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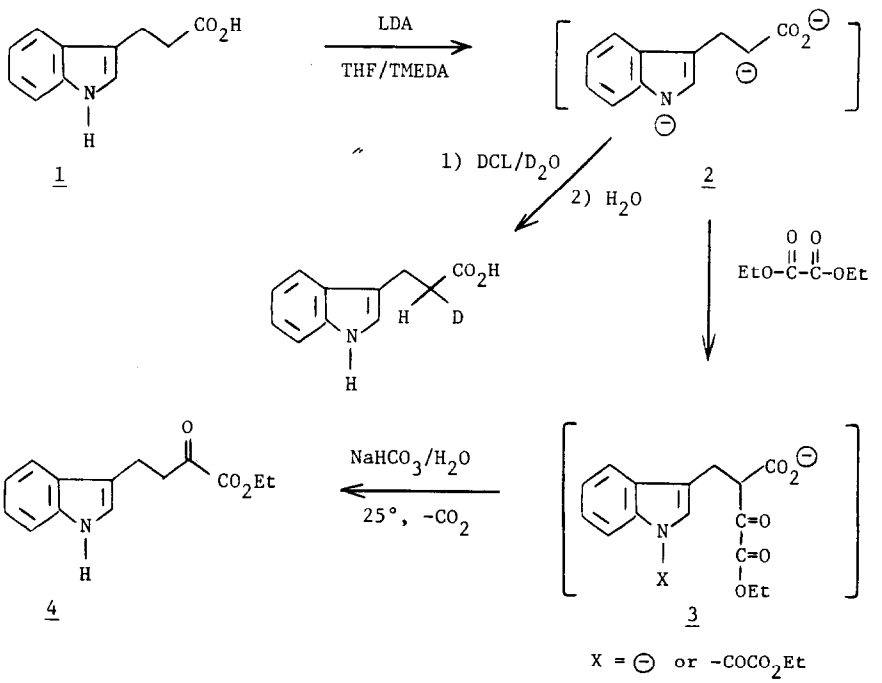
A ONE-STEP SYNTHESIS OF ETHYL 4-(β-INDOLYL)-2-KETOBUTYRATE VIA POLYANION CHEMISTRY AND ITS CONVERSION INTO ANGIOTENSIN CONVERTING ENZYME INHIBITORS

David G. Hangauer Jr.

Merck Sharp & Dohme Research Laboratories
P. O. Box 2000, Rahway, New Jersey 07065

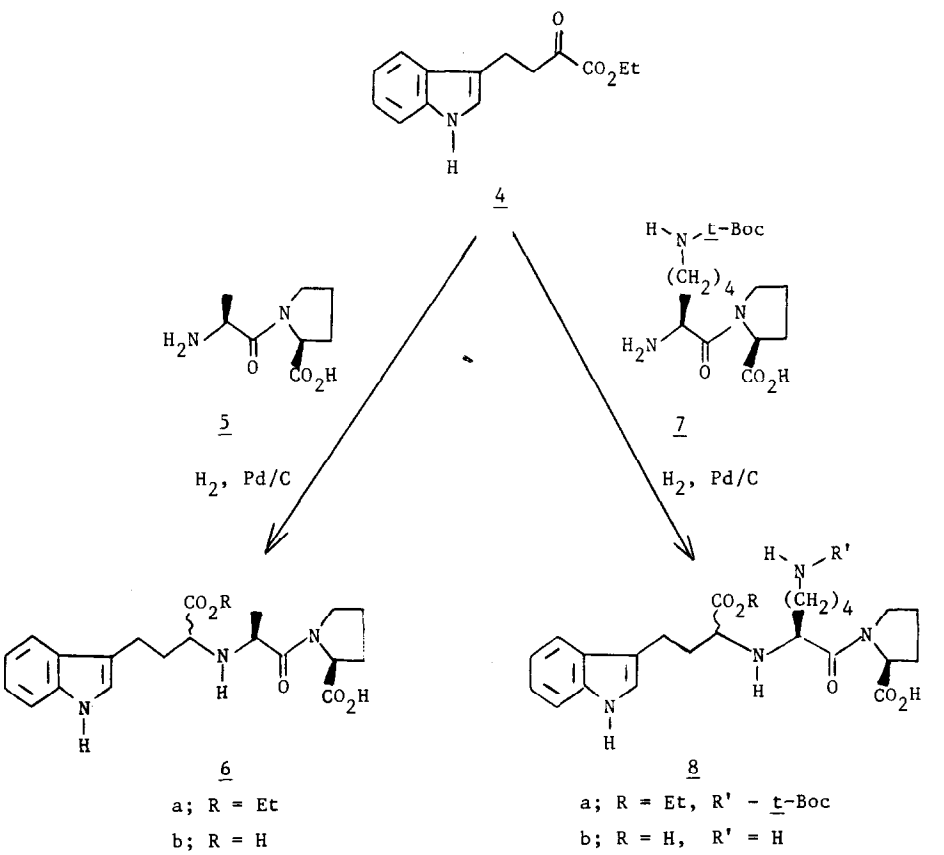
Summary: The trianion of 3-(β-indolyl)-propionic acid was condensed with diethyl oxalate to give ethyl 4-(β-indolyl)-2-ketobutyrate which, upon coupling with various dipeptides, gave potent angiotensin converting enzyme inhibitors.

Recently, α-anions of carboxylate salts have become viable synthons[1]. Such dianions have been reacted with various electrophiles such as alkyl halides[1], isocyanates[2], acid chlorides[3], esters[1] and ketones[1]. Herein we wish to report the condensation of the trianion of 3-(β-indolyl)-propionic acid (1)[4,5] with diethyl oxalate to give the α-ketoester 4. To our knowledge this is the first example of a "one-pot" synthesis of α-ketoesters[6] from carboxylic acids and may be of general utility. In addition, a blocking group on the indole nitrogen was unnecessary with this approach.



The trianion 2 was formed by reacting the indole acid 1 with 4.5 equiv of LDA in THF/TMEDA and slowly heating the reaction from -78° to 50° over a 3 hour period. Inversely quenching this intermediate into dilute DCl/D_2O (0°) and subsequent washing with H_2O results in α-deuteration (NMR). Inverse addition of the trianion 2 to diethyl oxalate (excess) in THF at -78° and allowing the temperature to rise to -40° over 1.5 hours presumably produces intermediate 3. A final inverse quench into saturated $NaHCO_3$ (25°) for 0.5 hour and extraction with ether followed by HCl and brine washes produced the crude α-ketoester 4. Decarboxylation occurs *in situ* and any N-acylated material is hydrolyzed upon aqueous quench. Purification by "flash chromatography"[7] (7/3-hexanes/ethyl acetate) results in a 55% yield of crystalline 4 (mp 109-110°)[8]. This reaction can be routinely run on a 10 g scale. In the absence of TMEDA, the trianion 2 is insoluble and inverse quenching into diethyl oxalate does not produce α-ketoester 4.

Compound 4 was coupled with L-alanyl-L-proline (5)[9] *via* a catalytic reductive amination[10] to produce the adduct 6a[12] in 70% yield (purified on a Sephadex LH-20 column using MeOH) as a *ca.* 1/1 mixture of diastereomers. The ester 6a was saponified (NaOH, H_2O, MeOH, 25°) and



the resulting diacid 6b[12,13] isolated in 65% yield by adsorption on a phosphonic acid resin (Bio-Rex 63) followed by elution with 2% pyridine/H_2O and subsequent freeze drying. Diacid 6b proved to be a highly potent angiotensin-converting enzyme (ACE) inhibitor[11] with an IC_{50} of 7×10^{-9}M [15].

Ketoester 4 was also coupled with t-Boc-L-lysyl-L-proline (7)[9] by catalytic reductive amination to give the adduct 8a[12] in 60% yield (Sephadex LH-20, MeOH). The t-Boc group was removed (TFA, 0°) and the ester saponified (NaOH, H_2O, MeOH, 25°) to give another potent ACE inhibitor 8b[12,13] ($IC_{50} = 4 \times 10^{-9}$M)[15] as a ca. 1/1 mixture of diastereomers in 75% overall yield (isolation procedure same as for 6b).

As previously demonstrated[11] α-ketoesters are useful synthetic intermediates, having provided short and convergent routes to a variety of ACE inhibitors. Additionally, α-ketoester 4 was made available through a "one-pot" reaction whereas earlier attempts using more classical (and lengthy) chemistry failed[14].

Acknowledgement: The author extends his gratitude to Drs. Patchett, Tristram and Wyvratt for helpful discussions relating to the chemistry and medicinal chemistry germane to this paper. We also thank Dr. E. H. Ulm for IC_{50} determinations.

NOTES AND REFERENCES

1. For an excellent review see P. L. Creger, "Annual Reports in Medicinal Chemistry," Vol. 12, Academic Press, New York (1977), Chapter 12.
2. A. P. Krapcho and W. P. Stephens, J. Org. Chem., 45, 1106 (1980).
3. A. P. Krapcho, D. S. Kashdan and E. G. E. Jahngen, Jr., J. Org. Chem., 42, 1189 (1977).
4. Fluka A.G.
5. We were prompted to report our results in part by the recent publication W. Adam and K. Takayama, J. Org. Chem., 45, 447 (1980), which describes the reactions of α-lithio-3-indolylacetate synthons with alkyl halides and ketones.
6. For reviews of synthetic methods towards α-ketoesters and α-ketoacids see; (a) D. Barton and W. D. Ollis, "Comprehensive Organic Chemistry," T. O. Sutherland, ed., Permagon Press, New York, N.Y. (1979), Vol. 2, p. 779, (b) D. St. C. Black, G. M. Blackburn and G. A. R. Johnston, in "Rodd's Chemistry of Carbon Compounds," S. Coffey, ed., Elsevier, Amsterdam (1965), 2nd edn., chapter 16, (c) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods," Interscience, New York, N.Y. (1974), Vol. 2.
7. W. C. Still, M. Kahn and A. Mitro, J. Org. Chem., 43, 2923 (1978).
8. Recrystallized from $CHCl_3$/hexanes. ^{1}H NMR (60 MHz, $CDCl_3$); δ1.3 (t, 3H, J = 6 Hz), 3.2 (m, 4H), 4.3 (q, 2H, J = 6 Hz), 7.5 (m, 6H): IR (KBr); 3350, 1730 cm^{-1}: MS (m/e); 245 (M^+), 216 (M^+-Et), 172 (M^+-CO_2Et), 144 (M^+-$COCO_2$Et): C, H, N; theory; C, 68.56, H, 6.16, N. 5.71, found; C, 68.18, H, 6.14, N, 5.58.
9. Prepared by standard peptide methodology using N,N'-dicyclohexylcarbodiimide as the coupling agent and appropriate blocking groups. Also available from Chemical Dynamics

Corp., South Plainfield, N. J.

10. The dipeptide (1 eq.) and α-ketoester (2.2 eq.) are dissolved in absolute ethanol, then pulverized 4A sieves (large excess) and 10% Pd/C are added. The mixture is hydrogenated on a Parr hydrogenator at 40 psig. and 25° until a fluorescamine test indicates all of the primary amine has been consumed.
11. For other ACE inhibitors of this structural type see A. A. Patchett et al., Nature, 288, 280 (1980).
12. A satisfactory NMR, IR and MS was obtained for these compounds.
13. A satisfactory combustion analysis and/or high resolution MS was obtained for these compounds.
14. D. G. Hangauer, Jr., E. D. Thorsett and M. J. Wyvratt, unpublished results.
15. The assay method is described in reference 11.

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