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A new synthesis of spiropyrrolidine–tetralones via an unexpected formal ring-contraction of 4-disubstituted piperidine to 3-disubstituted pyrrolidine

Upul K. Bandarage *, Robert J. Davies

Department of Medicinal Chemistry, Vertex Pharmaceutical Inc., 130 Waverly Street, Cambridge, MA 02139, USA

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ABSTRACT

We have developed an efficient synthesis of novel racemic spiropyrrolidine–tetralones via an unexpected ring-contraction reaction of a 4-disubstituted piperidine to 3-disubstituted pyrrolidine. We suggest that intramolecular quaternization of the piperidine nitrogen of compound **7** occurs to form a bridged bicyclic quaternary ammonium salt intermediate **10**. The ring opening of **10** with cyanide resulted in pyrrolidine **9**. The synthesis of racemic spiropyrrolidine–tetralone **15** is described as well as the related spiropiperidine–indanone, **1b**.

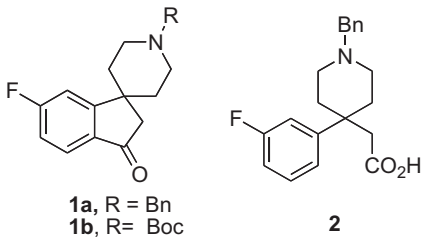
Compounds containing spirocyclic functionalities have been widely utilized in pharmaceutical research due to their biological properties.[1] For example, acylated spiropiperidine–indanone derivatives have been reported as potential melanocortin receptor (MC4R) agonists to treat a variety of diseases such as obesity,[2] and sexual dysfunctions.[3] Furthermore, spiropiperidine–tetralones have been investigated as potential delta opioid receptor agonists.[4] Recently, we reported the use of spiroindane derivatives as potential muscarinic receptor modulators.[5]

As the addition of fluorine to specific locations on drug-like molecules has successfully led to improvements in a variety of properties including enhanced binding interaction, brain penetration, metabolic stability, and extended biological half-life,[6] we became interested in preparing the fluorine containing spiropiperidine–indanone **1b** (Fig. 1).

It was speculated that the spirocyclic functionality could be constructed via an intramolecular Friedel–Crafts cyclization of the carboxylic acid precursor **2**. As illustrated in Scheme 1, our efforts focused on a six step synthesis to make the key nitrile intermediate **8**, which could be hydrolyzed to carboxylic acid **2**. The nitrile **8** could be synthesized from commercially available 2-(3-fluorophenyl) acetonitrile **3**.

The treatment of **3** with excess sodium hydride followed by sequential alkylation with bis-(2-chloroethyl)-*N*-benzylamine[7] provided tertiary nitrile **4** in 77% yield. Acid hydrolysis of nitrile **4**, followed by in situ esterification of the resulting carboxylic acid afforded ester **5** in 86% yield. Lithium aluminum hydride reduction of ester **5**, followed by reaction with methane sulfonyl chloride provided mesylate **7** in 94% yield. Upon heating mesylate **7** with sodium cyanide at 80 °C in DMSO, a major product was formed in 77% yield. Surprisingly, the ^{1}H NMR spectrum was not consistent with the structure of **8**, as the four distinct sets of peaks from the piperidine ring system were absent. Instead, the ^{1}H NMR was consistent with the pyrrolidine propanenitrile **9**.

The proposed mechanism for the formation of **9** is shown in Scheme 2. Intramolecular quaternization of the piperidine nitrogen results in the formation of the bridged bicyclic quaternary ammonium salt **10**. Addition of nucleophilic cyanide can now facilitate ring opening of **10** to produce compound **9**. If the piperidine nitrogen of compound **6** is protected as a carbamate instead of benzyl group, the quaternization and ring opening would be unlikely to occur. When the piperidine nitrogen is deactivated with a Boc group in substrates similar to **6**, no ring-contraction was observed.



1a, R = Bn
1b, R= Boc

2

Figure 1. Spiropiperidine–indanone and proposed cyclization precursor **2**.

* Corresponding author. Tel.: +1 617 444 6882; fax: +1 617 444 7827.
E-mail address: upul_bandarage@vrtx.com (U.K. Bandarage).

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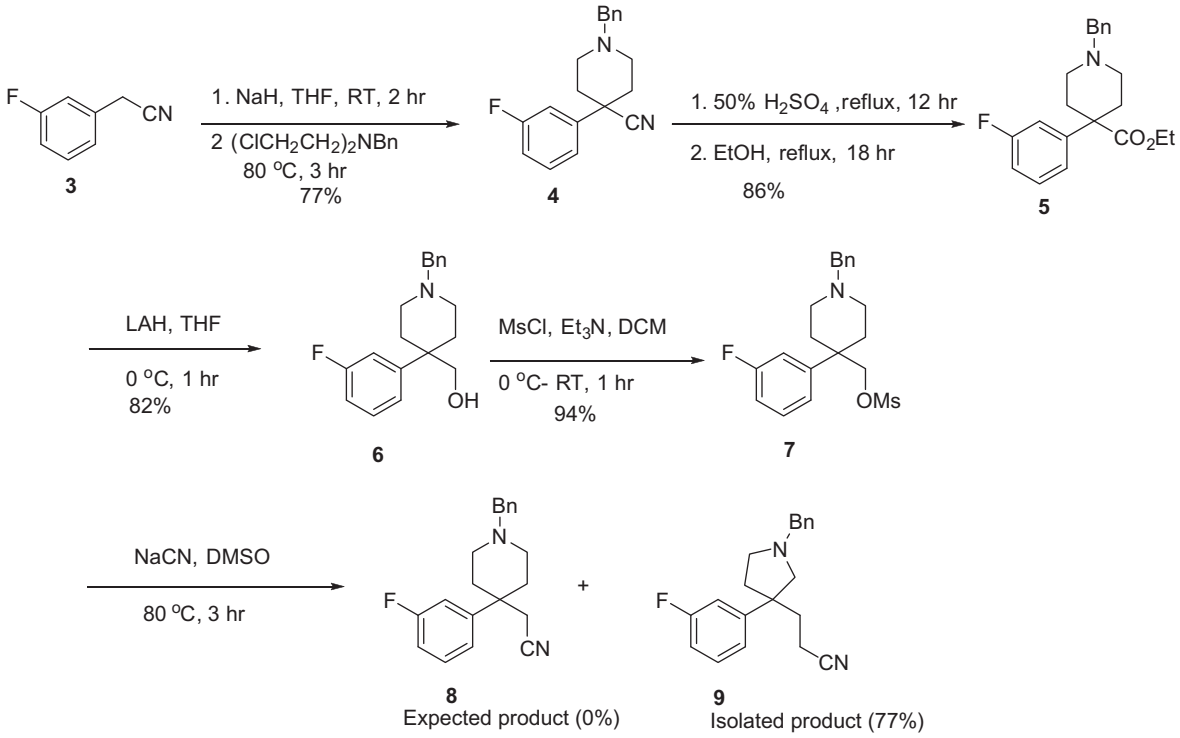
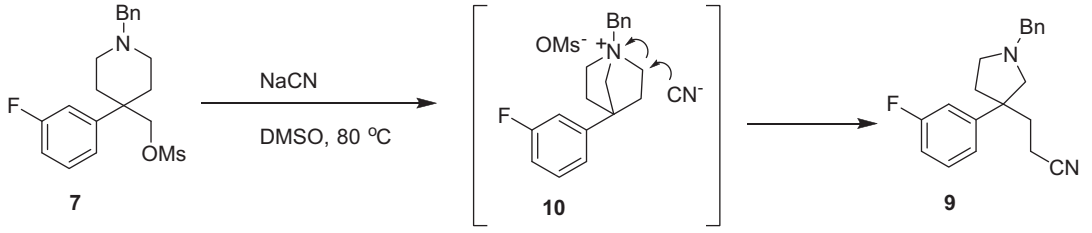


Scheme 1. The proposed synthesis of nitrile **8**.



Scheme 2. The proposed mechanism of formation of pyrrolidine **9** via ring opening of the bicyclic quaternery salt **10**.

Instead, the desired piperidine nitrile was isolated in high yield. The opening of bridged bicyclic quaternary[8] salts with nucleophiles is unusual and there are relatively few examples of ring contractions via bicyclic salts in the literature. Della and Smith[9] reported the ring opening of the bicyclic quaternary salt **11** with strong nucleophiles such as phenylselenide anion in DMSO at 100 °C to form the 3-disubstituted pyrrolidine **12**. (Fig. 2) The authors suggest that nucleophilic substitution on the ring carbon is facilitated by relief of ring strain.

With nitrile **9** in hand, this intermediate was converted into the spiropyrrolidine–tetralone **15** over four steps in good yield. (Scheme 3). Nitrile **9** was hydrolyzed with 6 N HCl to provide carboxylic acid **13**. Conversion of **13** into the corresponding acid chloride, followed by $AlCl_3$ assisted Friedel–Crafts cyclization resulted in the formation of spiropyrrolidine–tetralone core **14** in 81% yield. Removal of the benzyl group in the presence of Boc anhydride afforded the novel racemic Boc protected spiropyrrolidine–tetralone **15** in 66% yield.

We then sought to synthesize our initial target, spiropiperidine–indanone **1b**, via a different synthetic route utilizing alternate chemistry[10] as illustrated in Scheme 4. Knoevenagel condensation of commercially available *N*-Boc-4-piperidone with ethyl cyanoacetate provided compound **16** in 76% yield. Subsequent 1,4 conjugate addition with 3-fluoromagnesium bromide in the presence of CuCN in THF provided compound **17** in 91% yield. Decarboxylation, followed by base-catalyzed hydrolysis afforded carboxylic acid **18** (55% yield, two-steps). Treatment of acid **18** with Eaton's reagent facilitated intramolecular cyclization with concomitant loss of the Boc protecting group. The Boc group was re-installed in situ by addition of NaOH and followed by Boc anhydride to obtain **1b**.

The ^{1}H NMR spectra of compounds **15** and **1b** show significantly different splitting patterns for the aliphatic region confirming that these are different products. The ^{1}H NMR spectrum[11] (in CD_3OD) of **15** showed six distinct multiplets at 3.68 (1*H*), 3.58 (1*H*), 3.53 (2*H*), 2.75 (2*H*), 2.23 (3*H*), and 2.10 (1*H*) ppm for the pyrrolidine and the tetralone ring systems. However, the ^{1}H NMR spectrum[12] (in CD_3OD) of **1b** was consistent with four pairs of multiplets at 4.18, 2.94,

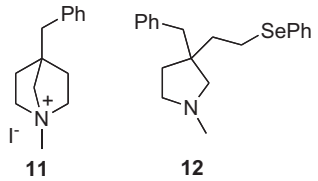
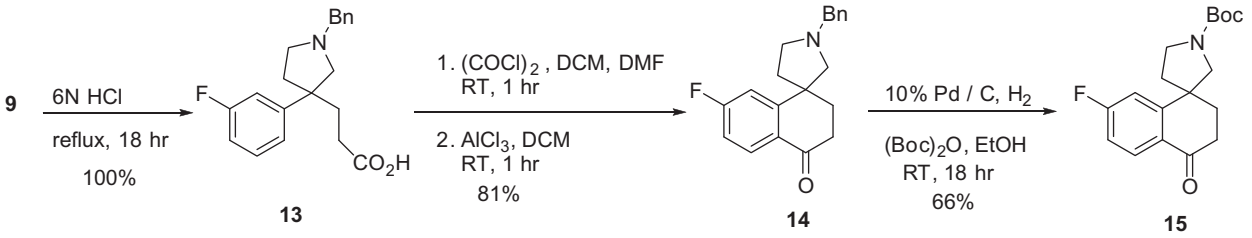
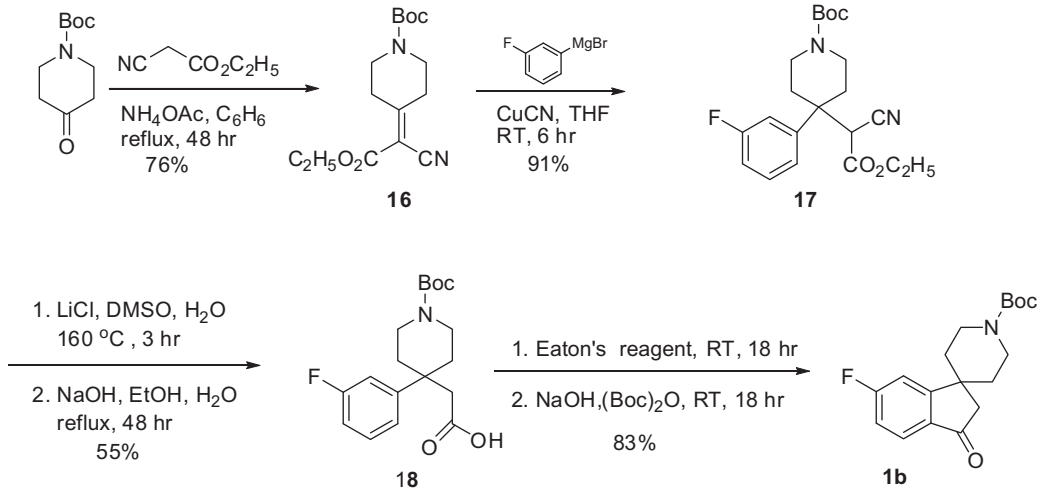


Figure 2. Bicyclic quaternary salt and ring contracted pyrrolidine.



Scheme 3. Formation of Spiropyrrolidine-tetralones.



Scheme 4. Second route to synthesis of spiropiperidine–indanone.

1.97, and 1.55 ppm corresponding to the desired piperidine ring system and at 2.74 ppm a two proton singlet for the indanone methylene group.

In conclusion, we have developed an efficient, high yielding reaction sequence to generate novel spiropyrrolidine–tetralone ring systems via an unexpected ring opening of a bridged bicyclic ammonium salt intermediate with a nitrile nucleophile. These new spiropyrrolidine–tetralones have the potential to be utilized as key building blocks for a variety of drug discovery programs in medicinal chemistry.

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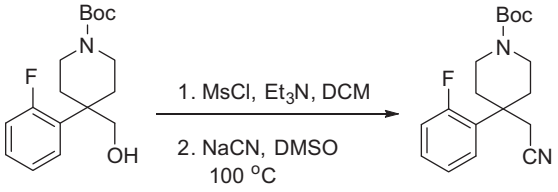
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.142.

References and notes

1. Limanto, J.; Shultz, C. S.; Dorner, B.; Desmond, R. A.; Devine, P. N.; Krska, S. W. *J. Org. Chem.* **2008**, *73*, 1639–1642. and references therein.
2. He, S.; Ye, Z.; Dobbelaar, P. H.; Sebhat, I. K.; Guo, L.; Liu, J.; Jian, T.; Lai, Y.; Franklin, C. L.; Bakshi, R. K.; Dellureficio, J. P.; Hong, Q.; Tsou, N. N.; Weinberg, D. H.; MacNeil, T.; Tang, R'; Strack, A. M.; Tamvakopoulos, C.; Peng, Q.; Miller, R. R.; Stearns, R. A.; Chen, H. Y.; Chen, A. S.; Fong, T. M.; Wyvratt, M. J., Jr.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4305–4399.
3. He, S.; Ye, Z.; Dobbelaar, P. H.; Sebhat, I. K.; Guo, L.; Liu, J.; Jian, T.; Lai, Y.; Franklin, C. L.; Bakshi, R. K.; Dellureficio, J. P.; Hong, Q.; Tsou, N. N.; Ball, R. G.; Cashen, D. E.; Martin, W. J.; Weinberg, D. H.; MacNeil, T.; Tang, R.; Tamvakopoulos, C.; Peng, Q.; Miller, R. R.; Stearns, R. A.; Chen, H. Y.; Chen, A. S.; Strack, A. M.; Fong, T. M.; MacIntyre, D. E.; Wyvratt, M. J.; Nargued, R. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2106–2110.
4. Chu, G.; Le Bourdonnec, B.; Gu, M.; Saeui, C. T.; Dolle, R. E. *Tetrahedron* **2009**, *65*, 5161–5167.
5. Makings, L. R.; Garcia-Guzman B. M.; Hurley, D. J.; Drutu, I.; Raffai, G.; Bergeron, D. M.; Nakatani, A.; Termin, A. P.; Silina, A. U.S. 2007043023.
6. For the recent review see Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 359–4368.
7. Weng, Z.; Li, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1256–1259.
8. 

9. Della, E. W.; Smith, P. A. *J. Org. Chem.* **1999**, *64*, 1798–1806.
10. Guo, L.; Hf, S.; Jian, T.; Lai, Y.; Liu, J.; Nargund, R. P.; Sebhat, I.K.; Ujjinwalla, F.; Yf, Z.; PCT 2004089307.
11. Compound **15** ^{1}H NMR (CD_3OD, 500 MHz) δ 8.05–8.08 (m, 1*H*), 7.07–7.14 (m, 2*H*), 3.68 (m, 1*H*), 3.58 (m, 1*H*), 3.50–3.53 (m, 2*H*), 2.68–2.78 (m, 2*H*), 2.21–2.25 (m, 3*H*), 2.08–2.19 (m, 1*H*), 150 (s, 9*H*).
12. Compound **1b** ^{1}H NMR (CD_3OD, 500 MHz) δ 7.73 (dd, J = 8.5, 5.3 Hz, 1*H*), 7.39 (dd, J = 9.1, 2.2 Hz, 1*H*), 7.19 (t m, 1*H*), 4.18 (m, 2*H*), 2.94 (s, 2*H*), 2.74 (s, 2*H*), 1.97 (m, 2*H*), 1.55 (m, 2*H*), 1.49 (s, 9*H*).