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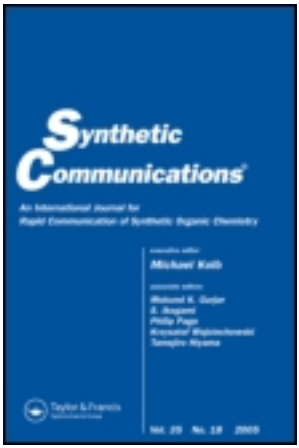

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Facile Synthesis of β-Azidocyclopropanecarboxylates by MIRC Reaction

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Facile Synthesis of β-Azidocyclopropanecarboxylates by MIRC Reaction

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Abstract: Two β-azidocyclopropanecarboxylates are readily synthesized from β-bromoalkyliden malonates via a Michael–initiated ring closure (MIRC) reaction in moderate yields, which are regarded as precursors of β-aminocyclopropanecarboxylic acids.

Keywords: MIRC, cyclopropane, β-azido acid

The overwhelming importance of α-amino acids in biologically relevant processes has also been manifested for many cyclopropane-containing derivatives.[1] With the growing realization that some β-amino acids also display significant biological activities[2] and because the latter are valuable constituents in peptides, β-cyclopropyl-substituted analogues have attracted widespread attention in recent years. In addition, cyclopropyl-modified β-alanines have been proved to be useful intermediates in organic syntheses and make use of the amino, the carboxyl, and the cyclopropyl group as reactive functionalities.[3]

Azido acids are versatile precursors for natural and nonnatural amino acids and can be incorporated into peptides and subsequently reduced to amino acids.[4] There are possibilities that β-azido acid **1** can be fused directly with a cyclopropane ring: the cyclopropyl group can be placed like

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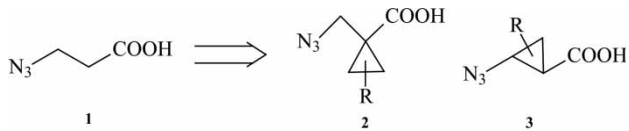
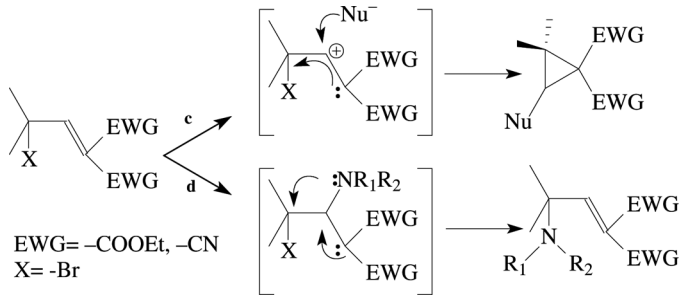
two geminal substituents in the α position of **1** as depicted in **2**, or incorporating the α and β positions as shown in **3**.



Of the methods available in the synthesis of cyclopropanes, the Michael-initiated ring closure (MIRC) reaction was used to synthesize 1-amino-cyclopropanecarboxylic acids.[5] It could be facile to synthesis of 2,2-dimethylcyclopropanes in mild conditions.

As the name of the reaction indicates, the process is started by a Michael addition of a nucleophile to an olefin, which is doubly activated by electron-withdrawing groups (EWG) in the α position and a leaving group (X) in the γ position. The intermediate carbanion produced by the addition of the nucleophile is thought to displace the leaving group to give the desired cyclopropane. It has been suggested that the mechanism of MIRC reactions of this type involve a nucleophilic displacement of the intermediate carbanion regardless of whether a primary, secondary, or tertiary halide is used. An S_N2 displacement may be operating with primary and possibly secondary halides, but cyclopropanes are often the only product for tertiary halides (see Scheme 1).

Not all the nucleophiles could be applied in the MIRC reaction. Some reported nucleophiles, such as sodium methoxide, potassium cyanide, sodium thiophenoxide, and sodium phenoxide, were chosen and corresponding cyclopropane derivatives were obtained. In recently years, alkyl imidazolyl sulfoxides[6] and $P(OR)_3$[7] were reported and the mechanisms were studied as new nucleophiles. In the MIRC reaction, some carbon–oxygen, carbon–carbon, and carbon–sulfur bonds could be formed in the cyclopropane skeleton, except for carbon–nitrogen bond. Only exclusively substitution products were obtained when primary and secondary amines were used as nucleophiles.[8] The MIRC reaction was affected by the stability of substituted



Scheme 1.

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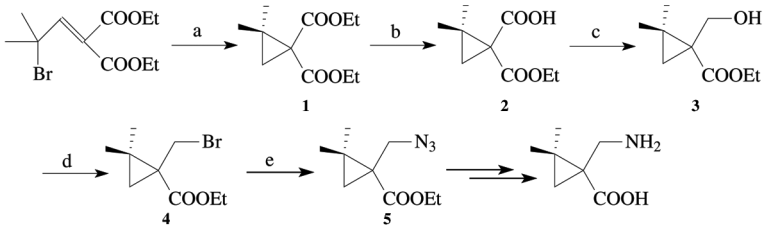
cyclopropane. Donor electrons of nitrogen are the major reason of instability of donor-acceptor substituted cyclopropanes.[3] There are two other successful examples: one is the synthesis of aminopurine-substituted cyclopropane by MIRC reaction,[9] another is 4-formylimidazole as a nitrogen nucleophile.[10] That is because of the absence of a lone electron in the related reaction system, which has been involved in the conjugated system (see Scheme 1).[9]

$NaBH_4$ and $LiAlH_4$ were also used as nucleophiles, and corresponding substituted cyclopropanes were obtained. The cyclopropane **1** from diethyl 2-bromo-2-methyl-propylidene malonate offered a simple but most effective entry into α-2,2-dimethylcyclopropane-β-azido acid **5**. Monoester **2** could be obtained by hydrolysis in alkali solution and subsequently reduced to give **3** by reduction of a mixed anhydride. Hydroxy group was converted to azido group easily when PBr_3 or MsCl was used (see Scheme 2).

In the work, sodium azide serves as a good nucleophile group reacted by the MICR reaction. The azidocyclopropane **6** was also obtained when the diethyl 2-bromo-2-methyl-propylidene malonate and one equivalent of NaN_3 were refluxed in ethanol for 10–12 h in moderate yields. The crude product **6** could be obtained by chromatography over silica gel. It is hazardous to distill because azide compounds can explode. When cyanoacetate was used, **6b** was also obtained (see Scheme 3).

However, nearly all the attempts to reduce the azido group into the amino group were not successful when ester existed, because of cyclopropane ring opening. Reduction of the carbonyl group (ester and acid) and azido group at the same time by strong reductants such as $LiAlH_4$ also failed. After saponification, selective reduction of monoester **7** could proceed in good yield. Using $NaBH_4/CaCl_2$ in EtOH as the reducing agent, the β-azidocyclopropane acid **8** was obtained. The compound **9** was prepared by reduction of a mixed anhydride[11] (see Scheme 4).

In our research for β-cyclopropane amino acids, especially peptides, these new cyclopropane derivatives as a new series of cyclopropane frameworks were useful building blocks in pharmaceutical design.



Scheme 2. (a) $NaBH_4$, EtOH, rt; (b) NaOH, EtOH, rt; (c) $CICOOH_3$, $NaBH_4$, $-78^{\circ}C$; (d) PBr_3, Pyr; (e) NaN, DMF.

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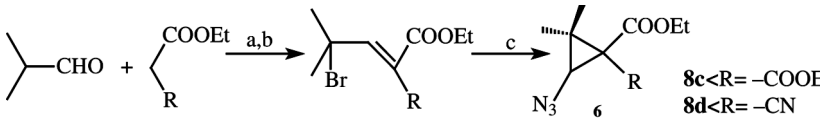

Scheme 3. (a) Piperidine, acetic acid, benzene; (b) NBS, AIBN, CCl_4; (c) NaN_3, EtOH, reflux.

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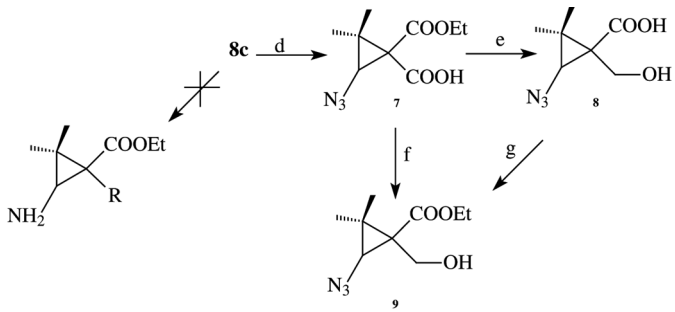
EXPERIMENTAL

Analytical Instrument

Melting points were uncorrected XT-4 melting point measurement and uncorrected. H^1NMR spectra were recorded using Varian Mercury VX-300 (300 MHz) spectrometer in $CDCl_3$ solution with TMS as internal standard. IR spectra were measured on KBr plates with 170-SX-FT-ir spectrometer.

Knoevenagel condensation of aldehydes with ethyl malonate in benzene in the presence of piperidine acetate gave diethyl alkylidenemalonates, which were brominated with *N*-bromo succinimide (NBS). The product bromoalkyliden malonate could be used without further purification.

Ethyl 2-azido-3,3-dimethylcyclopropanedicarboxylate 6a: A mixture of bromoalkyliden malonate (24.86 g, 84.8 mmol) and sodium azide (5.52 g, 84.9 mmol) in ethanol (150 mL) was reflux for 8 h. During this time, reaction progress was monitered by TLC. When the starting materials disappeared, most of the ethanol was removed under reduced pressure. Then the mixture was poured into ice water and extracted by dichloromethane (3×50 mL). The organic phase was washed with water and brine and dried by $MgSO_4$. After concentration and purification by column chromatography on silica gel (ethyl acetate/petroleum ether 1:6), the light green liquid product **6a** (16.97 g, 78.4%) was obtained. IR (film) cm^{-1}: 1728, 2112. **^{1}H**



Scheme 4. (d) NaOH, EtOH, rt; (e) $Ca(BH_4)_2$, EtOH, rt; (f) $CICOOCH_3$, $NaBH_4$, -78°C THF; (g) $SOCl_2$, EtOH.

NMR (300 Hz, $CDCl_3$, ppm): 1.220, 1.256 (dd, 6H, 2 × —C**H**$_3$), 1.298–1.252 (t, 6H, —C**H**$_3$, J = 13.8), 3.651 (s, 1H, —C**H**—), 4.211–4.243 (m, 4H, —C**H**$_2$—, J = 4.9). **^{13}C** NMR ($CDCl_3$, ppm): 14.150 (—CH_2**C**H_3), 14.17 (—CH_2**C**H_3), 17.95 (—**C**H_3), 19.58 (—**C**H_3), 30.82 (—**C**H-N_3), 42.80 [—**C**$(COOEt)_2$], 51.67 (—**C**Me_2), 61.50 (—**C**H_2CH_3), 61.97 (—**C**H_2CH_3), 165.35 (—**C**OOEt), 167.45 (—**C**OOEt).

Ethyl 1-cyano-2-azido-3,3-dimethylcyclopropanecarboxylate 6b: **6b** was obtained by a similar procedure. 72.6%. IR (film) cm^{-1}: 1728, 2112, 2244. **^{1}H** NMR (300 Hz, $CDCl_3$, ppm): 1.203, 1.159 (s, 6H, 2 × —C**H**$_3$), 1.350 (t, 3H, —C**H**$_3$), 3.675 (s, 1H, —C**H**—), 4.210–4.264 (m, 2H, —C**H**$_2$—).

2-Azido-3,3-dimethyl-1-(ethoxycarbonyl)cyclorpoane-1-dicarboxylic acid 7: To a solution of diethyl 2,2-dimethylcyclopropane-1,1-dicarboxylic ester **6a** (17.65 g, 69.2 mmol) in EtOH (70 mL) was added 1 N aqueous NaOH (70 mL). After stirring for 12 h at room temperature, ethanol was evaporated in vacuo. The residual was added to water (20 mL) and then extracted by ether (2 × 20 mL). The water layer was acidified by means of a saturated $KHSO_4$ solution and extracted with EtOAc (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give monoester **7** (8.48 g, 54%). Crystal mp 108–110°C. IR (KBr) cm^{-1}: 1745, 1694, 2117. **^{1}H** NMR (300 Hz $CDCl_3$, ppm): 1.262, 1.315 (dd, 6H, 2 × —C**H**$_3$), 1.356 (t, 3H, —C**H**$_3$), 3.781–3.814 (d 1H, —C**H**—), 4.255–4.298 (m, 4H, 2 × —C**H**$_2$—), 10.863(br, 1H, —COO**H**). **^{13}C** NMR (CDCl3, ppm): 14.196 (—CH_2**C**H_3), 18.296 (—**C**H_3), 19.631 (—**C**H_3), 32.818 (—**C**H—N_3), 42.627 (—**C**—COOEt), 52.777 (—**C**Me_2), 62.192 (—**C**H_2CH_3), 165.592 (—**C**OOEt), 173, 438 (—**C**OOH).

Ethyl 2-azido-3,3-dimethyl-1-(hydroxymethyl)cyclorpoane-1-carboxylate 9: Et_3N (3.2 mL) was added at 0°C to a stirred solution of monoester **7** (3.54 g, 15.59 mmol) in THF (30 mL), and then methyl chloroformate (1.2 mL) was introduced dropwise at the same temperature. The reaction was allowed to proceed for 1 h, and then the reaction mixture was filtered and the precipitate was washed with cooled THF. Filtrate was cooled to −78°C, $NaBH_4$ (2.36 g, 62.4 mmol) was introduced portionwise, and methanol (10 mL) was added dropwise over 30 min. After 1 h more at the same temperature, the cooling bath was removed and 10% HCl solution was added slowly until no residual $NaBH_4$ remained. Evaporation of THF, extravtion with CH_2Cl_2 (3 × 20 mL), drying ($MgSO_4$), evaporation, and column chromatography on silica gel (ethyl acetate/petroleum ether 1:6) provided the colorless liquid **9**: (2.97 g, 89.6%). IR (film) cm^{-1}: 3431, 2107, 1728. **^{1}H** NMR: 4.276–4.071 (m, 2H, —C**H**$_2$—), 3.878–3.836 (d, H, —C**H**$_2$O, J = 12.3), 3.707–3.666 (d, H, —C**H**$_2$O, J = 12.3), 2.560 (s, broad, H, O**H**, D_2O-disappear), 3.058 (s, H, —C**H**—N_3), 1.345–1.166 (m, 3H, —CH_2C**H**$_3$), 1.211 (s, 3H,—C**H**$_3$), 1.255 (s, 3H,—C**H**$_3$).

2-Azido-3,3-dimethyl-1-(hydroxymethyl)cyclorpoane-1-carboxylic acid 8: A solution of KOH (1.08 g, 19.2 mmol) and of $CaCl_2$ (4.3 g, 38.7 mmol) in EtOH (30 mL) was mixed to a solution of monoester **7**

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(1.7 g, 7.49 mmol) in EtOH (10 mL). The mixture was cooled to 0°C and then suspension of $NaBH_4$ (2 g, 52.88 mmol) in EtOH (20 mL) was added with stirring. The reaction was allowed to proceed for 17 h at rt, then cooled to 0°C. Addition of 10% HCl solution at the same temperature to attain pH2–3, evaporation of EtOH, adding of water, saturation with NaCl, extraction with CH_2Cl_2, drying ($MgSO_4$), and then evaporation provided practically pure **8** (0.95 g, 68.6%) as an oil that crystallized slowly upon standing. Mp 82–83° C. IR (KBr) cm^{-1}: 3372, 2104, 1693. ^{1}**H** NMR (300 Hz, $CDCl_3$, ppm): 1.291 (s, 3H, —C**H**$_3$), 1.258 (s, 3H, —C**H**$_3$), 3.665 (s, 1H, —C**H**—), 3.885–3.801 (d, H, —C**H**$_2$═, J = 12.3), 4.029–3.988 (d, H, —C**H**$_2$—, J = 12.3). ^{13}**C** NMR ($CDCl_3$, ppm): 176.6 (—**C**OOH), 59.81 (—**C**H$_2$—OH), 52.02(—**C**Me$_2$), 39.26 (—**C**—COOH), 31.47(—**C**H-N$_3$), 21.79(—**C**H$_3$), 17.03 (—**C**H$_3$).

Synthesis of ethyl 2,2-dimethyl-1-(azidomethyl)cyclorpoane-1-carboxylate 5: Bromoalkyliden malonate was the starting material and was ring-closed with sodium borohydride in absolute ethanol to afford ethyl 2, 2-dimethylcyclopropane dicarboxylate **1**. Then, **2**, **3** were obtained after monosaponification and reduction by a similar procedure. To a solution of **3** in anhydrous methylene chloride and dried pyridine was added PBr_3 dropwise at 0°C. The mixture was stirred at room temperature overnight. After the usual workup, light oil **4** was obtained. Then, a solution of **4** in DMF was treated with NaN_3 at room temperature for 6 h and **5** was obtained:

2: Colorless oil. 64%. IR (film) cm^{-1}: 3090–2642, 1730, 1689. ^{1}**H** NMR: 8.275 (s, broad, H, OH),4.302–4.174 (m, 2H, —C**H**$_2$CH$_3$), 1.791–1.711 (m, 3H, —CH$_2$C**H**$_3$), 1.279 (s, 3H, —C**H**$_3$), 1.325 (s, 3H, —C**H**$_3$), 1.181–1.259 (m, 2H, —C**H**$_2$—).

3: colorless liquid. 80.6%. IR (film) cm^{-1}: 3461, 1717, 1030. ^{1}**H** NMR: 2.751 (s, broad, H, —O**H**, D_2O-disappear), 4.193–4.123 (m, 2H, —C**H**$_2$CH$_3$, J = 14.1), 1.162 (s, 3H, —C**H**$_3$,), 1.271 (s, 3H, —C**H**$_3$), 1.205–1.260 (m, 3H, —C**H**$_3$), 3.958–3.918 (m, H, —CH$_2$O, J = 12), 3.546–3.582 (m, H, —C**H**$_2$O, J = 12), 1.348–1.333 (d, H, —C**H**$_2$—), 0.681–0.667 (d, H, —C**H**$_2$—, J = 4.2).

5: colorless liquid. 69.3%. IR (KBr) cm^{-1}: 2110, 1734. ^{1}**H** NMR (300 Hz, $CDCl_3$, ppm): 1.119 (s, 3H, —C**H**$_3$), 1.165(s, 3H, —C**H**$_3$), 0.702–0.686(d, H, —C**H**$_2$—, J = 4.8), 1.426–1.411(d, H, —C**H**$_2$—, J = 4.8), 1.236–1.212 (t, 3H, —C**H**$_3$, J = 3.6), 4.152–4.113 (m, 2H, —C**H**$_2$—, J = 4.8), 3.374–3.418 (d, H, —C**H**$_2$—,J = 13.2), 3.591–3.635 (d, H, —C**H**$_2$—, J = 13.2).

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