

α -AMINO KETONES FROM AMINO ACIDS AS PRECURSORS FOR THE KNORR PYRROLE SYNTHESIS[§]

James M. Hamby* and John C. Hodges

Parke-Davis Pharmaceutical Research, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105-2430, U.S.A.

Abstract- A useful and versatile modification of the Knorr pyrrole synthesis is described. Key α -amino ketone intermediates for the Knorr condensation were readily prepared from the *N*-methoxy-*N*-methylamides of amino acids and condensed with 1,3-dicarbonyl compounds to afford tetrasubstituted pyrroles in good yields.

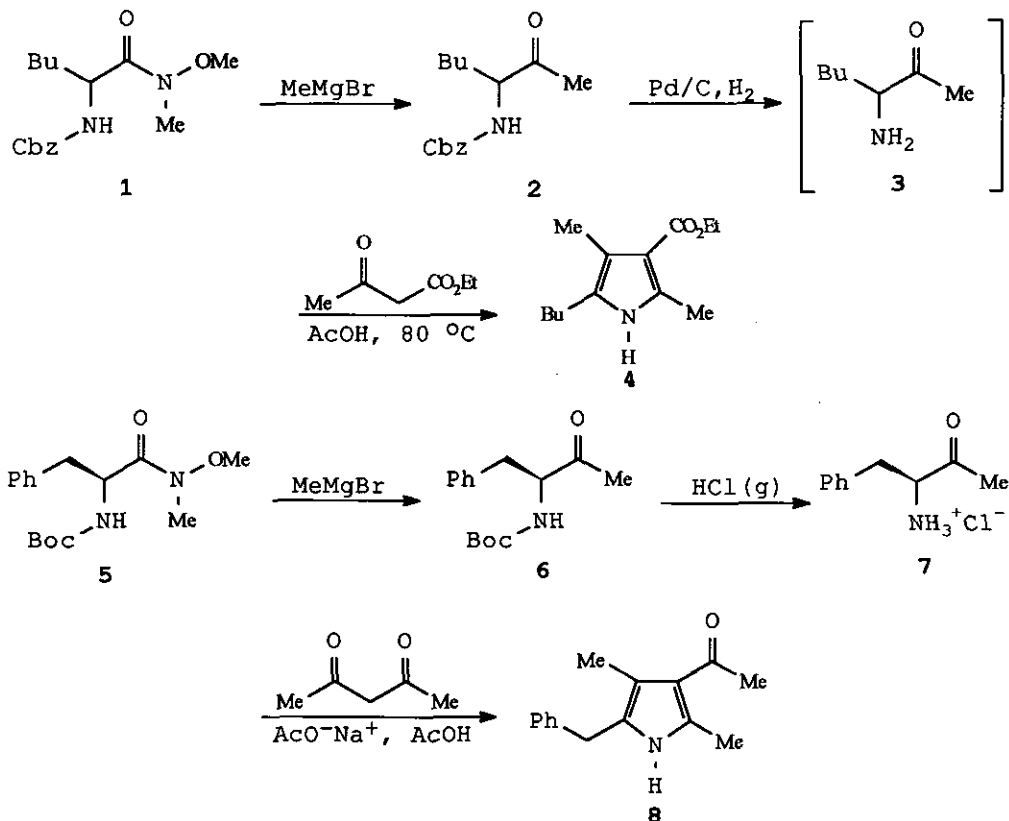
The Knorr condensation is an important method with wide application for the preparation of substituted pyrroles.¹ The method involves the condensation of an α -amino ketone with a 1,3-dicarbonyl compound such as a β -keto ester or β -diketone in acetic acid. The α -amino ketone reactant is usually prepared by the *in situ* nitrosation of an active methylene compound followed by reduction of the resulting oximino intermediate. The *in situ* formation of α -amino ketone intermediates in the Knorr condensation limits the scope of the reaction to less functionalized α -amino ketones that can be prepared by *in situ* nitrosation methods. Other reports in the literature have described modified Knorr condensations employing preformed α -amino ketone reagents.^{1,2} However, these reports are relatively few and are generally restricted to simpler α -amino ketones that can be facilely prepared. The preparation of more elaborate α -amino ketones and thereby, more diversely substituted pyrroles, is hindered by the lack of versatile synthetic methodology for preparation of stable α -amino ketones.³

Herein is described both a facile and versatile synthesis of tetrasubstituted pyrroles utilizing α -amino ketone intermediates prepared by the method of Weinreb from amino acid precursors.⁴ The reaction of *N*-methyl-*N*-methoxy amides with organometallic reagents is a well-known method for the preparation of ketones.⁴ Furthermore, the application of this method to *N*-methyl-*N*-methoxy amino acid amides provides a simple and versatile route to important α -amino ketone building blocks for the Knorr pyrrole synthesis.

The *N*-methoxy-*N*-methylamides of *N*-Cbz-(D,L)-norleucine (**1**)⁵ and *N*-Boc-(L)-phenylalanine (**5**)⁶ were prepared by the mixed anhydride method.⁷ The amide (**1**) was treated with excess methylmagnesium bromide solution in ether

[§] Dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

to afford the corresponding Cbz protected α -amino ketone (**2**) in 95% yield. The subsequent catalytic hydrogenation of **2** over 20% palladium on charcoal was performed in the presence of ethyl acetoacetate in acetic acid liberating the free amino ketone (**3**) *in situ*. The condensation was completed by filtering the catalyst and heating the reaction mixture at 80 °C for 1 h to afford the expected pyrrole (**4**) in 64% yield. Compound (**4**) has been previously prepared in the literature by the *in situ* reduction of 3-oximino-2-heptanone with zinc dust in the presence of ethyl acetoacetate in acetic acid (% yield not reported).⁸



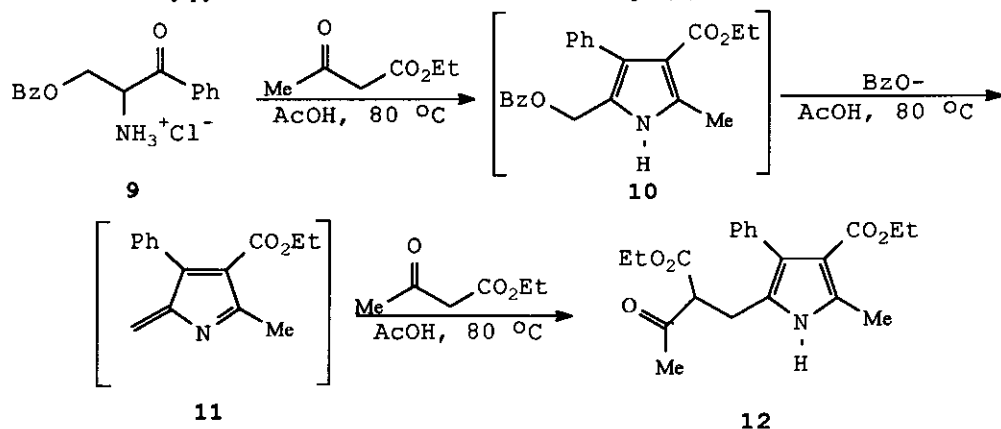
In a cognate procedure, the Boc amide (**5**) was reacted with methylmagnesium bromide to afford the protected α -amino ketone (**6**) in 74% yield. The Boc protecting group was cleaved by bubbling HCl gas through a methylene chloride solution of **6** furnishing the HCl salt of the free α -amino ketone (**7**) in 74% yield. The HCl salt (**7**) was stable at ambient temperature and could be stored for long periods of times without any special precautions. The Knorr condensation was accomplished by heating the salt (**7**) with one equivalent of sodium acetate and a three fold

excess of acetylacetone in acetic acid at 80 °C for 2 h to give **8** in 79% yield. The only product isolated from the reaction mixture was that of the expected Knorr condensation product.

Although both the above methods provided good yields of pyrroles, the latter method was preferred. The highly crystalline amino ketone HCl salts prepared in our laboratory were found to be stable at ambient temperature for months and provided the cleanest products in the highest yields. Nevertheless, the former method, is also a useful modification of the Knorr condensation particularly when the α -amino ketone is sensitive to the acid cleavage of a Boc protecting group.

It was anticipated that heating **6** in acetic acid would cleave the Boc protecting group *in situ* and in the presence of acetylacetone undergo the Knorr condensation directly to give **8**. The reaction, however, was unsuccessful. The disappearance of starting material as monitored by tlc proceeded slowly at 80 °C and heating overnight resulted in the formation of a complex mixture of products.

Jones *et al.* reported the inability of the Knorr synthesis to furnish α -trifluoromethylpyrroles from the condensation of ethyl 4,4,4-trifluoroacetoacetate with an *in situ* formed α -amino ketone.⁹ The failure of the Knorr condensation under these conditions was attributed by Jones to the formation of stable hemiaminal intermediates which do not readily eliminate water to form pyrroles.⁹ In agreement with the above account, we also were unable to prepare the expected α -trifluoromethylpyrrole from the condensation of **7** with ethyl 4,4,4-trifluoroacetoacetate.



Interestingly, the condensation of the α -amino ketone salt (**9**) prepared from *N*-Boc-*O*-benzyl-(L)-serine by the latter method with ethyl acetoacetate gave the unexpected product (**12**) in 48% yield. The reaction most likely proceeds as anticipated forming the expected product (**10**) which further reacts by eliminating benzyl alcohol to

form the electrophilic intermediate (11). The reactive intermediate (11) then goes on to add another molecule of ethyl acetoacetate to furnish the product (12). This unexpected observation warrants further investigation to determine the scope and limitations of this reaction.

The wide variety of amino acids commercially or synthetically available in combination with the Weinreb reaction provides a plethora of α -amino ketone intermediates for the Knorr synthesis of pyrroles. Since the chirality of the amino acid precursor is not of concern, the least expensive, most readily available, or most easily prepared form of the amino acid can be utilized for this reaction. Moreover, the modification of the Knorr pyrrole synthesis reported herein allows for the preparation of α -amino ketone intermediates not readily accessible from *in situ* nitrosation methods. Since α -amino ketones are important building blocks in general, it may be possible to extend this methodology to the synthesis of other heterocyclic systems such as imidazoles and isoxazoles.

EXPERIMENTAL

The starting amino acids (D,L)-norleucine, *N*-Boc-(L)-phenylalanine, and *N*-Boc-*O*-benzyl-(L)-serine were purchased from Bachem Inc. Methylmagnesium bromide and phenylmagnesium bromide were purchased from Aldrich Chemical Company as 3M solutions in ether. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. ^1H Nmr spectra were obtained in CDCl_3 solution on a Varian XL-200 or Bruker AM 250 using TMS as an internal standard. Mass spectra were recorded on a Finnigan 4500 mass spectrometer. Silica gel 60 PF₃₅₄ plates were used for thin layer chromatography, and spots were visualized with uv light or iodine vapor.

(±)-Benzyl [1-[(*N*-methoxy-*N*-methylamino)carbonyl]pentyl]carbamate (1).⁵ To a solution of *N*-Cbz-(D,L)-norleucine (20.24g, 0.076 mol) in CH_2Cl_2 (140 ml) at -78°C was added *N*-methylpiperidine (9.08 g, 0.092 mol) followed by ethyl chloroformate (9.11g, 0.084 mol) and the mixture stirred for 10 min. A solution of *O,N*-dimethylhydroxylamine-HCl (8.19g, 0.084 mol) and *N*-methylpiperidine (8.32 g, 0.084 mol) in CH_2Cl_2 (70 ml) was added dropwise over a period of 1 h to the cold reaction mixture. The reaction was allowed to warm to room temperature, extracted twice with 0.5 N HCl and once with a saturated solution of NaHCO_3 . The organic layer was dried (MgSO_4), filtered, and evaporated under reduced pressure to give 22.0g of 1 (93% yield) as a clear viscous oil

which crystallized upon standing. mp 36-38 °C. $^1\text{H-Nmr}$ δ : 0.88 (t, $J=6.9, 3\text{H}$), 1.28-1.34 (m, 4H), 1.57-1.72 (m, 2H), 3.21 (s, 3H), 3.78 (s, 3H), 4.71-4.80 (br s, 1H), 5.04-5.16 (m, 2H), 5.32 (br d, $J=9.1$, 1H), 7.26-7.36 (m, 5H). Ms m/z : (EI^+) 309 ($\text{M}+1$). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4$: C, 62.32; H, 7.84; N, 9.08. Found C, 62.54; H, 7.86; N, 9.38.

(+)-Benzyl (1-acetylpentyl)carbamate (2). To a solution of the *N*-methoxy-*N*-methyl amide (1) (20.0 g, 64.86 mmol) in anhydrous ether (200 ml) at 0 °C was added a 3 M solution of methylmagnesium bromide (55 ml, 160 mmol) in ether dropwise over a 30 min period. A white gum precipitated from the mixture and dry THF (80 ml) was added to facilitate the stirring. The reaction was allowed to warm to room temperature, stirred for 2 h, and then quenched at 0 °C with a saturated aqueous solution of NH_4^+Cl^- (80 ml) keeping the temperature below 10 °C. The resulting mixture was allowed to warm to room temperature and diluted with ethyl acetate. The organic layer was washed 1 N citric acid, a saturated NaHCO_3 solution, and again with brine. After drying over anhydrous MgSO_4 , the filtrate was evaporated under reduced pressure to give 16.26g (95%) of 2 as a viscous oil. $^1\text{H-Nmr}$ δ : 0.89 (t, $J=6.94$, 3H), 1.20-1.40 (m, 4H), 1.50-1.65 (m, 1H), 1.81-1.95 (m, 1H) 2.21 (s, 3H), 4.31-4.47 (m, 1H) 5.10 (s, 2H), 7.26-7.36 (m, 5H). Ms m/z : (CI , CH_4+NH_3) 264 ($\text{M}+1$). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_3 \cdot 0.15 \text{ EtOAc}$: C, 67.75, H, 8.09; N, 5.06. Found C, 67.76; H, 7.71; N, 4.97.

Ethyl 5-butyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (4). A suspension of 2 (3.0 g, 11.39 mmol), ethyl acetoacetate (2.22 g, 17.0 mmol), and 20% palladium on charcoal in acetic acid (30 ml) was shaken in a Parr reactor under an atmosphere of hydrogen (19.3 psi) for 44 min at which time tlc (30% ethyl acetate in heptane) indicated all the starting material had reacted. The reaction mixture was filtered through celite and washed with acetic acid. The filtrate was heated at 80 °C for 1 h, turning the solution dark. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography eluting with 30% ethyl acetate in heptane to afford 1.62 g (64%) of 4 as a yellow solid. Recrystallization from heptane afforded an analytical sample: mp 92-93 °C (lit.,⁸ mp 92-93 °C). $^1\text{H-Nmr}$ δ : 0.91 (t, $J=7.2, 3\text{H}$), 1.24-1.38 (m, 2H), 1.34 (t, $J=7.1$, 3H), 1.42-1.55 (m, 2H), 2.16 (s, 3H), 2.46 (s, 3H), 2.40-2.50 (m, 2H), 4.26 (q, $J=7.1$, 1H), Ms m/z : (EI^+) 223 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_2$: C, 69.92; H, 9.48; N, 6.27 Found C, 70.03; H, 9.55; N, 6.22.

(S)-Benzyl (2-oxo-1-phenylmethylpropyl)carbamate (6). To a solution of *N*²-Boc-*N*-methoxy-*N*-methyl-(L)-phenylalaninamide⁶ (5.0 g, 16.21 mmol) in anhydrous ether (50 ml) kept at 5 °C was added dropwise a 3 M

solution of methylmagnesium bromide in ether (13.5 ml, 40.53 mmol) with stirring. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was quenched by the careful addition of a saturated aqueous solution of ammonium chloride at 5 °C and diluted with ethyl acetate. The resulting suspension was filtered through celite washing the filter cake with ethyl acetate. The organic layer was separated from the filtrate, washed with brine, dried (Mg SO₄), and filtered. Evaporation of the filtrate afforded the crude product which was purified by flash chromatography (20% ethyl acetate in heptane) to give 3.16 g, (74% yield) of **6** as a white solid. mp 55-57 °C. ¹H-Nmr δ: 1.42 (s, 9H), 2.14 (s, 3H), 2.94-3.14 (m, 2H), 4.53-4.56 (m, 1H), 5.12 (br d, 1H, NH), 7.14-7.34 (m, 5H), Ms m/z: (CI, CH₄+NH₃) 263 (M+1). Anal. Calcd for C₁₅H₂₁NO₃: C, 68.42; H, 8.04; N, 5.32. Found C, 68.65; H, 7.96; N, 5.19.

3-Amino-4-phenyl-2-butanone monohydrochloride (7). Hydrogen chloride gas was bubbled through a solution of **6** (3.16 g, 13.66 mmol) in CH₂Cl₂ (100 ml) for 6 min at 5 °C. The reaction mixture was allowed to warm to room temperature then stirred for 3 h. The solvent was removed under reduced pressure and the residue suspended in ether. The insoluble product was collected by filtration, washed with ether, and dried *in vacuo* to afford 2.03g (74% yield) of **7** as a white solid. mp 130-132 °C. ¹H-Nmr δ: 1.42 (s, 9H), 2.14 (s, 3H), 2.94-3.14 (m, 2H), 4.53-4.56 (m, 1H), 5.12 (br. d, 1H, NH), 7.14-7.34 (m, 5H). Ms m/z: (CI, CH₄+NH₃) 263 (M+1). Anal. Calcd for C₁₀H₁₃NO·HCl: C, 60.15; H, 7.07; N, 7.01. Found C, 60.30; H, 6.92; N, 6.76.

(2,4-Dimethyl-5-phenylmethyl-1H-pyrrol-3-yl)ethanone (8). A mixture of **7** (0.5 g, 2.5 mmol), acetylacetone (0.75 g, 7.51 mmol), and sodium acetate (0.21 g, 2.5 mmol) in glacial acetic acid (5 ml) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with brine, a saturated solution of sodium bicarbonate, and again with brine. The organic layer was dried (MgSO₄), filtered, and evaporated to afford the crude product. Crystallization from an ethyl acetate-heptane mixture furnished 0.45 g (79% yield) of analytically pure **8** as a white solid. mp 164-165 °C. ¹H-Nmr δ: 2.27 (s, 3H), 2.42 (s, 6H), 3.87 (s, 2H), 7.26-7.32 (m, 5H), 7.70 (brs, 1H, NH). Ms m/z: (EI⁺) 227 (M+1). Anal. Calcd for C₁₅H₁₆NO: C, 79.61; H, 7.13; N, 6.19. Found C, 79.3; H, 7.53; N, 6.14.

(S)-Benzyl [2-oxo-2-phenyl-1-[benzyloxymethyl]ethyl]carbamate (13). A solution of *O*-benzyl-*N*^α-Boc-(L)-serine *N*-methoxy-*N*-methylamide¹⁰ (22.26 g, 65.78 mmol) from above in dry THF (220 ml) at ambient temperature

was treated with a 3 M solution of phenylmagnesium bromide in ether (54.8 ml, 164 mmol) dropwise over a period of 40 min. The reaction mixture was stirred overnight, cooled to 5 °C, and quenched by the careful addition of 1N HCl. The resulting suspension was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with a saturated solution of NaHCO₃ and brine. The ethyl acetate layer was dried (MgSO₄), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with a gradient of 10-30% ether in heptane to afford 21.0g (90% yield) of **13** as a viscous oil. ¹H-Nmr δ: 1.45 (s, 9H), 3.78 (d, J=3.9 Hz, 2H), 4.36 (d, J=12.3 Hz, 1H), 4.46 (d, J=12.3 Hz, 1H), 5.38-5.41 (m, 1H), 5.72 (br d, J=7.7 Hz, 1H), 7.05-7.62 (m, 9H), 7.92 (d, J=7.4 Hz, 2H). Ms m/z: (Cl, CH₄+NH₄) 356 (M+1). Anal. Calcd for C₂₁H₂₅NO₄·0.16 C₇H₁₆: C, 71.53; H, 7.48; N, 3.77. Found C, 71.63; H, 7.12; N, 3.72.

(S)-2-Amino-1-phenyl-3-benzyloxy-1-propanone monohydrochloride (9). Hydrogen chloride gas was bubbled through a solution of the above ketone (**13**) (5.0 g, 14.07 mmol) in CH₂Cl₂ (150 ml) 5 °C with stirring for 6 min. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. The solvent was removed under reduced pressure and the residue suspended in ether. The insoluble product was filtered and washed with ether to afford 3.69 g, (90% yield) of **9** as a crystalline white salt. mp 181-182 °C. ¹H-Nmr (DMSO-d₆) δ: 3.88-3.91 (m, 2H), 4.34 (d, J=12.3 Hz, 1H), 4.48 (d, J=12.3 Hz, 1H), 5.41 (br s, 1H), 7.10-7.12 (m, 3H), 7.12-7.25 (m, 2H), 7.55-7.61 (m, 2H), 7.71-7.77 (m, 1H), 8.04-8.07 (m, 2H), 9.54 (br s, 3H). Ms m/z: (Cl, CH₄+NH₄) 256 (M+1). Anal. Calcd for C₁₆H₁₇N₂O₄·HCl: C, 65.86; H, 6.22; N, 4.80. Found C, 65.58; H, 6.11; N, 4.80.

Ethyl 5-(2-ethoxycarbonyl-3-oxobutyl)-2-methyl-4-phenyl-1H-pyrrole-3-carboxylate (12). A solution of **9** (0.5 g, 1.71 mmol), sodium acetate (0.141 g, 1.71 mmol), and ethyl acetoacetate (0.67 g, 5.14 mmol) was heated at 70 °C for 3 h. The solvent was removed under reduced pressure and the residue dissolved in ethyl acetate. The organic layer was washed with brine, a saturated solution of NaHCO₃, and again with brine. The ethyl acetate layer was dried (MgSO₄), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with a gradient of 20-30% ethyl acetate in heptane to afford 0.29g (48% yield) of **12** as an orange viscous oil. ¹H-Nmr δ: 1.01 (t, J=7.2 Hz, 3H), 1.23 (t, J=7.1, 3H), 2.12 (s, 3H), 2.50 (s, 3H), 2.95 (d, J=6.4 Hz, 2H), 3.61 (t, J=6.4 Hz, 1H), 4.04 (q, J=7.2 Hz, 2H), 4.11-4.20 (m, 2H), 7.19-7.36 (m, 5H) 8.70 (br s, 1H). Ms m/z: (EI⁺) 371 (M⁺). Anal. Calcd for C₂₁H₂₅NO₅: C, 67.91; H, 6.78; N, 3.77. Found C, 67.92; H, 7.00; N, 3.78.

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