Pergamon

Tetrahedron Letters 40 (1999) 9189–9193

TETRAHEDRON LETTERS

Synthesis of substituted pyrrolidines by sequential radical cyclization and *N*-acyliminium ion reactions

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Received 2 September 1999; revised 30 September 1999; accepted 3 October 1999

Abstract

Readily available *N*-acyl-2-pyrrolines are converted into functionalized α-alkoxy-β-iodopyrrolidines by *N*-iodosuccinimide promoted alcohol addition to the enamine group. These compounds are readily cyclized using a sodium cyanoborohydride–catalytic tributylstannane system affording functionalized pyrrolidines in good yields. The cyclized products undergo *N*-acyliminium ion reactions, such as $BF_3 \cdot OEt_2$ mediated addition of allyltrimethylsilane. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: pyrrolidines; radical reactions; cyclizations; *N*-acyliminium ion reactions.

The widespread occurrence and biological activity of pyrrolidines in natural products and pharmaceuticals have made them important targets for synthetic chemists.[1] The development of new strategies that allow for pyrrolidine functionalization is therefore of great interest. Recent work from our laboratory has explored the use of *N*-acylated cyclic enamines **1** as versatile precursors for the formation of functionalized nitrogen heterocycles.[2,3] The precursors **1** are readily accessible from the corresponding cyclic amines, lactams or their acyclic equivalents. Differential and regiocontrolled functionalization of the alkene in **1** is then possible through electrophilic attack at the β-position and nucleophilic attack at the α-position. We are particularly interested in annulation and *N*-acyliminium ion reactions using **1**. In this report we describe preliminary results using a two-step approach for the formation of the bicycles **3**, via functionalization of **1** with **2** followed by free-radical cyclization, and the subsequent utility of **3** as *N*-acyliminium ion precursors (Scheme 1).

Intramolecular radical cyclizations constitute a well-established strategy for the construction of five- and six-membered rings for carbocycles and heterocycles,[4] and usually proceed with moderate to high stereoselectivity.[5] Thus, while direct annulation reaction of **1** and **2** to **3** is clearly a challenging prospect,

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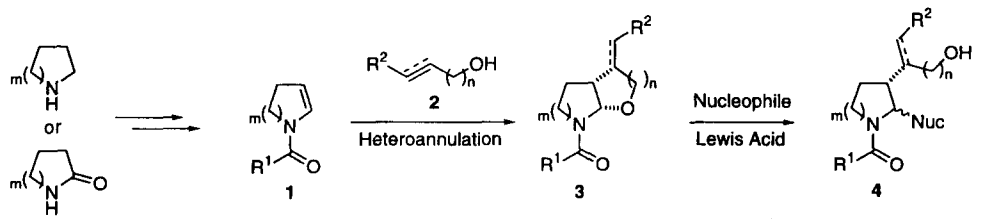
PII: S0040-4039(99)01971-1



Scheme 1.

an indirect route using a free-radical cyclization should allow for the formation of the new ring in **3**.[6,7] *N*-acyl-2-pyrroline **1**[8] was chosen as a representative precursor, and converted by iodoetherification to the free-radical precursor **5** (Table 1).[9] This was achieved by treatment of **1** and **2** with *N*-iodosuccinimide at low temperature, affording the *trans*-α-alkoxy-β-iodopyrrolidines **5** in good yields.[10]

Free-radical cyclizations of **5** were accomplished using a sodium cyanoborohydride–catalytic tributylstannane system[11] to give the bicyclic products **3** (Table 1).[12] The reactions occurred in moderate to high yields, except for the 6-*exo* ring closures in which reduced products were also formed (Table 1, Entries 3 and 8). The cyclizations were highly regiospecific with only the *cis*-fused 5-*exo* or 6-*exo* products being obtained, starting from the hexenyl and heptenyl radicals, respectively. For 5-*exo*-trig cyclizations onto alkene traps, cyclization proceeds preferentially through the lowest energy '*endo*' (1,5-*cis*) transition state, leading to the *cis*-substituted bicyclo[3.3.0] systems (Table 1, Entries 5–7).[13,14] As the size of the substituent increases, the steric interaction in the *endo* position become larger and the selectivity diminishes. For 6-*exo*-trig ring closure, lower selectivity in favour of the *trans* product was observed (Table 1, Entry 8), resulting from cyclization through the '*exo*' (1,6-*trans*) transition state, in accordance with similar examples.[5]

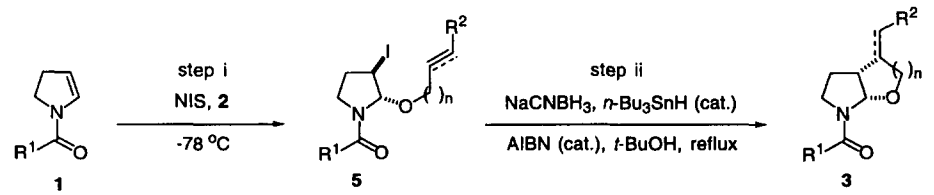
The C–O bond of the bicyclic pyrrolidine unit **3** can be used for further transformations. For instance, reduction of compound **3** using lithium aluminium hydride[15] gave the substituted pyrrolidine **6** (Scheme 2). More significantly, **3** can be utilized as an *N*-acyliminium ion precursor in C–C bond-forming reactions,[16] as exemplified by the reaction with allyltrimethylsilane/$BF_3 \cdot OEt_2$ to give **7**, which occurred with moderate diastereoselectivity in favour of the *cis*-isomer (Scheme 2).[16,17]

In summary, we have demonstrated that bicyclic pyrrolidines **3**, can be obtained by radical cyclization of *trans*-α-alkoxy-β-iodopyrrolidines **5** using a catalytic tributylstannane protocol. The radical precursors **5** are readily prepared by *N*-iodosuccinimide promoted iodoetherification of *N*-acyl-2-pyrrolines **1**. The adducts **3** are useful precursors for further transformations to form substituted pyrrolidines. Ongoing studies to extend this methodology to the synthesis of more highly substituted *N*-heterocycles will be reported in due course.

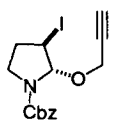
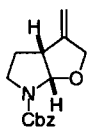
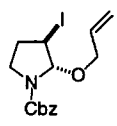
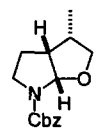
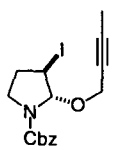
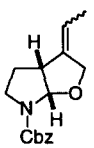
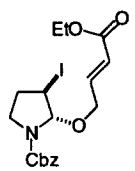
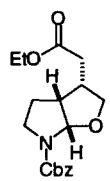
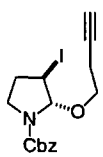
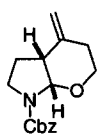
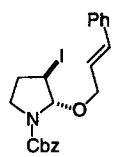
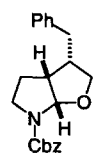
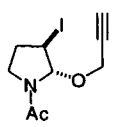
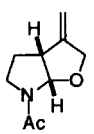
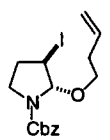
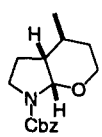
Acknowledgements

This work was supported by the Fundação para a Ciência e Tecnologia (FCT, project PRAXIS XXI PCEX/C/QUI/53/96 and a Ph.D grant for M.N.M., ref. PRAXIS XXI BD/9040/96) and the National Science and Engineering Research Council (NSERC) of Canada. R.A.B. gratefully acknowledges AstraZeneca and AstraZeneca R&D Montréal, Bio-Méga/Boehringer Ingelheim Recherche Inc., the Environmental Science and Technology Alliance Canada, Merck Frosst, the Ontario Research and Development Challenge Fund and Uniroyal Chemicals Inc., for additional support. We thank Dr. A. B. Young for mass spectroscopic analyses.

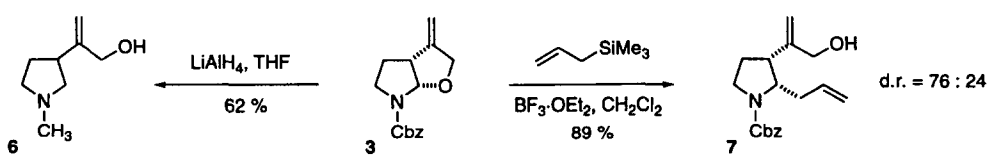
Table 1
Representative examples for the conversion of *N*-acyl-2-pyrrolines **1** into bicyclic pyrrolidines **3**



1 **5** **3**

Entry	5 (step i)	Yield[a] (%)	3 (step ii)	Yield[a] (%)	Entry	5 (step i)	Yield[a] (%)	3 (step ii) (major isomer)	Yield[a] (%)	d.r.[f]
1		80		71	5		65		92[d]	95:5
2		65		74[b]	6		62		82[d]	80:20
3		75		46[c]	7		74		60[d]	74:26
4		83		75	8		62		30[d,e]	60:40

(a) Yield of pure product isolated by flash chromatography. (b) Isolated as a 1:1 mixture of *E/Z*-isomers. (c) The corresponding reduced product was also isolated in 37% yield. (d) Isolated as a mixture of two diastereoisomers. (e) The corresponding reduced products were also isolated in 26% yield. (f) d.r. determined by ^{1}H NMR.



6 **3** **7**

Scheme 2.

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12. *Representative iodoetherification*: (Step i, Entry 1) A solution of *N*-iodosuccinimide (698 mg, 2.95 mmol) and propargyl alcohol (172.0 μl, 2.95 mmol) in dry dichloromethane (20 ml) under nitrogen was cooled to −78°C. *N*-(Benzyloxy)carbonyl-2-pyrroline **1** (500 mg, 2.46 mmol) in dry dichloromethane (3 ml) was added dropwise and the resulting mixture was stirred for 10 min and then poured into a cold saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted once with dichloromethane. The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification by column chromatography (SiO_2, 10% EtOAc:90% hexane) afforded *trans*-3-iodo-2-propynyloxy-*N*-(benzyloxy)carbonyl-pyrrolidine **5** (760 mg, 80%) as a colourless oil; R_f=0.5 (10% EtOAc:90% hexane); IR (film) ν 3290, 3032, 2955, 2117, 1710, 1586, 1498, 1404, 1286, 1193, 1113, 1052, 972, 915, 771, 696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.33 (m, 5H, phenyl), 5.63–5.54 (m, 1H, N-C*H*-O), 5.19 (s, 2H, (O=C)-CH_2-Ph), 4.33–4.31 (m, 2H, O-CH_2-C), 4.12 (d, *J*=3.6 Hz, 1H, CH_2-C*H*-I), 3.71–3.49 (m, 2H, N-CH_2-CH_2), 2.48–2.11 (m, 3H, CC-H and CH_2-CH-I); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.3, 154.2, 136.0, 135.8, 128.2, 127.9, 127.8, 127.5, 94.9, 94.2, 79.5, 79.1, 74.5, 74.3, 67.2, 67.0, 56.3, 55.6, 44.7, 44.5, 33.4, 32.5, 26.7, 25.9; HRMS (EI) *m/z*: calcd for (M^+), requires: 385.0175. Found: 385.0173. *Representative radical cyclization*: (Step ii, Entry 1) *trans*-3-iodo-2-propyloxy-*N*-(benzyloxy)carbonyl-pyrrolidine **5** (400 mg, 1.04 mmol) in dry *t*-BuOH (5 ml) was added dropwise to a stirred mixture of $NaCNBH_3$ (82 mg, 1.3 mmol), Bu_3SnH (15 μl, 0.05 mmol) and AIBN (17.4 mg, 0.104 mmol) in dry *t*-BuOH (16 ml) under nitrogen at 80°C. The reaction mixture was refluxed for 14 h. Three portions of benzene (3×5 ml) were added and the azeotropic mixture was removed under reduced pressure. The residue was taken up in dichloromethane and filtered through Celite to remove the white precipitate. Purification by column chromatography (SiO_2, 20% EtOAc:80% hexane) afforded *cis*-6-methylene-2-aza-8-oxa-bicyclo[3.3.0]octane **3** (192 mg, 71%) as a colourless oil; R_f=0.36 (20% EtOAc:80% hexane); IR (film) ν 3040, 2953, 1709, 1411, 1356, 1272, 1170, 1113, 1057, 1024, 888, 769, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.24 (m, 5H, phenyl), 5.89–5.84 (m, 1H, N-C*H*-O), 5.26–5.02 (m, 4H, 2H: (O=C)-CH_2-Ph, 2H: =CH_2), 4.40 (s, 2H, CH_2-O), 3.68–3.63 (m, 1H, CH_2-C*H*-C=), 3.42–3.29 (m, 2H, N-CH_2-CH_2), 2.07–1.84 (m, 2H, -CH_2-CH_2-CH); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.4, 149.7, 136.7, 128.4, 128.0, 127.8, 127.7, 105.7, 93.0, 92.4, 71.1, 66.9, 47.5, 46.5, 45.6, 45.4, 31.0, 30.7; HRMS (EI) *m/z*: calcd for (M^+), requires: 259.1208. Found: 259.1195.

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14. The stereochemistry of cyclized products for entries 5 to 8 was assigned by a combination of 1D NMR and 2D NMR NOESY experiments performed at high temperatures in 1,1,2,2-tetrachloroethane-d_2 (for entry 7 toluene-d_8 was used).
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