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ASYMMETRIC SYNTHESIS OF N-SUBSTITUTED α-AMINO ESTERS

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Summary. A one pot procedure converting chiral silyl ketene acetals to N-substituted α-amino esters by amination with ethyl azidoformate is described.

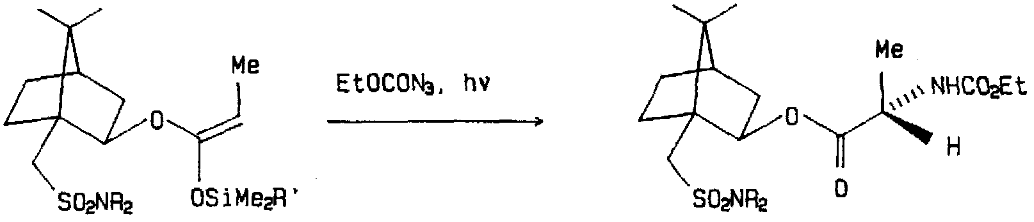
In recent years we have reported the direct amination by nitrene and azide of enamines, enol silyl ethers and silyl ketene acetals to produce N-substituted α-amino ketones[1] and α-amino esters[2] respectively.

The use of optically active enamines, prepared from (S)-proline derivatives, allowed the asymmetric formation of 2-(ethoxycarbonylamino)cyclohexanone of R configuration with high enantiomeric excess (e.e.).[3]

Asymmetric synthesis of α-amino or α-hydrazino esters starting from silyl ketene acetals[4] either by direct amination[5] or through α-chloro esters[6] have been recently reported. Here we propose a further, simple, one pot methodology for the chiral formation of a C-N bond, namely the preparation of an ester of N-(ethoxycarbonyl)alanine as the main product from the photolysis of ethyl azidoformate ($EtOCON_3$)[7] in a pentane solution[8] of optically active silyl ketene acetals.

The chiral auxiliaries employed were both the 10-sulphamido isobornyl derivatives introduced by Oppolzer[9] and now commercially available. The chiral silyl ketene acetals were prepared according to the literature procedure, starting from the chiral ester obtained by reaction of propionyl chloride and the chiral alcohol in the presence of AgCN.[10] The silylation reaction was performed under conditions known to give mainly the E configuration product.[11]

The best chemical yield (77 %) and the highest diastereoselectivity (70 %) were observed in the photolysis of $EtOCON_3$ (0 °C, Hanovia medium pressure lamp) in a pentane solution (0.6 M) of the silyl ketene acetal 1 having R′ equal to tert-butyl. The quantitative separation of the diastereomeric products was easily accomplished by silica gel chromatography reaching 97 % of purity. After this separation and further purification by HPLC, the ^{1}H-NMR spectrum of the pure diastereomer 2 was recorded and used to estimate the diastereomeric excess (d.e.) of the crude reaction mixture. The values so obtained were in very good agreement with those obtained by HPLC analyses, and with the amounts of separated compounds.



1 **2**

Starting from the silyl ketene acetal 1 (R' = methyl)[12] we obtained mainly a derivative of (S)-alanine but in lower chemical yield,[13] and d.e.. Its absolute configuration was proved by comparison with the compound prepared by esterification of (S)-N-(ethoxycarbonyl)alanine[14] with the (1S,2R) chiral alcohol, in the presence of AgCN.

Table. Photolysis of $EtOCON_3$ in the chiral silyl ketene acetals 1

R	R'	chiral auxiliary configuration	configuration of new chiral C	chemical yields %	d.e.
cyclohexyl	*tert*-butyl	(1S,2R)	S	77	70
cyclohexyl	methyl	(1S,2R)	S	14	50
cyclohexyl	methyl	(1R,2S)	R	38	53

Photolysis of $EtOCON_3$ in a pentane solution of the silyl ketene acetal enantiomer of 1 (R′ = methyl), prepared from the (1R,2S) chiral alcohol, confirmatively gave as the main product (38 % chemical yield) the ester of (R)-N-(ethoxycarbonyl)alanine (d.e. = 53 %), enantiomer of 2.

The facial selectivity observed in this reaction is the same than that observed during the attack of other electrophiles on the same substrates.[9] Preferential attack from the less hindered face has been confirmed by X-ray data and N.O.E. experiments.[12]

The chiral alcohol could be regenerated by the transesterification procedure described in the literature.[6]

General Procedure

A solution of ethyl azidoformate (0.6 ml, 5.1 mmol) and silyl ketene acetal (2.5 mmol) in dry pentane (4 ml), in an atmosphere of argon, was photolysed in a quartz vessel using a medium pressure Hanovia PCR lamp (100 W). When the ketene band (1680 cm^{-1}) disappeared in the IR spectrum, the pentane was distilled *in vacuo*. The crude mixture was analysed by HPLC (hexane/ethyl acetate = 9:1) and by ^1H NMR, then chromatographed on silica gel (hexane/ethyl acetate = 9:1) giving the product in the yields reported in table with a d.e. more than 97 %. By HPLC (hexane/ethyl acetate = 9:1) the major diastereomer was isolated in quantitative d.e.. 2: $[\alpha]_D$ -35, enantiomer of 2: $[\alpha]_D$ +35; IR($CHCl_3$): 3430, 1715 cm^{-1}; ^1H NMR($CDCl_3$): δ 0.88 (s, 3H), 0.97 (s, 3H), 1.23 (t, 3H), 1.42 (d, 3H), 1.58-2.06 (27H), 2.68 (d, J=13.5 Hz, 1H), 3.21 (m, 3H), 4.09 (q, 2H), 4.33 (q, 1H), 5.01 (m, 1H), 5.41(m, 1H). ^{13}C NMR($CDCl_3$): δ 14.58, 18.80, 19.90, 20.37, 25.17, 26.40, 26.45, 26.95, 30.31, 32.81, 39.32, 44.43, 49.16, 49.58, 54.00, 57.62, 60.84, 63.67, 79.39, 155.68, 171.31; *m/z* calcd. for $C_{28}H_{48}N_2O_6S$ 540.3221, found 540.3214. The minor diastereomer (*ca.* 80 %) was obtained by chromatography. ^1H NMR: δ 0.88 (s, 3H), 0.98 (s, 3H), 1.23 (t, 3H), 1.47 (d, 3H), 1.58-2.06 (27H), 2.63 (d, J=13.5 Hz, 1H), 3.22 (m, 3H), 4.09 (q, 2H), 4.28 (m, 1H), 4.92 (m, 1H), 5.29 (m, 1H).

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