from Clariant (France).

(9) Alks, V.; Sufrin, J. R. *Synth. Commun.* **1989**, *19*, 1479.

(10) Condensation of **2** with acetamide in acetone gave moderate yield. Schmitt, M.; Bourguignon, J.-J.; Barlin, G. B.; Davies, L. P. *Aust. J. Chem.* **1997**, *50*, 719.

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Table 1. **Preparation of 3: HOAc effect on conversion in *i*-PrOAc at 55 °C**

entry	HOAc (equiv)	ratio[12] of **3** vs **2**
1	0.0	4.5:1
2	0.05	24:1
3	0.25	23:1
4	0.4	40:1
5	0.5	71:1
6	0.6	39:1
7	1.0	23:1

supersaturation.[11] Once >95% conversion was achieved, the batch was then cooled to ambient temperature. Thus, without any aqueous workup, the desired product was isolated in 85% yield and >99% purity through simple filtration.

To convert **3** to its corresponding chloride **4**, the use of a combination of $SOCl_2$ and *i*-PrOAc[13] made the process practical and effective. Within 1 h at 30−35 °C, the chlorination was complete[12] (>99% conversion) in the presence of 1.1 equiv of $SOCl_2$. Without isolation of the intermediate **4**, most of the HCl formed during the reaction, as well as unreacted $SOCl_2$, was removed via distillation with *i*-PrOAc *in vacuo* before 1.05 equiv of $P(OMe)_3$ was added. The desired product **1** was obtained effectively via a Michaelis−Arbuzov reaction at 55 °C. Again, the use of a combination of *i*-PrOAc and heptane was chosen for direct isolation/crystallization of **1** from the crude reaction mixture without any aqueous workup. Through simple filtration, **1** was obtained in 94% isolated yield.

This two-step process could also be carried out in one-pot without isolating the aminal **3**.[14] However, the overall isolated yield was decreased by approximately 15%.

In summary, a practical preparation of ethyl *N*-acyl-2-(dimethoxyphosphoryl)glycinate (**1**) has been developed. The easily operated, two-step process afforded **1** in 80% overall isolated yield. Suitable for large-scale preparation, this process does not generate any aqueous waste.

Experimental Section

Acetylamino Hydroxy Acetic Acid Ethyl Ester (3). A slurry of $AcNH_2$ (55 g, 0.931 mol), ethyl glyoxalate (50 wt % in toluene, 200 g, 0.978 mol), and AcOH (21.3 mL, 0.372 mol) in *i*-PrOAc (770 mL) and heptane (440 mL) was heated to 55−60 °C for 1 h. The resulting homogeneous solution was seeded with <500 mg of the seeds and aged for additional 3 h at 55−60 °C to form a thick slurry. The slurry was cooled to ambient temperature and aged for 2 h before filtration. The white solid was filtered, and the wet cake was washed with 50% *i*-PrOAc in heptane (200 mL × 2). Drying by suction gave 127 g of the desired product as white solid; 85% yield.[15] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 7.8 Hz, 1 H), 5.60 (d, J = 7.8 Hz, 1 H), 4.81 (s, br, 1 H), 4.28 (q, J = 7.2 Hz, 2 H), 2.05 (s, 3 H), 1.32 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 169.8, 72.2, 62.7, 23.3, 14.2.

Ethyl *N*-Acyl-2-(dimethoxyphosphoryl)glycinate (1). To a slurry of **3** (100 g, 0.680 mol) in *i*-PrOAc (1.0 L) at ambient temperature was added $SOCl_2$ (54.4 mL, 0.748 mol) dropwise over 30 min. The reaction mixture was aged at 30−35 °C for 1 h, and the solution was concentrated *in vacuo* to about 500 mL. The solution was further distilled at constant volume (~500 mL) by feeding *i*-PrOAc (~600 mL). Then, the solution was diluted to ~1 L with *i*-PrOAc and warmed to 55 °C. $P(OMe)_3$ (84 mL, 0.714 mol) was added dropwise over 1 h. The resulting solution was aged at 55 °C for 3−4 h. The batch was then concentrated *in vacuo* to a volume of 450 mL while the internal temperature was kept between 30−40 °C to maintain a homogeneous solution. The solution was seeded with <500 mg of the seeds at 30 °C, and heptane (700 mL) was added dropwise at 25−30 °C over 2 h. Then, the slurry was aged at 0−5 °C for 2 h before filtration. The wet cake was washed with 20% *i*-PrOAc in heptane (250 mL × 2). Drying by suction gave 153 g of **1** as white solid; 94% yield, >99% purity. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, J = 9.0 Hz, 1 H), 5.20 (dd, J = 9.0, 22.3 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 3.80 (d, J = 10.6 Hz, 3 H), 3.78 (d, J = 10.6 Hz, 3 H), 2.04 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (d, J = 6.0 Hz), 166.8 (d, J = 2.4 Hz), 62.6, 54.2 (d, J = 6.8 Hz), 54.1 (d, J = 6.8 Hz), 50.3 (d, J = 147.6 Hz), 22.8, 14.1.

Supporting Information Available

^{1}H and ^{13}C NMR spectra of **1** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) It is recommended to seed the batch at 55−60 °C to relieve supersaturation and obtain a stirrable slurry during the reaction.

(12) Unless otherwise mentioned, the ratio and conversion were determined by high performance liquid chromatography (HPLC) analysis: Zorbax RX-C8 column, 4.6 mm × 250 mm, 5 μm particle size, 45 °C, mobile phase: aq H_3PO_4/MeCN; flow rate: 0.5 mL/min; detection: UV absorbance at 205 nm.

(13) Xu, F.; Simmons, B.; Reamer, R. A.; Corley, E.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2008**, *73*, 312.

(14) A quantity of 0.1 equiv of HOAc was used.

(15) The spectroscopic data (^{1}H and ^{13}C NMR) are identical with those reported.[4c,9]