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Synthesis of new ionic liquids from α-, β-alanine and α-iodo ketones

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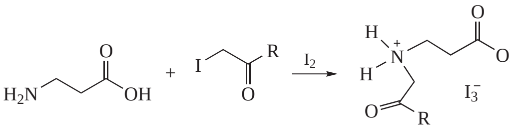
The one-pot reaction of α-, β-alanine with 1-iodopropan-2-one, 2-iodo-1-phenylethanone and 2-iodo-1-(2-thienyl)-ethanone and elemental iodine proceeds without solvents and basic media to afford a novel family of ionic liquids with triiodide counteranion.



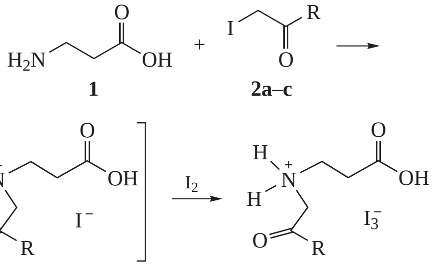
R = Me, Ph, 2-thienyl

A search for new approaches to chemical modification of semi-synthetic amino acids and a study of biological activity are among the standing challenges of modern organic synthesis. Such amino acids are known to be in-demand building blocks for the synthesis of biologically active compounds,[1] bionanomaterials in tissue engineering, markers for drug transport in live organisms,[2] biopolymers for target diagnostics and cancer therapy,[3] design of antimicrobial and antidepressant pharmaceuticals.[4]

The most straightforward method for the preparation of modified amino acids involves alkylation of natural amino acids with alkyl halides in the presence of alkalis. The interaction of α- and β-alanine with 1-bromobutane in the presence of sodium hydroxide in ethanol furnishes mono-N-alkylated amino acids.[3] Similarly, cesium carbonate[5] and lithium hydroxide[6] were employed as bases in these reactions.

In the present work, we have studied reaction of β-alanine with aliphatic, aromatic and heteroaromatic α-iodo ketones without basic media and solvents. The attempts to involve α-chloro-substituted ketones in β-alanine alkylation were unsuccessful.

The reaction of β-alanine **1** with 1-iodopropan-2-one **2a** proceeds as the alkylation at the amino group with the formation of monoiodide **A**, which further reacts with molecular iodine, generated upon reduction of the iodo ketone **2** with hydrogen iodide evolved during the reaction, to deliver *N*-(2-carboxyethyl)-2-oxopropylammonium triiodide **3a** in 21% yield (Scheme 1).[†] The formation of hydrogen iodide is confirmed by the appearance of acetone signals in the ^{1}H and ^{13}C NMR spectra of the reaction mixture at 2.00 (Me) and 27.29 (Me), and 207.58 ppm (C=O), respectively.



1 **2a–c**

A **3a–c**

a R = Me
b R = Ph
c R = 2-thienyl

Scheme 1

To extend the reaction scope and to evaluate the alkylating ability of aliphatic, aromatic and heteroaromatic α-iodo ketones, we have carried out the reaction of β-alanine **1** with 2-iodo-1-phenylethanone **2b** and 2-iodo-1-(2-thienyl)ethanone **2c**. It could be assumed that the negative inductive effect of the carbonyl group and the presence of the aromatic ring in iodo ketones **2b** and **2c** would increase electrophilicity of the methylene group that would allow the N-alkylation products to be obtained in high yields. However, it turns out that the yields of triiodides **3b**,**c** do not substantially change (17.5 and 17%, respectively). Apparently, the experimental data evidence that the reaction mixture contains insignificant amounts of molecular iodine. To check this assumption, we implemented the reaction between β-alanine **1** and iodo ketones **2a**,**b** in the presence of molecular iodine, the yields of liquid salts **3a**,**b** being increased up to 40 and 45% (see Scheme 1).

The conditions of β-alanine alkylation with α-iodo ketones also tolerate α-alanine. The reaction of α-alanine **4** with 1-iodo-

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[†] The reaction course and compounds purity were monitored by TLC using Silufol UV-254 sheets (acetone as eluent). Elemental analysis was performed on an automatic Thermo scientific Flash 2000 CHNS-analyzer. UV spectra were recorded on a UV-Vis Lambda 35 (MeCN) spectrometer. ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded on Bruker DPX-400 and Bruker AV-400 spectrometers (400.13, 100.61 and 40.56 MHz, respectively) in acetone-d_6. ^{1}H and ^{13}C NMR chemical shifts were measured relative to TMS, ^{15}N NMR signals were determined relative to nitromethane. 2D ^{1}H-^{15}N NMR spectra were recorded using the HMBC-gp ^{1}H–^{15}N correlation method.

Reaction of amino acids **1**, **4** *with iodo ketones* **2a–c** *(general procedure).* (*a*) Equmolar amounts of amino acids **1** or **4** were added to heated (45 °C) iodo ketones **2a–c** under argon. The mixture was stirred at 45–50 °C for 6 h for β-alanine and for 15 h for α-alanine until iodo ketones **2a–c** disappeared (^{1}H, ^{13}C NMR). The formed triiodides **3a–c**, **5** were isolated on a chromatographic column (10 × 900 mm) filled with silica gel MN Kieselgel 60 (0.063–0.2 mm). Acetone was used as an eluent.

Reaction of amino acids **1**, **4** *with iodo ketones* **2a**,**b** *in the presence of elemental iodine (general procedure).* (*b*) Equmolar amounts of β-alanine **1**, **4** were added to heated (45–50 °C) iodo ketones **2a**,**b** under argon. After 30 min, equmolar amount of elemental iodine was added to the reaction mixture. Further the reaction was carried out similar to protocol (*a*).

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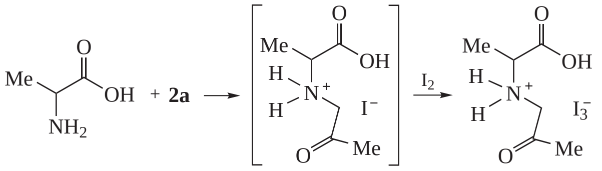
propan-2-one **2a** gives rise to liquid *N*-(1-carboxyethyl)-2-oxopropylammonium triiodide **5** in 18% yield. In the presence of molecular iodine, the yield of ionic liquid **5** grows higher (39%). However, α-alanine appears to be less reactive and the reaction requires a longer time for its completion. In this case and in other experiments, duration of the reaction was monitored (NMR) by disappearance of iodo ketones **2a–c** in the reaction mixture (Scheme 2).



4 **5**

Scheme 2

Relatively low yields of triiodides **3a–c**, **5** are due to the competitive polycondensation of the amino acids leading to alanine oligopeptides, which were not isolated as individual compounds. Products **3a–c**, **5** were purified taking into account their significantly different solubility in acetone as well as exposing time on the chromatographic column (eluent acetone).

Triiodides **3a–c**, **5** are viscous purple oils, which ensure homogeneity of the medium and act as solvents in the reaction. They represent a novel type of ionic liquids, which can find application as surfactants,[7] catalysts,[8] solvents of organic and bioorganic synthesis.[9–11] Earlier it was reported that triiodide anions were formed during alkylation of *N*-haloazoles with iodoalkanes,[12] iodo ketones[13] and iodomethylsiloxanes,[14] and during iodocyclization of triazole[15] or quinoline[16] in the presence of molecular iodine.[15,16] The triiodides of liquid amino acid family were synthesized herein for the first time.

The structure of ionic liquids **3a–c**, **5** has been proved by the elemental analysis data, ^{1}H, ^{13}C, ^{15}N NMR and UV techniques. In the ^{1}H NMR spectra of compounds **3a–c**, **5**, proton signals of the methylene fragments appear in the region 4.1–4.6 ppm at quaternized nitrogen atom. In the ^{13}C NMR spectra of ionic liquids **3a–c**, **5**, carbon signals of the carboxyl and carbonyl moieties are observed at 170.65–171.34 and 189.92–194.34 ppm, respectively. The 2D NMR {^{1}H–^{15}N}HMBC spectrum shows cross-peaks of nitrogen atom with protons of the methylene group for **3a**,**b**, the methylene and methine for **5** at –(180.5–181.6) and –177.6 ppm, respectively. The UV spectra of triiodides **3a–c**, **5** contain absorption bands at 291, 361 nm, which are characteristic of the (I_3^-) anion.[17]

In conclusion, the reaction of α-, β-alanine with α-iodo ketones paves an avenue to the synthesis of novel ionic liquids. The solvents- and bases-free reaction proceeds as N-alkylation and formation of the triiodide in a one synthetic operation.

The main results were obtained using the equipment of Baikal Analytic Center of Collective Use, SB RAS.

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N-*(2-Carboxyethyl)-2-oxopropylammonium triiodide* **3a**. (*a*) From **1** (0.4 g, 4.4 mmol) and **2a** (0.81 g, 4.4 mmol), 0.49 g (21%) of dark-red oil was obtained (R_f = 0.87, acetone). ^{1}H NMR, δ: 1.56 (s, 3H, Me), 2.97 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.6 Hz), 3.03 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.6 Hz), 4.10 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.3 Hz), 7.98 (br.s, 3H, NH$_2$, OH). ^{13}C NMR, δ: 23.19 (Me), 31.27 (*C*H$_2$COOH), 43.64 (NCH$_2$), 58.78 (N*C*H$_2$CO), 171.35 (COOH), 192.86 (C=O). ^{15}N NMR, δ: –180.5. Found (%): C, 13.52; H, 2.31; I, 71.95; N, 2.32. Calc. for $C_6H_{12}I_3NO_3$ (%): C, 13.68; H, 2.30; I, 72.26; N, 2.66.

(*b*) From **1** (0.4 g, 4.4 mmol), **2a** (0.81 g, 4.4 mmol) and molecular iodine (1.12 g, 4.4 mmol), 0.95 g (41%) of **3a** was obtained.

N-*(2-Carboxyethyl)-2-oxo-(2-phenyl)ethylammonium triiodide* **3b**. (*a*) From **1** (0.2 g, 2.2 mmol) and **2b** (0.56 g, 2.2 mmol), 0.23 g (17%) of dark-red oil was obtained (R_f = 0.83, acetone). ^{1}H NMR, δ: 2.95 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.6 Hz), 2.98 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.6 Hz), 4.10 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.2 Hz), 7.47–7.68 (m, 5H, Ph), 8.33 (br.s, 3H, NH$_2$, OH). ^{13}C NMR, δ: 30.95 (*C*H$_2$COOH), 43.47 (NCH$_2$), 64.96 (N*C*H$_2$CO), 127.57 (*o*-Ph), 128.34 (*m*-Ph), 132.73 (*i*-Ph), 133.87 (*p*-Ph), 170.91 (COOH), 192.83 (C=O). ^{15}N NMR, δ: –181.6. Found (%): C, 22.75; H, 2.48; I, 64.21; N, 2.85. Calc. for $C_{11}H_{14}I_3NO_3$ (%): C, 22.43; H, 2.40; I, 64.64; N, 2.38.

(*b*) From **1** (0.2 g, 2.2 mmol), **2b** (0.56 g, 2.2 mmol) and molecular iodine (0.57 g, 2.2 mmol), 0.59 g (45%) of **3b** was obtained.

N-*(2-Carboxyethyl)-2-oxo-2-(2-thienyl)ethylammonium triiodide* **3c**. From **1** (0.3 g, 3.3 mmol) and **2c** (0.83 g, 3.3 mmol), 0.34 g (17 %) of dark-red oil was obtained (R_f = 0.85, acetone). ^{1}H NMR, δ: 2.98 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.3 Hz), 3.04 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.3 Hz), 4.11 (t, 2H, CH$_2$, $^{3}J_{HH}$ 6.2 Hz), 7.20 (dd, 1H, CH, $^{3}J_{HH}$ 5.1 Hz, $^{3}J_{HH}$ 4.3 Hz), 7.86 (d, 1H, CH, $^{3}J_{HH}$ 5.1 Hz), 7.86 (d, 1H, CH, $^{3}J_{HH}$ 4.3 Hz). ^{13}C NMR, δ: 29.78 (*C*H$_2$COOH), 43.40 (NCH$_2$), 60.00 (N*C*H$_2$CO), 128.23 (C-4), 132.81 (C-5), 133.81 (C-3), 144.35 (C-2), 170.93 (COOH), 190.05 (C=O). ^{15}N NMR, δ: –180.7. Found (%): C, 18.45; H, 2.42; I, 63.61; N, 2.85; S, 5.58. Calc. for $C_9H_{12}I_3NO_3S$ (%): C, 18.17; H, 2.03; I, 63.99; N, 2.35; S, 5.39.

N-*(1-Carboxyethyl)-2-oxopropylammonium triiodide* **5**. (*a*) From **4** (0.3 g, 3.4 mmol) and **2a** (0.62 g, 3.4 mmol), 0.32 g (18%) of dark-red oil was obtained (R_f = 0.87, acetone). ^{1}H NMR, δ: 1.67 (d, 3H, Me, $^{3}J_{HH}$ 6.2 Hz), 1.69 (s, 3H, Me), 4.38 (t, 2H, CH$_2$, $^{3}J_{HH}$ 7.0 Hz), 5.13 (q, 1H, CH, $^{3}J_{HH}$ 6.2 Hz), 7.63 (br.s, 3H, NH$_2$, OH). ^{13}C NMR, δ: 15.61 (*Me*CH), 16.53 (*Me*CO), 49.47 (CH$_2$), 56.21 (CH), 170.59 (COOH), 194.34 (C=O). ^{15}N NMR, δ: –177.6. Found (%): C, 13.99; H, 2.42; I, 71.96; N, 2.85. Calc. for $C_6H_{12}I_3NO_3$ (%): C, 13.68; H, 2.30; I, 72.26; N, 2.66.

(*b*) From **4** (0.3 g, 3.4 mmol), **2a** (0.62 g, 3.4 mmol) and molecular iodine (0.86 g, 3.4 mmol), 0.69 g (39%) of **5** was obtained.