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ASYMMETRIC SYNTHESIS OF α-ALKYLATED α-AMINO ACIDS VIA SCHMIDT REARRANGEMENT OF α,α-BISALKYLATED β-KETO ESTERS

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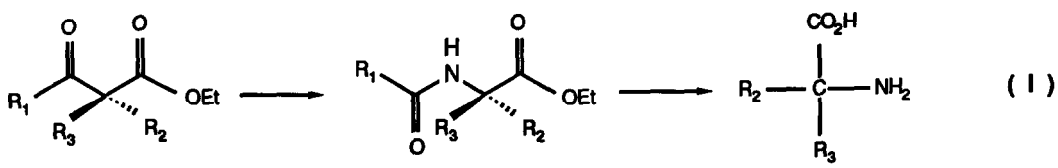
Abstract: α-Alkylated α-amino acids are obtained in high yield and optical purity through Schmidt rearrangement of optically active α,α-bisalkylated β-keto esters.

Because of their interesting biological properties, α-alkylated α-amino acids have generated considerable interest both with respect to their synthesis[1] and their role in bioorganic chemistry.

They are known to be powerful inhibitors of those enzymes that metabolize the corresponding α-unsubstituted proteinogenic amino acids.[2] α-Alkylated α-amino acids are also constituents of natural products such as the antibiotic, amicetin[3], and polypeptide antibiotics[4] such as antiamoebin I. Furthermore, this class of compounds is of importance in peptide chemistry, since introduction of an α-alkylated amino acid into peptide chains restricts the available range of backbone conformations.[5]

We have now been able to demonstrate[6] that the Schmidt rearrangement of optically active α,α-bisalkylated β-keto esters is a convenient method to generate α-alkylated α-amino acids in high yields and excellent optical purity (eq 1).

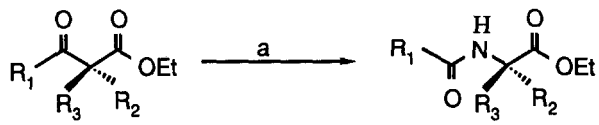


(I)

It is well-known that the Schmidt rearrangement of β-keto esters is a suitable methodology to synthesize α-amino acids in high yields.[7] Although several studies have revealed that the Schmidt rearrangement takes place with retention of configuration,[8] the rearrangement of optically active β-keto esters has not yet been studied.

Optically active β-keto esters[9] of high enantiomeric purity have recently become available[10] through diastereoselective alkylation of the lithio enamines of α-alkylated β-keto esters utilizing readily available L-valine tert-butyl ester as the chiral auxiliary. We synthesized several optically active α,α-dialkylated β-keto esters[11] and subjected them to the Schmidt rearrangement.[12] We obtained the corresponding N-acyl amino acids in excellent chemical yields (Scheme I). NMR experiments with racemic and optically active N-acyl α-amino

Scheme I



a. NaN_3, CH_3SO_3H, $CHCl_3$, 0.5-1 h.

entry	R_1	R_2	R_3	yield (%)	$[\alpha]_D$ *	e e % **
1	CH_3	CH_3	$PhCH_2$	95	-47.8°	>95
2	CH_3	CH_3		89	-49.3°	>95
3	$(CH_2)_4$		$PhCH_2$	97	+4.6°	>95
4	$(CH_2)_4$			71	+23.9°	>95
5	CH_3	CH_3	CH_2CO_2Me	88	-16.5°	70

* The optical rotations were taken in chloroform, c ≈ 1.

** ^{1}H-NMR with chiral shift reagent (Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium(III) derivative.

acids utilizing chiral shift reagents revealed that no detectable racemization had occurred during the Schmidt rearrangement. In the series of optically active N-acyl α-amino acids we only observed the presence of one of the two enantiomers by NMR entry 1-4 and, therefore, assigned them as possessing an enantiomeric excess (ee) of > 95%. The α-methylaspartic acid derivative (entry 5) was synthesized from the corresponding α,α-bisalkylated β-keto ester possessing an enantiomeric excess (ee) of 70%.[10]

With these results, we have now established for the first time that the Schmidt rearrangement of α,α-bisalkylated β-keto esters also proceeds with retention of configuration and little or no racemization.

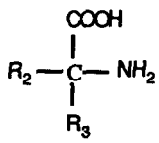
Hydrolysis of the N-acyl α-alkylated α-amino acid esters (eq 2) followed by treatment with propylene oxide in ethanol[13] produced the desired free D-amino acids in excellent yield and optical purity (Table 1). The ee values for D-α-methylphenylalanine, D-α-(2-naphthylmethyl)-

alanine, and D-α-methylaspartic acid were established by comparison with reported optical rotations.[14] The overall chemical yield for the three step synthesis, for example, of D-α-methylphenylalanine is 74%.[15]

(2)

a. H^+. b. propylene oxide, ethanol

Table I



entry	R_2	R_3	yield (%)	$[\alpha]_D$	e e %
1	CH_3	$PhCH_2$	95	+20.5° [a]	97.8
2	CH_3		89	+14.3° [b]	98.6
3	$(CH_2)_4CO_2H$	$PhCH_2$	99 [c]	+3.4° [b]	>95
4	$(CH_2)_4CO_2H$		88 [c]	+8.8° [d]	>95
5	CH_3	CH_2CO_2H	80	-37.7° [a]	69

a. The optical rotation was taken in H_2O, c ~1.

b. Optical rotation in 1 N HCl.

c. Isolated as HCl salt.

d. Optical rotation in 4 N HCl.

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(11) The β-keto esters of entry 1 and 5 (Scheme I) have been synthesized previously (see reference 10a). The β-keto esters of entry 2,3, and 4 were newly synthesized and displayed an enantiomeric excess (ee) of > 95% using NMR spectroscopy (chiral shift reagent).

(12) A typical procedure for the Schmidt rearrangement is give below: A solution of 1.06 mmol β-keto ester in 5 mL of chloroform was cooled to 0°C. After the addition of 10 mmol methanesulfonic acid, sodium azide (2-4 mmol) was added in small portions. The reaction mixture was then refluxed for 0.5-1 h, quenched into ice water, neutralized with ammonium hydroxide solution and extracted with ether (3 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using ethyl acetate/ hexanes as eluents.

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(15) All newly synthesized compounds were characterized by elemental analysis or HRMS and exhibited spectroscopic data in agreement with their structures.

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