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Asymmetric Addition of Ethyl Azidoformate to Optically Active Enamines. Reversal of Facial Selectivity Compared with (Ethoxycarbonyl)nitrene#1

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Abstract: Thermal reaction of ethyl azidoformate with proline-derived optically active enamines of cyclohexanone, followed by photolysis, proceeds with opposite facial selectivity to that observed using (ethoxycarbonyl)nitrene. A tentative explanation is proposed. The absolute configuration of the main product, 2-(ethoxycarbonylamino)cyclohexanone (**6**), was deduced by chemical correlation.

Recently, our attention has been focused on novel methods of asymmetric formation of carbon-nitrogen bond α to the carbonyl[2] and carboxyl[3] functionality.

2-(Ethoxycarbonylamino)cyclohexanone (**6**) is obtained in high enantiomeric excess (ee) when (ethoxycarbonyl)nitrene (NCO_2Et) generated from ethyl *N*-{[(4-nitrophenyl)sulfonyl]oxy}carbamate is reacted with proline-derived optically active enamines.[2] The chemical yields are quite low, due to a side reaction giving aminimides.[4]

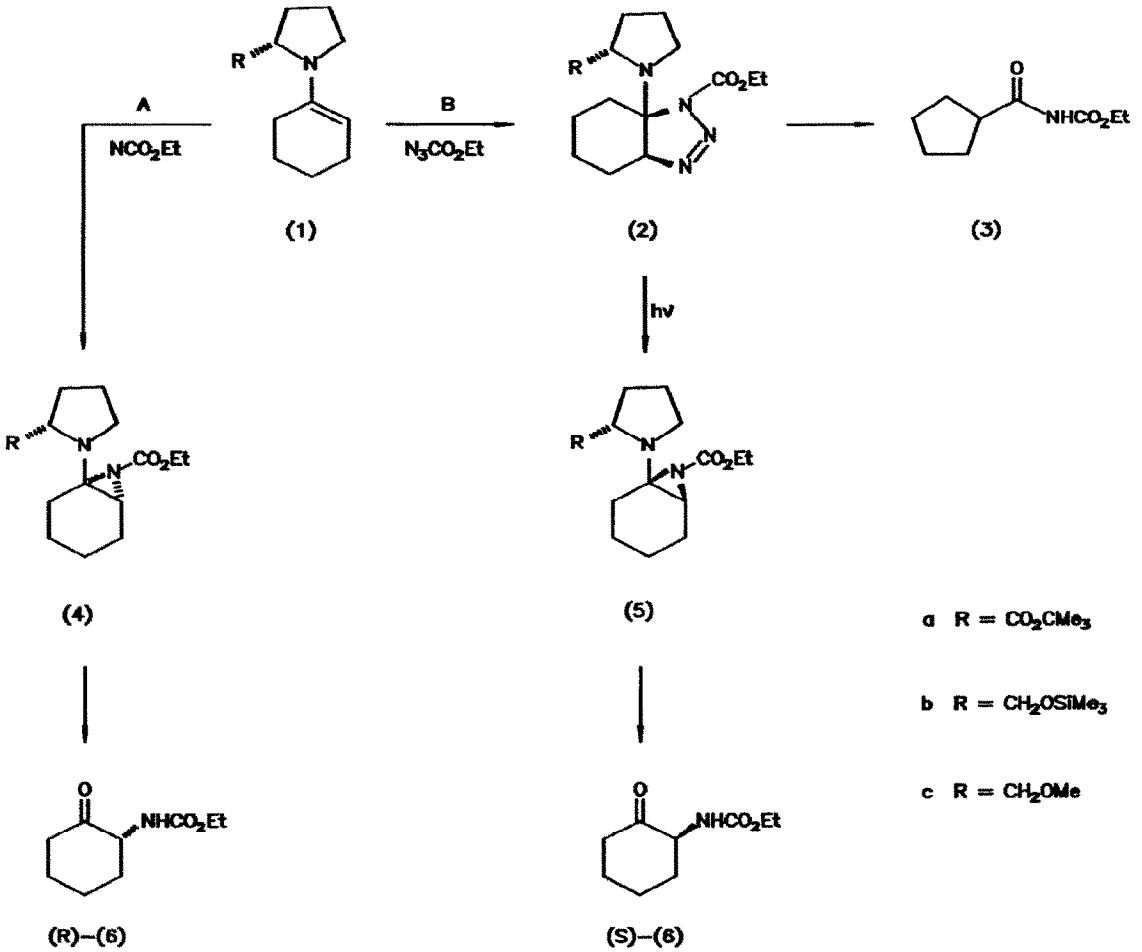
In order to improve the yields of (**6**) by avoiding attack on the nitrogen atom, an alternative route was tried, namely cycloaddition of ethyl azidoformate (N_3CO_2Et) to the same enamines, followed by photolysis.

Many addition reactions between azides and enamines have been reported.[5] Furthermore several examples of asymmetric synthesis based on cycloaddition reactions of chiral enamines are known.[6]

Reaction of ethyl azidoformate in the presence of chiral enamines (**1**), all having an (*S*) configuration, in refluxing dichloromethane was immediately followed by photolysis of the solution of the crude products. After silica gel chromatography, this sequence gave 2-(ethoxycarbonylamino)cyclohexanone (**6**) as the sole product, in chemical yields of 48 % (3 % ee), 51 % (35 % ee), and 40 % (18 % ee) respectively, starting from enamines (**1a**), (**1b**), and (**1c**). Interestingly, the major enantiomer (route B), possesses the opposite configuration to that observed in the nitrene reaction (route A).

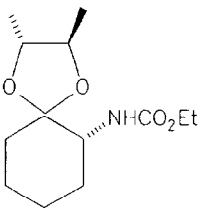
Formation of the α-amino ketone probably involves the loss of nitrogen from the expected triazoline (**2**) to give aziridine[7] (**5**) which undergoes hydrolysis to produce the final product. Competitive ring contraction, favoured by hydrolytic conditions,[8] to give *N*-(ethoxycarbonyl)cyclopentanecarboxamide (**3**) was minimized under the chosen reaction conditions.

Dedicated to Professor Giovanni Battista Marini-Bettolo on the occasion of his 75th birthday

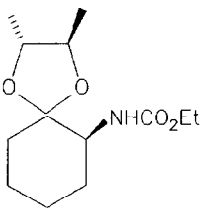


Only the major isomer is shown for products (2), (4), (5), and (6)

All attempts to isolate the triazoline resulted in its conversion into the undesired amide, thus providing an indirect proof of the proposed reaction sequence. The enantiomeric 2-(ethoxycarbonylamino)cyclohexanones (**6**) were converted into the diastereomeric acetals (**7**) and (**8**).[9] These compounds were easily purified by HPLC. Contrarily to what we previously reported,[2] the rule based on ^{13}C NMR spectra[10] does apply to these acetals, as confirmed by the chemical correlation (see below), indicating the absolute configurations shown in the formulae. The first eluted acetal (**7**) was hydrolysed to give the parent amino ketone (**6**) in 97 % ee, which showed $[\alpha]_D$ -40.38 (*c* 0.52, CH_2Cl_2) and a negative Cotton effect in the range 200-400 nm.



(**7**)



(**8**)

The absolute configuration of amino ketones was confirmed by conversion of (1*S*, 2*S*)-*trans*-2-aminocyclohexanol[11] into the *N*-(ethoxycarbonyl) derivative, followed by Jones oxidation. This gave a product identical in all respects to the major isomer obtained by the azide reaction (route B), $[\alpha]_D$ +37.50 (*c* 0.16, CH_2Cl_2).

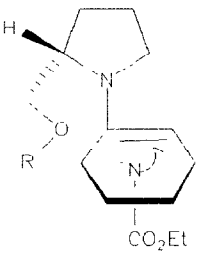
Table. 2-(Ethoxycarbonylamino)cyclohexanone (**6**) from enamines (**1**)

substrate	R	reagent	yield [%]	ee [%]	configuration
1a	CO_2CMe_3	NCO_2Et[a]	14	5	(*R*)
1a	CO_2CMe_3	N_3CO_2Et	48	3	(*S*)
1b	CH_2OSiMe_3	NCO_2Et[a]	12	52	(*R*)
1b	CH_2OSiMe_3	N_3CO_2Et	51	35	(*S*)
1c	CH_2OMe	NCO_2Et[a]	18	77	(*R*)
1c	CH_2OMe	N_3CO_2Et	40	18	(*S*)

[a] Ref. 2

The reverse facial selectivity[6b,12] observed can tentatively be attributed to the different steric[13] or stereoelectronic requirements of the reagents used. We can assume a preferential enamine conformation *anti* as reported for homoproline derivatives in the crystalline state.[14] Under this hypothesis the result

observed in the reaction with N_3CO_2Et might be understood as due to steric hindrance. In fact the highest value of ee (35 %) found is the one expected on the basis of steric effects for the addition to a monosubstituted pyrrolidine enamine, as suggested by Whitesell[15] and has been observed in the case of the bulky side chain (R = CH_2OSiMe_3).[16] The enamine prepared from cyclohexanone and *trans*-(-)-(2*R*, 5*R*)-2,5-dimethylpyrrolidine[17] failed to react with N_3CO_2Et. The main product from the nitrene route is derived from the attack on the opposite face of the enamine. The same direction of attack was observed in Michael-type reactions on similar substrates.[18] In our case we can not exclude a possible coordination of the nitrene with the ethereal oxygen atom[19] on the chiral auxiliary giving a transient complex as depicted in (**9**) (R = Me, $SiMe_3$). The stereochemistry of allylation of enamines is also rationalized by the formation of a complex.[20] The ee's observed in the reaction between (**1b**) (52 %) or (**1c**) (77 %) and NCO_2Et, higher than those expected for a non-C_2 symmetric enamine, and the absence of reaction between NCO_2Et and enamine derived from cyclohexanone and *trans*-2,5- dimethylpyrrolidine[2] seem in agreement with such a hypothesis. In addition we can note that the enamine (**1c**) having a less hindered oxygen atom with respect to (**1b**) gives the highest ee. Although discrete ylids have been observed only in reactions between nitrenes and nitrogen or sulphur substrates,[2,21] several reports indicate their possible intermediacy in the case of oxygenated substrates.[22] Possibly the chlorinated solvent (CH_2Cl_2)[23] also plays a role in favouring the transfer of the nitrene to the double bond. Accordingly, attempts to perform the reaction of (**1c**) with NCO_2Et in different solvents such as benzene and nitromethane failed to give (**6**) and only the product of attack on the nitrogen atom was observed.[24]



(**9**)

In conclusion we showed that starting from the same optically active enamines and using a different reagent it is possible to change the diastereoselectivity of a new C-N bond formation.

EXPERIMENTAL

The equipment used and the characterization of products (**7**) and (**8**) have been previously reported.[2] The enamines (**1a**),[25] (**1b**),[26] and (**1c**)[27]and ethyl azidoformate (*CAUTION! can decompose explosively at 160 °C and its vapours are toxic*)[28] were prepared according to literature methods. Optical rotations were recorded at the sodium D line with a Perkin-Elmer 241 polarimeter (1-cm cell). CD spectra (in hexane) were obtained on a JASCO J-500 A spectropolarimeter (0.1-cm cell). UV spectra (in hexane) were performed on a Perkin-Elmer Lambda 5 spectrophotometer (1-cm cell). The separations by HPLC were done with a Violet Clar 002 instrument equipped with a IOTA Jobin-Yvon differential refractometer. Solvents were HPLC-grade.

Reaction of Ethyl Azidoformate with Enamines. General Procedure. Ethyl azidoformate (10 mmol) and the enamine (10 mmol) in 10 ml of dichloromethane were refluxed in an atmosphere of nitrogen. When the azide band disappeared in the IR spectrum, the crude product was photolysed in a quartz vessel under an atmosphere of nitrogen at room temperature, using a medium pressure Hanovia PCR lamp (100 W). After 18 h, the mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel with

benzene - ethyl acetate (4:1) giving (**6**)[29] in the yields indicated in the Table: ^{13}C NMR, δ 14.51 (CH_3), 24.06 (C-5), 27.88 (C-4), 35.84 (C-3), 41.01 (C-6), 59.37 (C-2), 60.85 (CH_2O), 155.93 (COO), 207.10 (CO). The ee's were measured through the acetals,[2] which were separated by HPLC with hexane - ethyl acetate (4:1) : (**7**), 97 % de, $[\alpha]_D$ +8.01 (*c* 0.72, CH_2Cl_2), ^{13}C NMR δ 14.71 (CH_3CH_2), 16.11 and 17.57 (CH_3CH), 23.28 (C-5), 23.86 (C-4), 29.69 (C-3), 36.02 (C-6), 54.98 (C-2), 60.63 (CH_2O), 77.93 and 79.59 (CH_3CH), 108.39 (C-1), 156.35 (CO); (**8**), 82 % de, $[\alpha]_D$ -7.84 (*c* 0.51, CH_2Cl_2), ^{13}C NMR coincident with (**7**) except δ 16.61 and 17.93 (CH_3CH), 22.82 (C-5), 30.82 (C-3), 36.12 (C-6), 54.10 (C-2), 77.92 and 80.08 (CH_3CH).

(R)-2-(Ethoxycarbonylamino)cyclohexanone (6). To a solution of pure (**7**) (16 mg, 0.062 mmol) in pentane (1 ml) at room temperature 0.31 ml of 3 M HCl was added slowly. The reaction was monitored by GLC and after 3 h the solution was poured into a saturated NaCl solution and extracted with pentane. The organic layer was dried over sodium sulphate and concentrated. Purification of the crude product by HPLC with hexane - ethyl acetate (4:1) yielded (*R*)-(**6**) (5.2 mg, 45 %, 97 % ee), $[\alpha]_D$ -40.38 (*c* 0.52, CH_2Cl_2); UV, λ_{max} 277 (ε = 42 $dm^3mol^{-1}cm^{-1}$); CD, 284 ($\Delta\varepsilon$ -1.00).

(1*S*, 2*S*)-*trans*-2-(Ethoxycarbonylamino)cyclohexanol. To a solution of (1*S*, 2*S*)-*trans*-2-aminocyclohexanol[11] (0.27 g, 2.35 mmol) in 4 ml of benzene ethyl chloroformate (0.34 ml, 3.5 mmol) and triethylamine (0.5 ml, 3.5 mmol) were added dropwise and simultaneously so that the temperature remained between 10 and 20 °C. The resulting mixture was stirred an additional 2.5 h at room temperature and then filtered. The filtrate was evaporated and the residue was purified by HPLC with hexane - ethyl acetate (7:3) giving the title compound (0.335 g, 76 %), $[\alpha]_D$ -5.97 (*c* 0.67, CH_2Cl_2), whose racemic form is known.[30]

(*S*)-2-(Ethoxycarbonylamino)cyclohexanone (6). To a solution of (1*S*, 2*S*)-*trans*-2-(ethoxycarbonylamino)cyclohexanol (0.16 g, 0.85 mmol) in 3.6 ml of acetone cooled to 0 °C, 0.35 ml of a Jones solution (prepared from 0.267 g of CrO_3 in 0.23 ml of concentrated H_2SO_4 diluted to 1 ml with water) was added with stirring over a period of 5 min. Nitrogen was bubbled through all solvents and reagents before and during the reaction. The solution was allowed to stir at room temperature for an additional 10 min and then 0.14 ml of methanol was added. The chromium salts were filtered off and washed with acetone. The filtrate was evaporated and the residue dissolved in dichloromethane was washed with saturated NaCl solution and dried over Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was purified by HPLC with hexane - ethyl acetate (7:3) giving (*S*)-(**6**) (0.14 g, 88 %, 95 % ee), $[\alpha]_D$ +37.50 (*c* 0.16, CH_2Cl_2).

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