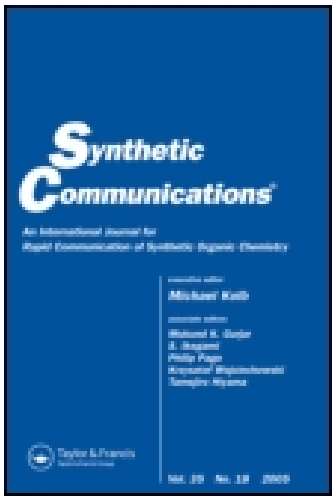


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis and Characterization of Some α,β-Didehydroamino Acid Derivatives

Guifa Su [a b] , Chengxue Pan [b] , Hengshan Wang [b] & Longmei Zeng [a]
[a] College of Chemistry & Chemical Engineering , Zhongshan University , Canton, P.R. China
[b] College of Chemistry & Chemical Engineering , Guangxi Normal University , 15 Yucai Rd., Guilin, 541004, P.R. China
Published online: 16 Aug 2006.

To cite this article: Guifa Su , Chengxue Pan , Hengshan Wang & Longmei Zeng (2004) Synthesis and Characterization of Some α,β-Didehydroamino Acid Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:4, 665-671, DOI: 10.1081/SCC-120027714

To link to this article: http://dx.doi.org/10.1081/SCC-120027714

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 4, pp. 665–671, 2004

Synthesis and Characterization of Some α,β-Didehydroamino Acid Derivatives

Guifa Su,[1,2,*] Chengxue Pan,[2] Hengshan Wang,[2] and Longmei Zeng[1]

[1]College of Chemistry & Chemical Engineering, Zhongshan University, Canton, P.R. China
[2]College of Chemistry & Chemical Engineering, Guangxi Normal University, Guilin, P.R. China

ABSTRACT

A mild Horner–Wadsworth–Emmons reaction is described. Treatment 4-substituted cyclohexanones with trimethyl 1-(*N*-benzyloxycarbonyl) phosphonoacetate afforded the corresponding α,β-didehydroamino acid derivatives.

Key Words: HWE olefination; Substituted cyclohexanones; Trimethyl 1-(*N*-benzyloxycarbonyl)phosphonoacetate; DBU; α,β-Didehydroamino acid.

*Correspondence: Guifa Su, College of Chemistry & Chemical Engineering, Guangxi Normal University, 15 Yucai Rd., Guilin 541004, P.R. China; Fax: 86-773-5833630; E-mail: su_gf@sina.com.

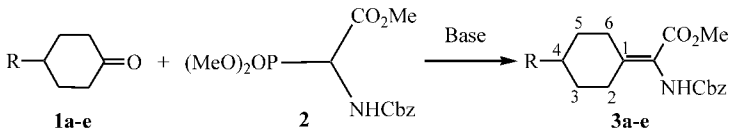
DOI: 10.1081/SCC-120027714 0039-7911 (Print); 1532-2432 (Online)

The introduction of an α,β-didehydroamino acid (DDAA) residue into a peptide sequence causes a significant limitation of possible side chain orientations and strongly induces folded conformations. α,β-Didehydroamino acid have been used as structural modifications in the design of model peptides with well-defined structures.[1–6]

A straightforward synthesis of DDAA derivatives is the Horner–Wadsworth–Emmons olefination of aldehydes with N-acyl-2-dialkoxyphosphorylglycine esters in aprotic solvents and in the presence of strong bases. The typical method is condensation in CH_2Cl_2 at $-70^{\circ}C$ with addition of potassium *tert*-butoxide, but ketones do not react.[7,8]

From 1984, some researchers used tertiary amine bases such as diisopropylethylamine (DIPEA),[9] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[9,10] tetramethylguanidine (TMG),[10] and triethylamine,[11] to generate the phosphinate carbanion, which then was treated with carbonyl compounds, typically aldehydes (1 : 1 ratio methyl ketones were unreactive under these conditions[11]). The mild reaction conditions permit the substrates that racemize easily or are base-sensitive to remain unaffected. Schmidt and coworkers used excess ketone as solvent, DBU as base and realized the condensation of 2-butanone, cyclohexanone and acetone with trimethyl 1-(*N*-alkoxycarbonyl)phosphonoacetate.[10]

Here we wish to report the Horner–Wadsworth–Emmons olefinations of several 4-substituted cyclohexanones **1** with trimethyl 1-(*N*-benzyloxycarbonyl)phosphono-acetate **2** in the presence of a tertiary amine such as DBU or TMG (Sch. 1 and Table 1). All α,β-didehydroamino acid derivatives **3** are new compounds.



1a-e **2** **3a-e**

Scheme 1. R = **a**: Me; **b**: Ph; **c**: ^{t}Bu; **d**: —$OCH_2CH_2CH_2O$—; **e**: EtOOC.

From Table 1 we could conclude:

1. Reactivity of 4-substituted cyclohexanone: **1e** –**1d** > **1a** > **1b** > **1c**, the reactivity is a function of the steric hindrances of the substituent.
2. The molar ratio between substituted cyclohexanone and trimethyl 1-(*N*-benzyloxy-carbonyl)phosphonoacetate affected the formation of DDAA. Excess ketone facilitates the olefination and increases the yield (Entry 1–2, 5–7).

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Table 1. Synthesis of **3a–3e**.

Entry	R	Base	**1**/**2**	Solvent	Temperature	Time (h)	Yield (%)
1	Me	DBU	1/1	CH_2Cl_2	r.t.	87	25
2	Me	DBU	1.4/1	CH_2Cl_2	r.t.	46	52
3	Me	DBU	1.4/1	THF	r.t.	46	50
4	Me	TMG	1.4/1	THF	r.t.	93	44
5	Me	DBU	2/1	CH_2Cl_2	r.t.	72	56
6	Me	DBU	3/1	CH_2Cl_2	r.t.	72	64
7	Me	DBU	4/1	CH_2Cl_2	r.t.	31	75
8	Me	DBU	4/1	CH_3CN	r.t.	71	67
9	Ph	DBU	4/1	CH_2Cl_2	r.t.	77	68
10	OCH_2CH_2O	DBU	4/1	CH_2Cl_2	r.t.	85	83
11	EtOOC	DBU	4/1	CH_2Cl_2	r.t.	85	86
12	^{t}Bu	DBU	4/1	CH_2Cl_2	r.t.	77	42
13	^{t}Bu	DBU	4/1	CH_2Cl_2	r.t.	134	60

3. DBU was a better base than TMG and CH_2Cl_2 was a better solvent than THF (Entry 2–4).

So, the optimal reaction conditions are: solvent CH_2Cl_2; base DBU; molar ratio **1**/**2** = 4/1; reaction temperature room temperature; reaction time about 3 days.

In conclusion, the presented mild olefination procedure provides a convenient alternative to traditional Horner–Wadsworth–Emmons techniques,[7,8] especially with base-sensitive substrates.

EXPERIMENTAL SECTION

General Considerations

All reactions with air- or moisture-sensitive reactions were carried out in oven- or flamed-dried glassware under a positive pressure of dry Ar. Liquid reagents and solvents were purified by distillation shortly before use according to literature. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F_{254} precoated, glass backed plates. The plates were visualized using ultraviolet light (254 nm), anisaldehyde solution or iodine as appropriate. Flash column chromatography was carried out using Merck 60

silica gel (70–240 μm). IR spectra were recorded in Mattson Genesis FT IR Spectrophotometer, NMR spectra were recorded in Bruker-ARX300 or Varian Unity-300 apparatus (^{13}C: 75 MHz). M.p. were determined in Gallenkamp apparatus (uncorrected).

Synthesis of 3: General Procedure

To a solution of trimethyl 1-(*N*-benzyloxycarbonyl)phosphonoacetate **2** (332 mg, 1 mmol) in the appropriate solvent was added base dropwise. 10 min later, the respective carbonyl compound **1** was added. The reaction times are listed in Table 1. The reaction solution was then diluted with AcOEt (20 mL), washed with 1N of H_2SO_4 (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (**3a**, **3b**: eluent: hexane/AcOEt = 7/1, then 6/1. **3c**: eluent: hexane/AcOEt = 4/1. **3d**: eluent: hexane/AcOEt = 3/1. **3e**: eluent: hexane/AcOEt = 4/1, then 2/1).

3a: White solid, M.p. 90–91°C, R_f 0.25 (hexane/ethyl acetate 4/1, v/v), IR (nujol, *v*, cm^{-1}): 3303 (N–H), 1717 (C═O), 1693 (amide), 1645 (C═C), 1516, 751, 698 (Ar). ^{1}H NMR ($CDCl_3$, δ, ppm): 7.4–7.2 (m, 5H, C_6H_5), 5.84 (s, 1H, N*H*), 5.14 (s, 2H, OCH_2), 3.70 (s, 3H, OCH_3), 3.39 (br d, *J* = 14.1 Hz, 1H, eqatorial 2- or 6-H), 2.68 (br d, *J* = 14.1 Hz, 1H, eqatorial 2- or 6-H), 2.2–1.7 (m, 4H, eqatorial 3,5-H and axial 2,6-H), 1.7–1.5 (m, 1H, 4-H), 1.2–1.1 (m, 2H, axial 3,5-H), 0.91 (d, *J* = 6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 165.55 (–CO_2Me), 155.02 (–NH–CO_2–), 151.33 (cyclohexyl *C*1), 136.51 (Cbz *C*1), 128.49, 128.49, 128.11, 128.07, 128.07 (phenyl, *C*2–C6), 118.72 (═*C*–CO_2Me), 67.19 (–OCH_2Ph), 51.57 (–OCH_3), 35.75, 35.35 (cyclohexyl *C*2, *C*6), 32.08 (cyclohexyl *C*4), 30.63, 29.72 (cyclohexyl *C*3, *C*5), 21.35 (CH_3). Anal. calcd. for $C_{18}H_{23}NO_4$ (317.38): C, 68.12; H, 7.30; N, 4.41. Found: C, 68.26; H, 7.21; N, 4.38.

3b: White solid, M.p. 145–148°C, R_f 0.18 (hexane/ethyl acetate 4/1, v/v), IR (nujol, *v*, cm^{-1}): 3321 (N–H), 1706 (C═O), 1634 (C═C), 1510, 746, 694 (Ar). ^{1}H NMR ($CDCl_3$, δ, ppm): 7.4–7.1 (m, 10H, 2 C_6H_5), 5.89 (s, 1H, N*H*), 5.14 (s, 2H, OCH_2), 3.71 (s, 3H, OCH_3), 3.7–3.5 (m, 1H, Ph–C*H*), 2.9–2.7 (m, 2H, eqatorial 2,6-H), 2.2–2.0 (m, 4H, eqatorial 3,5-H and axial 2,6-H), 1.7–1.5 (m, 2H, axial 3,5-H). ^{13}C NMR ($CDCl_3$, δ, ppm): 165.51 (–CO_2Me), 155.03 (–NH–CO_2–), 150.27 (cyclohexyl *C*1), 145.95 (–Ph, *C*1), 136.45 (Cbz, *C*1), 128.54, 128.54, 128.45, 128.45, 128.20, 128.13, 128.13, 126.82, 126.82, 126.24 (10C, C2-C6 in phenyl and Cbz), 119.17 (═C–CO_2Me), 67.32 (–OCH_2Ph), 51.71 (–OCH_3), 44.05 (Ph-*C*H, cyclohexyl *C*4), 34.81, 34.45 (cyclohexyl *C*2, *C*6), 31.20, 30.28 (cyclohexyl *C*3,

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

*C*5). Anal. calcd. for $C_{23}H_{25}NO_4$ (379.45): C, 72.80; H, 6.64; N, 3.69. Found: C, 72.89; H, 6.58; N, 3.63.

3c: White solid, M.p. 122–123°C, R_f 0.26 (hexane/ethyl acetate 4/1, v/v), IR (nujol, *v*, cm^{-1}): 3309 (N–H), 1725, 1710 (C═O), 1648 (C═C), 1515, 750, 700 (Ar). ^{1}H NMR ($CDCl_3$, δ, ppm): 7.4–7.3 (M, 5H, C_6H_5), 5.79 (s, 1H, N*H*), 5.13 (s, 2H, OCH_2), 3.69 (s, 3H, OCH_3), 3.50 (br d, $J = 13.5$ Hz, 1H, eqatorial 2- or 6-H), 2.75 (br d, $J = 13.5$ Hz, 1H, eqatorial 2- or 6-H), 2.0–1.8 (m, 4H, eqatorial 3,5-H and axial 2,6-H), 1.3–1.0 (m, 3H, ^{t}Bu-CH and axial 3,5-H), 0.84 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, δ, ppm): 165.57 ($-CO_2Me$), 155.04 ($-NH-CO_2-$), 150.93 (cyclohexyl *C*1), 136.47 (phenyl *C*1), 128.52, 128.52, 128.12, 128.08, 128.08 (5C, phenyl C2-C6), 118.90 ($=C-CO_2Me$), 67.23 ($-OCH_2Ph$), 51.65 ($-OCH_3$), 47.90 (cyclohexyl *C*4), 32.93, 31.81 (cyclohexyl *C*2, *C*6), 30.72 ($C(CH_3)_3$), 28.72, 28.39 (cyclohexyl *C*3, *C*5), 27.53 ($C(CH_3)_3$). Anal. calcd. for $C_{21}H_{29}NO_4$ (359.46): C, 70.17; H, 8.13; N, 3.90. Found: C, 70.02; H, 8.19; N, 3.93.

3d: Orange solid, M.p. 88–90°C, R_f 0.25 (hexane/ethyl acetate 2/1, v/v), IR (nujol, *v*, cm^{-1}): 3336 (N–H), 1720 (C═O), 1692 (amide), 1502, 756, 700 (Ar). ^{1}H NMR ($CDCl_3$, δ, ppm): 7.34 (s, 5H, C_6H_5), 5.88 (s, 1H, N*H*), 5.14 (s, 2H, OCH_2Ph), 3.96 (s, 4H, OCH_2CH_2O), 3.70 (s, 3H, OCH_3), 2.9 (m, 2H, eqatorial 2,6-H), 2.5 (m, 2H, eqatorial 3,5-H), 1.8 (m, 4H, axial 2,6-H and axial 3,5-H). ^{13}C NMR ($CDCl_3$, δ, ppm): 165.32 ($-CO_2Me$), 154.93 ($-NH-CO_2-$), 148.78 (cyclohexyl C1), 136.43 (phenyl *C*1), 128.53, 128.53, 128.19, 128.12, 128.12 (phenyl 5C, *C*2-*C*6), 119.62 ($=C-CO_2Me$), 108.08 (cyclohexyl *C*4), 67.31 ($-OCH_2Ph$), 64.45, 64.45 ($-OCH_2CH_2O$), 51.72 ($-OCH_3$), 35.10, 34.75 (cyclohexyl *C*2, *C*6), 28.16, 26.99 (cyclohexyl *C*3, *C*5). Anal. calcd. for $C_{19}H_{23}NO_6$ (361.39): C, 63.15; H, 6.41; N, 3.88. Found: C, 63.04; H, 6.48; N, 3.91.

3e: Pale yellow solid, M.p. 77–79°C, R_f 0.16 (hexane/ethyl acetate 4/1, v/v), IR (nujol, *v*, cm^{-1}): 3291 (N–H), 1725 (C═O), 1693 (amide), 1511, 743, 693 (Ar). ^{1}H NMR ($CDCl_3$, δ, ppm): 7.4–7.2 (m, 5H, C_6H_5), 5.84 (s, 1H, N*H*), 5.12 (s, 2H, OCH_2Ph), 4.12 (q, 2H, $J = 7.2$ Hz, OCH_2Me), 3.67 (s, 3H, OCH_3), 3.4–3.2 (m, 1H, eqatorial 2- or 6-H), 2.7–2.2 (m, 3H, eqatorial 2- or 6-H, eqatorial 3,5-H), 2.1–1.9 (m, 3H, axial 2,6-H and EtO_2C-CH), 1.8–1.6 (m, 2H, axial 3,5-H), 1.23 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 174.65 ($-CO_2Et$), 165.31 ($-CO_2Me$), 154.92 ($-NHCO_2-$), 149.36 (cyclohexyl *C*1), 136.40 (phenyl *C*1), 128.52, 128.52, 128.18, 128.10, 128.10 (phenyl 5C, *C*2-*C*6), 119.51 ($=C-CO_2Me$), 67.30 ($-OCH_2Ph$), 60.29 ($-CO_2CH_2Me$), 51.70 ($-OCH_3$), 42.10 (cyclohexyl C4), 29.50, 29.33 (cyclohexyl *C*2, *C*6), 28.85, 28.59 (cyclohexyl *C*3, *C*5), 14.18 (CH_3CH_2O-). Anal. calcd. for $C_{20}H_{25}NO_6$ (375.42): C, 63.99; H, 6.71; N, 3.73. Found: C, 64.07; H, 6.65; N, 3.77.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

ACKNOWLEDGMENTS

Financial support from the Foundation of Educational Bureau of the Guangxi Zhuang Autonomous Region, People's Republic of China and the International Cooperation Agency of Spain are gratefully acknowledged.

REFERENCES

1. Pietrzynski, J.; Rzeszotarska, B.; Ciszak, E.; Lisowski, M.; Kibica, Z.; Boussard, G. Conformational investigation of α,β-dehydropeptides. 7. Conformation of Ac-Pro-δAla-$NHCH_3$ and Ac-Pro-(*E*)-δ Abu-$NHCH_3$: comparison with (*Z*)-substituted α,β-dehydropeptides. Int. J. Petide Protein Res. **1996**, *48* (4), 347–356.
2. Broda, M.A.; Rzeszotarska, B.; Smelka, L.; Rospenk, M. Conformational investigation of α β-dehydropeptides. 8. *N*-acetyl-α,β-dehydroamino acid N′ methylamides: conformation and electron density perturbation from infrared and theoretical studies. J. Peptide Res. **1997**, *50* (5), 342–351.
3. Jain, R.; Chauhan, V.S. Conformational characteristics of peptides containing α,β-dehydroamino acid residues. Biopolymers **1996**, *40* (1), 105–119.
4. Aleman, C. Effect of the environment and role of the $\pi-\pi$ stacking interactions in the stabilization of the 3(10)-helix conformation in dehydroalanine oligopeptides. Int. J. Peptide Protein Res. **1995**, *46* (5), 408–418.
5. Dey, S.; Mitra, S.N.; Singh, T.P. Design of peptides using α,β-dehydro-residues: synthesis, crystal structure and molecular conformation of *Boc-L*-Val-δ Phe-δ Phe-*L*-Val-OCH_3. Biopolymers **1996**, *39* (6), 849–857.
6. Inai, Y.; Kurashima, S.; Okdo, Y.; Hirabayashi, T.; Yokota, K. Conformational preference in β-aryldehydroalanine. Synthesis and conformational study of tripeptides containing β-aryldehydroalanine residues. Bull. Chem. Soc. Jpn. **1996**, *69* (6), 1687–1694.
7. Schmidt, U.; Lieberknecht, A.; Schanbacher, U.; Beuttler, T.; Wild, J. Amino acids and peptides. 36. Dehydroamino acids. 16. Facile preparation of *N*-acyl-2-(diethoxyphosphoryl)glycine esters and their use in the synthesis of dehydroamino acids-esters. Angew. Chem. Int. Ed. Engl. **1982**, *21* (10), 770–777.
8. Schmidt, U.; Lieberknecht, A.; Wild, J. Amino acids and peptides; XLIII. Dehydroamino acids; XVIII. Synthesis of dehydroamino acids and amino acids from *N*-acyl-2-(dialkyloxyphosphinyl) glycine esters. Synthesis **1984** (1), 53–60.

9. Blanchette, M.A.; Choy, W.; Davis, J.T.; Essenfeld, A.P.; Masamune, S.; Roush, W.P.; Sakai, T. Horner-Wadsworth-Emmons reaction: use of lithium chloride and an amine for base sensitive compounds. Tetrahedron Lett. **1984**, *25* (21), 2183–2186.
10. Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. Amino acids and peptides. 81. Diastereoselective formation of (*Z*)-didehydroamino acid esters. Synthesis **1992** (5), 487–490.
11. Rathke, M.W.; Nowak, M. Horner-Wadsworth-Emmons modification of the Wittig reaction using triethylamine and lithium or magnesium salts. J. Org. Chem. **1985**, *50* (15), 2624–2626.

Received in the USA August 14, 2003

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016