Modification of the Aza-Robinson Annulation for the Synthesis of 4-Methyl-Benzo[*c*]quinolizin-3-ones, Potent Inhibitors of Steroid 5α-Reductase 1

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We have recently reported on the synthesis and biological evaluation of a series of benzo[*c*]quinolizin-3-ones (Figure 1), a novel class of potent and selective 5α-reductase type 1 inhibitors,[1] which could find application in the treatment of some androgen-dependent skin disorders such as acne, alopecia, male pattern baldness, and hirsutism.[2] We based the synthesis of the inhibitors on the Lewis-acid promoted Mannich−Michael tandem reaction of *N*-Boc iminium ions with 2-silyloxybutadiene derivatives. Because 4,4a-unsaturated compounds **1** (1*H*-series), with a methyl group at 4 position, were revealed to be the most potent inhibitors, we envisioned that a synthetic strategy based on an aza-Robinson annulation-type reaction could be more useful for the preparation of **1** in large scale as an alternative to the previously reported methodology.

The aza-Robinson methodology has not been widely used for the synthesis of heterocyclic compounds. Due to the low reactivity of the lactam C═O toward C-nucleophiles, the oxygen must in fact be replaced by a sulfur atom to have a more reactive thiocarbonyl group which can undergo, under specific conditions, the cyclization reaction. There are only a few examples of application of this methodology to the synthesis of *N*-bridgehead heterocycles: indolizinones and quinolizinones have been prepared by Danishefsky and other authors,[3] who made use of a Rh(II)-catalyzed reaction of α-diazoketones with a thiolactam for the ring closure step (Scheme 1, eq 1). However, the use of diazomethane for the preparation of the α-diazoketone could be a limitation for the application of the methodology to a large scale synthesis.

Another possibility is the conversion of the thiolactam into an iminium ion which then undergoes attack by the

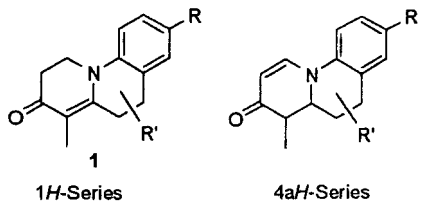
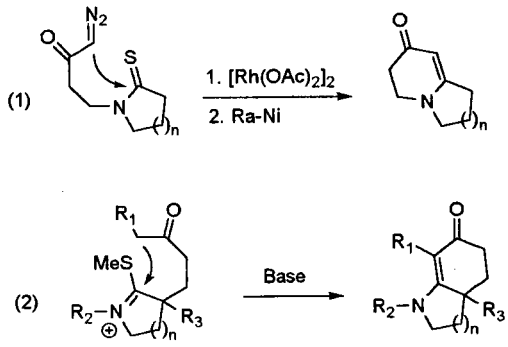


Figure 1.

Scheme 1



C-nucleophile on the side chain (Scheme 1, eq 2). This methodology has been already described by Heathcock[4] and other authors;[5] however, in the reported examples, the side chain bearing the C-nucleophile was on the α-carbon to the C═S group, thus leading to indole and quinoline derivatives. Tethering the side chain at the N atom and then performing the cyclization onto the adjacent carbon by nucleophilic addition to the thioiminium ion would instead afford N-bridgehead heterocycles. We therefore decided to apply this strategy to the synthesis of **1** (wherein R = H, Me, Cl, and R′ = H) starting from lactams **2a**−**c** (Scheme 2) prepared from the corresponding anilines as already described.[1] The conversion of **2a**−**c** to the corresponding thiolactams **3a**−**c** (93%) was achieved by the Lawesson reagent in boiling toluene.[6] N-Alkylation of thiolactams **3a** with ethyl vinyl ketone to give **4a** was quite troublesome, since it always also gave, to a variable extent, S-alkylated compounds **5a** (easily identifiable by the triplet at about 3.3 ppm in the ^{1}H NMR spectrum of the crude reaction mixture) as byproduct. There are only a few examples of N-alkylation of thiolactams with Michael acceptors.[3b,7] In all cases the alkylating agents were α,*β*-unsaturated esters, and S-alkylation has not been reported. However, in our case, the formation of **5a** could be favored by the conjugation of the thioimine moiety with the aromatic ring. We studied the reaction of **3a** with ethyl vinyl ketone under different conditions in order to reduce the extent of S-alkylation: the use of DBU as a base,[5] in THF at 0 °C, after 2 h led to the formation of both **4a** and **5a** in 42 and 27% yield, respectively, after chromatographic purification (see Experimental Section). The use of

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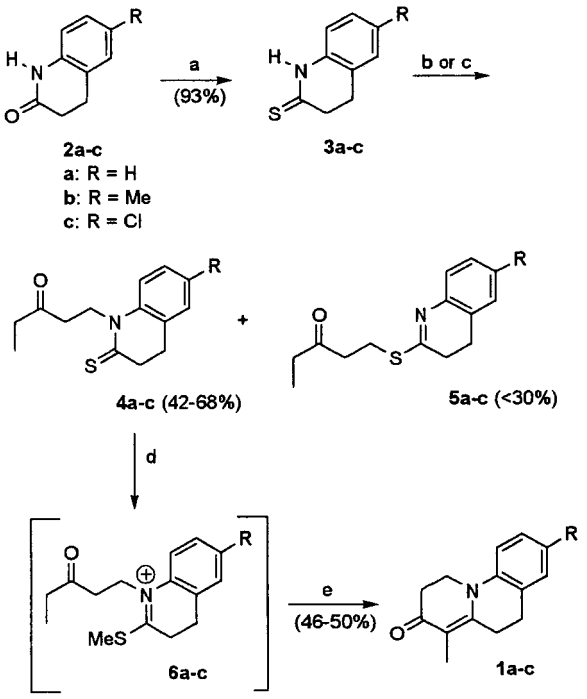
Scheme 2[a]



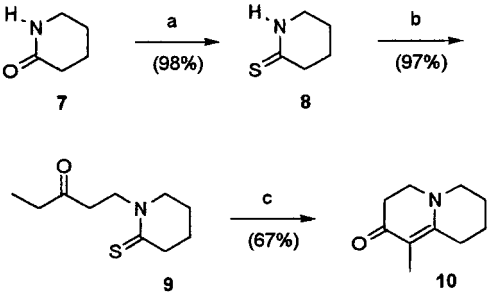
[a] (a) Lawesson's reagent, toluene, reflux, 15 min; (b) ethyl vinyl ketone, K_2CO_3, 18-C-6, THF, 0 to 25 °C; (c) DBU, ethyl vinyl ketone, THF, 0 °C, 2.5 h; (d) Me_2SO_4, toluene, reflux, 15 min; (e) DBU, reflux, 20 min.

NaOH[3b] or NaH[7] as bases for N-deprotonation in THF instead caused a decrease in the yields of the N-alkylated product if compared with the reaction with DBU. Better results were obtained with K_2CO_3 in anhydrous THF and in the presence of a catalytic amount of 18-crown-6. Although under these conditions a certain amount of the S-alkylated byproduct was also formed, it was possible to reduce completely the S-alkylation by slow addition of an excess of ethyl vinyl ketone at 0 °C during a period of 2 h. Under these conditions, N-alkylated compounds **4a**−**c** were obtained in 53−68**%** yield after chromatographic purification.

The last step was performed by treating **4a**−**c** with Me_2SO_4 (1.7 equiv) in boiling toluene in order to generate thioiminium ions **6a**−**c**. The formation of **6a**−**c** (a dark-red oil that separates from toluene) was very fast if compared with other cases (15 min vs 16 h) reported in the literature.[5] Ring closure was finally attained by addition to the boiling suspension containing **6a**−**c** of DBU (1.7 equiv), which resulted in the rapid (20 min) dissolution of the red oil and formation of **1a**−**c** (obtained in 46−50% yield after chromatography). A major difference of this procedure from the strategy depicted in Scheme 1 (reaction 2) is that, in the reported examples,[4,5] the cyclization was done using iminium ions that could not isomerize to the corresponding enamines because the adjacent carbon atom was quaternary. In our case this isomerization is possible; however, we did not find the enamine in the crude reaction mixtures (by ^{1}H NMR analysis) or after chromatography. Presumably, decomposition of the thioiminium ion has instead occurred, which lowered the yields to a certain extent.

To extend the scope of this work to thioiminium ions not conjugated to an aromatic ring, we applied the procedure to thiolactam **8**[3b] (Scheme 3) which was N-alkylated with ethyl vinyl ketone to give compound **9** by the usual protocol. The reaction was faster (30 min) and afforded **9** in very good yield (97%). No traces of the S-alkylated compound were detected in this case. Ring closure finally gave quinolizinone **10** in 67% yield after chromatographic purification.

Scheme 3[a]



[a] (a) Lawesson's reagent, toluene, reflux, 15 min; (b) ethyl vinyl ketone, K_2CO_3, 18-C-6, THF, 0 to 25 °C; (c) Me_2SO_4, toluene, reflux, 15 min; then DBU, reflux, 20 min.

In conclusion we have shown that our modification of the aza-Robinson annulation is applicable to the synthesis of *N*-bridgehead heterocyclic compounds. In particular this procedure is suitable for the large-scale preparation[8] of the potent 5α*R*-1 inhibitors 4-methyl-1*H*-benzo[*c*]-quinolizin-3-ones **1b**,**c** by using inexpensive starting materials and reagents and in only three steps.

Experimental Section

Lactams **2a**−**c** were prepared as reported.[1] Anhydrous THF and toluene were distilled over Na/benzophenone.

6-Chloro-3,4-dihydro-(1*H*)-quinoline-2-thione (3c). A mixture of **2c** (28.2 g, 155.3 mmol) and Lawesson's reagent (32.4 g, 77.7 mmol) was suspended in anhydrous toluene (200 mL) and then refluxed under nitrogen atmosphere for 15 min. The solution was then cooled to room temperature and evaporated. The residue was purified by flash chromatography on silica gel (eluant CH_2Cl_2−light petroleum ether, 2:1, R_f 0.34) providing **3c** (28.6 g) in 93% yield as a pale yellow solid: mp 210−212 °C; ^{1}H NMR ($CDCl_3$) δ 9.90 (br s, 1 H), 7.20 (m, 2 H), 6.81 (d, J = 7.2 Hz, 1 H), 3.09 (m, 2 H), 2.88 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 199.0 (s), 135.0 (s), 128.4 (s), 127.2 (d), 126.8 (d), 126.3 (s), 117.0 (d), 38.4 (t), 24.0 (t); MS *m*/*z* (%) 197 (M^+, 39), 51 (100); IR ($CDCl_3$) 1519, 1483 cm^{-1}. Anal. Calcd for C_9H_8NClS: C, 54.66; H, 4.08; N, 7.08. Found: C, 54.77; H, 3.97; N, 6.83.

6-Chloro-1-(3-oxopentyl)-(1*H*)-3,4-dihydroquinolin-2-thione (4c). Compound **3c** (4.5 g, 22.8 mmol), anhydrous K_2CO_3 (7.3 g, 52.4 mmol) (kept at 140 °C for 12 h before use), and 18-crown-6 (0.78 g, 2.96 mmol) were suspended in anhydrous THF (380 mL). After cooling to 0 °C, a first portion of ethyl vinyl ketone (3.06 mL, 30.78 mmol) was added dropwise under stirring and nitrogen atmosphere. After the addition was complete, the solution was left at 0 °C for 5 min and then at room temperature for 1 h. The solution was cooled again to 0 °C, and a second portion of ethyl vinyl ketone (3.06 mL, 30.78 mmol) was added. The solution was left under stirring for 3 h at room temperature, monitoring the reaction by TLC. Then, sodium sulfate was added, and the solution was filtered and concentrated, providing crude **4c** which was purified by chromatography on silica gel (eluant ethyl acetate−light petroleum ether, 1:10, R_f 0.20) affording pure **4c** (3.40 g) in 53% yield as a pale yellow solid: mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.22−7.10 (m, 2 H), 7.04 (d, J = 8.8 Hz, 1 H), 4.71 (dd, J = 8.8, 6.6 Hz, 2 H), 3.14 (m, 2 H), 2.97 (t, J = 7.7 Hz, 2 H), 2.75 (m, 2 H), 2.48 (q, J = 7.4 Hz, 2 H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.3 (s), 200.0 (s), 137.7 (s), 130.9 (s), 130.0 (s), 128.1 (d), 127.6 (d), 117.3 (d), 45.5 (t), 42.0 (t), 38.3 (t), 36.3 (t), 24.7 (t), 7.6 (q); MS *m*/*z* (%) 281

(8) Up to 0.5 kg of **1c** was prepared using this strategy.

(M^+, 17), 57 (100); IR ($CDCl_3$) 1708, 1424, 1390 cm^{-1}. Anal. Calcd for $C_{14}H_{16}NOClS$: C, 59.67; H, 5.72; N, 4.97. Found: C, 59.54; H, 5.89; N, 4.58.

4-Methyl-8-chloro-2,3,5,6-tetrahydro-(1*H*)-benzo[*c*]quinolizin-3-one (1c). Compound **4c** (3.0 g, 10.7 mmol) was suspended under nitrogen atmosphere in anhydrous toluene (29 mL), and then freshly distilled Me_2SO_4 (1.71 mL, 18.1 mmol) was added dropwise by a syringe at room temperature and under stirring. After the addition was complete, the flask was placed into an oil bath at 140−150 °C. After refluxing for 15 min, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.71 mL, 18.1 mmol) was added dropwise by a syringe and the resulting solution refluxed for a further 20 min. Then it was cooled to room temperature, diluted with CH_2Cl_2 (120 mL), and washed with water (100 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated, affording a crude oil which was purified by flash chromatography (eluant ethyl acetate−light petroleum ether, 1:1, R_f 0.28) providing **1c** (1.21 g) in 46% yield as an oil which solidified on standing: mp 108−110 °C; ^{1}H NMR ($CDCl_3$) δ 7.23−7.11 (m, 2 H), 6.87 (d, J = 8.8 Hz, 1 H), 3.90 (t, J = 7.5 Hz, 2 H), 2.76−2.64 (m, 6 H), 1.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 190.6 (s), 155.4 (s), 139.0 (s), 128.3 (s), 127.7 (d), 127.3 (d), 126.5 (s), 113.9 (d), 106.4 (s), 45.1 (t), 35.3 (t), 26.1 (t), 24.7 (t), 10.1 (q); MS *m*/*z* (%) 247 (M^+, 100); IR ($CDCl_3$) 1648, 1569 cm^{-1}. Anal. Calcd for $C_{14}H_{14}NOCl$: C, 67.82; H, 5.70; N, 5.66. Found: C, 67.98; H, 6.00; N, 5.48.

6-Methyl-3,4-dihydro-(1*H*)-quinoline-2-thione (3b). Prepared as reported above. Starting from **2b** (879 mg, 5.5 mmol), chromatography (CH_2Cl_2: light petroleum ether, 2:1, then only CH_2Cl_2 to elute **3b**) of the crude reaction mixture afforded pure **3b** (900 mg, 93%) as a pale yellow solid: mp 148 °C; ^{1}H NMR ($CDCl_3$) δ 9.55 (br s, 1 H), 7.00 (m, 2 H), 6.71 (d, J = 7.3 Hz, 1 H), 3.07 (t, J = 7.0 Hz, 2 H), 2.82 (t, J = 7.0 Hz, 2 H), 2.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.0 (s), 134.6 (s), 128.6 (d), 127.9 (d), 124.9 (s), 115.5 (d), 38.8 (t), 24.4 (t), 20.8 (q); MS *m*/*z* (%) 177 (M^+, 94), 176 (100); IR ($CDCl_3$) 1486 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90. Found: C, 67.41; H, 6.57; N, 7.71.

6-Methyl-1-(3-oxopentyl)-(1*H*)-3,4-dihydroquinolin-2-thione (4b). Prepared as reported above. Starting from thiolactam **3b** (900 mg, 5.1 mmol), chromatography of the crude reaction mixture (ethyl acetate−light petroleum ether, 1:9, R_f 0.20) afforded pure **4b** (903 mg, 68%) as a pale yellow solid: mp 70−71 °C; ^{1}H NMR ($CDCl_3$) δ 7.08−6.82 (m, 3 H), 4.74 (t, J = 6.6 Hz, 2 H), 3.11 (m, 2 H), 2.99 (t, J = 7.7 Hz, 2 H), 2.72 (t, J = 7.7 Hz, 2 H), 2.49 (q, J = 7.3 Hz, 2 H), 2.29 (s, 3 H), 1.06 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.4 (s), 199.6 (s), 136.5 (s), 134.7 (s), 128.9 (d), 128.3 (s), 128.1 (d), 115.8 (d), 45.4 (t), 42.4 (t), 38.4 (t), 36.3 (t), 24.8 (t), 20.6 (q), 7.6 (q); MS *m*/*z* (%) 261 (M^+, 77), 204 (100); IR ($CDCl_3$) 1707, 1401, 1359 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NOS$: C, 68.92; H, 7.33; N, 5.36. Found: C, 68.98; H, 7.00; N, 5.03.

4,8-Dimethyl-2,3,5,6-tetrahydro-(1*H*)-benzo[*c*]quinolizin-3-one (1b). Prepared as reported above. Starting from **4b** (350 mg, 1.34 mmol), chromatography (ethyl acetate−light petroleum ether, 1:1, R_f 0.25) of the crude reaction mixture afforded pure **1b** (152 mg, 50%) as an oil which solidifies on standing. ^{1}H NMR ($CDCl_3$) δ 7.06−6.83 (m, 3 H), 3.91 (t, J = 7.7 Hz, 2 H), 2.73−2.61 (m, 6 H), 2.30 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 190.3 (s), 156.8 (s), 138.1 (s), 131.4 (s), 128.4 (d), 128.0 (d), 126.6 (s), 112.8 (d), 105.3 (s), 45.0 (t), 35.3 (t), 26.4 (t), 24.7 (t), 20.4 (q), 10.0 (q); MS *m*/*z* (%) 227 (M^+, 100); IR ($CDCl_3$) 1652, 1573 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.25; H, 7.59; N, 6.16. Found: C, 79.34; H, 7.72; N, 6.09.

3,4-Dihydro-(1*H*)-quinoline-2-thione (3a). Prepared as reported above. Starting from **2a** (804 mg, 5.5 mmol), chromatography (CH_2Cl_2: light petroleum ether, 2:1, then only CH_2Cl_2 to elute **3a**) of the crude reaction mixture afforded pure **3a** (829 mg, 93%) as a pale yellow solid: mp 93−94 °C; ^{1}H NMR ($CDCl_3$) δ 9.85 (br s, 1 H), 7.25−7.00 (m, 3 H), 6.85 (d, J = 7.7 Hz, 1 H), 3.09 (m, 2 H), 2.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 200.2 (s), 136.2 (s), 128.2 (d), 127.7 (d), 125.2 (s), 125.0 (d), 115.7 (d), 38.8 (t), 24.4 (t); MS *m*/*z* (%) 163 (M^+, 68), 162 (100); IR ($CDCl_3$) 1485 cm^{-1}. Anal. Calcd for C_9H_9NS: C, 66.22; H, 5.56; N, 8.58. Found: C, 66.54; H, 5.43; N, 8.21.

1-(3-Oxopentyl)-(1*H*)-3,4-dihydroquinolin-2-thione (4a). Thiolactam **3a** (750 mg, 4.6 mmol) was dissolved in 5 mL of anhydrous THF, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (826 μl, 5.52 mmol) was added, and, while cooling at 0 °C, ethyl vinyl ketone (550 μl, 5.52 mmol) was added dropwise under stirring and nitrogen atmosphere. After 2.5 h at 0 °C, the solvent was evaporated, and the residual oil was diluted with CH_2Cl_2 (30 mL) and washed with 5% citric acid, $NaHCO_3$ (satd), and water. The organic layer was dried over sodium sulfate, filtered, and evaporated, obtaining a crude oil which was chromatographed (ethyl acetate−light petroleum ether, 1:9) affording pure **4a** (477 mg, 42%, R_f 0.26) and S-alkylated **5a** (303 mg, 27%, R_f 0.38).

4a: mp 61 °C; ^{1}H NMR ($CDCl_3$) δ 7.25−7.00 (m, 4 H), 4.75 (dd, J = 8.8, 6.3, 2 H), 3.15 (m, 2 H), 3.00 (t, J = 7.9 Hz, 2 H), 2.77 (m, 2 H), 2.48 (q, J = 7.3 Hz, 2 H), 1.06 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.4 (s), 200.1 (s), 138.7 (s), 128.9 (s), 128.1 (d), 127.7 (d), 124.9 (d), 115.7 (d), 45.3 (t), 42.2 (t), 38.3 (t), 36.2 (t), 24.7 (t), 7.5 (q); MS *m*/*z* (%) 247 (M^+, 43), 190 (100); IR ($CDCl_3$) 1706, 1400 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.77; H, 7.12; N, 5.41.

5a: pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2 H), 7.05 (m, 2 H), 3.31 (t, J = 7.0 Hz, 2 H), 2.89 (t, J = 7.0 Hz, 2 H), 2.72 (m, 2 H), 2.43 (m, 4 H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.9 (s), 168.1 (s), 144.2 (s), 127.4 (d, 2 C), 126.7 (s), 125.5 (d), 125.2 (d), 41.8 (t), 36.0 (t), 29.9 (t), 24.4 (t), 23.1 (t), 7.7 (q).

4-Methyl-2,3,5,6-tetrahydro-(1*H*)-benzo[*c*]quinolizin-3-one (1a). Prepared as reported above. Starting from **4a** (504 mg, 2.0 mmol), chromatography (ethyl acetate−light petroleum ether, 2:1, R_f 0.34) of the crude reaction mixture afforded pure **1a** (217 mg, 50%) as an oil which solidified on standing: mp 88−89 °C;^{1}H NMR ($CDCl_3$) δ 7.25−6.94 (m, 4 H), 3.93 (t, J = 7.7 Hz, 2 H), 2.80−2.63 (m, 6 H), 1.83 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 190.7 (s), 156.3 (s), 140.5 (s), 127.9 (d), 127.8 (d), 126.7 (s), 121.8 (d), 112.8 (d), 105.9 (s), 45.0 (t), 35.5 (t), 26.3 (t), 24.8 (t), 10.1 (q); MS *m*/*z* (%) 213 (M^+, 98), 212 (100); IR ($CDCl_3$) 1622, 1553 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.83; H, 7.09; N, 6.57. Found: C, 78.67; H, 7.34; N, 6.29.

1-(3-Oxopentyl)piperidine-2-thione (9). Prepared as reported for **4c**, but the reaction was left under stirring for 30 min at room temperature after the second addition of vinyl ethyl ketone. Starting from **8** (500 mg, 4.33 mmol), pure **9** (844 mg, 97%) was obtained after chromatography (CH_2Cl_2, R_f 0.25) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.10 (t, J = 6.6 Hz, 2 H), 3.49 (t, J = 6.2 Hz, 2 H), 2.95 (m, 4 H), 2.44 (q, J = 7.3 Hz, 2 H), 1.84 (m, 2 H), 1.68 (m, 2 H), 1.03 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.7 (s), 199.7 (s), 52.2 (t), 50.3 (t), 41.9 (t), 38.6 (t), 36.2 (t), 23.0 (t), 20.5 (t), 7.8 (q); MS *m*/*z* (%) 199 (M^+, 27), 142 (100); IR ($CDCl_3$) 1705, 1413 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.01; H, 8.76; N, 7.13.

1-Methyl-3,4,6,7,8,9-hexahydroquinolizin-2-one (10). Prepared as reported for **1c**. Starting from **9** (500 mg, 2.51 mmol), pure **10** (278 mg, 67%) was obtained after chromatography (CH_2Cl_2−MeOH, 19:1, R_f 0.27) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.25 (t, J = 7.7 Hz, 2 H), 3.12 (t, J = 5.5 Hz, 2 H), 2.37 (m, 4 H), 1.70 (m, 2 H), 1.62 (s, 3 H), 1.61 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 188.7 (s), 1.60.3 (s), 103.1 (s), 50.7 (t), 50.3 (t), 35.1 (t), 26.9 (t), 22.7 (t), 19.6 (t), 9.4 (q); MS *m*/*z* (%) 165 (M^+, 83), 136 (100); IR ($CDCl_3$) 1600, 1546 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.47; H, 9.03; N, 8.21.

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