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Synthesis of Protected, Chiral α,α-Disubstituted α-Amino Acids *via* a Beckmann Rearrangement

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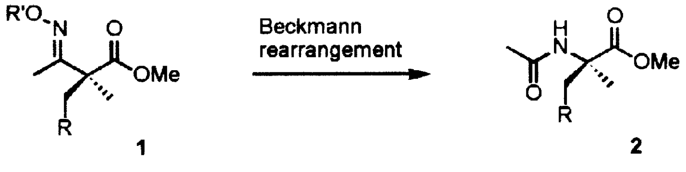
Abstract: The synthesis of chiral, nonracemic, fully protected α,α-disubstituted α-amino acids *via* the Beckmann rearrangement of tosylated oximes **1** is described. The desired amino acids were obtained in good yields with excellent enantioselectivities in relatively few steps. © 1998 Elsevier Science Ltd. All rights reserved.

The synthesis of chiral non-racemic α-amino acids[1,2] continues to challenge an ever growing group of organic chemists. The interest in these compounds lies in their role as building blocks for natural and man-made proteins and peptides. Further interest in the synthesis of unnatural amino acids has been generated by the observation that conformational constraints can be imparted upon peptides by the incorporation of specific amino acid residues,[3] and many methods have been developed for the synthesis of these compounds. Of the methods developed for the preparation of amino acids, however, few can be utilized for the synthesis of α,α-disubstituted amino acids,[4-8,9] and even fewer can be considered practical and general methods capable of incorporating a wide variety of functional groups into α,α-disubstituted amino acids.[10,11] As a result, there is a need to improve and expand the organic chemists' arsenal for the synthesis of these important building blocks.

The Beckmann rearrangement is known to occur with retention of configuration at the migrating carbon.[12,13] Hence, rearrangement of chiral, non-racemic compounds such as **1** should afford *N*-acetyl amino esters **2** with high enantioselectivities (eq. 1). This strategy for the synthesis of amino acids has found limited use by Westermann,[14] who reported the synthesis of enantiomerically pure, protected α,α-disubstituted α-amino acids starting from cyclic β-ketoesters. A related approach utilizing a Schmidt rearrangement has also been reported by Georg.[15] Herein, we report our studies on the synthesis of protected chiral, non-racemic α,α-disubstituted α-amino acids *via* a Beckmann rearrangement starting with acyclic β-ketoesters.



(1)

The synthesis of the protected α,α-disubstituted α-amino acids through the Beckmann rearrangement is illustrated by the preparation of (*R*)-*N*-acetyl-α-methylphenylalanine methyl ester **6** (Scheme 1). β-Ketoesters like **3** were prepared enantiomerically pure according to the procedure described by Koga,[16] and oximes were formed using standard conditions ($HONH_2$•HCl, NaOAc, MeOH, rt, 10-15 h). Initially, we performed the

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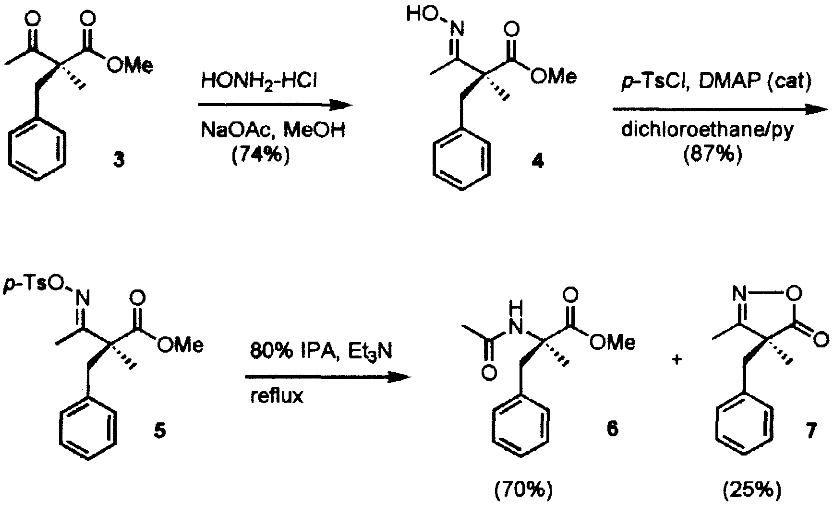
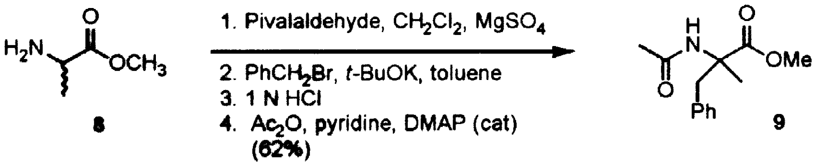
rearrangement of oxime **4** directly by treatment with PCl_5 in ether followed by an aqueous workup, but this reaction resulted in the formation of numerous impurities and the yield of **6** was low (30-40%). Consequently, oxime **4** was tosylated (*p*-TsCl, DMAP (cat), dichloroethane/pyridine, 60 °C, 10-15 h) to afford **5** as a single isomer in good yield. Tosylate **5** was then submitted to the Beckmann rearrangement (refluxing isopropanol/water, 4:1 $^{v}/_{v}$, with 1 equiv of triethylamine, 8-12 h) to afford **6**[17] together with undesired isoxazolone 7. Purification by silica gel chromatography gave pure **6** in 70% yield.

Scheme 1. Synthesis of (*R*)-N-acetyl-α-methylphenylalanine methyl ester **6**



The formation of isoxazolones from β-ketoesters[18,19] or their corresponding oximes[20,21] is well precedented, but to the best of our knowledge the formation of isoxazolones from tosylated oximes like **5** has not been previously reported. Numerous efforts were made to minimize the formation of undesired isoxazolone 7. The rearrangement was performed using solvents such as ethanol, methanol, butanol, acetic acid, pyridine and THF, and the amount of water in the mixture was varied with no improvement on the yield. Changing the amount or type of base resulted in no improvement. Similarly, changing the ester functionality from methyl to ethyl, isopropyl or *tert*-butyl esters proved detrimental to the reaction.[22] Finally, it was observed that mesylates gave a slightly inferior yield than the corresponding tosylates such as **5**.

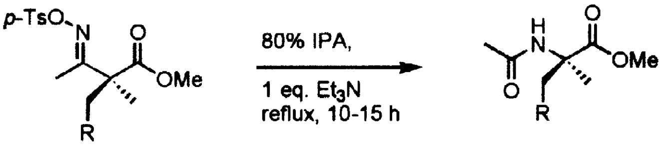
To confirm the enantiospecificity of the Beckmann rearrangement, the corresponding racemic protected α,α-disubstituted α-amino acids were synthesized as shown in eq 2. These racemic amino acids were analyzed and resolved by chiral HPLC (Chiralpak AD column, hexane/ethanol/diethylamine 85:15:0.5, 1 mL/min) and their traces were used as a reference to analyze the chiral, non-racemic products. In this manner, it was determined that compounds such as **6** were obtained with 95-99 % ee's.

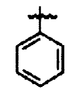
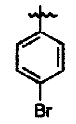
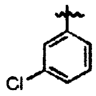
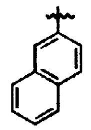


(2)

Scheme 2 shows a list of the protected chiral, non-racemic α,α-disubstituted α-amino acids prepared using the methodology described above.

Scheme 2.



entry	R	% yield	$[\alpha]_D^{25}$	% ee[23]
1		70	+ 89.8	99.7
2		65	+ 101.1	98.5
3		66	+ 113.9	99.0
4		57	+ 92.0	97.8
5		51	+ 13.6	95.0

In conclusion, we have demonstrated a novel method for the synthesis of fully protected, chiral α,α-disubstituted α-amino acids *via* a Beckmann rearrangement. The desired amino acids were obtained in good yields with excellent enantioselectivities in relatively few steps. Consequently the methodology presented here should prove itself useful for the synthesis of α,α-disubstituted amino acids.

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16. a) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718. b) The optical purity of the resulting β-ketoesters was determined by chiral HPLC (Chiralpak AS column, hexanes/ethanol, 100:0.5 $^{v}/_{v}$, 1.5 mL/min).
17. Synthesis of **6**: Triethylamine (153 μL, 1.10 mmol) was added dropwise to a stirred suspension of tosylate **5** (429 mg, 1.10 mmol) and isopropanol/water (11 mL, 4:1 $^{v}/_{v}$) at room temperature. The resulting mixture was refluxed for 12 h, allowed to reach ambient temperature and concentrated under reduced pressure. Aqueous workup (dichloromethane, water, brine, Na_2SO_4) afforded an oil. Flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) afforded 190 mg (70%) of **6** as a colorless oil (R_f = 0.21, 2:1 hexanes/ethyl acetate) and 55.0 mg (25%) of undesired **7** (R_f = 0.07). **6**: $[\alpha]_D^{25}$ = + 89.8 (c = 0.50, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.93 (s, 3H), 3.17 (d, J = 13.6 Hz, 1H), 3.48 (d, J = 13.6 Hz, 1H), 3.75 (s, 3H), 6.20 (br, 1H), 7.04 (d, J = 8.0 Hz), 7.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 23.7, 40.9, 52.4, 60.8, 126.7, 128.0, 129.7, 16.3, 169.5, 174.2.
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22. The distribution of products correlates with the ability of the ester R group to stabilize a positive charge. Therefore the mechanism probably involves nucleophilic attack of the ester carbonyl oxygen into the oxime nitrogen.
23. The optical purity of the products was determined by chiral HPLC (Chiralpak AD column, hexane/ethyl acetate/diethyl amine, 85:15:0.5 $^{v}/_{v}$, 1 mL/min), and was found to be consistent with the optical purity of the starting β-ketoesters.