A Two-Step Synthesis of 2-Spiropiperidines

Samuel D. Griggs,[a] Nathan Thompson,[a] Daniel T. Tape,[b] Marie Fabre,[a] and Paul A. Clarke\*[a]

[a] Mr. S. D. Griggs, Mr. N. Thompson, Miss M. Fabre, Dr. P. A. Clarke,  
Department of Chemistry,  
University of York,  
Heslington, York, UK, YO10 5DD.  
E-mail: paul.clarke@york.ac.uk

[b] Dr. D. T. Tape,  
Flexible Discovery Unit,  
GlaxoSmithKline Medicines Research Centre,  
Gunnels Wood Road, Stevenage, UK, SG1 2NY.

Supporting information for this article is given via a link at the end of the document.

**Abstract:** A general two-step synthesis of 2-spiropiperidines has been developed. -Amino--ketoesters can be reacted with cyclic ketones to generate 2-spiropiperidines in good to excellent yields. The 2-spiropiperidines formed occupy an under-explored region of 3D-chemical space and are novel scaffolds for use in drug discovery programs. These 2-spiropiperidines can be further functionalized to generate small highly *sp3*-rich structures which exhibit an excellent likeness to lead-molecules in drug discovery.



Traditional drug discovery programs rely on the identification and synthesis of small molecule leads which can be elaborated into potential drug candidates. Recently it has been recognized that a very large proportion of these molecules are comparatively two-dimensional structures containing a high proportion of *sp* and *sp2*-hybridised carbons,[1] and hence, there has been a drive to develop new routes to access the relatively under-explored *sp3*-rich area of chemical space.[2] Consequently, several tools have been developed to assess the degree of 3-dimensionality of small molecules, these include Principle Moments of Inertia (PMI) analysis,[3] Plane of Best Fit analysis[4] and, more recently, Lead Likeness And Molecular Analysis (LLAMA).[5] There is a growing consensus that out of all the *sp3*-rich structural types spirocyclic molecules hold a privileged position,[6] as they are conformationally well defined which allows the functionality on the spirocycle to be elaborated in well-defined directions.[7],[8] Furthermore, we identified that a highly desirable, yet under represented subset of spirocyclic systems is the 2-spiropiperidine unit. While routes for the synthesis of spirocyclic oxetanes[9] and other 4-membered rings,[10] indolenines[11] andethers[12],[13] have been developed, and the advent of SnAP and SLAP reagents has led to the facile synthesis of spirocyclic morpholines, piperazines and piperidines,[14],[15] there are limited methods for the synthesis of 2-spiropiperidines,[16]  with the vast majority of spiropiperidines being spirofused at either the 3- or 4-positions.[16]

In this paper we report a general, expedient and operationally simple two-step route for the synthesis of 2-spiropiperidines, which builds on our extensive expertise in the development of the Maitland-Japp[17] and aza-Maitland-Japp reactions[18] (Scheme 1). The 2-spiropiperidines synthesized occupy the *sp3*-rich area of chemical space as assessed by PMI analysis and have a good “lead-likeness” as assessed by LLAMA.

**Scheme 1.** The aza-Maitland-Japp reaction

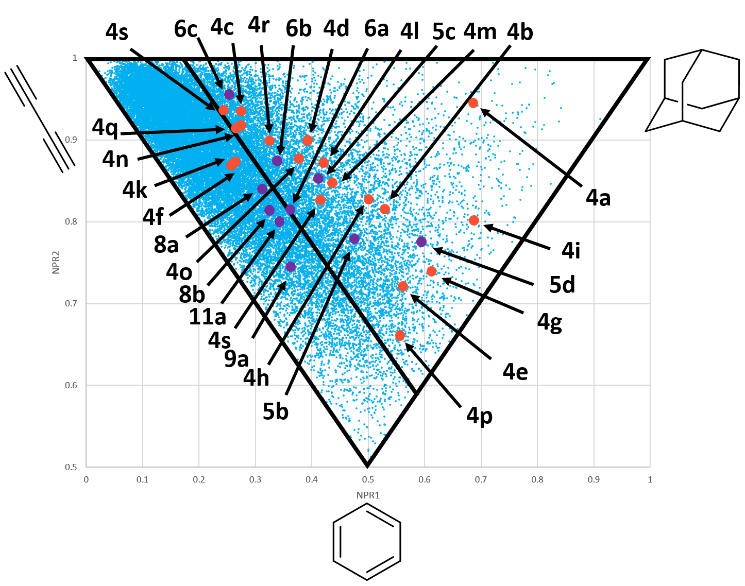
Initial studies focused on adapting the one-pot aza-Maitland-Japp synthesis of highly functionalized piperidines from diketene, *N*-tosyl imines and aldehydes (Scheme 1a).[18b] However, we were unable to extend this reaction to the synthesis of 2-spiropiperidines, as the *N*-tosyl group was either eliminated in the Mannich-like step or it inhibited the cyclisation step when ketones were used. These problems were overcome by the use of *N*-Boc imines and the Weiler dianion[19] (Scheme 1b). We rationalized that the Boc group would still increase the electrophilicity of the azamethine carbon, as the tosyl group had, and that it could easily be removed before cyclisation. Known aryl *N*-Boc imines were prepared from the corresponding aryl aldehydes *via* the procedure of Lam.[20] However, the other *N*-Boc imines used were relatively unstable and so were generated *in situ* from the *N*-Boc sulfone precursor **1** (Figure 1).*N*-Boc sulfone precursors **1** were treated with the Weiler dianion and the resultant *N*-Boc--amino--ketoesters **2** were isolated. Removal of the *N*-Boc group was achieved by treatment with HCl in dioxane and the -amino--ketoester**·**HCl salt was “cracked” in the presence of a ketone **3** with NaHCO3, which promoted cyclisation and yielded 2-spiropiperidines **4** (Figure 1). *N*-Boc sulfone precursors **1a-j** derived from a range of medicinal chemistry relevant aldehydes were prepared, including 3-pyridyl **1g**, 4-methyl thiazole **1h**, *N*-methyl-4-pyrazole **1i** and 4-cyanophenyl **4j** from the GSK aldehyde library.[21] Acetone and a selection of cyclic (4-6 membered ring) ketones containing *O*, *S* or *N*-heteroatoms all reacted smoothly with the -amino--ketoester to give the desired piperidines **4a-s**. The two-step procedure is easy to carry out and robust as is demonstrated by the synthesis of 2-spiropiperidine **4h** on a 1.5 g scale. The piperidines existed as a mixture of diastereomeric methyl esters, with the relative stereochemistry shown predominating, and there was no evidence of the diastereomers interconverting during chromatographic purification. Interestingly, in the major diastereomer the methyl ester is axial, presumably to alleviate a destabilizing steric interaction with the protons on the adjacent spiro-ring (Figure 2).

**Figure 1.** 2-Spiropiperidine scaffolds. Spirocyclisation reactions were run on 100 mg scale with the exceptions of **2e**, **2g** and **2h** which were synthesised on 5 g scale and **4h** which was synthesised on 1.5 g scale. The ratio of diastereomers was determined by 1H NMR of the crude reaction mixture.

2-Spiropiperidines **4a-s** were subjected to PMI analysis to determine their degree of 3-dimensionality. As can be seen in Figure 3, almost all of the spirocycles **4a-4s** reside in the under-explored area of chemical space, making these molecules more 3-dimensional than 75% of the structures in the comparison library of 35,270 lead-like molecules from the ZINC database.[22]



G:\Piperidine Project\Sam Griggs\Xray pac1626 Griggs\pac1626 new for paper.tif**Figure 2.** X-ray crystal structure of **4j** with thermal ellipsoids shown at 50% CCDC Number 1549997.

****

**Figure 3.** PMI plot of **4a-4s** (orange) and **5a-11** (purple) on a library of 35,270 ‘lead-like’ molecules out of the 6,053,287 molecules from the ZINC database[22] (blue). This lead-like set has 250≤mw≤350, clogP ≤3.5, number of rotatable bonds ≤7 and an overall charge of 0 or +1 at physiological pH. 75% of the population of this library lies to the left of the line.

With a procedure in place for the synthesis of a range of substituted 2-spiropiperidines, we wished to demonstrate the versatility of the scaffold by carrying out a series of transformations, which would enable them to be converted into lead-like structures. To this end the transformations investigated were the reduction of the ketone carbonyl with NaBH4 which generated alcohols **5a-d**, and the conversion of the ester to an amide **6a-c** (Figure 4). Amides **6a-c** were formed directly from the esters following the amidation procedure of Woodward.[23] Of particular note is the formation of propargyl amide **6a**, which installed the functionality required for the spirocyclic scaffold to participate in azide-alkyne “Click” chemistry.[24] Tertiary amine **7a** was formed by reaction of **5c** with Ag2O and MeI in 50% yield. The removal of the ester group by LiOH in THF/H2O promoted decarboxylation and yielded **8a-c**, reductive amination of the ketone function with propargyl amine and NaBH(OAc)3 gave **9a**, Wittig methylenation of the carbonyl generated **10a**, and epoxidation of carbonyl through sulfoxonium ylide addition, generated a tri-spirocyclic system **11a** (Figure 4).

**Figure 4.** Functionalization of 2-spiropiperidines

The lead-likeness of all of these structures was assessed using the LLAMA protocol[5] (Figure 4). LLAMA assigns a lead-likeness value to molecules, where the lower the value, the more lead-like the molecule is. Penalties are applied to a molecule’s LLAMA score if the molecule has >1 aromatic rings or functional groups which are deemed too reactive to be present in a lead molecule. As can be seen **6a-c**, **8-11a** all have low LLAMA values (≤3) indicating that these molecules are highly lead-like. Molecules **5a-d** and **7a** have LLAMA values of ≥5 showing that they are less lead-like. Further analysis of these values and structures, indicated that these high LLAMA scores are due to the presence of the ester functionality which carries a significant penalty (+5) due to its reactivity. However, as we have shown the ester group can be removed or converted to an amide these molecules still have significant potential as lead precursors.



In summary, we have developed a simple and robust procedure for the synthesis of novel 2-spiropiperidine scaffolds, which occupy the under-explored region of *sp3*-rich chemical space. The properties of these molecules in terms of new defined vectors for functionalization make these molecules highly desirable in drug discovery programs. Further functionalization of these scaffolds generated molecules which are highly lead-like, as assessed by LLAMA. As such we believe this work will be of great interest to synthetic and computational chemists involved in drug discovery programmes.

Acknowledgements

We thank the Department of Chemisty, University of York, GlaxoSmithKline (SDG) and the ERASMUS+ program (MF) for financial support and Dr. Adrian Whitwood for X-ray analysis.

Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** spirocyclic • piperidine • scaffolds • Maitland-Japp • medicinal chemistry

[1] a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752-6756; b) F. Lovering, *Med. Chem. Commun*. **2013**, *4*, 515-519.

[2] For over views see: a) C. J. O’Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev*. **2012**, *41*, 4444-4456; b) A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Muller, A. Piechot, D. Tzalis, *Drug Discov. Today* **2015**, *11*, 1310-1316; c) J. Meyers, M. Carter, N. Y. Mok, N. Brown, *Future Med. Chem*. **2016**, *8*, 1753-1767.

[3] W. H. B. Sauer, M. K. Schwarz, *J. Chem. Inf. Comput. Sci*. **2003**, *43*, 987-1003.

[4] N. C. Firth, N. Brown, J. Blagg, *J. Chem. Inf. Model*. **2012**, *52*, 2516-2525.

[5] I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden, A. Nelson, *Chem. Commun*. **2016**, *52*, 7209-7212.

[6] F. Voss, S. Schunk, H. Steinhagen, *RSC Drug Discovery Series* **2016**, *50*, *Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation*, 439-458, Ed. S. Bräse.

[7] Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673-3682.

[8] G. Müller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe, J. Bajorath, *Chem. Eur. J.* **2017**, *23*, 703-710.

[9] a) G. Wuitschik, M. Rogers-Evans, A. Buckl, M. Bernasconi, M. Märki, T. Godel, H. Fischer, B. Wagner, I. Parrilla, F. Schuler, J. Schneider, A. Alker, W. B. Schweizer, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2008**, *47*, 4512-4515; b) M. Gurry, P. McArdle, F. Aldabbagh, *Molecules*, **2015**, *20*, 13864-13874.

[10] E. M. Carreira, T. C. Fessard, *Chem. Rev*. **2014**, *114*, 8257-8322.

[11] a) M. J. James, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2016**, *55*, 9671-9675. b) A. K. Clarke, M. J. James, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed*. **2016**, *55*, 13798-13802; c) M. J. James, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J*. **2016**, *22*, 2856-2881. d) S. J. Chambers, G. Coulthard, W. P. Unsworth, P. O’Brien, R. J. K. Taylor, Chem. Eur. J. 2016, 22, 6496-6500.

[12] T. Xu, N. A. Savage, G. Dong, *Angew. Chem. Int. Ed*. **2014**, *53*, 1891-1895.

[13] K. Adams, A. K. Ball, J. Birkett, L. Brown; B. Chappell, D. M. Gill, P. K. T. Lo, N. J. Patmore, C. R. Rice, J. Ryan, P. Raubo, J. B. Sweeney, *Nature Chem*. **2017**, *9*, 396-401.

[14] a) W.-Y. Siau, J. W. Bode, *J. Am. Chem. Soc*. **2014**, *136*, 17726-17729; b) K. Geoghegan, J. W. Bode, *Org. Lett*. **2015**, *17*, 1934-1937; c) S.- Y. Hsieh, J. W. Bode, *Org. Lett*. **2016**, *18*, 2098-2101.

[15] For an over view see: C.-V. T. Vo, J. W. Bode, *J. Org. Chem*. **2014**, *79*, 2809-2815.

[16] Y. Troin, M. E. Sinibaldi, *Targets in Heterocyclic Systems: Chemistry and Properties*, Italian Chemical Socciety (Rome), **2009**, *13*, 120-146.

[17] a) P. A. Clarke, K. Ermanis, *Curr. Org. Chem*. **2013**, *17*, 2025-2037; b) P. A. Clarke, P. B. Sellars, N. M. Nasir, *Org. Biomol. Chem.* **2015**, *13*, 4743-4750; c) P. A. Clarke, N. M. Nasir, P. B. Sellars, A. M. Peter, C. A. Lawson, J. L. Burroughs, *Org. Biomol. Chem*. **2016**, *14*, 6840-6852.

[18] P. A. Clarke, A. V. Zaytzev, A. C. Whitwood, *Tetrahedron Lett*. **2007**, *48*, 5209-5212; b) P. A. Clarke, A. V. Zaytsev, T. W. Morgan, A. C. Whitwood, C. Wilson, *Org. Lett.* **2008**, *10*, 2877-2880; c) P. A. Clarke, A. V. Zaytsev, A. C. Whitwood, *Synthesis* **2008**, 3530-3532.

[19] S. N. Huckin, L. Weiler, *Tetrahedron Lett.* **1971**, *50*, 4835-4838.

[20] D. Best, S. Kujawa, H. W. Lam, *J. Am. Chem. Soc*. **2012**, *134*, 18193-18196.

[21] For GSK compounds for lead oriented synthesis, contact [free.buildingblocks@gsk.com](mailto:free.buildingblocks@gsk.com)

[22] J. J. Irwin, T. Sterling, M. M. Mysinger, E. S. Bolstad, R. G. Coleman, *J. Chem. Inf. Model.* **2012**, *52*, 1757–1768.

[23] N. Dubois, D. Glynn, T. McInally, B. Rhodes, S. Woodward, D. J. Irvine, C. Dodds, *Tetrahedron* **2013**, *69*, 9890-9897.

[24] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599; b) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210-216.

**Entry for the Table of Contents** (Please choose one layout)

Layout 1:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| COMMUNICATION | | | | |
| **Spiro-tastic!** 2-Spiropiperidines are readily synthesised in good to excellent yields via a two-step procedure. These molecules constitute novel 3D-scaffolds for use in drug discovery programs, occupying an under-populated region of chemical space. The 2-spiropiperidines formed can be readily modified into lead-like molecules. |  |  |  | Samuel D. Griggs, Nathan Thompson, Daniel T. Tape, Marie Fabre and Paul. A. Clarke\*  Page No. – Page No.  A Two-Step Synthesis of 2-Spiropiperidines |
|  |  |