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Practical Synthesis of Structurally Important Spirodiamine Templates

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Practical Synthesis of Structurally Important Spirodiamine Templates

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Abstract: A general, concise, four-step synthetic sequence for the preparation of spirodiamine templates is described herein.

Keywords: α-aza-bicyclo templates, α-"N"-bearing spirodiamies, spirodiamines

INTRODUCTION

The incorporation of spiro-bicyclic ring systems into many bioactive molecules is one of the key strategies in modern medicinal chemistry. This is due primarily to their structural rigidity along with feasibility for further structural elaboration through three-dimensional drug space. A recent survey reveals the popularity of the spirodiamine scaffolds with heteroatom attached directly to the nearby spiro-carbon atom as shown in Fig. 1. For example, the [6,6]-spiro scaffold **A** showed pharmacological activity on synaptic conductance and was believed to confer neurotoxic activities.[1] The recent interest in [5,7]-aza-bicyclic system **B** stemmed from the successful use of aza-siprolactams as beta-turn mimetics.[2] Furthermore, the discovery of quinolone antibacterial agents containing the [5,5]-spirodiamine moiety (e.g., compound **C**) has garnered further interest in the synthesis of such aza-spiro scaffolds (see Fig. 1).

Prompted by intriguing biological and pharmacological activities exhibited by the spirodiamine scaffolds as shown in Fig. 1, we decided to devise practical synthetic routes for those α-nitrogen-containing spirodiamines as outlined in Fig. 2, namely [5,5]-, [6,5]-, [5,6]-, and [6,6]-scaffolds.

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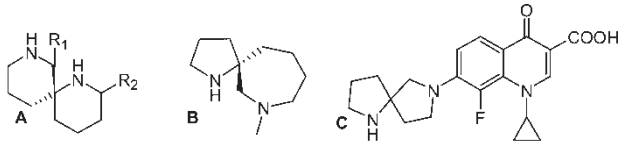


Figure 1. Examples of spirodiamine structures.

We believe that these structural motifs can be incorporated into diverse biologically active molecules.

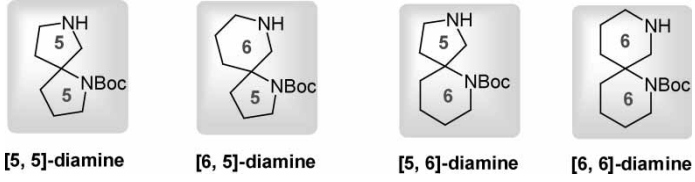


Figure 2. Spirodiamine templates of interest.

Despite their growing popularity in medicinal chemistry, a practical synthetic method directed toward spirodiamines with α-heteroatom is sub optimal. For example, the reported four-step procedure (consisting of *C*-alkylation, cyano reduction, second ring closure, and amido-reduction) for the synthesis of [5,5]-spiro template as shown in Fig. 3 suffers from poor overall yield (only 2.6%).[3]

With the intention of designing a high-yielding and general methodology, we have devised an efficient route as shown in Scheme 1.[4] In this event, *N*-Boc proline **1** was converted to its carboxamide **2** (60%) and thereafter the cyano derivative **3** in 85% yield *via* trifluoro acetic anhydride/triethyl amine (TFAA/TEA)-mediated dehydration reaction. Treatment of **3** with lithium diisopropyl amine (LDA) followed by 1-bromo-2-chloro-ethane led to the *C*-1 alkylated compound **4** (55%), which was further transformed to the [5,5]-spirodiamine template **5** (90%) via Raney Ni–mediated cyano

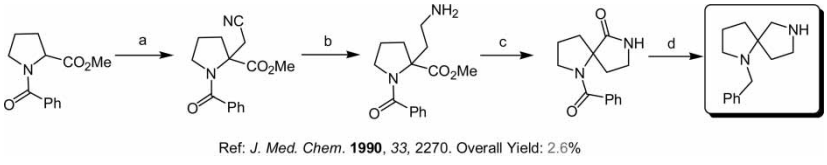
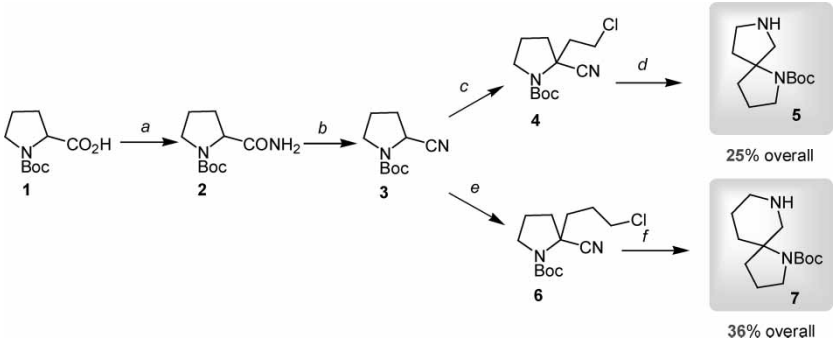


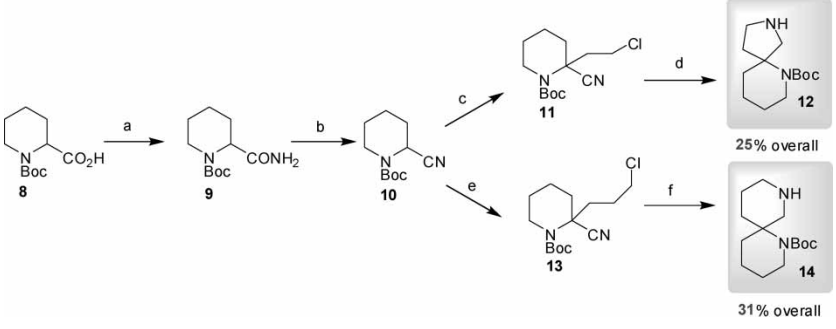
Figure 3. Literature route toward the synthesis of [5,5]-template: (a) $ClCH_2CN$, LDA, 40%; (b) H_2, Raney Ni; (c) heat, 36% two steps; (d) LAH, 18%.



Scheme 1. Efficient synthetic routes for [5,5]- and [5,6]-templates: (a) *i*-PrOC (O)Cl, NH_3-H_2O, 60%; (b) TFAA, Et_3N, 85%; (c) LDA, $BrCH_2CH_2Cl$, 55%; (d) H_2, Raney Ni, NH_3-H_2O, 90%; (e) LDA, $ClCH_2CH_2CH_2Cl$, 75%; (f) H_2, Raney Ni, NH_3-H_2O, 95%.

reduction and subsequent ring closure. Following the same sequence as described for the target template **5**, compound **3** was subjected to *C*-alkylation with $ClCH_2CH_2CH_2Cl$ to afford the desired *C*-1 alkylated product **6** in 75% yield. This intermediate was further converted to the target [6,5]-spirodiamine template **7** via an one-pot process in 95% yield. It is worthwhile to mention that the four-step overall yields for the templates **5** and **7** are 25 and 36%, respectively. This represents a significant improvement over that reported (2.6%) in Ref. [3].

Following the same strategy as outlined in Scheme 1, the syntheses of [5,6]- and [6,6]-spirodiamines employed *N*-Boc pipcolic acid **8** as the starting material. A two-step procedure was used to convert the acid **8** into its *C*-1 cyano derivative **10** in 50% overall yield. Subsequent C-1 alkylation on **10**



Scheme 2. Efficient synthetic routes for [6,5]- and [6,6]-templates: (a) *i*-PrOC (O)Cl, NH_3-H_2O, 60%; (b) TFAA, TEA, 89%; (c) LDA, $BrCH_2CH_2Cl$, 50%; (d) H_2, Raney Ni, NH_3-H_2O, 92%; (e) LDA, $BrCH_2CH_2CH_2Cl$, 65%; (f) H_2, Raney Ni, NH_3-H_2O, 90%.

with appropriate alkyl halides afforded the expected products **11** (50%) and **13** (65%), which were further converted to the desired templates **12** (92%) and **14** (90%) via Raney Ni–mediated cyano reduction and ammonia–water–mediated ring-closure reaction. The overall four-step yields for the [5,6]- and [6,6]-spirodiamine templates are 25% and 31% (Scheme 2).

In summary, we have designed an efficient four-step sequence for the preparation of α-nitrogen containing spirodiamine templates **5**, **7**, **12**, and **14**. The overall yields for the target templates range between 25 and 36%. It is conceivable that the synthetic route reported herewith will allow for synthesis of related spirodiamines bearing different ring sizes.

EXPERIMENTAL

Unless otherwise mentioned, reagents were obtained commercially and used without further purification. ^{1}H NMR, ^{13}C NMR and ^{1}H-13C HMQC were taken with Bruker AM-400 Hz spectrometer in $CDCl_3$. MS was taken with Shimadzu 2010.

tert-Butyl 2-Carbamoylpyrrolidine-1-carboxylate (2)

A solution of Boc-proline (10.75 g, 0.05 mol) and Et_3N (22.5 g, 0.225 mol) in dichloromethane (50 ml) was cooled to -30°C and then treated with isopropyl chloroformate (12.2 g, 0.1 mol) at -30°C. After complete addition, the resulting mixture was stirred at -30 to -20°C for 30 min, and this mixture was treated with conc. $NH_3 \cdot H_2O$ (11 ml, 0.15 mol) at -30°C in a period of 30 min. This mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was washed with water (3×50 ml), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **2** (6.45 g, yield 60%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 5.50–7.01 (m, 2H), 4.87 (m, 1H), 4.35 (m, 1H), 3.44 (m, 1H), 1.75–1.99 (m, 4H), 1.43 (s, 9H): MS (m/z): 215 (M + 1).

tert-Butyl 2-Cyanopyrrolidine-1-carboxylate (3)

A solution of compound **2** (10.70 g, 0.05 mol) in dichloromethane (300 ml) and Et_3N (22.7 g, 0.225 mol) was cooled to 0°C and then treated with TFAA (21.0 g, 0.1 mol) at 0°C. After complete addition, the mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was washed with water (3×50 ml), 0.5 M HCl, and aqueous $NaHCO_3$; dried over Na_2SO_4; filtered; and concentrated under reduced pressure to give compound **3** (8.33 g, yield 85%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 4.43 (m, 1H), 3.31–3.55 (m, 2H), 1.96–2.30 (m, 4H), 1.49 (s, 9H): MS (m/z): 197 (M + 1).

tert-Butyl 2-(2-Chloroethyl)-2-cyanopyrrolidine-1-carboxylate (4)

A solution of n-BuLi (2.5 M, 12 ml, 0.03 mol) in THF was added to a solution of diisopropylamine (5.6 ml, 0.04 mol) in THF (30 ml) under an N_2 atmosphere at $-78^{\circ}C$. After 30 min, compound **3** (4.91 g, 0.025 mol) was added to the mixture at $-78^{\circ}C$. After complete addition, the resulting mixture was stirred at $-78^{\circ}C$ for 45 min. 1-Bromo-2-chloro-ethane (4.1 ml, 0.05 mol) was added to the mixture at $-78^{\circ}C$. After complete addition, the mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was quenched by aqueous NH_4Cl and extracted with EtOAc (50 ml × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude compound **4** (5.4 g) as a brown liquid. The crude product was purified by silica column chromatography to afford compound **4** (3.5 g, yield 55%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): 3.41–3.95 (m, 4H), 2.21–2.65 (m, 2H), 1.71–2.35 (m, 4H), 1.50 (s, 9H): MS (m/z): 203 (M-23), 259 (M + 1).

tert-Butyl 1,7-Diazaspiro[4.4]nonane-1-carboxylate (5)

A solution of compound **4** (1.1 g, 4.4 mmol) in methanol (40 ml) and conc. $NH_3 \cdot H_2O$ (2.8 ml) was stirred with Raney Ni (1 g) under an H_2 atmosphere (30 psi) at $50^{\circ}C$ for 6 h. After filtrating off Raney Ni, the filtrate was concentrated under reduced pressure to give compound **5** (1.0 g, yield 90%). ^1H NMR (400 MHz, $CDCl_3$): 3.20–3.50 (m, 3H), 2.16–2.67 (m, 4H), 1.62–1.89 (m, 5H), 1.49 (s, 9H): ^{13}C NMR (400 MHz, $CDCl_3$): 154.7, 81.1, 67.4, 53.7, 47.8, 46.0, 39.8, 36.1, 28.5, 23.2; ^1H-^{13}C HMQC: H3.22, 3.48/C53.7; H3.23, 2.67/C47.8; H2.16, 2.43/C47.8; H2.23, 1.89/C46.0; H1.76, 1.80/C36.1; H1.62, 1.70/C23.2; MS (m/z): 227 (M + 1).

tert-Butyl 2-(3-Chloropropyl)-2-cyanopyrrolidine-1-carboxylate (6)

General procedure for compound **4** was followed to afford the title product. ^1H NMR (400 MHz, $CDCl_3$): 3.31–3.75 (m, 4H), 2.35–2.51 (m, 2H), 1.70–2.25 (m, 6H), 1.51 (s, 9H): MS (m/z): 295 (M + 23).

tert-Butyl 1,7-Diazaspiro[4.5]decane-1-carboxylate (7)

General procedure for compound **5** was followed to afford the title product. ^1H NMR (400 MHz, $CDCl_3$): 2.80–3.48 (m, 6H), 1.60–2.67 (m, 8H), 1.49 (s, 9H): ^{13}C NMR (400 MHz, $CDCl_3$): 154.3, 80.3, 62.3, 48.3, 43.4, 37.3, 31.4, 28.7, 28.5, 21.8, 20.8; ^1H-^{13}C HMQC: H3.48, 3.02/C48.3; H3.15, 2.92/C43.4; H3.20, 2.80/C37.3; H2.67, 2.25/C31.4; H2.05, 1.90/H28.7; H1.98, 1.85/21.8; H1.65, 1.60/C20.8; MS (m/z): 241 (M + 1).

tert-Butyl 2-Carbamoylpiperidine-1-carboxylate (9)

General procedure for compound **2** was followed to afford the title product. ^{1}H NMR (400 MHz, $CDCl_3$): 6.12 (m, 2H), 4.70 (m, 1H), 4.11 (m, 1H), 2.70 (m, 1H), 2.25 (m, 1H), 1.46 (s, 9H), 1.38–1.70 (m, 5H): MS (m/z): 229 (M + 1).

tert-Butyl 2-Cyanopiperidine-1-carboxylate (10)

^{1}H NMR (400 MHz, $CDCl_3$): 5.25 (m, 1H), 4.02 (m, 1H), 3.61 (m, 1H), 2.98 (m, 1H), 1.45–1.85 (m, 6H), 1.47 (s, 9H): MS (m/z): 155 (M-56), 211 (M + 1), 233 (M + 23).

tert-Butyl 2-(2-chloroethyl)-2-cyanopiperidine-1-carboxylate (11)

General procedure for compound **4** was followed to afford the title product. ^{1}H NMR (400 MHz, $CDCl_3$): 3.75 (d, 1H), 3.64 (t, 2H, $J = 10$ Hz), 3.10 (m, 1H), 2.50 (m, 1H), 2.05 (m, 1H), 1.45–1.70 (m, 6H), 1.51 (s, 9H): MS (m/z): 217 (M-56), 295 (M + 23).

tert-Butyl 2,6-Diazaspiro[4.5]decane-6-carboxylate (12)

General procedure for compound **5** was followed to afford the title product. ^{1}H NMR (400 MHz, $CDCl_3$): 2.99–3.69 (m, 6H), 1.52–2.18 (m, 8H), 1.43 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): 156.2, 80.4, 62.3, 58.3, 43.0, 41.2, 36.8, 29.6, 28.4, 23.5, 20.5; ^{1}H-^{13}C HMQC: H3.69, 2.89/C58.3; H3.21, 3.20/C43.0; H3.45, 3.05/C41.2; H2.18, 1.95/C36.8; H2.00, 1.93/C29.6; H1.72, 1.59/C23.5; H1.65, 1.52/C20.5; MS (m/z): 241 (M + 1).

tert-Butyl 2-(3-chloropropyl)-2-cyanopiperidine-1-carboxylate (13)

General procedure for compound **4** was followed to afford the title product. ^{1}H NMR (400 MHz, $CDCl_3$): 3.75 (dd, 1H, $J = 4$ Hz), 3.59 (tetra, 2H, $J = 6.4$ Hz), 3.10 (m, 1H), 2.14–2.20 (m, 2H, $J = 5.2$ Hz), 1.60–2.05 (m, 8H), 1.51 (s, 9H): MS (m/z): 231 (M-56), 309 (M + 23).

tert-Butyl 1,8-Diazaspiro[5.5]undecane-1-carboxylate (14)

General procedure for compound **5** was followed to afford the title product. ^{1}H NMR (400 MHz, $CDCl_3$): 2.44–4.01 (m, 6H), 1.50–1.75 (m, 10H), 1.43 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): 156.4, 81.6, 63.4, 52.3, 42.0, 36.8,

29.4, 28.7, 28.5, 28.4, 24.6, 19.0; ^{1}H-^{13}C HMQC: H4.01, 3.25/C52.3; H3.55, 2.46/C42.0; H3.16, 2.65/C36.8; H1.58, 1.55/C29.4; H1.75, 1.65/C28.5; H1.70, 1.63/C28.4; H1.68, 1.59/C24.6; H1.50, 1.55/C19.0; MS (m/z): 255 (M + 1).

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