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Diastereoselectivity in the Overman rearrangement of *O*-cyclohexylideneethylimidates

Ieva Jaunzeme,[a,b] Aigars Jirgensons,[b,*] Valerjans Kauss[b] and Eduards Liepins[a,b]

[a]*Faculty of Material Science and Applied Chemistry, Riga Technical University, Riga LV-1048, Latvia*
[b]*Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia*

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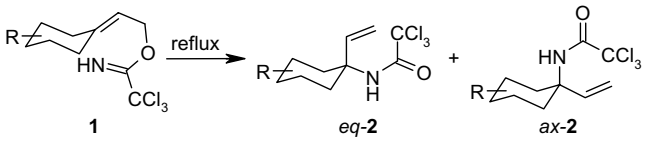
Abstract—Conformationally biased cyclohexylideneethanols were prepared and converted to trichloroacetimidates, which then were subjected to the thermal Overman rearrangement. The rearrangement of axially unshielded imidates was unselective, providing isomeric amides in equal ratio. The axial face shielding in the 3,3,5-trimethylcyclohexylidene system resulted in highly selective nitrogen attack from the equatorial side.

The aza-Claisen rearrangement of *O*-allyltrichloroacetimidates to *N*-allyltrichloroacetamides (the Overman rearrangement), performed thermally or catalyzed by soft Lewis acids, is a convenient method to prepare allyl amine derivatives.[1] The thermal Overman rearrangement constitutes one of the few alternatives for introducing an amino group at a tertiary carbon atom.[2] We found it to be the method of choice for the synthesis of 1-vinylaminocyclohexanes as NMDA receptor antagonists.[3] However, in imidates of type **1** nitrogen can attack the double bond from either the axial or the equatorial side resulting in isomeric amides **2** (Fig. 1).

The stereochemical outcome of the rearrangement was difficult to predict, since only a few examples have been reported where remarkable selectivity was induced by remote substituent effects.[2b–f] The closest example was the stereoselective introduction of an amido group in a conformationally biased cyclohexene in Isobe's total synthesis of tetrodotoxin. In this case, shielding of the equatorial face favored axial attack of the imidate nitrogen, while simultaneous axial and equatorial shielding resulted in the undesired 1,3-rearrangement product.[2d–f] Limited information on the stereochemical aspects of the Overman rearrangement prompted our investigations in this field.



1 *eq*-**2** *ax*-**2**

Figure 1. Formation of isomeric amides *eq*-**2** and *ax*-**2** from imidates **1**.

We chose the 4-*tert*-butyl- and 4-phenylcyclohexylidene systems as conformationally biased models for axially unshielded attack, and the 3,3,5-trimethylcyclohexylidene system for axially shielded attack of the nucleophile at C-1.[4]

Cyclohexylideneethanols **4a–c** were prepared from cyclohexanones **3a–c** by converting them into unsaturated esters, which were subsequently reduced (Scheme 1). 3,3,5-Trimethylcyclohexanone (**3c**) gave a mixture of isomeric alcohols *E*-**4c** and *Z*-**4c** in the ratio 2:1. These were converted to a mixture of the corresponding 4-nitrobenzoates which were resolved by crystallization. Cleavage of the 4-nitrobenzoyl group provided allylic alcohols *E*-**4c** and *Z*-**4c** with de's of 73% and 68%, respectively.[5] The diastereomeric purity of alcohols *E*-**4c** and *Z*-**4c** was sufficient to evaluate the effect of the double bond geometry on the stereoselectivity of the Overman rearrangement (vide infra). The double bond geometry in isomer *Z*-**4c** was determined based on the NOE studies.

Allylic alcohols **4a**,**b** and *E*-**4c**, *Z*-**4c** were converted to trichloroacetimidates **1a**,**b** and *E*-**1c**, *Z*-**1c**, which were

* Corresponding author. Tel.: +371 7543535; fax: +371 7553142; e-mail: aigars@osi.lv

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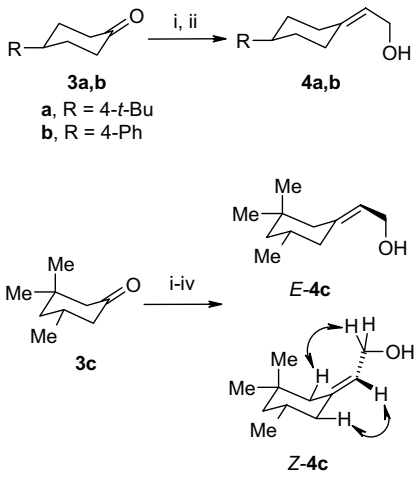
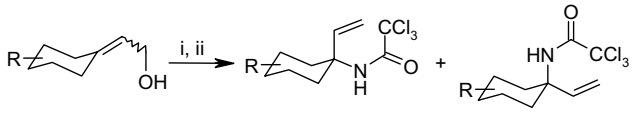


Scheme 1. Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2Et$ (1.2 equiv), NaOEt, EtOH, rt; (ii) DIBAL-H (2.2 equiv), Et_2O, 0 °C, **4a** 70%, **4b** 71%, **4c** 80% over two steps; (iii) *o*-$NO_2C_6H_4COCl$, Py, 0 °C, 89%; (iv) K_2CO_3, MeOH, rt, 2 h, 78%.

isolated and immediately subjected to thermal rearrangement (Scheme 2). The ratio of the resulting trichloroacetamidocyclohexanes *eq*-**2a**–**c** and *ax*-**2a**–**c** was determined by GC–MS analysis prior to workup, and the products were then isolated as mixtures of isomers (Table 1). The rearrangement of trichloroacetimidates **1a**,**b** derived from 4-phenyl- and 4-*tert*-butylcyclohexylideneethanols (**3a**,**b**) was unselective, providing isomeric amides *eq*-**2a**,**b** and *ax*-**2a**,**b** in equal ratios. However, the rearrangement of trichloroacetimidates *E*-**1c** and *Z*-**1c** gave predominantly amide *eq*-**2c**. Notably, the geometry of the double bond in imidates *E*-**1c** and *Z*-**1c** had little impact on the ratio of isomers *eq*-**2c** and *ax*-**2c**.

To determine the configuration of the major trichloroacetamide *eq*-**2c**, it was hydrolyzed to amine **5** (Scheme 3), crystallized to give a de >95% and studied by NMR spectroscopy.[6] Large vicinal coupling constants

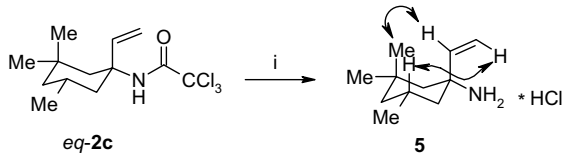


Scheme 2. Reagents and conditions: (i) Cl_3CCN (1.1 equiv), NaH (10 mol %), Et_2O, −10 °C; (ii) *o*-xylene, reflux, 10 h.

Table 1. Stereochemical results of the Overman rearrangement

Alcohol **4**	Ratio *eq*-**2**:*ax*-**2**	Yield[a] (%)
a	1:1	70
b	1:1	72
E-**c**	12:1	58
Z-**c**	19:1	28[6]

[a] Isolated yields in two steps from alcohol **4**.



Scheme 3. Reagents and conditions: (i) (a) NaOH, DMSO; (b) HCl, 68%.

between 4-CH_{ax} and 6-CH_{ax} ($J = 12.5$ Hz) indicated the chair conformation of compound **5**.[7] The amino group is cis oriented with respect to 5-CH_3, as was indicated by NOE measurements.

The high selectivity in the rearrangement of conformationally biased imidates *E*-**1c** and *Z*-**1c** confirmed that axial face shielding of the cyclohexane directs nitrogen attack from the equatorial side. Kinetic control was proved by the fact that the ratio of the trichloroacetamides *eq*-**2c** and *ax*-**2c** (enriched with minor isomer *ax*-**2c**, 2:1) remained unchanged after heating the mixture for 10 h. This suggests that the isomer distribution depends on the energy differences of the diastereomeric transition states. Axial face shielding by 3-CH_{3ax} occurs provided that nitrogen attacks C-1 nondistorted from sp^2 geometry—a situation that is similar to nucleophilic addition to cyclohexanones. This is the case if the rearrangement is concerted and proceeds through an early (reactant-like) transition state, as supported by the evidence of exothermic nature of the process.[1b] A planar allylic part in an ion-pair transition state for the Overman rearrangement was proposed by semi-empirical calculations[8] and could also be used to explain the observed stereochemical results.

In summary, we have demonstrated that axial face shielding induces stereoselective nitrogen attack from the equatorial side during the Overman rearrangement of trichloroacetimidates derived from 2-cyclohexylideneethanols. With this information in hand, we have prepared a series of 1,3,3,5-tetrasubstituted aminocyclohexanes possessing an equatorially positioned amino group as NMDA receptor antagonists, the studies of which will be reported elsewhere.

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5. *Z*-**4c**: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.77$ (s, 3H, 3-CH_{3ax}), 0.87 (d, $J = 6.3$ Hz, 3H, 5-CH_3), 0.96 (d, $J = 12.7$, 1H, 4-CH_{ax}), 0.96 (s, 3H, 3-CH_{3eq}), 1.36–1.42 (m, 2H, 4-CH_{eq} and 6-CH_{ax}), 1.56 (d, $J = 13.7$ Hz, 1H, 2-CH_{ax}), 1.61 (m, 1H, 5-CH_{ax}) 2.14 (d, $J = 11.0$ Hz, 1H, 6-CH_{eq}), 2.24 (d, $J = 13.1$ Hz, 1H, 2-CH_{eq}), 4.09 (dd, $J = 6.8$, 5.8 Hz, 2H, CH_2O), 5.45 (m, 1H, =CH). *E*-**4c**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.79$ (s, 3H, 3-CH_{3ax}), 0.91 (d, $J = 6.6$ Hz, 3H, 5-CH_{3eq}), 0.85–1.05 (m, 1H, 4-CH_{ax}), 0.94 (s, 3H, 3-CH_{3eq}), 1.18 (s, 1H, OH), 1.15–2.00 (m, 5H, 2-CH_2, 6-CH_{ax}, 4-CH_{eq}, 5-CH_{ax}), 2.57 (d, $J = 13.2$ Hz, 1H, 6-CH_{ax}), 4.17 (d, $J = 6.8$ Hz, 2H, CH_2O), 5.33 (t, $J = 7.0$ Hz, 1H, =CH).
6. The low isolated yield of amide **2c** from *Z*-**4c** may be due to the very small scale. The rearrangement of the imidate derived from the mixture of isomeric alcohols *E*-**4c** and *Z*-**4c** (*E*/*Z* = 3:1) gave trichloroacetamides *eq*-**2c** and *ax*-**2c** (*eq*/*ax* = 16:1) in 63% total yield.
7. **5**: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.87$ (s, 3H, 3-CH_{3eq}), 0.88–0.95 (m, 1H, 4-CH_{ax}), 0.93 (d, 3H, $J = 7.0$ Hz, 5-CH_3), 0.95 (s, 3H, 3-CH_{3ax}), 1.31–1.38 (m, 2H, 2-CH_{ax} and 4-CH_{eq}), 1.67 (d, 1H, $J = 13.2$ Hz, 6-CH_{ax}), 1.70 (m, 1H, 5-CH_{ax}), 1.97 (d, 1H, $J = 13.2$ Hz, 2-CH_{eq}), 2.30 (d, 1H, $J = 12.3$ Hz, 6-CH_{eq}), 5.41 (d, 1H, $J = 10.5$ =CH_{2trans}), 5.62 (d, 1H, $J = 17.6$ Hz, =CH_{2cis}), 6.02 (dd, 1H, $J = 17.6$, 10.5 Hz, =CH), 8.25 (3H, br s, NH_3^+; ^{13}C NMR (150 MHz, $CDCl_3$): 22.07 (5-CH_3), 25.14 (5-CH), 26.66 (3-CH_{3ax}), 31.99 (3-C), 33.89 (3-CH_{3eq}), 40.86 (4-CH_2), 47.23 (2,6-CH_2), 57.67 (1-C), 119.27 (=CH_2), 138.28 (=CH).
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