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Trianion Synthon Approach to Spirocyclic Heterocycles

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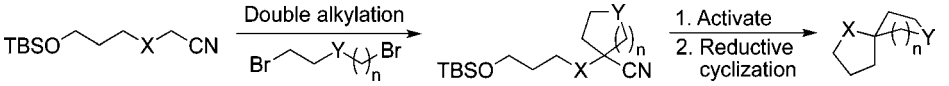
ABSTRACT



A variety of spirocyclic heterocycles have been constructed by a double-alkylation and reductive cyclization approach utilizing α-heteroatom nitriles as trianion synthons. The method provides access to heteroatom-substituted spirocycles in a variety of ring sizes that are found in natural products and are important in pharmaceutical lead development and optimization.

Spirocyclic frameworks are important motifs found in natural products and in medicinal lead compounds. These complex structures have a well-defined three-dimensional spatial arrangement that exhibit specificity of action with biological receptors and enzymes.[1] Spirocycic frameworks have been the target of several synthetic methods[2] aimed at the construction of structurally diverse natural and non-natural molecules. Described herein is a general strategy for the construction of spiro-heterocycles based on a reductive cyclization process.[3]

Efficient construction of spirocyclic heterocycles is important in the synthesis of natural products[4] and pharmaceutical targets (Figure 1).[5] The assembly of carbocyclic[6,7] and, especially, heterocyclic[8] frameworks by double alkylation of α-heteronitriles is an underdeveloped transformation. Nitrile anions are competent nucleophiles that have been applied to the formation of complex molecules using nitrile anion alkylation methodology.[9] Based on the double alkylation/reductive cyclization strategy we developed for the lepadiformine alkaloids,[7] we set out to extend this method to the synthesis of diverse spirocyclic heterocycles.

Synthesis of a variety of spirocyclic frameworks begins with double alkylation of a bis-electrophile (**6**) with the appropriate nitrile partner (e.g., **5**). Subsequent deprotection with TBAF and phosphorylation with diethyl chlorophosphate and *N*-methylimidazole[10] generated the cyano

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(2) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, *2*, 165–193.

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(4) (a) Biard, J. –F.; Guyot, S.; Roussakis, C.; Verbist, J.-F. *Tetrahedron Lett.* **1994**, *35*, 2691–2694. (b) Issa, H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trainto, A.; Higa, T. *Mar. Drugs* **2005**, *3*, 78–83. (c) Hirasawa, Y.; Morita, H.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3389–3391. (d) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870. (e) Burnell, R. H.; Mootoo, B. S. *Can. J. Chem.* **1961**, *39*, 1090. (f) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. H. *Tetrahedron* **1993**, *49*, 8645–8656. (g) Blackman, A. J.; Li, C. *Aust. J. Chem.* **1994**, *47*, 1355–1361. (h) Blackman, A. J.; Li, C. *Aust. J. Chem.* **1995**, *48*, 955–965. (i) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37–44. (j) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. PCT Int. Appl. WO 91 13,887, 1991; *Chem Abstr.* 1992, *116*, 39780t.

(5) (**1**) Sanofi-Aventis, Fr, WO2009EP04393, 2009 June 18. (**2**) GlaxoSmithKline LLC, USA, WO2010US46782, 2010 August 26. (**3**) Ghosh, A. K.; Krishnan, K.; Walters, D. E.; Cho, W.; Cho, H.; Koo, Y.; Trevino, J.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 979–982. (**4**) Glaxo Group Limited, UK, WO2008EP53595, 2008 March 27. (a) The Boots Company PLC, USA, US5610161, 1997 March 11. (b) Targacept, Inc., USA, WO2006034089, 2006 March 30. (c) Takeda Chemical Industries, Ltd., USA, US5591849, 1997 January 7.

(6) Guillaume, D.; Brum-Bousquet, M.; Aitken, D. J.; Husson, H.-P. *Bull. Soc. Chim. de Fran* **1994**, *131*, 391–396.

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(9) (a) Fleming, F. F.; Zhang, Z. *Tetrahedron* **2005**, *61*, 747–789. (b) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1–23 and references cited therein.

(10) Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409–2411.

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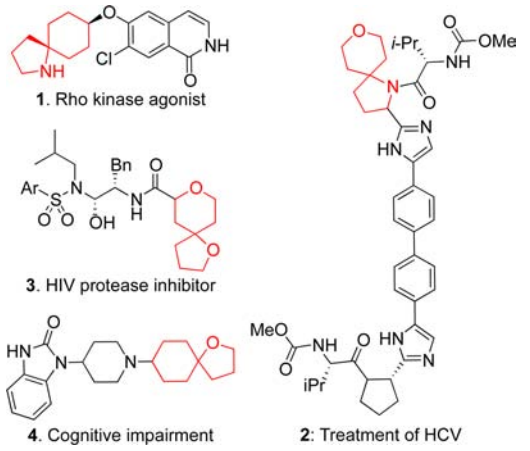
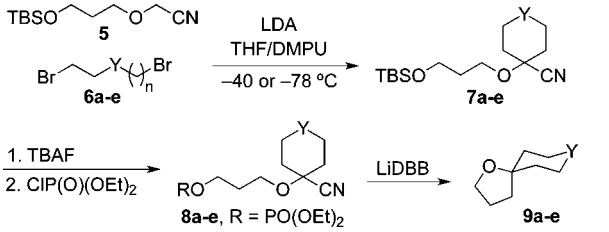


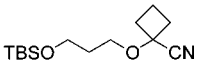
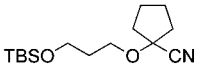
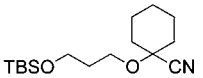
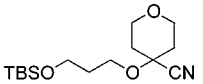
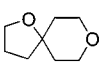
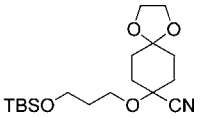
Figure 1. Spirocyclic rings in pharmaceutical targets.

phosphate intermediate (**8**). Reductive decyanation with cyclization afforded spirotetrahydrofurans **9a**–**e** (Table 1). The double alkylation led to good yields of cyclobutanenitrile **7a**, cyclopentanenitrile **7b**, and cyclohexanenitrile **7c** (entries 1–3). The tetrahydropyranyl adduct **7d** was readily accessed from the double alkylation with 2,2′-dibromodiethyl ether (entry 4). Synthesis of the ketal cyclohexanenitrile **7e** was achieved in moderate yield using protected 1,5-dibromopentan-3-one **6e** (entry 5). The deprotection and phosphorylation steps were efficient in all cases. The reductive decyanation generates an intermediate tertiary alkyllithium reagent that cyclizes with displacement of the phosphate. The reductive cyclization in all cases proceeded with very good yield. For the volatile products **9a** and **9b**, the yields were estimated by GCMS analysis with an internal standard. Attempts to isolate **9a** from residual THF were unsuccessful as the boiling point and polarity are too similar.

In a similar fashion, the use of aminonitrile **10** provided spiropyrrolidines **13a**–**g** (Table 2). The cyclobutane nitrile **11a** was obtained in a modest yield from the double-alkylation step. The double alkylation reactions to produce unsubstituted cyclopentane **11b** and cyclohexanenitrile **11c** were more efficient (entries 2 and 3). Double alkylation with 1,6-dibromohexane gave a mixture of the desired cycloheptanenitrile **11g**, and an alkylation–elimination product in an overall 18% yield and was not investigated further. As above, the THP–aminonitrile product **11d** was isolated in good yield using dielectrophile **6d**. Use of protected 1,5-dibromopentan-2-one **6f** (entry 7) resulted in a moderate yield due to concomitant formation of a bis-alkylated aminonitrile byproduct (19% yield). The reductive lithiation and cyclization of the N-Boc aminonitriles were all effective, but yields were more varied than in the spirotetrahydrofuran examples in Table 1. Construction of the aliphatic spiropyrrolidines proceeded in moderate to good yield irrespective of the carbocyclic ring size. Cyclization to provide unsymmetrically substituted spirocycle **13f** also proceeded in moderate yield. In the case of **12e**, the reductive cyclization proceeded in an unexpectedly low

Table 1. α-Oxonitrile Double Alkylation and Spirocyclization



entry	alkylation (yield)	deprotect (yield)	phosphate (yield)	reductive cyclization (yield)
1	 **7a** 61%	79%	**8a** 98%	 **9a** (98)[a]
2	 **7b** 81%	93%	**8b** 90%	 **9b** (94)[a]
3	 **7c** 96%	82%	**8c** 91%	 **9c** 89%
4	 **7d** 67%	76%	**8d** 84%	 **9d** 80%
5	 **7e** 51%	85%	**8e** 98%	 **9e** 88%

[a] Yield estimated by GCMS analysis using decane as an internal standard. Isolated yield of **9b** was 56%.

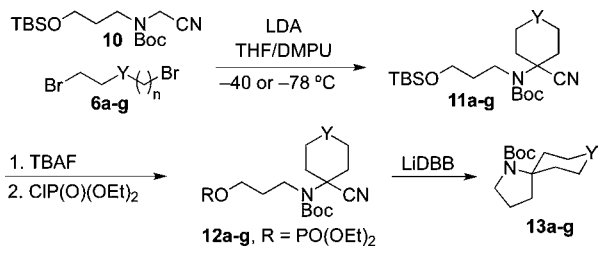
37% yield to afford **13e**. In most instances, no side products were observed or isolated in these reductive cyclization reactions. In a few cases, reduced starting material containing a terminal olefin was observed as a byproduct (≤10%), which was inseparable from the desired product by chromatography.[11]

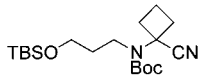
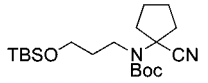
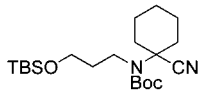
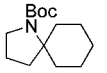
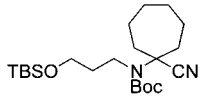
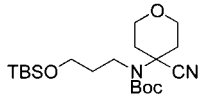
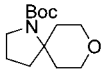
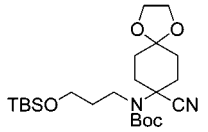
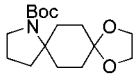
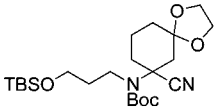
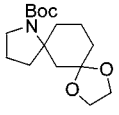
The reductive cyclizations developed to date all use 2.2 equiv of the lithium di-*tert*-butyl biphenylide (LiDBB), which limits the practical scale of the reaction. We have investigated the cyclization using catalytic di-*tert*-butylbiphenyl (DBB) and lithium metal.[12] The source of lithium metal was important with lithium powder proving more efficient than lithium wire, sheet, or granules. Equation 1 shows an example on 1.23 g scale using 10 mol % of DBB run at 0 °C, which proceeds in good yield. Using catalytic

(11) Removal of the elimination byproduct can be accomplished by dihydroxylation using OsO_4 and NMO in acetone/water followed by column chromatography.

(12) (a) Guijarro, D.; Yus, M. *Tetrahedron* **1994**, *50*, 3447–3452. (b) Ramon, D.; Yus, M. *Tetrahedron* **1992**, *48*, 3585–3588. (c) Gomez, C.; Lillo, V. J.; Yus, M. *Tetrahedron* **2007**, *93*, 4655–4662.

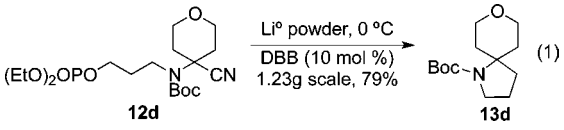
Table 2. α-Aminonitrile Double Alkylation and Spirocyclization[a]



entry	alkylation (yield)	deprotect (yield)	phosphate (yield)	reductive cyclization (yield)
1	 **11a** 25%	83%	**12a** 86%	 **13a** 69%
2	 **11b** 63%	91%	**12b** 91%	 **13b** 56%
3	 **11c** 79%	86%	**12c** 89%	 **13c** 70%
4	 **11g** 18%[a]	n/a	n/a	n/a
5	 **11d** 63%	92%	**12d** 90%	 **13d** 79%
6	 **11e** 62%	86%	**12e** 89%	 **13e** 37%
7	 **11f** 57%	95%	**12f** 61%	 **13f** 62%

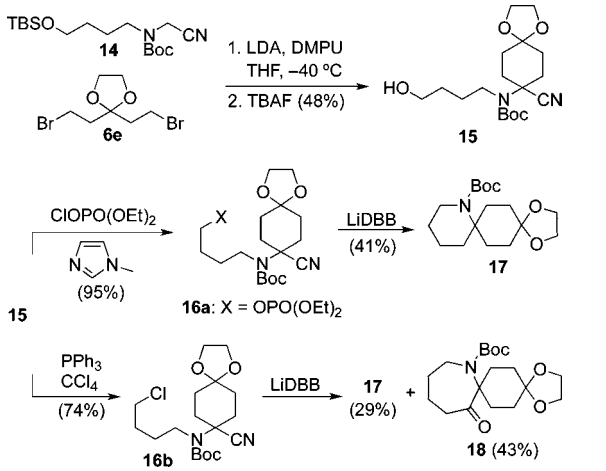
[a] Cycloheptane **11g** was isolated as a 1:1 mixture with an elimination byproduct.

DBB and noncryogenic temperatures makes the cyclization step amenable to scale-up.



Spiropiperidine and azepinone frameworks are also accessible by this method. Reaction of nitrile **14**, which contains one more methylene unit than nitrile **10**, with dibromide **6e** resulted in alcohol **15** after double alkylation and deprotection (Scheme 1). Formation of the phosphate **16a**, followed by reductive cyclization generated the spiropiperidine **17** in moderate yield. The chloride **16b** was prepared from **15** to test the effect of the leaving group on the spirocyclization. Reductive lithation of **16b** led to the formation of both the expected spiropiperidine **17** (29%) and the unexpected spiroazepinone **18** in 43% yield. Compound **18** arose by competitive lithiation of the alkyl chloride and cyclization onto the nitrile. We have previously observed competitive lithation of alkyl chlorides with *N*-benzyl aminonitriles,[13] but not with the more easily reduced *N*-Boc aminonitriles. Formation of azepinone **18** would be enhanced by using a more easily reduced halide such as bromide. Spiropiperidines are available in moderate yield using the reductive decyanation and cyclization strategy.

Scheme 1. Cyclizations to Piperidines and Azipinones

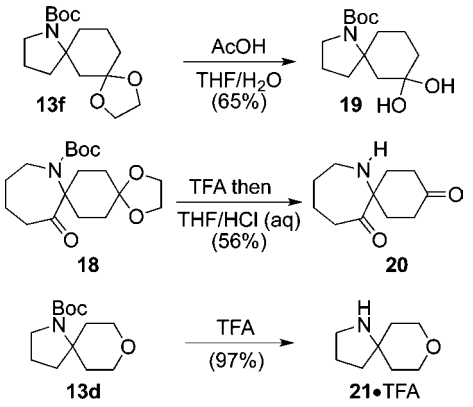


Spiroacetals **13f** and **17** both incorporate protected secondary amines and ketones. Selective deprotection by treatment of **13f** with acetic acid in THF/H_2O led to removal of the 1,3-dioxolane protecting group to provide the hydrated ketone **19** in 65% yield (Scheme 2). Acid-mediated removal of the nitrogen Boc group of **18** with TFA led to a 2:1 mixture of deprotected aminoacetal and amine **20**. Dilution of the crude mixture in THF and 1 M HCl provided the ketoamine **20** in 56% yield. In simple cases, acidic removal of the *N*-Boc group proceeded without issue (i.e., **13d** to **21**). Further transformations of these types of spirocycles to give valuable medicinally relevant compounds have been reported.[14,5b]

(13) Bahde, R. J.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4017–4020.

(14) (a) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387–8390. (b) Nagumo, S.; Matoba, A.; Ishii, Y.; Yamaguchi, S.; Akutsu, N.; Nishijima, H.; Nishida, A.; Kawahara, N. *Tetrahedron* **2002**, *58*, 9871–9877. (c) Sanofi-Aventis, Fr, WO2009156092, 2009 December 30. (d) Sunovion Pharmaceuticals, Inc., USA, WO2011075699, 2011 June 23. (e) Rotta Research Laboratorium S.p.A., Italy, US6075033, 2000 June 13.

Scheme 2. Deprotection of Spirocycles



We have presented a general strategy to construct spirocyclic heterocycles. The key step is a reductive lithiation and cyclization of a nitrile phosphate to form the spirocyclic pyrrolidine, piperidine, or tetrahydrofuran ring. The reactions were successful with different heteroatoms and a number of ring sizes. This method will be useful in natural products synthesis and in medicinal chemistry. We are continuing to explore the selectivity and scope of this strategy.

Acknowledgment. We thank NIGMS (GM43854) for their support of this program and Vertex for a Vertex Fellowship (MAP).

Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.