Pergamon

Tetrahedron Letters, Vol. 35, No. 20, pp. 3417-3420, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0537-8

The Formation of 3-Methyl-1a,7b-dihydro-1H-cycloprop[*c*]isoquinoline from *trans*-*N*-[2-(2-Acetylphenyl)cyclopropyl]-2-(trimethylsilyl)ethylcarbamate

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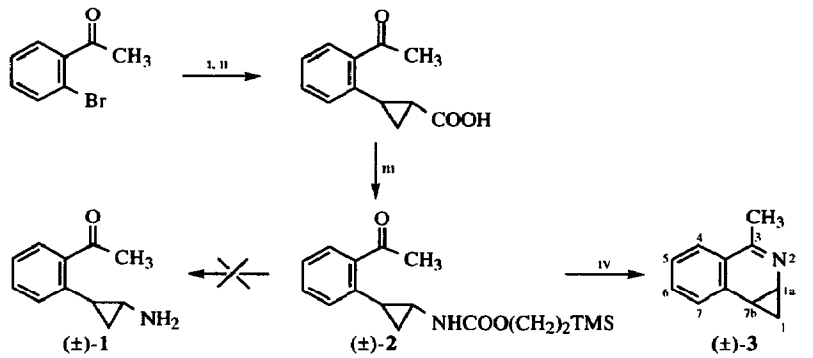
Abstract: *3-Methyl-1a,7b-dihydro-1H-cycloprop[c]isoquinoline is formed from trans-2-(2-acetylphenyl)cyclopropylamine generated in situ. The mechanism for this reaction appears to involve the formation of a cis-arylcyclopropylamine via a homoconjugated intermediate.*

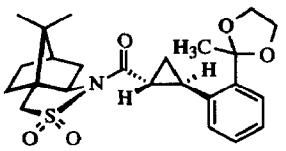
As part of a current synthetic programme aiming to produce 2-arylcyclopropylamines with ability to stimulate 5-HT_{1A}-receptors[1] we attempted to form amino derivative (±)-**1** by treatment of (±)-**2**[2] with fluoride ion[3]. This deprotection reaction produces a primary *trans*-2-arylcyclopropylamine from several other derivatives closely related to (±)-**2**.[2] However, the only product isolated from the reaction mixture was isoquinoline derivative (±)-**3**[4] and no (±)-**1** was observed. Apparently, the stereochemistry of the cyclopropyl ring moiety had isomerized from *trans* to *cis* and ring closure had occurred, possibly by a condensation reaction.



i: Methyl acrylate, (o-tolyl)$_3$P, Pd(OAc)$_2$, Et$_3$N (91 %). ii: 1. CH_2N_2, Pd(OAc)$_2$; 2. NaOH/H_2O (59 %).
iii: 1. Ethylchloroformate, Acetone; 2. NaN_3/H_2O; 3. Δ; 4.Trimethylsilylethanol (73 %). iv: TBAF (34 %).

The structure of (±)-**3** was confirmed by its characteristic spectroscopic properties:[4] NOE-measurements confirmed the *cis*-stereochemistry of the ring junction between the cyclopropyl and the isoquinoline moieties and the NMR signal of the *endo*-C1 hydrogen of (±)-**3** appears at δ 0.25 ppm, a chemical shift expected for a proton positioned in an anisotropic pseudoaromatic field.[5] Further, the appearence of a signal at δ 172.1 ppm in the ^{13}C-NMR spectrum of (±)-**3** is consistent with an iminecarbon.

Previously described syntheses of derivatives of cycloprop[c]isoquinoline have predominantly been utilizing intramolecular cycloadditions with iminocarbenes generated from nitrile ylides by either photochemical ringopening of azirines[6-9] or by 1,3-dehydrochlorination of imidoylchlorides.[10,11] A few examples of cyclizations of *cis*-N-acyl-2-phenylcyclopropylamines[12,13] and isothiocyanates[14] have also been reported.



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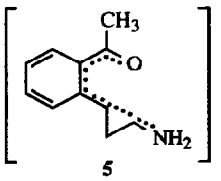
In order to investigate the mechanism of the observed ring forming reaction we prepared the enantiopure (1*R*,2*S*)-**2**[15] from **4**,[16] and treated it with TBAF. The resulting product was identical to that formed from racemic **2** demonstrating that both stereogenic centres of the cyclopropyl moiety participate in the isomerization reaction. This indicates that the homoconjugated intermediate **5** is formed during the reaction. An alternative intermediate **6**, formed from **1** via a 1,7-homosigmatropic hydride shift,[17-20] was rejected because of the inability of **1** to obtain a proper geometry for hydride transfer.[21,22]



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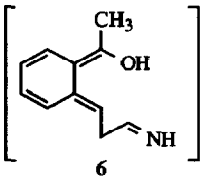

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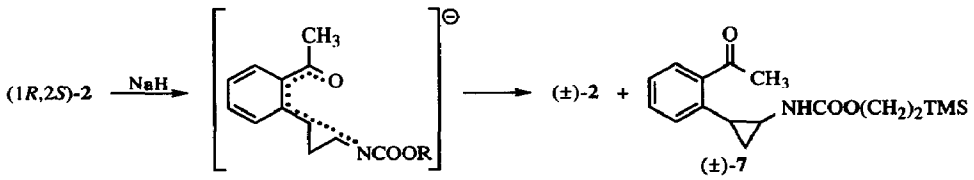
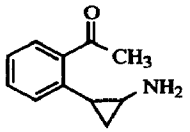
Further evidence for the participation of intermediate **5** in the ring forming reaction was obtained by an experiment in which (1*R*,2*S*)-**2** was treated with catalytic amounts of sodium hydride in THF during 24 h. The resulting mixture consisted of **2** and **7** in a 93:7 ratio according to NMR- and GC/MS-analysis. The optical rotation of this mixture was negligible ($[\alpha]_D$ -2.4°) as compared to that of the starting material ($[\alpha]_D$ -71.8°), demonstrating that both *trans/cis* isomerization and racemization had almost certainly taken place. Most likely, the observed *cis/trans* ratio corresponds to the thermodynamic equilibrium mixture.

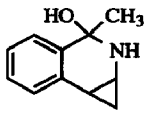


(±)-**7**

On the basis of the above observations, the following mechanistic scheme may be proposed: Deprotection of (1*R*,2*S*)-**2** gives the amine (1*R*,2*S*)-**1** which is in rapid equilibrium with its enantiomer and both enantiomers of the *cis*-isomer **8** via the achiral homoconjugated **5** (a similar *cis/trans*-isomerization has been observed in the aminocyclopropyl sulfoxide system[23]). The thermodynamically less favoured *cis*-isomer **8** has the ability to attack the carbonyl function and form aminol **9** which loses water, thus providing the driving force for the reaction.



(±)-**8**



(±)-**9**

Acknowledgement:
Support for this study was provided by grants from the Swedish Natural Science Research Council and the Swedish Board for Industrial and Technical Development.

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4. Spectroscopic data: Compound (±)**3**·HCl: mp 235-237 °C; ^{1}H-NMR (270 MHz, CD_3OD): δ 8.13 (1H, d, J = 8.1 Hz), 7.88-7.75 (2H, m), 7.57 (1H, dd, J = 7.3 and 7.3 Hz), 3.82 (1H, ddd, J = 3.6, 7.2 and 7.4 Hz), 2.90 (1H, ddd, J = 5.8, 7.2 and 9.7 Hz), 2.80 (3H, s, $C\underline{H}_3$), 2.09 (1H, ddd, J = 5.5, 7.4 and 9.7), 0.25 (1H, ddd, J = 3.6, 5.5 and 5.8 Hz); ^{13}C-NMR (270 MHz, CD_3OD): δ 172.1, 141.1, 138.8, 132.8, 130.2, 129.0, 122.7, 35.2, 20.8, 20.1 and 10.1; Anal. Calcd for $C_{11}H_{11}N$·HCl. Calcd: C, 68.22; H, 6.24; N, 7.23. Found: C, 68.35; H, 6.45; N, 7.30.
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15. Synthesis of (1*R*,2*S*)-**2**: $Ti(i\text{-}PrO)_4$ (3.1 ml, 10.4 mmol) was added to compound **4** (3.5 g, 7.8 mmol) in benzyl alcohol (10 ml) and the mixture was heated to 150 °C for 2 h. The crude mixture was purified by column chromatography (Al_2O_3: Et_2O) and the volatiles were evaporated. The crude mixture of i-propyl and benzyl esters was dissolved in aqueous 2 M NaOH (50 ml), MeOH (50 ml) and THF (50 ml). The mixture was stirred for 5 h at room temperature and concentrated. The remaining alkaline aqueous layer was washed with Et_2O (4x120 ml), acidified with 5 M HCl, extracted with Et_2O (3x120 ml), dried ($MgSO_4$) and concentrated. The crude acid was purified by flash chromatography (SiO_2: Et_2O-light petroleum 2:3 + 2.5 % HOAc) to afford the pure (1*R*,2*R*)-2-(2-acetylphenyl)cyclopropane carboxylic acid (0.47g, 29 %); mp 53-56 °C; $[\alpha]_D$ -171.8° (c = 1, CH_2Cl_2); ^{1}H-NMR (270 MHz, $CDCl_3$): δ 10.26 (1H, broad s), 7.65 (1H, dd, J = 1.3 and 7.6 Hz), 7.40 (1H, ddd, J = 1.3, 7.6 and 7.6 Hz), 7.30 (1H, ddd, J = 1.3, 7.6 and 7.6 Hz), 7.13 (1H, d, J = 7.6), 3.13-3.05 (1H, m), 2.61 (3H, s, $COC\underline{H}_3$), 1.82-1.74 (1H, m), 1.70-1.63 (1H, m) and 1.40-1.33 (1H, m); ^{13}C-NMR (270 MHz, $CDCl_3$): δ 201.7, 179.5, 139.3, 138.6, 131.6, 128.9, 127.4, 126.7, 29.7, 25.7, 23.4 and 16.7; Anal. Calcd for $C_{12}H_{12}O_3$. Calcd: C, 70.58; H, 5.92. Found: C, 70.55; H, 6.25.
Ethyl chloroformate (0.18 ml, 1.9 mmol) was added to a stirred and cooled (-10 °C) solution of the above acid (0.25 g, 1.2 mmol) and triethyl amine (0.24 ml, 1.7 mmol) in dry acetone (10 ml). After 2 h, a solution of NaN_3 (0.14 g, 2.1 mmol) in H_2O (12 ml) was added and the solution was concentrated. The residue was extracted with toluene (4x10 ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude acylazide thus obtained was dissolved in dry toluene (4 ml) and heated to 90 °C (bath temperature) for 1 h. The mixture was concentrated and the residue was dissolved in 2-(trimethylsilyl)ethanol (0.7 ml, 4.9 mmol) and heated to 60 °C for 24 h. The mixture was concentrated and the crude carbamate was purified by flash chromatography (SiO_2: Et_2O-light petroleum 1:2) to afford the pure TMS-carbamate (1*R*,2*S*)-**2** (0.31 g, 80 %) as an oil; $[\alpha]_D$ -71.8° (c = 1, CH_2Cl_2); ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.71 (1H, dd, J = 1.3 and 7.6 Hz), 7.42 (1H, ddd, J = 1.6, 7.6 and 7.6 Hz), 7.29 (1H, ddd, J = 1.3, 7.6 and 7.6 Hz), 7.20 (1H, d, J = 7.6 Hz), 5.34 (1H, broad s, N$\underline{H}$), 4.17 (2H, dd, J = 8.6 and 8.6 Hz, O$C\underline{H}_2$), 2.62 (3H, s, $COC\underline{H}_3$), 2.55-2.46 (2H, m), 1.27-1.17 (2H, m), 1.00 (2H, dd, J = 8.6 and 8.6 Hz, C-$C\underline{H}_2$-Si), 0.04 (9H, s, Si($C\underline{H}_3$)$_3$); ^{13}C-NMR (270 MHz, $CDCl_3$): δ 201.6, 157.3, 140.0, 138.4, 131.9, 129.4, 128.9, 126.2, 63.0, 32.5, 29.6, 24.0, 17.7, 15.5 and -1.5 (3C); Anal. Calcd for $C_{17}H_{25}NO_3Si$. Calcd: C, 63.91; H, 7.89; N, 4.38. Found: C, 63.5; H, 7.50; N, 4.00.
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(*Received in UK* 4 *February* 1994; *revised* 14 *March* 1994; *accepted* 17 *March* 1994)