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# A practical method for the synthesis of pyrrolizidine, indolizidine and pyrroloazepinolizidine nucleus

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**Abstract**—The alkylation of α,ω-dibromoalkanes, with the sodium salt of succinimide, followed by the reduction with sodium borohydride gives the respective *N*-ω-bromoalkyl-5-hydroxy-2-pyrrolidinones. These substrates are precursors of *N*-acyliminium ions under acidic conditions. The condensation of these intermediates with ethyl malonate in the presence of $TiCl_4$ and diisopropylethylamine following the intramolecular cyclization provides a convenient route to substituted pyrrolizidinone, indolizidinone and pyrroloazepinolizidinone nucleus in a good yield.


Nitrogen containing heterocycles are abundant in nature and exhibit diverse and important biological properties.[1,2] These heterocycles include an important group of azabicyclic alkaloids, among them, pyrrolizidines,[3] indolizidines,[4] and the perhydroazaazulene ring containing pyrroloazepinolizidines.[5] Not surprisingly, members of this class have attracted considerable attention, and several reviews concerning their synthesis and biological properties have been published.[6] Many syntheses of these compounds are reported for both racemic and enantiomerically pure forms. It might therefore appear that sufficient methods are available for preparing these compounds. The elaboration of ring-fused heterocycles based on internal nucleophilic displacement,[7] intramolecular conjugate addition,[8] intermolecular amide formation,[9] double cyclization processes,[10] transannular reactions,[11] dipolar cycloaddition,[12] ring closing metathesis[13] or upon cascade sequences such as cationic cyclization,[14] radical cyclization,[15] tandem Heck processes,[16] allows the rapid and stereocontrolled synthesis of azabicyclic skeletons. Small modifications of the structure of pyrrolizidines, indolizidines and pyrroloazepinolizidines induce significant changes in their biological activity. It is therefore justified to develop improved methodologies to generate more substituted congeners of these azabicyclic systems.

In the above context, the acyliminium ions especially the cyclic versions thereof are widely used for the synthesis of nitrogen containing heterocyclic compounds[17] and nitrogen containing natural products.[18] ω-Hydroxylactams are the most frequently used precursors of cyclic *N*-acyliminium ions, and they are typically prepared by the reduction of the corresponding imides with sodium borohydride. Subsequent treatment of the hydroxy compounds with Lewis or protic acids generates the very reactive *N*-acyliminium species.[19]

We first considered that the intramolecular trapping of an *N*-acyliminium species by an ester enolate[20] would provide a short and convergent route to the desired bicyclic five-membered N-containing systems.[21] To this end, succinimide was N-alkylated with ethyl 4-bromobutyrate (NaH/DMF) and imide **1** (Scheme 1) thus produced, was reduced with sodium borohydride at a low temperature to the *N*-acyliminium species precursor **2** (52% yield in two steps). A prolonged contact of the solutions of **2** with either trifluoroacetic acid or titanium tetrachloride at 0 °C gave none of the expected pyrrolizidinone **4** and a small amount (24% yield) of

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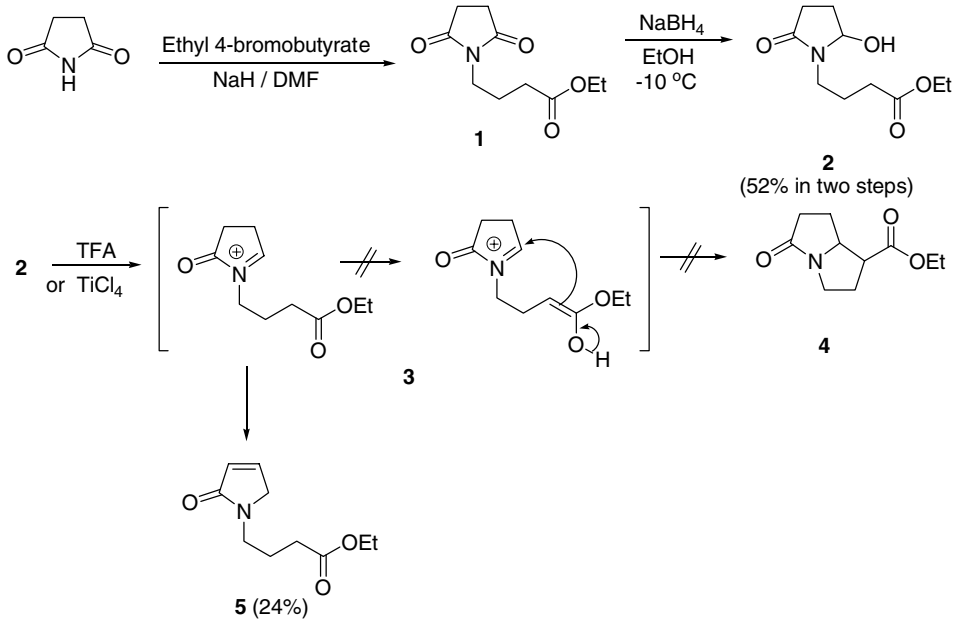
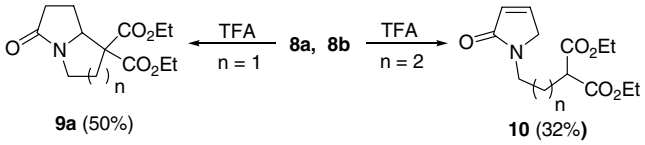



**Scheme 1.** Synthesis of *N*-acyliminium species precursor **2**.

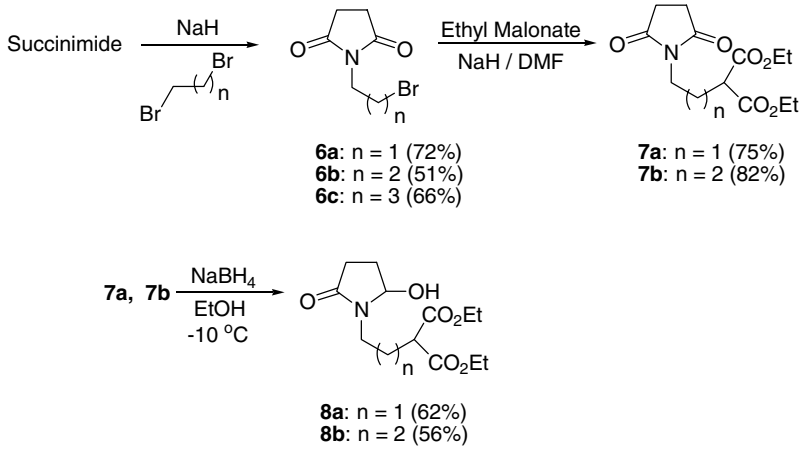
3-pyrrolin-2-one **5** as the only isolable product. Unfortunately the yield for this compound was not improved (Scheme 1).

We next considered that the enolates of the malonate[22] analog **8a** and its homolog **8b** (Scheme 2) might more effectively trap the *N*-acyliminium species in the intramolecular sense. These compounds were obtained by sodium borohydride reduction of **7a**,**b**, which had been prepared by the alkylation of the corresponding *N*-ω-bromoalkylsuccimides **6a**,**b** with the sodium salt of diethyl malonate in DMF solution. The bromo compounds **6a**–**c** were prepared from succinimide and the appropriate α,ω-dibromoalkanes using sodium hydride as the base in DMF (51–72% yields) at room temperature. Treatment of 5-hydroxy-2-pyrrolidinone **8a** with TFA in $CH_2Cl_2$ solution at room temperature did indeed produce 2-pyrrolizidinone **9a** (Scheme 3; 50% yield), but the homologous compounds **8b** under similar conditions gave pyrroline-2-one derivative **10** as the major product.[23]

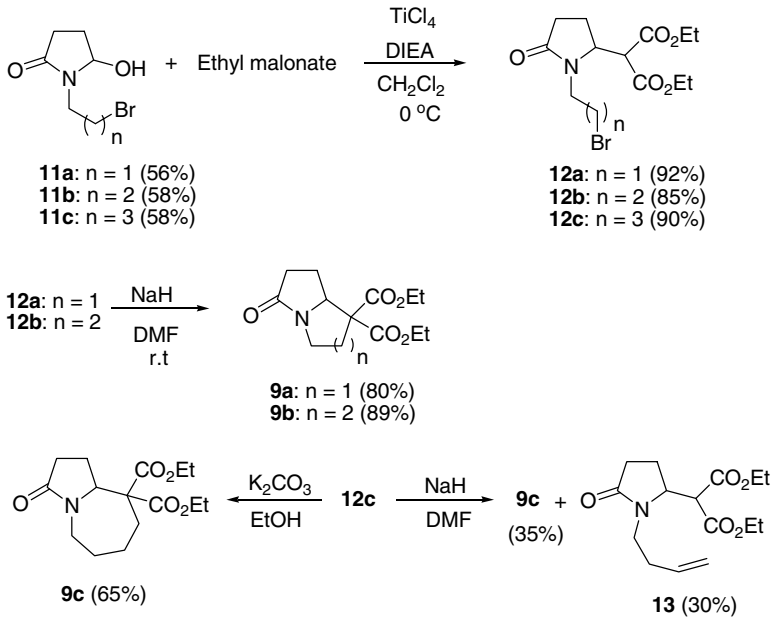



**Scheme 3.** Treatment of 5-hydroxy-2-pyrrolidinone **8a** and **8b** with TFA.

Given the results described above, we opted to try a different synthetic approach. Thus, 5-hydroxy-2-pyrrolidinones **11a**–**c** (Scheme 4) were synthesized (56–58% yields) from ω-bromoalkylsuccinimides **6a**–**c** by reduction with sodium borohydride in the usual way.[24] 5-Hydroxypyrrolidinones **11** have a good stability and can be purified by silica-gel column chromatography.




**Scheme 2.** Synthesis of *N*-acyliminium species precursor **8**.




**Scheme 4.** Synthesis of azabicyclic nucleus **9a**, **9b** and **9c**.

The combination of titanium tetrachloride and diisopropylethyl amine (DPEA) had been efficiently used in the stereoselective formation of nucleophilic enolates,[25] it was thought that ethyl malonate might react in an analogous manner. This supposition was correct. The reaction of **11** with ethyl malonate in the presence of two equivalents each of $TiCl_4$ and DPEA, efficiently afforded the required malonyl compounds **12a** (92%), **12b** (85%) and **12c** (90%). Compounds **12a** and **12b** underwent facile cyclization with sodium hydride in DMF solution giving pyrrolizidinone **9a** and indolizidinone **9b** in 80% and 89% yields, respectively. In contrast, the cyclization of **12c** to pyrroloazepinolizidinone **9c** took place much less efficiently (35%) under these conditions and olefin **13** was formed as a significant byproduct. When ethanolic potassium carbonate was used as the base, none of the elimination product was formed and the intramolecular cyclization product **9c** was obtained in a 65% yield.[23]

In summary, the synthesis of pyrrolizidinone **9a**, indolizidinone **9b** and pyrroloazepinolizidone **9c** systems has been devised. This synthetic approach to these bicyclic systems which are found in many natural products is particularly attractive because of its brevity and efficiency, and also because all of the starting materials are readily available and inexpensive.

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23. $^{1}$H NMR and $^{13}$C spectra were measured on a Bruker 300 MHz Advance instrument in $CDCl_3$ solution. Mass spectra on a Jeol JMS-Ax 505 HA mass spectrometer at 70 eV.
24. *5-Hydroxy-2-pyrrolidinones* **11**. These reductions were carried out as described below using a slightly modified version of that reported by Hubert et al.[19] To a stirred solution of **6** (1.0 equiv) in ethanol (10 mL/mmol) at −10 °C was added $NaBH_4$ powder (1.0 equiv) and the reaction mixture was stirred for 30 min. At this time 1 M ethanolic HCl (3 drops) was added and after a further 30 min $NaBH_4$ (1.0 equiv) was added, followed 30 min thereafter by another portion of 1 M ethanolic HCl (3 drops). This procedure of alternate additions of $NaBH_4$ and HCl was repeated until a total of 5.0 equiv of sodium borohydride had been added. The reaction mixture was maintained at −5 °C over night. The reaction mixture was poured onto ice and the product was extracted with $CH_2Cl_2$ (5 × 50). The organic layer was washed with ice water and the organic phase was dried over $Na_2SO_4$. The solvent was removed under vacuum, and the product was purified by silica gel column chromatography to afford the respective 5-hydroxy-2-pyrrolidinone **11**.
Compound **11a**: $^{1}$H NMR ($CDCl_3$) $\delta$ 1.90–1.99 (m, 1H), 2.30–2.45 (m, 2H), 2.50–2.68 (m, 2H), 3.45–3.61 (m, 2H), 3.64–3.86 (m, 2H), 5.29–5.38 (m, 1H), 6.0 (br, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2 (C), 84.0 (CH), 42.4 ($CH_2$), 29.3 ($CH_2$), 28.7 ($CH_2$), 28.2 ($CH_2$); mass spectrum *m*/*z* 191 (40, $M^+$+2, –$H_2O$), 189 (40, $M^+$−$H_2O$), 96 (100).
Compound **11b**: $^{1}$H NMR ($CDCl_3$) $\delta$ 1.92–99 (m, 1H), 2.10–2.41 (m, 4H), 2.58–2.65 (m, 1H), 3.37–3.55 (m, 4H), 5.24–5.27 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2 (C), 83.7 (CH), 39.3 ($CH_2$), 31.13 ($2CH_2$), 28.9 ($CH_2$), 28.3 ($CH_2$); mass spectrum *m*/*z* 206 (99, $M^+$+2, –HO), 204 (100, $M^+$−HO).
Compound **11c**: $^{1}$H NMR ($CDCl_3$) $\delta$ 1.61–1.98 (m, 5H), 2.24–2.38 (m, 2H), 2.5–2.63 (m, 1H), 3.18–3.27 (m, 1H), 3.42–3.52 (m, 3H), 5.24–5.27 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2 (C), 84.0 (CH), 38.9 ($CH_2$), 33.4 ($CH_2$), 29.9 ($CH_2$), 29.0 ($CH_2$), 28.2 ($CH_2$), 26.2 ($CH_2$); mass spectrum *m*/*z* 235 (5, $M^+$+2), 233 (5, $M^+$), 154 (100).
Compound 5-(2′-malonyl)-2-pyrrolidinones **12**. To a solution of ethyl malonate (2.0 equiv) in $CH_2Cl_2$ (5.0 mL/mmol) was added at 0 °C $TiCl_4$ (2.2 equiv, 1.0 M in $CH_2Cl_2$) and the reaction mixture was stirred under argon for 10 min, diisopropylethylamine (2.0 equiv) was then added slowly at 0 °C and the mixture was stirred for 30 min, 5-hydroxy-2-pyrrolidinone **11** (1.0 equiv) in $CH_2Cl_2$ (1.0 mL/mmol) was added very slowly (30–60 min), and the resulting reaction was stirred overnight at room temperature. The reaction was quenched with saturated $NH_4Cl$ solution and the product was extracted with $CH_2Cl_2$ (3 × 50 mL). The extract was washed with brine and dried over $Na_2SO_4$. The solvent was removed under vacuum and the product was purified by column chromatography.
Compound **12a**: $^{1}$H NMR ($CDCl_3$) $\delta$ 1.27 (t, $J = 7.1$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 2.18–2.21 (m, 1H), 2.31–2.40 (m, 3H), 3.30 (td, $J = 14.4$, 6.6 Hz, 1H), 3.42–3.61 (m, 2H), 3.73 (d, $J = 5.0$ Hz, 1H), 4.06 (td, $J = 14.4$, 6.6 Hz, 1H), 4.20 (c, $J = 7.1$ Hz, 2H), 4.23 (c, $J = 7.1$ Hz, 2H), 4.41–4.43 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.7 (C), 167.1 (C), 167.0 (C), 62.1 ($CH_2$), 62.0 ($CH_2$), 57.28 (CH), 53.9 (CH), 42.8 ($CH_2$), 29.3 ($CH_2$), 28.4 ($CH_2$), 22.0 ($CH_2$), 14.0 ($2CH_3$); mass spectrum *m*/*z* 351 (7, $M^+$+2), 349 (7, $M^+$), 190 (100).
Compound **12b**: $^{1}$H NMR ($CDCl_3$) $\delta$ 1.28 (t, $J = 7.1$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 2H), 2.05–2.45 (m, 6H), 3.07 (ddd, $J = 14.1$, 6.0, 2.1 Hz, 1H), 3.40 (t, $J = 6.5$ Hz, 2H), 3.69–3.79 (m, 1H), 3.76 (d, $J = 4.5$ Hz, 1H), 4.21 (c, $J = 7.1$ Hz, 2H), 4.25 (c, $J = 7.1$ Hz, 2H), 4.28–4.31 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.5 (C), 167.1 (C), 166.9 (C), 61.9 ($CH_2$), 61.8 ($CH_2$) 57.2 (CH), 53.6 (CH), 39.9 ($CH_2$), 30.3 ($CH_2$), 30.2 ($CH_2$), 29.4 ($CH_2$), 21.6 ($CH_2$), 13.9 ($2CH_3$); mass spectrum *m*/*z* 365 (2, $M^+$+2), 363 (2, $M^+$), 204 (100).
Compound **12c**: $^{1}$H NMR ($CDCl_3$) $\delta$ 1.25 (t, 3H), 1.27 (t, 2H), 1.60–1.75 (m, 2H), 1.78–1.85 (m, 2H), 2.13–2.48 (m, 4H), 2.87 (ddd, $J = 13.5$, 7.9, 4.9 Hz, 1H), 3.43 (t, $J = 6.3$ Hz, 1H), 3.73 (d, $J = 4.9$ Hz, 1H), 3.68–3.77 (m, 1H), 4.19 (c, $J = 7.1$ Hz, 2H), 4.23 (c, $J = 7.1$ Hz, 2H), 4.25–4.31 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.3 (C), 167.2 (C), 167.0 (C), 61.9 ($CH_2$), 61.8 ($CH_2$), 56.3 (CH), 53.4 (CH), 39.5 ($CH_2$), 33.1 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 21.4 ($CH_2$), 14.0 ($CH_3$), 13.9 ($CH_3$); mass spectrum *m*/*z* 380 (8, $M^+$+2), 378 (8, $M^+$), 218 (100).
Compound **9a**: To a stirred suspension of sodium hydride (1.0 equiv, prepared from 50% suspension of NaH in mineral oil) in anhydrous DMF (10 mL/mmol) was added at room temperature 5-malonyl-2-pyrrolidinone **12** (1.0 equiv) in DMF (5 mL/mmol) and the resulting mixture was stirred during overnight. AcOEt was added and the mixture was washed with saturated $NH_4Cl$ solution, the organic phase was dried over $Na_2SO_4$, the solvent was removed under vacuum, and the product was purified by silica-gel column chromatography with hexane–ethyl acetate (50:50).
Compound **9a** was obtained as an oil in an 80% yield: $^{1}$H NMR ($CDCl_3$) $\delta$ 1.27 (t, $J = 7.0$ Hz, 3H), 1.28 (t, $J = 7.0$ Hz, 3H ), 1.86–1.99 (m, 1H), 2.27–2.46 (m, 3H), 2.58–2.69 (m, 2H), 3.12–3.20 (m, 1H), 3.79 (td, $J = 11.3$, 8.0 Hz, 1H), 4.17–4.29 (m, 4H), 4.42 (dd, $J = 7.3$, 6.2 Hz,

1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.4 (C), 169.3 (C), 169.1 (C), 65.6 (CH), 61.9 ($CH_2$), 61.8 ($CH_2$), 60.7 ($CH_2$), 40.9 (C), 34.7 ($CH_2$), 33.2 ($CH_2$), 21.6 ($CH_2$), 14.0 ($CH_3$), 13.9 ($CH_3$); mass spectrum $m/z$ 269 (20, $M^+$), 270 (43, M+H), 97 (100).

Compound **9b**: This compound was prepared in the same manner as described for **9a**. After column chromatography using hexane–ethyl acetate (50:50) **9b** was isolated as an oil in an 89% yield: $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, $J = 7.1$ Hz, 3H), 1.23 (t, $J = 7.1$ Hz, 3H), 1.41–1.66 (m, 2H), 1.89 (dt, $J = 13.7$, 4.0 Hz, 1H), 2.05–2.19 (m, 1H), 2.25–2.67 (m, 5H), 3.73 (dd, $J = 9.5$, 3.9 Hz, 1H), 4.06–4.22 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.9 (C), 169.8 (C), 168.6 (C), 61.7 ($CH_2$), 61.2 ($CH_2$), 60.8 (CH), 56.7 ($CH_2$), 39.3 (C), 31.5 ($CH_2$), 29.9 ($CH_2$), 20.3 ($CH_2$), 20.1 ($CH_2$), 14.0 ($CH_3$), 13.9 ($CH_3$); mass spectrum $m/z$ 283 (22, $M^+$), 210 (100).

Compound **9c**: To a solution of 5-malonyl-2-pyrrolidinone (1.0 equiv) in ethanol (7.5 mL/mmol) was added $K_2CO_3$ (5.0 equiv) at room temperature and the resultant suspension was stirred overnight. The reaction mixture was filtered through a pad of Celite and washed with ethyl acetate. After removal of the solvent in vacuo the product was purified by flash column chromatography on silica gel using hexane–AcOEt (50:50) to afford azepinolizidinone **9c** as an oil in a 65% yield $^1$H NMR ($CDCl_3$) $\delta$ 1.26 (t, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.63–1.91 (m, 7H), 2.22–2.28 (m, 1H), 2.34–2.40 (m, 2H), 3.04 (ddd, $J = 13.3$, 10.9, 1.7 Hz, 1H), 3.80 (td, $J = 14.0$, 3.6 Hz, 1H), 4.12–4.28 (m, 4H), 4.56 (dd, $J = 8.9$, 7.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.7 (C), 171.3 (C), 169.1 (C), 62.3 (CH), 61.7 ($CH_2$), 61.6 ($CH_2$), 60.2 ($CH_2$), 41.8 (C), 30.0 ($CH_2$), 29.7 ($CH_2$), 28.0 ($CH_2$), 24.9 ($CH_2$), 22.4 ($CH_2$), 14.0 ($2CH_3$); mass spectrum $m/z$ 297 (95, $M^+$), 184 (100).

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