New synthesis of 3,3-disubstituted piperidin-2-ones from esters and 1-(3-halopropyl)-2,5-dimethylpyrroles

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3,3-Disubstituted piperidin-2-ones were obtained by alkylation of carboxylic acid esters with 1-(3-halopropyl)-2,5-dimethylpyrroles using lithium diisopropylamide as a base followed by the removal of 2,5-dimethylpyrrole protection and intramolecular cyclization. The overall yields of the target products amounted to 78% in two synthetic steps.

Key words: piperidin-2-ones, esters, alkylation, protection groups, 2,5-dimethylpyrrole protection, cyclization.

A lactam fragment is found in natural compounds and is a structural part of many pharmaceuticals.[1—4] The introduction of a lactam fragment is used for the rational modification of known biologically active compounds.[5] Lactams are also the starting compounds for the synthesis of practically important polyamides.[6] Therefore, the development of new convenient and efficient methods for obtaining this class of compounds is still a challenge.

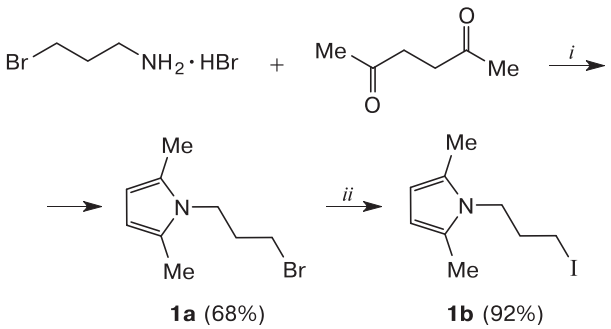
One of the synthetically and practically valuable types of lactams are 3,3-disubstituted piperidin-2-ones. Compound of this type possess anticonvulsant properties[7,8] and exhibit other types of biological activity.[9,10] The most commonly used general approaches to their synthesis are the alkylation of *N*-protected δ-valerolactams[11—14] or their 3-monosubstituted derivatives,[15—17] as well as the cyanoethylation of disubstituted acetic acid esters with subsequent reductive cyclization.[18—23] There are examples of the formation of 3,3-disubstituted piperidin-2-ones by reductive cyclization of δ-azido esters.[24] Note that despite the versatility and good yields of the final products, the last two approaches involve the use of highly toxic (acrylonitrile) or explosive (azides) reagents. Therefore, the development of alternative methods for the construction of 3,3-disubstituted piperidin-2-ones is of undoubted interest.

In continuation of our works[25—28] on the elaboration of new approaches to nitrogen heterocycles, we suggested that such lactams can be obtained by the alkylation of enolates of the corresponding esters with 1-(3-halopropyl)-2,5-dimethylpyrroles followed by the removal of the dimethylpyrrole protection[29] and intramolecular cyclization of δ-amino esters formed. The present work is devoted to the confirmation of this hypothesis and the development a new approach to the synthesis of six-membered lactams.

Results and Discussion

The starting 1-(3-bromopropyl)-2,5-dimethyl-1*H*-pyrrole (**1a**) was obtained by the condensation of commercially available 3-bromopropylamine hydrobromide with hexane-2,5-dione upon treatment with an equimolar amount of KOH gradually added to the reaction mixture (Scheme 1). In contrast to the procedure described earlier[29] using methanol as a solvent, we applied less toxic ethanol that practically did not affect the yield of the final product, which after vacuum distillation was 68%. It should be noted that such a yield is achieved only when the reaction was carried out under argon, while in air deep resinification of the reaction mixture occurs decreasing the yield of product **1a** to 30—35%. Most likely, this is explained by the high sensitivity of compound **1a** to oxygen, which is confirmed by its rapid polymerization in air accompanied by turning the color to deep red.

Scheme 1



Reagents and conditions: *i*. EtOH, KOH, reflux, 2 h; *ii*. NaI, acetone, 20 °C, 48 h.

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Bromide **1a** was converted to the corresponding iodide **1b** in 92% yield under the standard Finkelstein reaction conditions (NaI, acetone, room temperature) (see Scheme 1).

We showed that addition of an equimolar amount of bromide **1a** to a solution of lithium enolate, obtained by deprotonation of ethyl cyclohexanecarboxylate **2a** with lithium diisopropylamide in THF, at −60÷−50 °C followed by a slow warming-up of the resulting mixture to room temperature gave the corresponding alkylated ester **3a** (Scheme 2). According to the NMR spectra, the content of compound **3a** in the reaction mixture obtained after the standard aqueous work-up and removal of the solvent was ~90%. In a separate experiment, product **3a** was isolated pure in 82% yield by flash chromatography on silica gel.

We tested two methods for the cleavage of the 2,5-dimethylpyrrole protection in compound **3a** described in the work,[29] namely, the reflux in an aqueous ethanol solution in the presence of an excess of hydroxylamine hydrochloride and a similar process with the addition of 0.5 equiv. (based on the amount of hydroxylamine hydrochloride) of KOH. It turned out that in the first case, prolonged heating (48 h) of the reaction mixture did not cause a noticeable conversion of the starting ester, whereas in the second case, the reaction was completed in 24 h. According to the ^{1}H NMR spectrum of the reaction mixture recorded after the reflux for 24 h, the main products were hexane-2,5-dione dioxime and amino ester **4a** in a ratio of ~1 : 1. Despite the potential tendency to cyclize to the corresponding lactam **5a**, compound **4a** turned out to be quite stable and was isolated by vacuum distillation in 76% yield based on ethyl cyclohexanecarboxylate **2a**. The cyclization of ester **4a** to lactam **5a** was successfully accomplished by refluxing a solution of **4a** in *o*-xylene for 2 h; the yield of product **5a** after recrystallization was 87% (see Scheme 2).

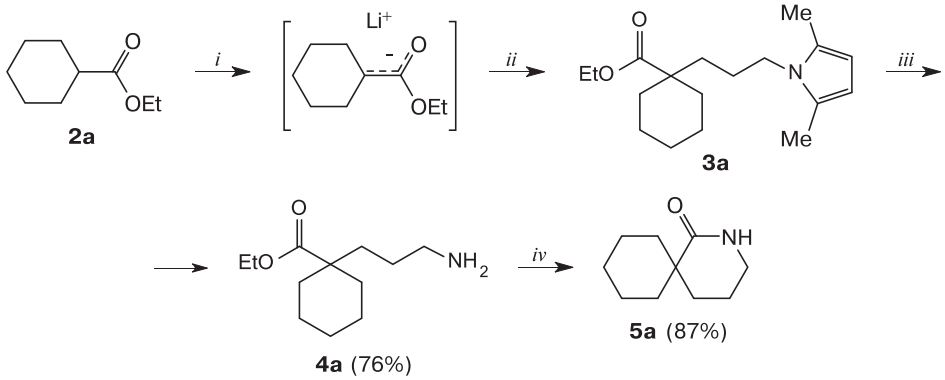
A fairly wide range of esters **2b—i** can be involved into similar transformations. Note that in these cases, in contrast to the reaction involving ethyl cyclohexanecarboxylate **2a**, the removal of the 2,5-dimethylpyrrole protection is accompanied by a spontaneous cyclization of amino esters **4b—i** to the corresponding lactams **5b—i** (Scheme 3). We studied the transformation **3**→**5** using ^{1}H NMR spectroscopy and ester **3e** as a model compound. The ^{1}H NMR spectra of reaction mixtures lacked the signals of amino ester **4e** thus indicating that the formation of compound **4e** is much slower than its cyclization to lactam **5e**.

Hexane-2,5-dione dioxime that resulted from the destruction of the pyrrole ring by hydroxylamine is easily separable by washing with an aqueous potassium hydroxide. This allowed us to obtain products **5** with a purity of more than 95% only by recrystallization.

When α,α-disubstituted esters **2b—g** were used as the starting compounds, the yields of the corresponding 3,3-disubstituted lactams were 62—78%. At the same time, an attempt to extend this approach to the synthesis of monosubstituted piperidin-2-ones from esters bearing two α-protons at the alkoxycarbonyl group was less successful. Thus, under similar conditions ethyl isovalerate **2h** gave 3-isopropylpiperidin-2-one **5h** in 32% yield only. Most likely, this is explained by the presence of an acidic α-proton in product **3h**, which can be involved into the exchange with the corresponding enolate to regenerate the starting ester **2h**. This assumption is confirmed by the NMR spectra of the reaction mixture, which demonstrate the absence of the signals for the starting ester **2h** and the presence of the intense signals for bromide **1a** and unidentified side products, whose pattern corresponds to the signals for self-condensation products of ester **2h**.

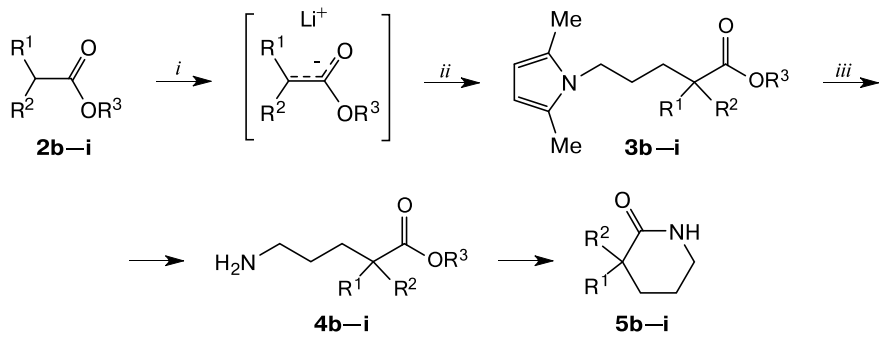
Replacing bromide **1a** as an alkylating agent with iodide **1b** did not improve the yield of compound **5h** significantly, which in this case amounted 35%.

Scheme 2



Reagents and conditions: *i*. Pr^i_2NLi, THF, −60÷−50 °C; *ii*. **1a**, THF, −50÷>20 °C; *iii*. EtOH, H_2O, $NH_2OH \cdot HCl$, KOH, reflux, 24 h; *iv*. *o*-xylene, reflux, 2 h.

Схема 3

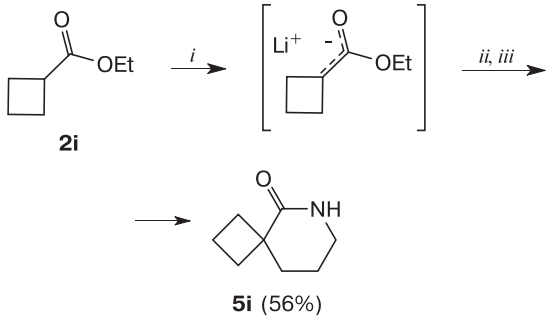


Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
2—5				**2—5**			
b	Me	Me	Et	**f**	$-(CH_2)_2N(Me)(CH_2)_2-$		Et
c	Me	Et	Et	**g**	$-(CH_2)_3N(Et)CH_2-$		Et
d	$-(CH_2)_2O(CH_2)_2-$		Me	**h**	Pr^i	H	Et
e	$-(CH_2)_4-$		Et	**i**	$-(CH_2)_3-$		Et

Reagents and conditions: *i*. Pr^i_2NLi, THF, −60÷−50 °C; *ii*. **1a**, THF, −50÷>20 °C; *iii*. EtOH, H_2O, $NH_2OH \cdot HCl$, KOH, reflux, 24—40 h.

Using this approach, we synthesized a new lactam **5i** bearing a spiro-fused four-membered ring from ethyl cyclobutanecarboxylate **2i** in 23% yield. According to the spectrum of the reaction mixture recorded after the alkylation step, the starting ester **2i** was completely consumed, while a large amount of unreacted bromide **1a** was present. Apparently, the strained cyclobutane enolate arising in the course of the reaction is involved not only into the substitution of the bromine atom in compound **1a**, but also into the side processes. Therefore, it could be expected that the replacement of bromide **1a** with a more active iodide **1b** would increase the yield of lactam **5i**. Indeed, the use of iodide **1b** allowed us to increase the yield of lactam to 56% based on ester **2i** (Scheme 4).

Scheme 4



Reagents and conditions: *i*. Pr^i_2NLi, THF, −60÷−50 °C; *ii*. **1b**, THF, −50÷>20 °C; *iii*. EtOH, H_2O, $NH_2OH \cdot HCl$, KOH, reflux, 24 h.

In conclusion, we proposed an original general approach to piperidin-2-ones substituted at the position 3 *via* alkylation of enolates of the corresponding esters with 1-(3-halopropyl)-2,5-dimethylpyrroles followed by the removal of the dimethylpyrrole protection by treatment with hydroxylamine. This approach is advantageous over the widely used syntheses by the reductive cyclization of γ-cyano esters since it does not require the use of highly toxic acrylonitrile or its derivatives.

Experimental

GLC analysis of starting compounds and products was performed on a Hewlett—Packard 5890 Series II instrument equipped with an HP-1 capillary column (30 m×0.153 mm) and a Hewlett—Packard 3396A automatic integrator. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200p spectrometer in $CDCl_3$ using residual signals of the solvent as references.

High-resolution lectrospray ionization (ESI) mass spectra were recorded on a Bruker micrOTOF II instrument. The measurements were performed in a positive ion mode (the capillary voltage was 4500 V). The scanning range of masses m/z was from 50 to 3000 Da, external or internal calibration (Electrospray Calibrant Solution, Fluka) was used. Compounds were syringed as solutions in acetonitrile at a flow rate of 3 μL min^{-1}. The nebulizer gas was nitrogen (4 L min^{-1}), the interface temperature was 180 °C.

Commercially available 3-bromopropylamine hydrobromide, hexane-2,5-dione, and esters **2a—e**,**h** were used as purchased. Ethyl 1-methylpiperidine-4-carboxylate (**2f**) was synthesized by reductive methylation of ethyl piperidine-4-carboxylate according to the procedure described in patent.[30] Ethyl 1-ethylpiperidine-3-carboxylate (**2g**) was prepared by alkylation of ethyl piperidine-3-carboxylate with iodoethane under conditions earlier described for the synthesis of ethyl 1-propylpiperidine-3-carboxylate.[31] Ethyl cyclobutanecarboxylate (**2i**) was synthesized by esterification of cyclobutanecarboxylic acid under earlier described conditions.[32] Tetrahydrofuran was dried by distillation over $LiAlH_4$ immediately prior to use.

1-(3-Bromopropyl)-2,5-dimethyl-1*H*-pyrrole (1a). A solution of KOH (7.4 g, 0.12 mol) in a mixture of ethanol (100 mL) and water (10 mL) was added to a refluxing solution of 3-bromopropylamine hydrobromide (21.9 g, 0.1 mol) and hexane-2,5-dione (11.4 g, 0.1 mol) in ethanol (80 mL) under argon over 30 min. The resulting mixture was refluxed with stirring for 2 h under argon, then cooled to room temperature, and poured into water (300 mL). The precipitated brown oil was extracted three times with CH_2Cl_2, the combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was evaporated. Compound **1a** (14.7 g, 68%) was isolated from the residue by vacuum distillation collecting the fraction with b.p. 85—89 °C (0.5 Torr). ^{1}H NMR, δ: 2.15—2.29 (m, 2 H, $NCH_2C\underline{H}_2CH_2Br$); 2.30 (s, 6 H, 2 CH_3); 3.46 (t, 2 H, $NCH_2CH_2C\underline{H}_2Br$, J = 6.3 Hz); 3.96 (t, 2 H, $NC\underline{H}_2CH_2CH_2Br$, J = 7.4 Hz); 5.83 (br.s, 2 H, 2 CH=). ^{13}C NMR, δ: 12.4 (2 CH_3), 30.2, 33.7 ($NCH_2\underline{C}H_2\underline{C}H_2Br$), 42.0 ($N\underline{C}H_2CH_2CH_2Br$), 105.2 (2 CH=), 127.4 (2 $\underline{C}CH_3$). The spectral data of compound **1a** are consistent with those published previously.[33]

Bromide **1a** is stable upon storage in a tightly closed vessel at low temperatures for several months, but it rapidly oxidizes in air.

1-(3-Iodopropyl)-2,5-dimethyl-1*H*-pyrrole (1b). Bromide **1a** (10.8 g, 0.05 mol) was added to a solution of anhydrous NaI (15 g, 0.1 mol) in anhydrous acetone (100 mL) and the resulting mixture was stirred for 48 h at room temperature under argon. The precipitate of sodium bromide was filtered off, washed with acetone (20 mL), and the filtrate was concentrated. Water (50 mL) and CH_2Cl_2 (50 mL) were added to the residue, the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, the solvent was evaporated to obtain a light red liquid (12.1 g, 92%), which according to the NMR spectroscopy data was iodide **1b** with a purity of ~95%. Found (%): C, 41.31; H, 5.23; N, 5.20. $C_9H_{14}IN$. Calculated (%): C, 41.08; H, 5.36; N, 5.32. ^{1}H NMR, δ: 2.07—2.25 (m, 2 H, $NCH_2C\underline{H}_2CH_2I$); 2.26 (s, 6 H, 2 CH_3); 3.19 (t, 2 H, $NCH_2CH_2C\underline{H}_2I$, J = 6.7 Hz); 3.86 (t, 2 H, $NC\underline{H}_2CH_2CH_2I$, J = 7.5 Hz); 5.74 (br.s, 2 H, 2 CH=). ^{13}C NMR, δ: 2.0 ($NCH_2CH_2\underline{C}H_2I$), 12.7 (2 CH_3), 34.4 ($NCH_2\underline{C}H_2CH_2I$), 44.1 ($N\underline{C}H_2CH_2CH_2I$), 105.5 (2 CH=), 127.5 (2 $\underline{C}CH_3$).

Ethyl 1-[3-(2,5-dimethyl-1*H*-pyrrolyl)propyl]cyclohexanecarboxylate (3a). A 1.6 *M* solution of Bu^{n}Li in hexane (13.7 mL, 22 mmol) was added to diisopropylamine (2.2 g, 22 mmol) in anhydrous THF (50 mL) at −50÷−60 °C under argon. The resulting mixture was stirred for 10 min at the same temperature followed by a dropwise addition of a solution of ethyl cyclohexanecarboxylate **2a** (3.12 g, 20 mmol) in THF (10 mL). After 10 min, bromide **1a** (4.32 g, 20 mmol) was added to the reaction mixture, the temperature was gradually raised to ambient, and the mixture was stirred for 2 h. Then, water (30 mL) and CH_2Cl_2 (50 mL) were added and the organic layer was separated. The aqueous layer was additionally extracted with CH_2Cl_2 (2×20 mL), the combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was evaporated. The residue was subjected to flash chromatography on silica gel (eluent hexane—Et_2O, 20 : 1→10 : 1) to isolate ester **3a** (4.77 g, 82%) as a dense yellow liquid. MS (ESI), found: m/z 292.2267, calculated for $[C_{18}H_{29}NO_2 + H]^+$: m/z 292.2271. ^{1}H NMR, δ: 1.10—1.68 (m, 12 H, 6 CH_2); 1.28 (t, 3 H, $C\underline{H}_3CH_2O$, J = 6.9 Hz); 2.02—2.16 (m, 2 H, $C_2\underline{H}H$, $C_6\underline{H}H$, *cyclo*-C_6); 2.22 (s, 6 H, 2 CH_3); 3.64—3.74 (m, 2 H, CH_2N); 4.17 (q, 2 H, OCH_2, J = 6.9 Hz); 5.79 (s, 2 H, 2 CH=). ^{13}C NMR, δ: 12.5 (2 CH_3 at pyrrole ring), 14.3 ($\underline{C}H_3CH_2O$), 23.1 (C(2), C(6) in *cyclo*-C_6), 25.7, 25.9 ($CH_2\underline{C}H_2CH_2N$, C(4) in *cyclo*-$C_6$), 34.1 (C(3), C(5) in *cyclo*-C_6), 37.3 ($\underline{C}H_2CH_2CH_2N$), 43.8 ($\underline{C}H_2N$), 46.5 (C(1) in *cyclo*-C_6), 60.1 (OCH_2), 105.1 (2 CH=), 127.2 (2 $\underline{C}CH_3$), 176.4 (C=O).

Ethyl 1-(3-aminopropyl)cyclohexanecarboxylate (4a). The residue obtained by concentration of the reaction mixture as described above was dissolved in a mixture of ethanol (60 mL) and water (20 mL), then hydroxylamine hydrochloride (5.52 g, 80 mmol) and powdered KOH (2.52 g, 45 mmol) were added. The mixture was refluxed under argon for 24 h and concentrated *in vacuo* to dryness. The residue was treated with CH_2Cl_2 (100 mL) and water (20 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with 25% aqueous KOH (100 mL), dried with anhydrous Na_2SO_4, and the solvent was evaporated. Vacuum distillation of the residue afforded compound **4a** (3.23 g, 76% based on ester **2a**) with a purity of ~93% as a colorless liquid, b.p. 88—92 °C (0.5 Torr). MS (ESI), found: m/z 214.1808, calculated for $[C_{12}H_{23}NO_2 + H]^+$: m/z 214.1802. ^{1}H NMR, δ: 1.05—1.54 (m, 14 H, 6 CH_2, NH_2); 1.18 (t, 3 H, CH_3, J = 7.1 Hz); 1.91—2.06 (m, 2 H, $C_2\underline{H}H$, $C_6\underline{H}H$); 2.55 (t, 2 H, $C\underline{H}_2NH_2$, J = 6.8 Hz); 4.06 (q, 2 H, OCH_2, J = 7.1 Hz). ^{13}C NMR, δ: 14.3 (CH_3), 23.2 (C(2), C(6) in *cyclo*-C_6), 25.9, 28.3 ($CH_2\underline{C}H_2CH_2NH_2$, C_4 in *cyclo*-C_6), 34.1 (C(3), C(5) in *cyclo*-C_6), 37.7 ($\underline{C}H_2CH_2CH_2NH_2$), 42.6 ($\underline{C}H_2NH_2$), 46.5 (C(1) in *cyclo*-C_6), 59.9 (OCH_2), 176.6 (C=O).

2-Azaspiro[5.5]undecan-1-one (5a). Amino ester **4a** (3.23 g, 15 mmol) was dissolved in *o*-xylene (40 mL) and the resulting solution was refluxed for 2 h. Then, the solvent was evaporated *in vacuo* and the dark solid residue was recrystallized from hexane—THF to obtain lactam **5a** (2.18 g, 87%) with a purity of >95%. MS (ESI), found: m/z 168.1388, calculated for $[C_{10}H_{17}NO + H]^+$: m/z 168.1383. ^{1}H NMR, δ: 1.19—1.68 (m, 8 H, 4 CH_2); 1.70—2.02 (m, 6 H, 3 CH_2); 3.20—3.34 (m, 2 H, NCH_2); 6.12 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.2 (C(4)), 20.9 (C(8), C(10)), 25.7 (C(9)), 29.0 (C(5)), 33.6 (C(7), C(11)), 36.3 (C(6)), 42.5 (C(3)), 178.8 (C=O).

Synthesis of piperidin-2-ones 5b—i from esters 2b—i (general procedure). A 1.6 *M* solution of Bu^{n}Li in hexane (13.7 mL, 22 mmol) was added to diisopropylamine (2.2 g, 22 mmol) in anhydrous THF (50 mL) at −50÷−60 °C under dry argon. The resulting mixture was stirred for 10 min at the same temperature followed by a dropwise addition of a solution of the corresponding ester **2** (20 mmol) in THF (10 mL). After 10 min, 1-(3-bromopropyl)-2,5-dimethylpyrrole (**1a**) (4.32 g, 20 mmol) or 1-(3-iodopropyl)-2,5-dimethylpyrrole (**1b**) (5.26 g, 20 mmol) was added to the mixture, the temperature was gradually raised to ambient, and the mixture was stirred for 2 h. Water (30 mL) and CH_2Cl_2 (50 mL) were added and the organic layer was separated. The aqueous layer was additionally extracted with CH_2Cl_2 (2×20 mL), the combined organic layers were dried with anhydrous Na_2SO_4, and the solvent was evaporated. The residue was dissolved in a mixture of ethanol (60 mL) and water (20 mL), followed by the addition of hydroxylamine hydrochloride (5.52 g, 80 mmol) and powdered KOH (2.52 g, 45 mmol). The reaction mixture was refluxed under argon for 24—40 h until the complete consumption of esters **3** (GLC monitoring). The solvent was evaporated *in vacuo* to dryness, CH_2Cl_2 (100 mL), water (20 mL) were added to the residue, the organic layer was separated, and the

aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with 25% aqueous KOH (100 mL), dried with anhydrous Na_2SO_4, the solvent was evaporated, and the residue was recrystallized from HF—hexane to give piperidones **5b—i**.

3,3-Dimethylpiperidin-2-one (5b) was obtained from ethyl isobutyrate (**2b**) and bromide **1a** in 78% yield. ^{1}H NMR, δ: 1.19 (s, 6 H, 2 CH_3); 1.59—1.68 (m, 2 H, CH_2); 1.70—1.84 (m, 2 H, CH_2); 3.22—3.31 (m, 2 H, NCH_2); 6.59 (br.s, 1 H, NH). ^{13}C NMR, δ: 19.4 (C(5)), 27.5 (2 CH_3), 36.0 (C(4)), 37.8 (C(3)), 42.9 (C(6)), 178.7 (C=O). The spectral data of compound **5b** agree with those published earlier.[11]

3-Ethyl-3-methylpiperidin-2-one (5c) was obtained from ethyl 2-methylbutanoate (**2c**) and bromide **1a** in 69% yield. ^{1}H NMR, δ: 0.90 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.4 Hz); 1.21 (s, 3 H, CH_3); 1.67—1.88 (m, 4 H, 2 CH_2); 1.42—1.63 (m, 2 H, $C\underline{H}_2CH_3$); 3.21—3.36 (m, 2 H, NCH_2); 6.24 (br.s, 1 H, NH). ^{13}C NMR, δ: 8.5 ($CH_2\underline{C}H_3$), 19.4 (C(5)), 25.5 (CH_3), 31.9 ($\underline{C}H_2CH_3$), 32.1 (C(4)), 41.2 (C(3)), 42.6 (C(6)), 178.5 (C=O). The spectral data of compound **5e** agree with those published earlier.[7]

9-Oxa-2-azaspiro[5.5]undecan-1-one (5d) was obtained from methyl tetrahydro-2*H*-pyran-4-carboxylate (**2d**) and bromide **1a** in 71% yield. MS (ESI), found: m/z 170.1183, calculated for $[C_9H_{15}NO_2 + H]^+$: m/z 170.1176. ^{1}H NMR, δ: 1.38 (dddd, 2 H, C(7)$\underline{H}$H, C(11)$\underline{H}$H, J = 13.8 Hz, J = 5.2 Hz, J = 3.2 Hz, J = 1.4 Hz); 1.69—1.86 (m, 4 H, C(4)H_2, C(5)H_2); 2.14 (ddd, 2 H, C(7)$\underline{H}$H, C(11)$\underline{H}$H, J = 13.8 Hz, J = 9.3 Hz, J = 4.1 Hz); 3.20—3.31 (m, 2 H, NCH_2); 3.61 (ddd, 2 H, C(8)$\underline{H}$H, C(10)$\underline{H}$H, J = 11.6 Hz, J = 9.3 Hz, J = 3.2 Hz); 3.87 (ddd, 2 H, C(8)$\underline{H}$H, C(10)$\underline{H}$H, J = 11.6 Hz, J = 5.2 Hz, J = 4.1 Hz); 6.64 (br.s, 1 H, NH). ^{13}C NMR, δ: 18.5 (C(4)), 31.2 (C(5)), 34.2 (C(7), C(11)), 38.5 (C(6)), 42.3 (C(3)), 63.4 (C(8), C(10)), 177.4 (C=O).

7-Azaspiro[4.5]decan-6-one (5e) was obtained from ethyl cyclopentanecarboxylate **2e** and bromide **1a** in 67% yield. ^{1}H NMR, δ: 1.41—1.89 (m, 10 H, 5 CH_2); 2.03—2.19 (m, 2 H, CH_2); 3.24—3.33 (m, 2 H, NCH_2); 6.48 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.2 (C(9)), 25.8 (C(2), C(3)), 34.5 (C(10)), 38.7 (C(1), C(4)), 42.5 (C(8)), 48.5 (C(5)), 179.4 (C=O). The spectral data of compound **5e** agree with those published earlier.[12]

9-Methyl-2,9-diazaspiro[5.5]undecan-1-one (5f) was obtained from ester **2f** and bromide **1a** in 65% yield. MS (ESI), found: m/z 183.1478, calculated for $[C_{10}H_{18}N_2O + H]^+$: m/z 183.1482. ^{1}H NMR, δ: 1.38—1.52 (m, 2 H, C(7)$\underline{H}$H, C(11)HH); 1.63—1.79 (m, 4 H, C(4)H_2, C(5)H_2); 2.01—2.19 (m, 4 H, C(7)$\underline{H}$H, C(8)$\underline{H}$H, C(10)$\underline{H}$H, C(11)HH); 2.22 (s, 3 H, NCH_3); 2.51—2.68 (m, 2 H, C(8)$\underline{H}$H, C(10)$\underline{H}$H); 3.15—3.28 (m, 2 H, C(3)H_2); 6.40 (br.s, 1 H, NH). ^{13}C NMR, δ: 18.8 (C(4)), 31.2 (C(5)), 33.6 (C(7), C(11)), 37.3 (C(6)), 42.4 (C(3)), 45.7 (CH_3), 51.8 (C(8), C(10)), 177.1 (C=O).

8-Ethyl-2,8-diazaspiro[5.5]undecan-1-one (5g) was obtained from ester **2g** and bromide **1a** in 62% yield. MS (ESI), found: m/z 197.1654, calculated for $[C_{11}H_{20}N_2O + H]^+$: m/z 197.1648. ^{1}H NMR, δ: 1.03 (t, 3 H, $NCH_2C\underline{H}_3$, J = 7.0 Hz); 1.45—1.98 (m, 8 H, C(4)H_2, C(5)H_2, C(10)H_2, C(11)H_2); 2.01—2.15 (m, 1 H, C(9)$\underline{H}$H); 2.31 (d, 1 H, C(7)$\underline{H}$H, J = 11.5 Hz); 2.39 (q, 2 H, $NC\underline{H}_2CH_3$, J = 7.0 Hz); 2.60 (d, 1 H, C(7)$\underline{H}$H, J = 11.5 Hz); 2.70—2.82 (m, 1 H, C(9)$\underline{H}$H); 3.18—3.32 (m, 2 H, C(3)H_2); 6.38 (br.s, 1 H, NH). ^{13}C NMR, δ: 11.9 ($NCH_2\underline{C}H_3$), 19.1 (C(4)), 20.9 (C(10)), 28.8 (C(11)), 32.0 (C(5)), 42.0 (C(6)), 42.3 (C(3)), 52.5, 53.9, 59.1 (C(7), C(9), $N\underline{C}H_2CH_3$), 177.1 (C=O).

3-Isopropylpiperidin-2-one (5h) was obtained from ester **2h** and bromide **1a** in 32% yield. ^{1}H NMR, δ: 0.83 (d, 3 H, CH_3, J = 6.9 Hz); 0.93 (d, 3 H, CH_3, J = 7.1 Hz); 1.43—1.94 (m, 4 H, C(4)H_2, C(5)H_2); 2.21 (ddd, 1 H, C(3)H, J = 10.5 Hz, J = 6.1 Hz, J = 3.8 Hz); 2.51 (d.sept, 1 H, C$\underline{H}$(CH_3)$_2$, J = 3.8 Hz, J = 6.9 Hz); 3.17—3.31 (m, 2 H, NCH_2); 6.72 (br.s, 1 H, NH). The spectral data of compound **5h** agree with those published earlier.[34]

A similar experiment with iodide **1b** instead of bromide **1a** gave lactam **5h** in 35% yield.

6-Azaspiro[3.5]nonan-5-one (5i) was obtained from ester **2i** and iodide **1b** in 56% yield. MS (ESI), found: m/z 140.1073, calculated for $[C_8H_{13}NO + H]^+$: m/z 140.1070. ^{1}H NMR, δ: 1.59—1.83 (m, 4 H, C(8)H_2, C(9)H_2); 1.86—2.09 (m, 4 H, C(2)H_2, C(1)$\underline{H}$H, C(3)$\underline{H}$H); 2.47—2.68 (m, 2 H, C(1)$\underline{H}$H, C(3)$\underline{H}$H); 3.19—3.32 (m, 2 H, NCH_2); 6.22 (br.s, 1 H, NH). ^{13}C NMR, δ: 15.8 (C(2)), 19.3 (C(8)), 30.6 (C(1), C(3)), 33.3 (C(9)), 42.5 (C(7)), 43.1 (C(4)), 177.2 (C=O).

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