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Stereoselective synthesis of *cis*-2-aryl- and 2-alkyl-1-chlorocyclopropanecarboxaldehydes

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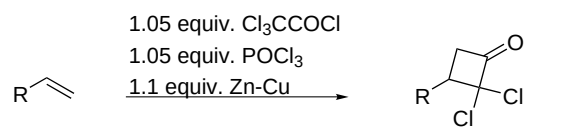
Abstract—The title compounds were stereoselectively synthesized via a semi-benzilic Favorskii rearrangement of 3-aryl- and 3-alkyl-2,2-dichlorocyclobutanols, obtained by stereoselective reduction of the corresponding cyclobutanones. This synthetic pathway, starting from the synthesis of 3-substituted-2,2-dichlorocyclobutanones can be performed in one day with total yields up to 60% after purification. Reduction of the cyclobutanones yielded only *cis*-3-substituted cyclobutanols. Taking into account the stereoselectivity of the rearrangement, 1-halocyclopropanecarboxaldehydes, of which very few articles have been published, can be seen as highly interesting building blocks for further elaboration. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Readily available 2-halogenated cyclobutanones exhibit interesting properties for ring transformation due to their pronounced electrophilicity and ring strain. This is proved by the numerous reactions described in the literature,[1] among which the well-known Favorskii rearrangement has been used to synthesize cyclopropanecarboxaldehydes.[2–9] Surprisingly, only very few publications are found to exist regarding 1-halocyclopropanecarboxaldehydes, which are interesting building blocks for further organic synthesis. In most cases the synthetic pathways have no stereochemical impact, thus chromatographic separation of the formed isomers is required. Only two publications were found concerning ring contraction of 2,2-dihalocyclobutanones towards 1-halocyclopropanecarboxaldehydes. One article describes the Favorskii rearrangement after chromatographic separation of a diastereomeric mixture of steroidal spirocyclobutanones towards the corresponding spirocyclopropane steroids[8] and a second publication deals with the ring contraction of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (the dichloroketene adduct of cyclopentadiene).[9] With our research, a general, easy synthesis of 2-substituted 1-halocyclopropanecarboxaldehydes is established. Up to now, α-halogenated cyclopropanecarboxaldehydes were (less efficiently) accessible via dihalocarbene addition to *O*-protected 2-halopropen-1-ols[10] or via a lithium–halogen exchange of geminal dihalocyclopropanes (synthesized via dihalocarbene addition to olefins) and subsequent reaction with formates or formamides.[11–13] Also, oxidation of mixtures of stereoisomers of 1-halocyclopropylmethanol derivatives leads to the corresponding α-halogenated aldehydes.[14] Another approach consists of a carbene addition to α-haloacrylates or derivatives.[15–17] With the latter method 5-(1-halocyclopropyl)-2,4-dienamides were synthesized and are patented as acaricidal and insecticidal compounds.[18,19]

2. Results and discussion

3-Substituted-2,2-dichlorocyclobutanones **2a–c** were easily synthesized via a [2+2]-cycloaddition of olefins **1a–c** to dichloroketene, generated from trichloroacetyl chloride and a Zn–Cu couple[20] (Scheme 1). The



1a R = Ph
1b R = 4-Cl-C_6H_6
1c R = *n*-Bu

2a-c 74-80%

Scheme 1.

Keywords: cyclopropanes; 1-chlorocyclopropanecarboxaldehydes; Favorskii rearrangement; cyclobutanones.

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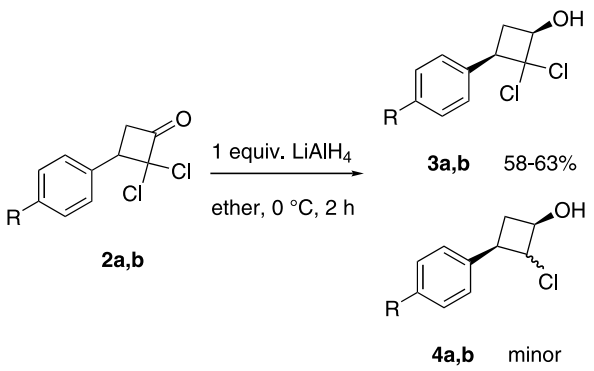
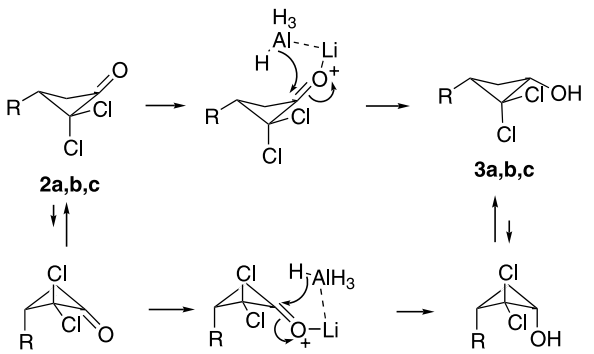
cyclobutanones **2a,b** thus obtained, were treated with reducing agents to give the corresponding 3-aryl-2,2-dichlorocyclobutanols **3** in a stereoselective way as shown in Scheme 2.



Scheme 2.

Reductions of non-halogenated 3-substituted cyclobutanones were previously described in the literature, where the resulting alcohols were mixtures of isomers.[21,22] In our experiments, reduction of the cyclobutanones **2a,b** with $LiAlH_4$ or $LiAlH(OtBu)_3$ yielded only *cis*-3-arylcyclobutanols **3** in yields around 60%. HPLC-separation of the crude reaction mixture from the reduction of cyclobutanone **2a** resulted in the isolation and characterization of 2-chloro-3-phenylcyclobutanol **4a** as a minor byproduct. A slight difference in the ratio of **3**/**4** was observed when the reaction was carried out using an excess of $LiAlH_4$, $LiAlH(OtBu)_3$ or $NaBH_4$. The ratio determined by gas chromatographic analysis was 85/15, 93/7 and 94/6, respectively.

The stereoselectivity of the reaction is not due to an *exo*-attack of hydride, but due to steric hindrance of the substituent in the 3-position. This effect appears to be more important than the favorable *exo*-attack of hydride to the cyclobutane ring with the substituent in the equatorial position, as shown in Scheme 3. *exo*-Attack yielding *cis*-substituted cyclobutanols is only possible when the substituent is in the thermodynamically less favorable axial position.



Scheme 3.

In order to determine unambiguously the stereochemistry by DIFNOE-NMR techniques, cyclobutanol **3b** was derivatized to the 3,5-dinitrobenzoate. In the case of 2,2-dichloro-3-(4-chlorophenyl)cyclobutyl 3,5-dinitrobenzoate **5** (yield 90% from **3b**) a significant Overhauser effect was observed between the hydrogen atoms in the 1- and 3-positions of the cyclobutane ring, which indicated that both hydrogens are positioned in *cis*-configuration (Fig. 1).

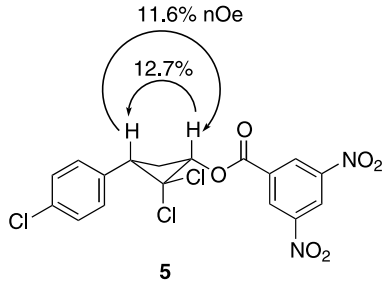
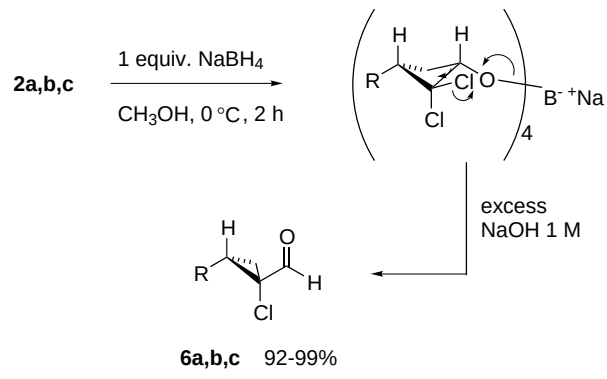


Figure 1.

In order to perform a ring contraction of *cis*-cyclobutanols **3**, the latter were treated with a 1 M solution of sodium hydroxide in water. The reduction of cyclobutanones **2** and subsequent ring contraction can be performed in one step, without purification of the cyclobutanols, by first adding $NaBH_4$ to the ketones **2** in methanol at 0°C and after an appropriate time, a basic workup (Scheme 4). When the reducing agent was added at higher temperatures, formation of a minor amount of 1-chlorocylopropylmethanols **7** was observed due to overreduction. This compound can also be obtained in high yield by reduction of the α-halogenated aldehydes **6** with $NaBH_4$ in methanol at 0°C.

Conia and Salaün[2,4] demonstrated in 1972 that the mechanism of the ring contraction of halogenated cyclobutanols involves a semi-benzilic Favorskii rearrangement where the hydroxyl function must be in the equatorial position.[23] The stereochemistry of the obtained cyclopropanecarboxaldehydes **6** was analyzed via DIFNOE experiments.



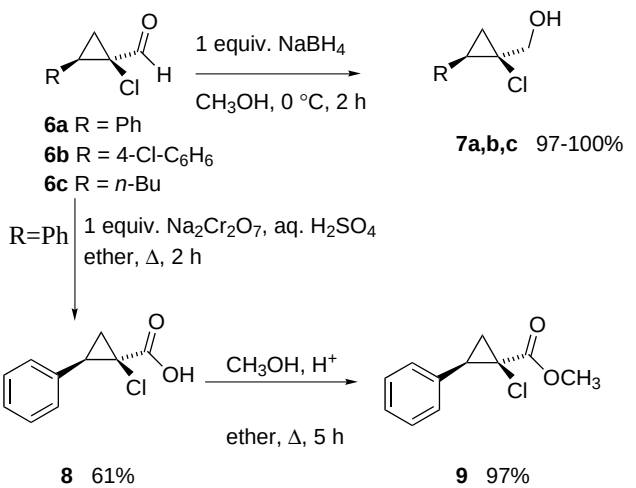
Scheme 4.

After distillation of cyclopropanecarboxaldehydes **6**, storage under inert atmosphere is needed, because after a while auto oxidation of the aldehydes takes place. Because no further reactions on 1-halocyclopropanecarboxaldehydes have been described, some simple transformations were performed leading to alternative routes to substituted cyclopropanes **7**, **8** and **9**. Controlled oxidation of the aldehydes and subsequent esterification was possible with sodium dichromate in acidic medium followed by normal esterification procedures (Scheme 5).

In conclusion, this paper describes an efficient and facile synthesis to *cis*-2-substituted 1-chlorocyclopropanecarbox-aldehydes **6** and derived products **7**–**9** in a stereoselective way. Keeping in mind the physiological activity of 2-halogenated cyclopropyldienamides and the very few articles published about this subject, this pathway provides interesting results for further elaboration of the cyclopropane chemistry.

3. Experimental

A typical procedure for the synthesis of aldehydes **6a,b,c** can be given with 1-chloro-2-phenylcyclopropanecarboxaldehyde **6a** as an example. To a cooled solution of 1.0 g (4.65 mmol) 2,2-dichloro-3-phenylcyclobutanone **2a** in 10 ml of methanol, 1 equiv. (0.18 g) of sodium borohydride was added in portions at 0°C. After stirring for 2 h at 0°C, 30 ml of a 1 M solution of sodium hydroxide in water was added and stirred for another 15 min at room temperature. After extraction of the reaction mixture with chloroform (3×20 ml), drying of the combined organic layers and evaporating of the solvent, a colorless oil was obtained in 100% yield. To remove impurities, aldehyde **6a** can be distilled at 58–60°C, 0.01 mmHg (colorless oil, 78%). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.87 (dd, $J=6.3$; 8.6 Hz, 1H), 2.17 (dd, $J=6.3$; 10.2 Hz, 1H), 3.00 (dd, $J=9.4$ Hz 2×, 1H), 7.20–7.38 (m, 5H), 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 23.4, 34.9, 53.2, 127.8, 128.3, 129.3, 133.6, 197.1; IR (KBr, cm^{-1}): 2837, 1717; MS (70 eV): m/z (%): 180/82 (M^+, 33); 145 (100); 127 (29), 117 (33), 116 (25), 115 (83), 91 (32).



Scheme 5.

3.1. 1-Chloro-2-phenylcyclopropanecarboxylic acid 8

Colorless solid, mp: 76.7°C, spectral data: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.84 (dd, $J=5.9$; 8.6 Hz, 1H), 2.23 (dd, $J=5.9$; 10.2 Hz, 1H), 3.17 (dd, $J=9.5$ Hz 2×, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 68 MHz, int. ref. 77.00 ppm): δ 24.0, 34.7, 44.2, 127.8, 128.2, 129.4, 133.8, 177.0; IR (KBr, cm^{-1}): 3414, 1693, 1636, 1617, 1498; MS (70 eV): m/z (%): 196/98 (M^+, 20); 116 (44), 115 (100).

3.2. Methyl 1-chloro-2-phenylcyclopropanecarboxylate 9

Colorless oil, $R_f=0.38$ (ethyl acetate/hexane:10/90), spectral data: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.78 (dd, $J=5.9$; 8.6 Hz, 1H), 2.16 (dd, $J=5.9$; 10.2 Hz, 1H), 3.09 (dd, $J=9.4$ Hz 2×, 1H), 3.84 (s, 3H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 68 MHz, int. ref. 77.00 ppm): δ 22.8, 33.2, 44.2, 52.8, 127.1, 127.7, 128.9, 133.9, 169.9; IR (KBr, cm^{-1}): 1724, 1606, 1500, 1437, 1283; MS (70 eV): m/z (%): 210/2 (M^+, 33); 178 (17), 174 (17), 131 (25), 116 (19), 115 (100).

Acknowledgements

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