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Synthesis of racemic *cis*-1-alkyl- and 1-aryl-2-aminocyclopropanecarboxylic esters

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Abstract—The title cyclic β-amino esters were synthesized stereo- and regioselectively. Starting from the corresponding 1-aryl- and 1-alkylcyclopropane-1,2-dicarboxylates, selective monosaponification and subsequent Curtius reaction leads to certain *cis*-1-alkyl- and 1-aryl-2-aminocyclopropanecarboxylic esters. These β-aminocyclopropanecarboxylate derivatives (β-ACCs) can be seen as useful building blocks for β-peptides.

1. Introduction

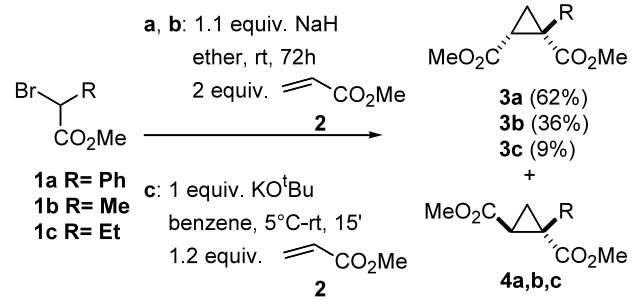
The interesting pharmacological properties of β-amino acids and their use in the synthesis of β-peptides have, especially in the last decade, renewed the interest of organic chemists.[1–4] The conformationally restricted β-aminocyclopropanecarboxylates (β-ACCs) are important building blocks in the synthesis of peptides with improved properties and in SAR studies.[5–12] Several synthetic methods have led to these vicinally push–pull-substituted cyclopropanes. Carbene or carbenoid addition to enamines or enaminocarbonyl compounds,[7,13–21] Michael addition of amines to cyclopropenecarboxylates,[22] oxidation of the corresponding hydroxymethylcyclopropylamines[8,9,23–27] and lithiation–substitution of cyclopropylamines are the most important methods described.[28] These methods suffer from drawbacks such as very low overall yield or stringent reaction conditions. A quite elegant method with good yields is the Curtius reaction applied at the corresponding cyclopropane-1,2-dicarboxylates.[10,27,29–34] Surprisingly this method has not been generalized towards alkyl- or aryl-substituted cyclopropane-1,2-dicarboxylates. Only ethyl (1*R*,2*R*)-2-(benzyloxycarbonylamino)-2-methylcyclopropane-1-carboxylate has been synthesized this way.[27]

In this report we wish to present our results of a one-step Curtius reaction starting from 1-aryl- and 1-alkylcyclopropane-1,2-dicarboxylates. In general, only few articles have appeared on the synthesis of alkyl- and aryl-substituted β-aminocyclopropanecarboxylic esters.[5,13,15,16,18,22,28] Most of them require carbene-type reactions or photolysis.

2. Results and discussion

The reaction between acrylates **2** and enolates derived from α-bromo esters **1** gives a ready access to *cis*-cyclopropanedicarboxylates **3** (major products) and *trans*-cyclopropanedicarboxylates **4** (d.r. >4:1) (Scheme 1).[35,36] Distillation and column chromatography enables the isolation of pure *cis*-1-aryl- and 1-alkylcyclopropane-1,2-dicarboxylates **3**.

The regioselective monosaponification of the least sterically hindered ester function in **3** with sodium hydrox-



Scheme 1.

Keywords: β-amino acids; β-aminocyclopropanecarboxylic acids; Curtius reaction.

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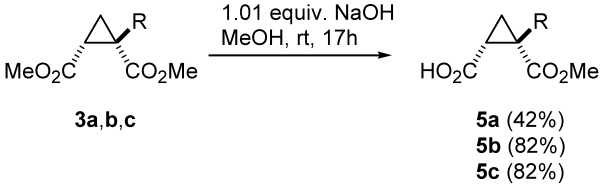
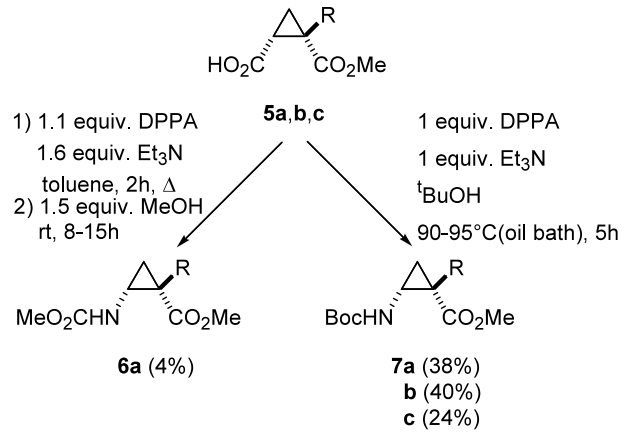
ide in methanol leads to 2-aryl- and 2-alkyl-2-(methoxycarbonyl)cyclopropane-1-carboxylic acids **5** (Scheme 2). This monosaponification has already been used in our research group for the synthesis of dimethyl-2,2-dialkylcyclopropane-1,1-dicarboxylates.[37] The spectral data of the phenyl derivative **5a**, which are in correspondence with literature data,[38] confirm that only reaction occurs at the least sterically hindered methoxycarbonyl group at position 2. The signal of the least sterically hindered methoxy group and, as a consequence, also the most deshielded signal (δ 3.77 ppm versus δ 3.66 ppm of the shielded methoxycarbonyl function on the phenyl-substituted carbon), disappeared completely. The same observations were made for methyl- and ethyl-substituted cyclopropanes **5b** and **5c**.

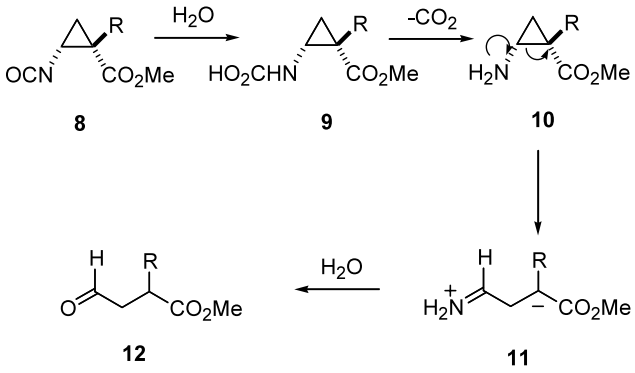
A modified Curtius rearrangement on the cyclopropanecarboxylic acids **5** finally led to the corresponding methyl 2-(alkoxycarbonylamino)-1-aryl- and 1-alkylcyclopropane-1-carboxylates **6** and **7** (Scheme 3). When a two-step modified version of the Curtius reaction was applied by treatment of **5a** with triethylamine and diphenyl phosphorazidate for 2 h reflux in toluene, followed by addition of methanol and subsequent stirring for 8–15 h, only a small amount of carbamate **6a** could be isolated from the reaction mixture with column chromatography. In the ^{1}H NMR spectra of most of the impure fractions was clearly present an aldehyde peak, probably arising from the ring-opened product **12**. The formation of this γ-keto ester is rationalised by formation of the carbaminic acid **9** from the intermediate isocyanate **8** and traces of water. This carbaminic acid **9** opens to the iminium salt **11** which underwent hydrolysis. This ring opening is inherent for 1,2-push–pull-substituted cyclopropanes (Scheme 4).[39] In order to avoid this ring opening the modified Curtius reaction was repeated under one-step conditions. Dry



Scheme 2.



Scheme 3.



Scheme 4.

tert-butanol was used instead of toluene, so that the formed isocyanate **8** would react in situ to the Boc-protected β-ACC derivative **7a**. Under these conditions, *cis*-methyl 1-aryl- and 1-alkyl-2-(*tert*-butoxycarbonylamino)cyclopropane-1-carboxylates **7** were isolated in better yields after column chromatography.

The *cis* configuration of **7a** was confirmed with DIFNOE-NMR experiments (Table 1, $CDCl_3$). The fact that after irradiation of proton H_c, the most shielded proton exhibits the highest NOE, proves that the proton in *cis* position of H_c is also positioned *cis* to the phenyl substituent (Fig. 1). This indicates that the carbamate function holds a *cis* position to the ester group.

Table 1. DIFNOE-NMR experiments on **7a**: irradiated protons and corresponding percentages NOE of the different protons ($CDCl_3$).

Irradiated proton	NOE (%)					
	H_a	H_b	H_c	N*H*	OCH_3	C_6H_5
H_a	–	20.5	6.5	0	1.3	8.1
H_b	24.6	–	Overlap[a]	6.4	Overlap[a]	6.0
H_c	8.1	2.2	–	1.6	0	7.8

[a] The total % NOE of H_c and OCH_3 was 2.2%; the signals were however not resolved enough to make a distinction and the use of C_6D_6 resulted, because of ASIS, in a better resolution of the signals of H_c and OCH_3, but in a worse resolution of the signals of H_b and the *tert*-butyl group.

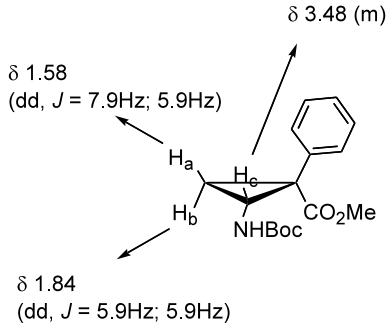
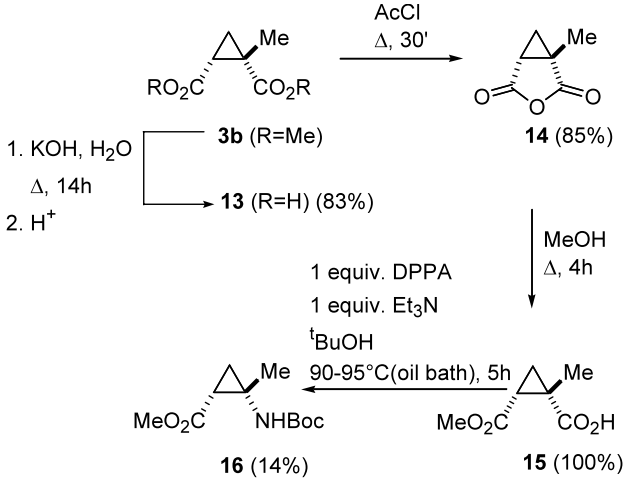


Figure 1.

The synthesis of the other regioisomer **16** was achieved via a four-step sequence. Treatment of the cyclopropane diester **3b** with a large excess of potassium hydroxide resulted in the diacid **13** which could be converted into the corresponding anhydride **14** by heating at reflux for a short period of time in acetyl chloride. Subsequent heating at reflux in methanol gave quantitatively *cis*-2-(methoxycarbonyl)-1-methylcyclopropane-1-carboxylic acid **15**. Also in this case, a complete regioselectivity of the nucleophilic addition of methanol to the least sterically hindered carbonyl group was observed. The final rearrangement under the same conditions as in the synthesis of 1-aryl- and 1-alkyl-substituted cyclopropanes **7**, resulted in the isolation of methyl 2-(*tert*-butoxycarbonylamino)-2-methylcyclopropane-1-carboxylate **16**, although in low yield, after chromatography and crystallisation (Scheme 5).

In conclusion, this paper describes a stereo- and regioselective synthesis of 1-methyl, 1-phenyl and 2-methyl 2-(alkoxycarbonylamino)cyclopropane-1-carboxylates. This makes certain β-ACC derivatives available which are of interest for further research in the fast-growing field of β-peptides and peptidomimetics.



Scheme 5.

3. Experimental

A typical procedure for the synthesis of methyl cyclopropanecarboxylates **7a–c** and **16** is given with *cis*-methyl 2-(*tert*-butoxycarbonylamino)-1-phenylcyclopropane-1-carboxylate **7a** as an example. To a solution of 0.5 g (23 mmol) of *cis*-2-methoxycarbonyl-2-phenylcyclopropane-1-carboxylic acid **5a** in 5 ml dry *tert*-butanol was added 0.23 g (23 mmol) of triethylamine and 0.62 g (23 mmol) of diphenyl phosphorazidate. The reaction mixture was heated for 5 h at 90–95°C (oil bath), the solvent was evaporated and 5 ml of water was added. After extraction with ethyl acetate (3×40 ml), the combined organic phases were washed with water and brine and dried ($MgSO_4$). Evaporation in vacuo resulted in a brown viscous oil which was subjected to column chromatography to obtain the resultant products.

3.1. *cis*-Methyl 2-(*tert*-butoxycarbonylamino)-1-phenylcyclopropane-1-carboxylate 7a

White crystals (253 mg, 38%), mp 97.0–98.0°C, $R_f = 0.30$, petroleum ether/EtOAc 4/1; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.47 (s, 9H), 1.58 (dd, $J = 5.9$, 7.9 Hz, 1H), 1.84 (dd, $J = 5.9$, 5.9 Hz, 1H), 3.48 (m, 1H), 3.62 (s, 3H), 5.26 (broad s, 1H), 7.24–7.36 (m, 3H), 7.46–7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 21.1, 28.3, 35.7, 39.2, 52.6, 79.9, 127.5, 128.3, 130.7, 138.4, 156.2, 172.0; IR (KBr, cm^{-1}): 3367, 1710; MS (70 eV): m/z (%): no M$^+$, 234 (5), 202 (6), 190 (12), 189 (7), 175 (10), 158 (100), 157 (21), 132 (26), 130 (45), 129 (42), 115 (12), 103 (31), 77 (9), 57 (82).

3.2. *cis*-Methyl 2-(*tert*-butoxycarbonylamino)-1-methylcyclopropane-1-carboxylate 7b

White crystals, mp 71.8–72.7°C, $R_f = 0.21$, petroleum ether/EtOAc 4/1; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.05 (dd, $J = 5.6$, 7.9 Hz, 1H), 1.32 (s, 3H), 1.37 (m, 1H), 1.43 (s, 9H), 3.10 (m, 1H), 3.71 (s, 3H), 5.24 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 19.0, 22.0, 24.9, 28.3, 39.0, 52.2, 79.6, 156.1, 173.7; IR (KBr, cm^{-1}): 3359, 1714; MS (70 eV): m/z (%): no M$^+$, 172 (9), 155 (6), 141 (5), 128 (13), 123 (6), 113 (14), 97 (42), 70 (19), 69 (12), 57 (100).

3.3. *cis*-Methyl 2-(*tert*-butoxycarbonylamino)-1-ethylcyclopropane-1-carboxylate 7c

Colorless oil, $R_f = 0.24$, petroleum ether/EtOAc 4/1 ; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 0.98 (t, $J = 7.3$ Hz, 3H), 1.05 (dd, $J = 5.8$, 7.8 Hz, 1H), 1.27 (m, 1H), 1.36 (m, 1H), 1.43 (s, 9H), 1.96 (dq, $J = 7.3$, 14.4 Hz, 1H), 3.10 (m, 1H), 3.72 (s, 3H), 5.20 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 11.3, 20.1, 26.4, 28.3, 31.2, 38.1, 52.0, 79.6, 156.0, 173.2; IR (NaCl, cm^{-1}): 3370, 1720; MS (70 eV): m/z (%): 243 (M$^+$, 0.05), 186 (8), 142 (10), 128 (14), 111 (46), 84 (17), 83 (20), 82 (12), 57 (100).

3.4. *cis*-Methyl 2-(*tert*-butoxycarbonylamino)-2-methylcyclopropane-1-carboxylate 16

White crystals, mp 82.7–83.3°C, $R_f = 0.20$, petroleum ether/EtOAc 4/1 ; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.13

(dd, $J=5.3$, 8.4 Hz, 1H), 1.40 (m, 1H), 1.42 (s, 9H), 1.46 (s, 3H), 1.84 (dd, $J=6.3$, 8.4 Hz, 1H), 3.67 (s, 3H), 4.98 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 21.9, 24.1, 27.6, 28.2, 37.6, 51.8, 79.6, 155.7, 171.3; IR (KBr, cm^{-1}): 3371, 1729, 1695; MS (ES, 3.5kV): m/z (%): 230 (M^++1, 7), 174 (32), 152 (12), 130 (100), 98 (25).

3.5. *cis*-Methyl 2-(methoxycarbonylamino)-1-phenylcyclopropane-1-carboxylate 6a

$R_f=0.25$, petroleum ether/EtOAc 7/3; ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.63 (dd, $J=5.9$, 8.6 Hz, 1H), 1.86 (dd, $J=5.9$, 6.3 Hz, 1H), 3.62 (s, 3H), 3.65 (m, 1H), 3.72 (s, 3H), 5.52 (broad s, 1H), 7.28–7.38 (m, 3H), 7.43–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 68 MHz): δ 21.2, 35.5, 39.5, 52.4, 52.7, 127.6, 128.4, 130.6, 138.1, 157.3, 172.1; IR (NaCl, cm^{-1}): 3350, 1726; MS (70 eV): m/z (%): 249 (M^+, 1), 248 (7), 218 (15), 217 (100), 190 (19), 189 (20), 174 (67), 159 (12), 158 (81), 144 (10), 131 (14), 130 (23), 129 (10), 115 (43), 103 (50), 86 (10), 84 (11), 77 (19), 59 (15).

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