Tetrahedron Letters, Vol.27, No.7, pp 831-834, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

ASYMMETRIC SYNTHESES OF α-AMINO ACIDS FROM α-HALOGENATED 10-SULFONAMIDO-ISOBORNYL ESTERS.[1]

Wolfgang Oppolzer *, Rafael Pedrosa, and Robert Moretti.
Département de Chimie Organique, Université de Genève, CH-1211 Genève, Switzerland.

Abstract : Treatment of chiral α-haloesters 2 with NaN_3 gave azidoesters 3 which on successive transesterification and hydrogenolysis furnished α-amino acids 5 and 9 in high e.e.

The synthesis of enantiomerically pure, unnatural or naturally occurring but scarcely accessible (2R)- or (2S)-α-aminoacids has attracted considerable attention in recent years [2]. We report here an entirely different approach to this biologically important class of compounds featuring asymmetric formation of the C(2)-N bond. Exploiting the simple and efficient π-face selective ester halogenation 1→2 [3] we envisaged an SN_2-type halide substitution by a nitrogen nucleophile followed by liberation of the carboxylic acid and amino groups thereby regenerating the auxiliary alcohol YH.

Our results are summarized in Schemes 1 and 2 as well as in the Table.

Scheme 1

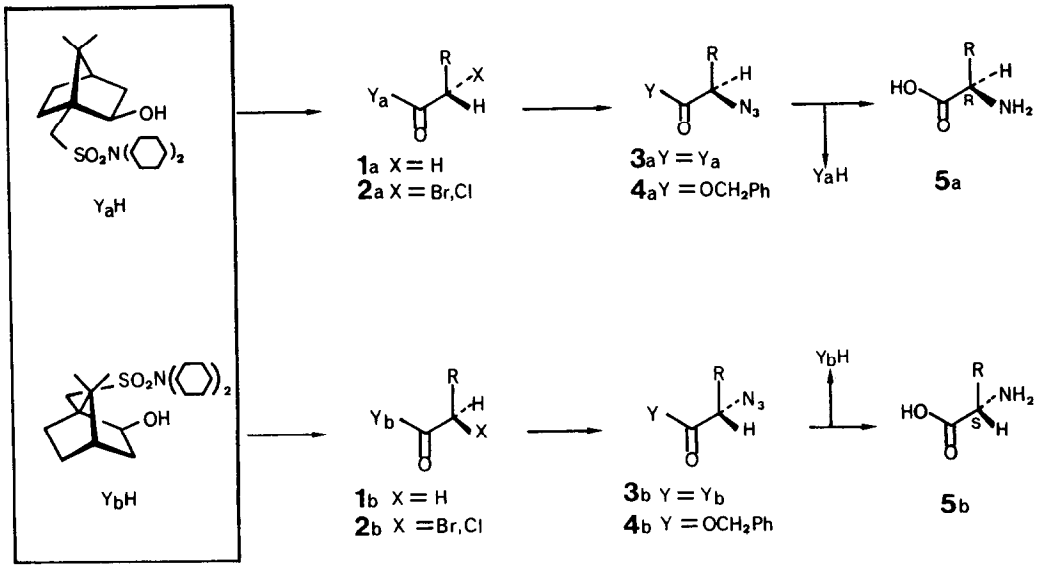


Table : Enantioselective Preparation of α-Amino Acids 5 from Esters 1 [4].

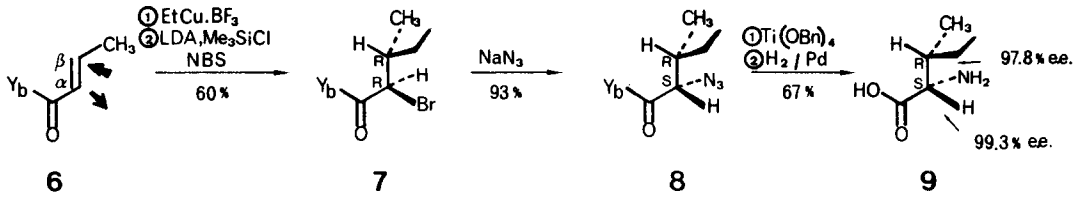
				Halogenation 1 → 2		Azide-Substitution 2 → 3		Transesterification/ Hydrogenolysis 3 → 4 → 5		
Entry	R	Auxiliary Y	X	Yield% cryst. (crude)	d.e.% cryst. (crude)	Yield% cryst. (crude)	d.e.% cryst. (crude)	Yield% overall	e.e.%	Conf.
1	C_2H_5	a	Cl	75(87)	>99	87(98)	-[iv]	72	94.0	(R)
2	nC_3H_7	a	Cl	75(82)	96.7	93(~100)	97(96.7)	87[iii]	93.8	(R)
3	nC_4H_9	a	Br	77	96	88(93)	96	72	94.0	(R)
4	$(CH_3)_2CHCH_2$	a	Cl	72(86)	≥96	81(97)	98(96)	80	96.0	(R)
5	nC_6H_{13}	a	Cl	82	≥94	89(96)[i)ii)]	100(94)[i)ii)]	78	98.0	(R)
6	$PhCH_2$	b	Br	80(92)	-[iv]	82(100)	98(91)	72[iii]	94.7	(S)
7	1-adamantyl-CH_2	b	Cl	54(64)	-[iv]	88(~100)	-[iv]	73	96.4	(S)

i) oil; ii) purified by flash chromatography; iii) recovery of YH by extraction after hydrogenolysis; iv) not determined.

Treatment of recrystallized chlorides or bromides 2 [4,5] with NaN_3 in DMF at r.t. or at +40° furnished smoothly azides 3 [5] in 93 to 100% yields. HPLC-analysis of crude 3 [6] revealed initial diastereomeric purities of 91 to 96.7% which were increased to 96-98% d.e. by crystallization or, in the case of azide 3, R=nC_6H_{13} (oil, entry 5, to ca. 100% d.e.), by flash chromatography. $Ti(OCH_2Ph)_4$-mediated transesterification of 3 regenerated the auxiliary YH which was separated by chromatography from the resulting benzyl esters 4 [5]. Stirring of 4 with 5% $Pd/BaSO_4$ under H_2 (1 atm) for 8 to 45 h entailed concomitant hydrogenolyses of the benzyloxy- and azide groups to furnish the amino acids 5 in 72 to 80% overall yield. Technically, it was preferable to remove the regenerated auxiliary by simple extraction after the hydrogenolysis step (entries 2 and 6). The depicted absolute configurations and enantiomeric purities (93.8 to 98 % e.e.) of amino acids 5 were readily determined by GC (chiral capillary column [7]) comparison of their N-trifluoroacetylisopropyl esters with those of racemic and enantiomerically pure authentic samples and further supported by chiroptic measurements [8]. Depending on the use of the antipodal auxiliaries Y_aH or Y_bH, either the expected (R)- (entries 1-5) or (S)- (entries 6,7) amino acids 5 were obtained. This is consistent with ≥99% inversion for the halide/azide substitutions 2 → 3 and ca. 99% retention for the transesterification/hydrogenolysis sequence 3 → 4 → 5.

We then turned our attention to the synthesis of the uncommon amino acid L-alloisoleucine 9 [9] (Scheme 2) which notably, is an essential precursor for the synthesis of the psychotropic ergot peptide eticriptine [10].

Scheme 2



6 **7** **8** **9**

Starting from crotonate 6 [5] the required two contigous stereocenters were generated efficiently using the same auxiliary Y_b which blocks the Cβ-*Re* face of 6. First, center C(3) was created by addition of $EtLi/CuI/BF_3.OEt_2$ (2 eq, -78° → r.t.) [11] to 6 to give, after crystallization, the β-adduct 1,R = (R)-$CH(CH_3)C_2H_5$ (89%) [5]. Subsequent treatment with LDA, Me_3SiCl and NBS [4,12] followed by three crystallizations afforded bromoester 7 (67%, HPLC: 2 peaks 99:1). Stirring 7 with NaN_3 in DMF at r.t. for 60 h gave, after work-up and crystallization, the (2S,3R)-azide 8 (93%, HPLC: 2 peaks 99.2:0.8). Transesterification, followed by chromatographic recovery of Y_bH and hydrogenolysis afforded L-alloisoleucine (9) in 67% yield from 8. GC-analysis of its N-trifluoroacetylisopropyl ester (chiral capillary column) confirmed the expected configuration and enantiomeric purity of crude 9: 2S (99.3% e.e.) / 3R (97.8% e.e.) [13].

In summary, we have described here a novel, enantioselective entry to α-amino acids which highlights the versatility of camphorsulfonic acid derived chiral auxiliaries in asymmetric synthesis.

Acknowledgements : Financial support of this work by the *Swiss National Science Foundation*, *Sandoz Ltd, Basel,* and *Givaudan SA,* Vernier is gratefully acknowledged. We thank Mr.*J.P.Saulnier*, Mr. *A.Pinto* and Mrs. *C. Clément* for NMR and MS measurements and particularly, Dr. *P. Dudfield* for preliminary experiments and Mr. *M. von Arx* and Mr. *T. Kobayashi* for their technical contribution.

REFERENCES AND NOTES.

1 Presented in part at the Autumn Meeting of the Swiss Chemical Society, Bern, October 1985, Abstr. OV I-4, p.10.

2 Reviews: D. Hoppe, *Nachr. Chem. Techn. Lab.* 1982, *30*, 783, 852; W.S. Knowles, *Acc. Chem. Res.* 1983, *16*, 106; U. Schöllkopf in "*Topics in Current Chemistry*" 1983, *109*, 65.

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4 Chlorides 2 and the starting esters 1 were prepared as described previously [3] (using freshly crystallized and rigorously dried NCS). For the preparation of bromides 2 and 7 solid N-bromosuccinimide (4.95 mmol) was added portionwise during 10 min to a stirred solution of the crude O-silyl ketene acetals derived from 1 (4.5 mmol) [3] in dry THF (35 ml) at -78°. Stirring of the mixture at -78° for 3h followed by aq. work-up and flash

chromatography gave crude α-bromoesters 2 or 7 which were crystallized from hexane or EtOH/EtOAc 5:1, respectively. NaN_3 (2 to 3 eq.) was stirred with 2 in DMF for 3 to 60 h at r.t. (entries 1,2,3,6,7 and Scheme 2) or at +40° (entries 4,5). Aq. work-up with hexane gave crude 3 or 8 which were crystallized from hexane. α-Azido esters 3 or 8 (2 mmol) were heated with $Ti(OCH_2Ph)_4$ (2 mmol) in benzyl alcohol (15ml) at +130° for 14 to 40 h; aq. work-up and chromatographic separation of YH (92 to 96%) gave benzyl ester 4. A mixture of 4 (2 mmol) and 5% $Pd/BaSO_4$ (250 mg) in EtOH (8 ml) or in EtOH/EtOAc 1:1 (entry 7) was stirred under H_2 (1 atm) at r.t. for 8 to 45 h. Filtration through Celite, washing of the insoluble residue with ether, followed by extraction with water (3 x 15 ml) at +50° or with MeOH (entry 7) and evaporation of the extracts and drying *in vacuo* gave α-aminoacids 5 or 9. In the case of entries 2 and 6 the crude transesterification mixture 4, + YH was submitted to the above hydrogenation conditions.Filtration and washing of the insoluble residue with chloroform gave the soluble auxilary YH; further extraction of the remaining insoluble residue with water at +50° gave α-amino acid 5.

[5] All new compounds were characterized by IR, ^{1}H-NMR and MS.

[6] HPLC analyses (*Merck, Lichrosorb Si 60*, 5 μm hexane), in comparison with the Cα-epimer mixtures obtained from epimer mixtures 1 [3] by treatment with NaN_3. However, 3, R=C_2H_5 and R=1-adamantyl-CH_2 (entries 1 and 7) could not be separated.

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[12] Chlorination of β-branched 1, R = (R)-$CH(CH_3)C_2H_5$ and subsequent chloride substitution by azide were intolerably slow.

[13] On GC-analysis [7] of (2RS,3RS)-9/(2RS,3SR)-9 all four stereoisomers were cleanly separated.

(Received in Germany 4 December 1985)