Tetrahedron Letters,Vol.31,No.2,pp 157-160,1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

PREPARATION AND WITTIG REACTIONS OF AN α-KETO AMINO ACID DERIVATIVE[1]

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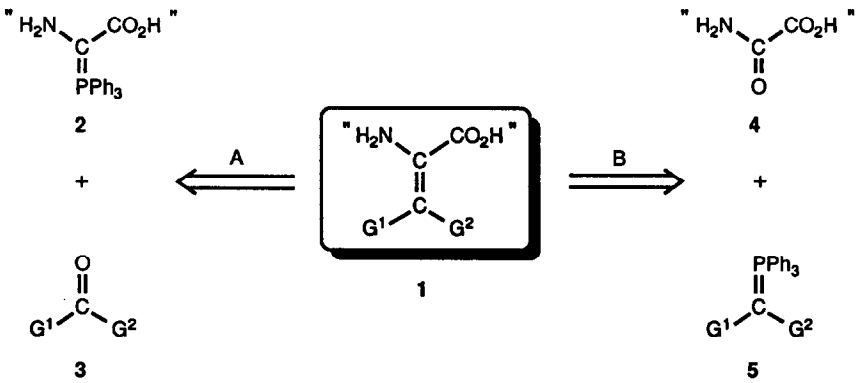
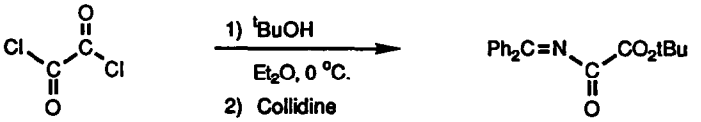
Dehydroamino acid derivatives **1** are an important class of compounds that include natural products, biosynthetic intermediates, substructural units in dehydro peptides and starting materials for the synthesis of α-amino acids.[2] Construction of the α,β carbon-carbon bond in these compounds by the Wittig olefination reaction[3] can provide versatile and complementary routes to derivatives of **1**. Thus, disconnection A yields the amino acid containing Wittig-type reagent **2** which can be reacted with aldehydes or ketones.[4] Disconnection B



involves a cationic amino acid derivative[5] in the form of a protected α-keto amino acid **4**, which could react with Wittig-type reagents **5**.[6] In addition to providing a route to normal carbon and hydrogen β-substituted alkene derivatives **1**, the latter approach could, in principal, lead to derivatives containing β-heteroatom substituents such as alkoxy or halogen which are not accessible by route A. Such compounds (**1**, G^1 or G^2 = OR or X) could themselves serve as useful starting substrates for further elaboration of the dehydroamino acid unit. We report here the preparation and Wittig olefination reactions of a stable α-keto amino acid synthon, compound **7**.

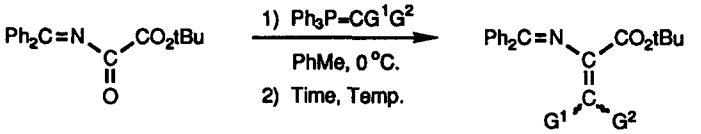
α-Keto derivative **7** is readily prepared in excellent yield in a one-pot, two step procedure from oxalyl chloride. Construction of the C_α-N bond is accomplished by reaction of the mixed ester-acid chloride (t-butyl

oxalyl chloride) with benzophenone imine in the presence of collidine.[7] Compound 7 is stable for several weeks at 0 °C although it decomposes by decarbonylation at room temperature.[8,9]



6 7 (89%)

Reaction of α-keto derivative **7** with Wittig reagents yields the desired dehydroamino acid derivatives protected as their benzophenone imine t-butyl esters (see Table).[10] Best results were obtained when the Wittig reagent was generated from the corresponding phosphonium halide in toluene by treatment with potassium hexamethyldisilazide (KHMDS).[11] It is possible to prepared dehydroamino acid derivatives **8a** - **8c** from



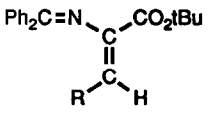
7 **8**

Table: Reaction of **7** with Wittig Reagents to Yield Dehydroamino Acid Derivatives **8**.

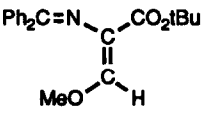
	Wittig Reagent[a]		Conditions[b]		Product **8**[c]		
Entry	G^1	G^2	Time (h)	Temp (°C.)	Yield (%)	Ratio[d]	$(^3J_{CH})^f$
a	Et	H	0.5	25	88	85:15	4.95; -
b	Ph	H	2.5	25	78	88:12	5.50; 11.00
c	CO_2Et	H	18	110	79	100:0	5.27; -
d	H	H	0.5	25	25	-	-
e	Me	Me	2	70	68	-	-
f	Me	Et	5	70	36	50:50[e]	-
g	MeO	H	0.5	25	90	60:40	2.09; 8.70
h	Cl	H	2.5	25	85	85:15	2.98; 9.49
i	Br	H	2.5	25	80	95:5	3.19; -

[a] Wittig reagents were generated by treatment of the corresponding triphenylphosphonium salt in toluene at room temperature with KHMDS for 30 minutes. See footnote 10 for general procedure. [b] Conditions for reaction of the phosphorane with compound **7**. [c]Starting substrate **7** and all products **8** gave satisfactory elemental or high resolution mass spectral analyses as well as NMR spectra consistent with the assigned structures. [d] Ratio of double bond diastereomers as determined by integration of vinyl proton in ^1H NMR. [e] Ratio determined by integration of vinyl methyl groups. [f] $^3J_{CH}$ major product; minor product. See text for discussion of double bond geometry.

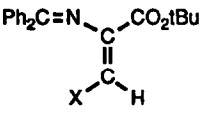
nonstabilized, semistabilized and stabilized phosphonium ylides (Table entries a, b and c, respectively) as well as β-unsubstituted (entry d)[12] and β,β-disubstituted (entries e and f) compounds **8**. Interestingly the β-heteroatom substituted vinyl ether **8g** and vinyl halides **8h** and **8i** are readily prepared from the appropriate phosphonium salt.



8a - 8c
(R = Et, Ph or CO_2Et)

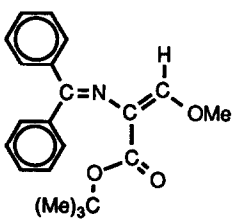


8g

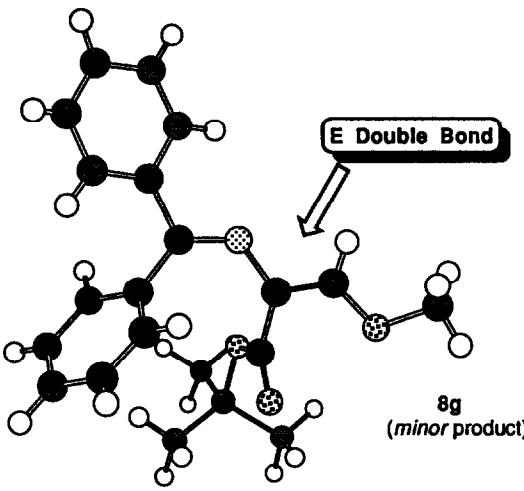


8h, 8i
(X = Cl, Br)

The configuration of the double bond in dehydroamino acid derivatives has been the subject of numerous studies.[13] The major products in this study (**8**) have been assigned the Z-configuration, as depicted above, based on the small (2.09 - 5.50 Hz) vicinal carbon-proton coupling constants ($^3J_{CH}$) of the major diastereomers compared with the larger (8.70 - 11.00 Hz) values of $^3J_{CH}$ for the minor diastereomers (see Table). These values are in agreement with the known relationship of the couplings of carbon atoms with alkene protons ($^3J_{trans} > {}^3J_{cis}$).[14]



8g
(*minor* product)



8g
(*minor* product)

Further support for these stereochemical assignments is provided by the crystal structure of the *minor* E-diastereomer **8g** (see above).[15] Research to determine the further scope of reactions of keto derivative **7** as well as dehydroamino acid derivatives **8** is in progress.

Acknowledgement. We gratefully acknowledge the National Institutes of Health (GM28193) and Eli Lilly and Company for support of this research. We thank Dr. J.E. Munroe for helpful discussions.

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3. For a recent excellent review on the Wittig olefination reaction, see: B.E. Maryanoff and A.B. Reitz, *Chem. Rev.*, **1989**, 89, 863.
4. (a) U. Schmidt, A. Lieberknecht, U. Schanbacher, T. Beuttler and J. Wild, *Angew. Chem., Int. Ed. Engl.*, **1982**, 21, 776; (b) R. Kober and W. Steglich, *Liebigs Ann.*, **1983**, 599.

5. For lead references on α-cationic amino acid equivalents, see: M.J. O'Donnell and W.D. Bennett, *Tetrahedron*, **1988**, 44, 5389.
6. (a) The first report of the Wittig olefination of an α-keto amino acid derivative appeared after this work was in progress; see: J.P. Bazureau and M. Le Corre, *Tetrahedron Lett.*, **1988**, 29, 1919. (b) More recently, compound **7** has been prepared and reacted with phosphoranes to prepare derivatives such as **8a - 8c**, see: J.P. Bazureau, D. Person and M. Le Corre, *Tetrahedron Lett.*, **1989**, 30, 3065.
7. Experimental Procedure for the preparation of **7**: freshly opened oxalyl chloride (2.0 g, 15.8.mmol) cooled to 0 °C. was added under nitrogen to an ice bath-cooled 100 mL round bottom flask equipped with a magnetic stirring bar containing anhydrous ether (30 mL). *t*-Butanol (1.17 g, 15.8 mmol) was added by pipette to the above solution and the resulting mixture was stirred for one hour. Collidine (4.6 mL, 4.2 g, 34.6 mmol) was then added dropwise with vigorous stirring (precipitate formed). Diphenylketimine (2.85 g, 15.8 mmol) was then added (more precipitate formed) and the resulting mixture was stirred at 0 °C. for ten minutes. The reaction mixture was poured into a separatory funnel containing ether (100 mL) and water (150 mL), the mixture was shaken, the layers were separated and the ethereal layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 4.35 g of a pale yellow solid **7** (89%) which was used without further purification (mp 71-72.5 °C.; hexane/tBuOMe, 60/40). Compound **7** can be stored under nitrogen at 0 °C. for several weeks without decomposition.
8. Attempts to prepare and use the ethyl ester derivative of **7** were not successful. This product readily decarbonylates to $Ph_2C{=}NCO_2Et$.[9]
9. Similar decarbonylations of α-keto esters are known, see: P.A. Levene and G.M. Meyer, *Organic Syntheses*, Coll. Vol. II, **1943**, 288.
10. General Experimental Procedure for the preparation of **8**: propyltriphenylphosphonium bromide (1.25 g, 3.23 mmol, previously dried in a vacuum oven overnight, 5 mm Hg at 50 °C.) and toluene (4 mL, stored over 4 Å molecular sieves) were added under nitrogen to a flame-dried 50 mL round bottom flask. Potassium hexamethyldisilazide (0.5 M in toluene, 6.5 mL, 3.23 mmol) was added dropwise at room temperature by syringe. After 0.1 mL of base had been added the solution was orange in color and went to a red-orange color after all the base had been added. The resulting solution was stirred for 30 minutes at room temperature, the reaction mixture was cooled to 0 °C. and keto compound **7** was added. The red-orange color dissipated and a yellow colored solution containing a fine solid dispersion resulted. The ice bath was removed, the solution was warmed to room temperature over 10 minutes and then stirred at room temperature for 20 minutes. The reaction mixture was concentrated *in vacuo*, ether (2 mL) followed by hexane (40 mL) were added, the solution was filtered and the filtrate ($Ph_3P{=}O$) was washed with hexane (2 x 10 mL). The filtrate was concentrated *in vacuo* to an oil which was subjected directly to flash chromatography on silica gel (90/10 hexane/EtOAc) to give **8a** (860 mg, 80%) as an 85:15 mixture of diastereomers [300 MHz ^1H NMR: major diastereomer 5.95δ (t); minor diastereomer 5.40δ (t)].
11. The reactivity of Wittig reagents generated from potassium bases and phosphonium salts has been noted: (a) M. Schlosser and K.F. Christmann, *Angew. Chem., Int. Ed. Engl.*, **1964**, 3, 636; (b) M. Nikaido, R. Aslanian, F. Scavo, P. Helquist, B. Akermark and J.-E. Backvall, *J. Org. Chem.*, **1984**, 49, 4738; (c) L. Fitjer and U. Quabeck, *Synth. Commun.*, **1985**, 15, 855.
12. This compound has recently been prepared by a different route, see: G. Tarzia, C. Balsamini, G. Spadoni and E. Duranti, *Synthesis*, **1988**, 514.
13. (a) Y.S. Rao and R. Filler, *Synthesis*, **1975**, 749; (b) A. Srinivasan, K.D. Richards and R.K. Olsen, *Tetrahedron Lett.*, **1976**, 891; (c) T.J. Nitz, E.M. Holt, B. Rubin and C.H. Stammer, *J. Org. Chem.*, **1981**, 46, 2667; (d) Y. Shimohigashi, T.J. Nitz, C.H. Stammer and T. Inubushi, *Tetrahedron Lett.*, **1982**, 23, 3235.
14. E. Breitmaier and W. Voelter, *Carbon-13 NMR Spectroscopy, 3rd ed*; VCH: Weinheim, 1987, pp 143-144.
15. Crystal data for **8g** (minor product): $C_{21}H_{23}NO_3$, space group Pcab, a = 17.979(11), b = 9.811(5), c = 20.187(10) Å; giving D_c = 1.259 g cm^{-3} for Z = 8. A total of 2341 unique intensities were collected. Final residuals were R(F) = 0.0802 and R_w(F) = 0.0693.

(Received in USA 27 September 1989)