Synthesis of Aza/Oxaspiro-γ-lactams by Radical Translocation Cyclization Reactions

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Received 5 March 2005

Abstract: A cascade radical translocation cyclization of the *N*-allyl-*N*-(2′-bromophenyl)amide moiety of heterocyclic carboxylic acids and its *N*-propynyl analogues were investigated. It provides a convenient method for the preparation of aza/oxaspiro-γ-lactams that are useful γ-turn mimetics in drug discovery.

Key words: radical translocation, [1,5]-hydrogen transfer, spiro-γ-lactams

Great efforts have been spent on the design and synthesis of conformationally constrained analogues (peptidomimetics) to improve the potency, selectivity, and metabolic stability of peptide-based drugs in recent years. Spirolactams **1**–**4** (Figure 1), with fixed angles resembling naturally occurring γ-turns of peptides, are of interest in the pursuit of peptidomimetic drugs.[1] Thus far, their synthesis has primarily involved intramolecular Mitsunobu reaction,[2] amide-coupling reaction,[3] or Michael addition followed by subsequent nitro-reductive cyclization reactions[4] to yield the bispirolactam skeleton. In addition, both solution and solid-phase synthesis of structurally similar spiro-oxindoles were reported.[5]

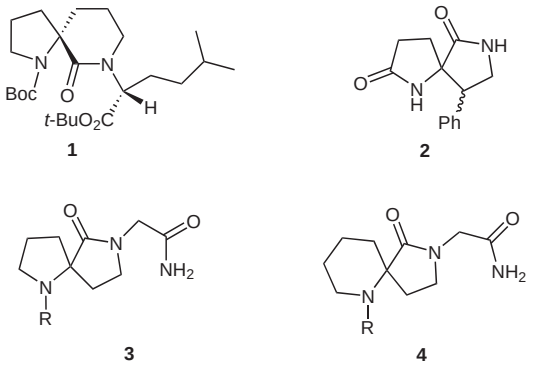
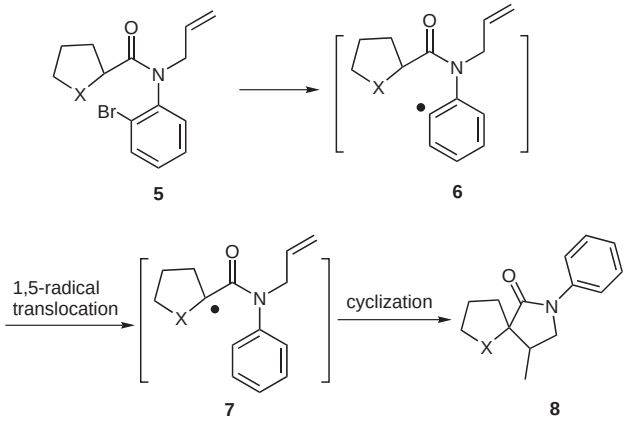


Figure 1 Spirolactam peptidomimetics

Over the last couple of decades, radical translocation reactions in which the key bond-forming radical was generated by intramolecular abstraction of an atom (usually hydrogen) or group by a radical center, which then subsequently reacts with a site normally unreactive towards external reagents have been well developed.[6] They have been employed in the synthesis of natural products with unusual structural features[7] and carbospirocarboncycles.[6b] To our knowledge no applications of radical translocation reactions in the preparation of aza/oxaspirolactams have been reported.

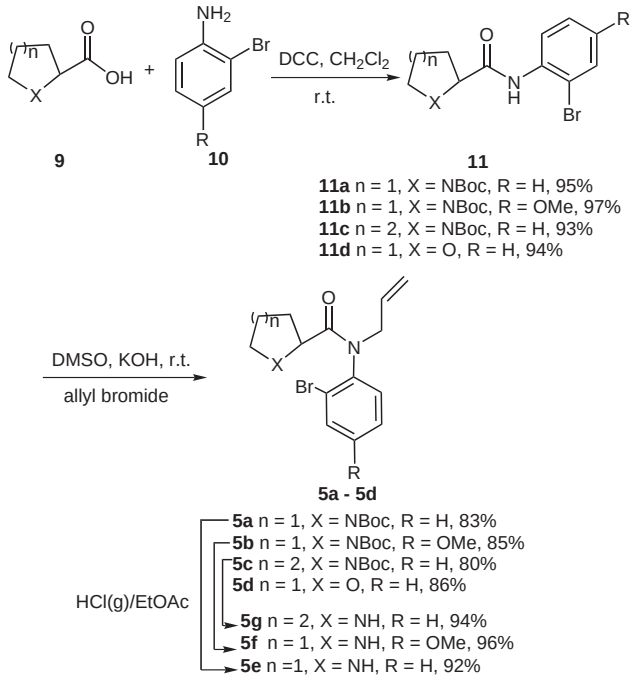
It is anticipated that the aza/oxaspiro-γ-lactam frameworks **8** could be constructed from amides **5** through radical translocation cyclization reactions (Scheme 1). This strategy involves a cascade of radical reactions initiated by generation of aryl radical **6** from its bromo precursor **5**. Radical **6** abstracts the α-proton on the heterocycle to yield new radical **7**. Radical **7** undergoes *exo* cyclization with the *N*-allyl double bond to give the spirolactam **8**. The details of the investigations are presented in this paper.



Scheme 1 Strategic approach to aza/oxaspiro-γ-lactams by radical translocation cyclization

Radical precursors **5** were prepared from readily available acids **9** according to Scheme 2. Acids **9** [*N*-Boc L-proline, (±)-*N*-Boc piperidine-2-carboxylic acid, or (±)-tetrahydrofuran-2-carboxylic acid] coupled with 2-bromo- or 4-methoxy-2-bromoaniline **10** to provide amides **11** in nearly quantitative yields. Amides **11** reacted with allyl bromide in the presence of potassium hydroxide in DMSO to afford radical precursors **5**. The Boc group of compounds **5** (**a**–**c**, X = *N*-Boc) was readily cleaved by hydrochloric acid in ethyl acetate to give unprotected **5** (**e**–**g**, X = NH) in good yields. Compounds **5a**, **5b**, **5e**, and **5f** were obtained in optically active form (**5a**: $[\alpha]_D^{20}$ = 153.2, **5b**: $[\alpha]_D^{20}$ = 142.6, **5e**: $[\alpha]_D^{20}$ = 28.0, **5f**: $[\alpha]_D^{20}$ = 27.4) from L-proline. The other precursors **5** were synthesized from racemic acids **9**.

SYNLETT 2005, No. 12, pp 1865–1868
Advanced online publication: 22.06.2005
DOI: 10.1055/s-2005-871563; Art ID: U06105ST

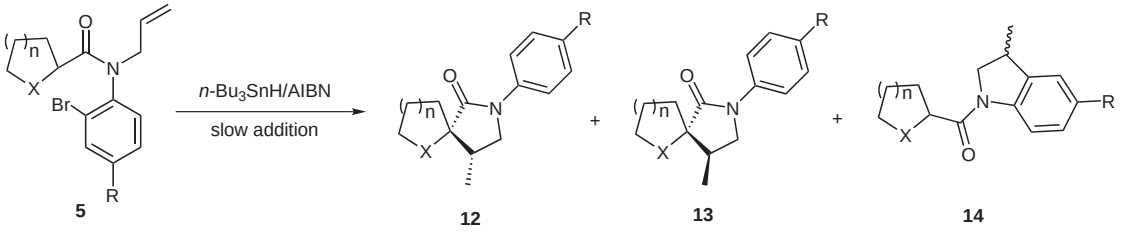


Scheme 2 Preparation of the radical precursors **5**

A routine method using AIBN[6c] as an initiator was applied to the radical reactions of compounds **5**;[8] translocation cyclization aza/oxaspirolactams **12** and **13**, along with non-translocation cyclization products **14** resulted. It was observed that the ratio of **12a**, **13a**, and **14a** was unchanged when the concentration of starting **5a** was varied (0.1 M, 0.05 M, 0.01 M). Several substrates **5** with different heteroatoms (X = N or O) on the ring, different ring size (n = 1 or 2), or different substituent on the nitrogen of the heterocycle (X = *N*-Boc or NH) were investigated. The results are summarized in Table 1. All the structures were determined on the basis of their ^{1}H and ^{13}C NMR spectra, LC-MS, and elemental analyses. The diastereomeric ratio (1:8–9) of **12** to **13** remained constant regardless of the N-substituent on the heterocycles (Table 1, entries 1, 2, 3, 5, 6, and 7), although Boc caused an increase in the yield of non-translocation cyclization products **14** (Table 1, entries 1, 2, and 3 vs 5, 6, and 7). Replacement of N with O resulted in an increase in the yield of product **12d** (Table 1, entry 4). Varying the ring-size from five to six (Table 1, entries 1 vs 3 and 5 vs 7) had no effect on the product ratio, neither did placing a methoxy group at the *para*-position of the phenyl ring (Table 1, entries 1 vs 2 and 5 vs 6). In the case of optically active substrates **5a**, **5b**, **5e**, and **5f** (Table 1, entries 1, 2, 5, and 6) no optical rotation of their corresponding products **12** and **13** was observed (**14** was not measured due to the small amount obtained), which indicated complete racemization at the initial chiral α-position. All these facts are consistent with a plane of symmetry at the translocated radical center at the α-position that is stabilized by the captodative effect with the adjacent heteroatom and carbonyl group.

The stereochemical configuration of compound **13f** was determined on the basis of X-ray diffraction analysis (Figure 2). Its NOESY spectrum (Figure 3) is consistent with the X-ray structure. As shown in Figure 3 there is a clear NOE effect between one of the protons at C-4 (1.91–2.03 ppm) and the methyl protons at C-9 (1.15 ppm) indicating that they are close to each other. The stereochemistry of **13b** was confirmed by its conversion to **13f** after treatment with hydrochloric acid in ethyl acetate.[9] The stereochemical structures of the rest of the products **12** and **13** were assigned by analogy with their NMR spectra. The stereochemical configuration of **14** was not determined.

Table 1 Cascade Radical Reaction of **5** Leading to Aza/Oxaspirolactam **12**, **13**, and Compound **14**



Entry	**5**	n	R	X	**12** (%)[a]	**13** (%)	**14** (%)
1	**a**	1	H	*N*-Boc	**a** (7)	**a** (52)	**a** (25)
2	**b**	1	OMe	*N*-Boc	**b** (7)	**b** (51)	**b** (22)
3	**c**	2	H	*N*-Boc	**c** (6)	**c** (50)	**c** (23)
4	**d**	1	H	O	**d** (25)	**d** (38)	**d** (23)
5	**e**	1	H	NH	**e** (7)	**e** (64)	**e** (9)
6	**f**	1	OMe	NH	**f** (7)	**f** (66)	**f** (8)
7	g	2	H	NH	**g** (7)	**g** (65)	**g** (9)

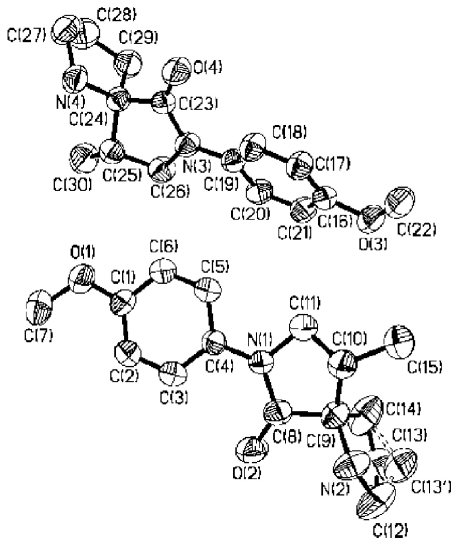


Figure 2 X-ray structure of compound **13f**

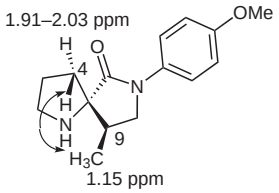


Figure 3 NOESY spectra of compound **13f**

The above radical transformations could be extended to *N*-propynyl analogues **15** of heterocyclic substrates. Unlike compounds **5**, precursors **15**, prepared in a similar procedure using 3-bromopropyne instead of allyl bromide, underwent only radical translocation cyclization to afford products **16** under similar conditions. As shown in Table 2, *exo*-cyclized products **16** were obtained in moderate to good chemical yields.

In summary, the *N*-allyl-*N*-(2′-bromoaryl)amide moiety of heterocyclic 2-carboxylic acids and their *N*-propynyl analogues were found to undergo radical translocation cyclization to form aza/oxaspirolactams in good yield. This approach provides a convenient methodology for the preparation of aza/oxaspirolactams that may be used as peptidomimetics in drug discovery.

Acknowledgment

This work was supported by a grant from Jilin Provincial Fund for Young Talented Scientists (No. 20010105) and by Changchun Discovery Sciences, Ltd.

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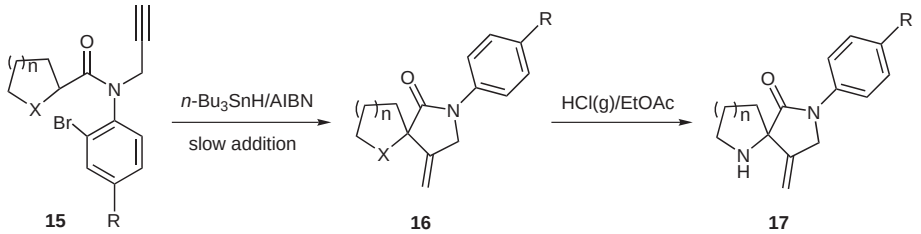
Table 2 Cascade Radical Reaction of **15** Leading to Aza/Oxaspirolactam **16**



Entry	**15**	X	n	R	**16** (%)	**17** (%)
1	**a**	*N*-Boc	1	H	**a** (80)	**a** (91)
2	**b**	*N*-Boc	2	H	**b** (75)	**b** (90)
3	**c**	*N*-Boc	1	OMe	**c** (79)	**c** (94)
4	**d**	O	1	H	**d** (55)	

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(8) Genenal procedure: To a stirred solution of **5** (2 mmol) in degassed toluene (50 mL), Bu_3SnH (0.688 mL, 2.4 mmol) and AIBN (33 mg, 0.2 mmol) in toluene (20 mL) were added dropwise over 7 h using a syringe pump under reflux. After addition, the solution was heated at reflux for a further 2 h. The solvent was removed, and the residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 5:1–1:1) to give products **12**, **13**, and **14** (order of elution).
Compound **12f**: 7%; light yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, 3 H, *J* = 7.2 Hz, 1.79–1.89 (m, 2 H), 1.92–2.04 (m, 2 H), 2.21–2.26 (m, 1 H), 2.87–2.95 (m, 1 H), 3.22–3.30 (m, 1 H), 3.34–3.38 (dd, 1 H, *J* = 3.6 Hz, *J* = 9.6 Hz), 3.80 (s, 3 H), 3.81–3.86 (dd, 1 H, *J* = 6.3 Hz, *J* = 9.8 Hz), 4.79 (br s, 1 H, D_2O exchangeable), 6.89 (d, 2 H, *J* = 9.0 Hz), 7.53 (d, 2 H, *J* = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.22, 26.10, 35.32, 37.67, 47.47, 52.97, 55.44, 71.07, 114.02, 121.26, 132.95, 156.49, 176.39; MS (ESI): *m*/*z* = 261.1 [M + H$^+$]; Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.02; H, 7.65; N, 10.83.
Compound **13f**: 66%; light yellowish solid; mp 82.4–83.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, 3 H, *J* = 7.2 Hz), 1.59–1.69 (m, 1 H), 1.76–1.86 (m, 1 H), 1.91–2.03 (m, 2 H), 2.31–2.39 (m, 1 H), 2.97–3.04 (m, 1 H), 3.23–3.30 (m, 2 H), 3.68–3.73 (m, 1 H, *J* = 7.5 Hz, *J* = 9.6 Hz), 3.80 (s, 3 H), 4.78 (br s, 1 H, D_2O exchangeable), 6.90 (d, 2 H, *J* = 9.0 Hz), 7.53 (d, 2 H, *J* = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.89, 26.26, 28.78, 39.34, 47.62, 52.08, 55.44, 70.64, 114.02, 121.09, 132.80, 156.47, 177.70; MS (ESI): *m*/*z* = 261.1 [M + H$^+$]; Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.97; H, 7.62; N, 10.51.
Compound **14f**: 8%; light yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, 3 H, *J* = 6.9), 1.78–1.89 (m, 2 H), 2.17–2.25 (m, 1 H), 2.88–2.91 (m, 1 H), 3.20–3.25 (m, 1 H), 3.44–3.58 (m, 2 H), 3.64–3.70 (m, 1 H), 3.80 (s, 3 H), 3.91–3.93 (m, 1 H), 4.18–4.32 (m, 1 H), 4.76 (br s, 1 H, D_2O exchangeable), 6.73 (d, 2 H), 8.10 (m, 1 H); MS (ESI): *m*/*z* = 261.1 [M + H$^+$].

(9) To a solution of **13b** (180 mg, 0.5 mmol) in EtOAc (4 mL) at r.t. was added a saturated solution of HCl in EtOAc (5 mL). After stirring for 2 h, the reaction was quenched with 30 % aq NaOH, and extracted with EtOAc (3 × 15 mL).The organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, and concentrated in vacuo to give **13f** (113 mg, 87%) as a light yellowish solid (mp 82.1–84.0 °C).