Published in final edited form as:

Org Lett. 2013 May 3; 15(9): 2226–2229. doi:10.1021/ol400788q.

Trianion Synthon Approach to Spirocyclic Heterocycles

Matthew A. Perry, Richard R. Hill, and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, Irvine, California 92697

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 Spirocyclic frameworks have been the target of several synthetic methods² aimed at the construction of structurally diverse natural and nonnatural 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 products⁴ and pharmaceutical targets (Figure 1).⁵ The assembly of carbocyclic^{6,7} and especially, heterocyclic⁸ 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*-methylimidazole¹⁰ generated the cyano 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 tetrahydropyran adduct **7d** was readily accessed from the double alkylation with 2,2'-dibromodiethylether (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 alkyl lithium reagent that cyclizes with displacement of the phosphate. The reductive cyclization in all cases proceeded with very good yield. For the volatile

srychnov@uci.edu.

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

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 37% 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 **6g** (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 symmetrically substituted spirocycle **13f** also proceeded in moderate yield. In the case of **12e**, the reductive cyclization proceeded in an unexpectedly low 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*-butylbiphenylide (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 1.23g scale using 10 mol% DBB run at 0 °C, which proceeds in good yield. Using catalytic DBB and non-cryogenic temperatures makes the cyclization step amenable to scale-up.

(1)

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. 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 lithiation 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 lithiation 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.

Spiroacetals **13f** and **17** both incorporate protected secondary amines and ketones. Selective deprotection by treatment of **13f** with acetic acid in THF/H₂O led to removal of the 1,3-dioxolane protecting group to provide the hydrated ketone **19** in 65% yield. 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}

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

References

1. Rajesh SM, Perumal S, Menendez JC, Yogeewari P, Sriram D. *Med Chem Commun.* 2011; 2:626–630.
2. Kotha S, Deb AC, Lahiri K, Manivannan E. *Synthesis.* 2009; 2:165–193.
3. (a) Takaoka LR, Buckmelter AJ, La Cruz TE, Rychnovsky SD. *J Am Chem Soc.* 2005; 127:528–529. [PubMed: 15643869] (b) La Cruz TE, Rychnovsky SD. *J Org Chem.* 2006; 71:1068–1073. [PubMed: 16438522] (c) La Cruz TE, Rychnovsky SD. *J Org Chem.* 2007; 72:2602–2611. [PubMed: 17346087] (d) Riberio CMR, Demelo SJ, Bonin M, Quirion JC, Husson HP. *Tetrahedron Lett.* 1994; 35:7227–7230.
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. [PubMed: 15355059] (d) Daly JW, Karle I, Myers CW, Tokuyama T, Waters JA, Witkop B. *Proc Natl Acad Sci USA.* 1971; 68:1870. [PubMed: 5288773] (e) Burnell RH, Mootoo BS. *Can J Chem.* 1961; 39:1090. (f) Blackman AJ, Li C, Hockless DCR, Skelton BH. *Tetrahedron.* 1993; 49:8645–8656. (g) Blackman AJ, Li C. *Aust J Chem.* 1994; 47:1355–1361. (h) Blackman AJ, 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. [PubMed: 8609083] (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. patent WO. 2009EP04393. 2009 Jun 18. (2) GlaxoSmithKline LLC, USA. patent WO. 2010US46782. 2010 Aug 26. (3) Ghosh AK, Krishnan K, Walters DE, Cho W, Cho H, Koo Y, Trevino J, Holland L, Buthod J. *Bioorg Med Chem Lett.* 1998; 8:979–982. [PubMed: 9871524] (4) Glaxo Group Limited, UK. patent WO. 2008EP53595. 2008 Mar 27. (a) The Boots Company PLC, USA. patent US. 5610161. 1997 Mar 11. (b) Targacept, Inc., USA. patent WO. 2006034089. 2006 Mar 30. (c) Takeda Chemical Industries, Ltd USA. patent US. 5591849. 1997 Jan 7.
6. Guillaume D, Brum-Bousquet M, Aitken DJ, Husson H-P. *Bull Soc Chim de Fran.* 1994; 131:391–396.
7. (a) Perry MA, Morin MD, Slafer BW, Wolckenhauer SA, Rychnovsky SD. *J Am Chem Soc.* 2010; 132:9591–9593. [PubMed: 20578697] (b) Perry MA, Morin MD, Slafer BW, Rychnovsky SD. *J Org Chem.* 2012; 77:3390–3400. [PubMed: 22413935]

8. Gharpure SJ, Reddy SRB. *Org Lett.* 2009; 11:2519–2522. [PubMed: 19445488]
9. (a) Fleming FF, Zhang Z. *Tetrahedron.* 2005; 61:747–789.(b) Fleming FF, Shook BC. *Tetrahedron.* 2002; 58:1–23. and references therein.
10. Soorukram D, Knochel P. *Org Lett.* 2004; 6:2409–2411. [PubMed: 15228291]
11. Removal of the elimination byproduct can be accomplished by dihydroxylation using OsO₄, 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 VJ, Yus M. *Tetrahedron.* 2007; 93:4655–4662.
13. Bahde RJ, Rychnovsky SD. *Org Lett.* 2008; 10:4017–4020. [PubMed: 18700774]
14. (a) Bonjoch J, Diaba F, Puigbó G, Peidró E, Solé D. *Tetrahedron Letters.* 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. patent WO. 2009156092. 2009 Dec 30. (d) Sunovion Pharmaceuticals, Inc., USA. patent WO. 2011075699. 2011 Jun 23. (e) Rotta Research Laboratorium S.p.A., Italy. patent US. 6075033. 2000 Jun 13.

Figure 1.
Spirocyclic rings in pharmaceutical targets

Scheme 1.
Cyclizations to Piperidines and Azipinones

Scheme 2.
Deprotection of Spirocycles

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%

^aYield estimated by GCMS analysis using decane as an internal standard. Isolated yield of **9b** was 56%.

Table 2

 α -Aminonitrile double alkylation and spirocyclization

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%

^aCycloheptane **11g** was isolated as a 1:1 mixture with an elimination byproduct.