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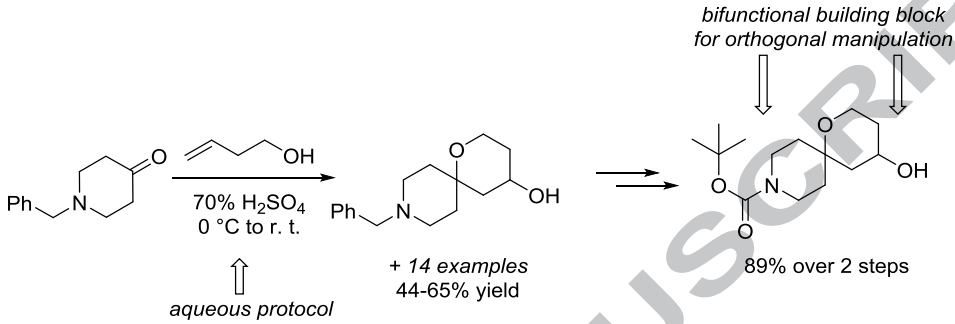


Spirocyclic Amino Alcohol Building Blocks Prepared *via* a Prins-Type Cyclization in Aqueous Sulfuric Acid

Alexey Lukin,[a] Darya Bagnyukova,[a] Natalya Kalinchenkova,[a] Nikolay Zhurilo,[a] and Mikhail Krasavin[*,b]

[a] *Lomonosov Institute of Fine Chemical Tehnologies, Moscow Technological University, 86 Vernadskogo Prospekt, Moscow, 117571 Russian Federation*

[b] *Saint Petersburg State University, Saint Petersburg, 199034 Russian Federation*

* Corresponding author; phone: + 7 931 3617872, fax: +7 812 428 6939.
E-mail: m.krasavin@spbu.ru

Abstract

A convenient Prins cyclization of various azacycloalkanones with homoallylic alcohol was achieved in aqueous sulfuric acid. The formal four-center, three-component reaction provides a facile and flexible entry into a range of spirocyclic amino alcohols which are valuable, 'high-F_{sp3}' motifs for drug design.

Keywords

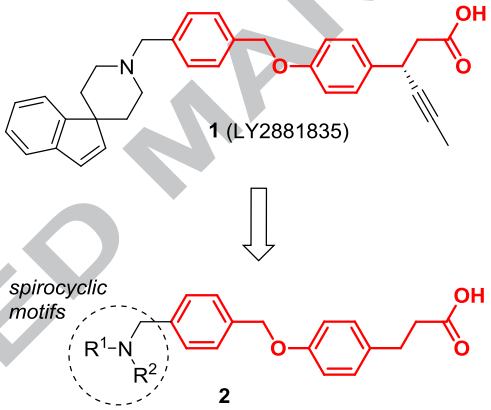
Prins spirocylization, amino alcohols, bifunctional building blocks, high-F_{sp3} scaffolds, privileged structures.

Spirocyclic motifs are valuable tools in drug design and their use in constructing small molecule bioactive compounds has delivered numerous advanced leads and clinically used compounds in diverse biotarget and therapeutic areas.[1] The privileged character[2] of spirocycles can be intuitively linked to the more pronounced three-dimensionality of spirocyclic scaffolds compared to their flat aromatic counterparts. The more 'shapely' character of small molecules intended to modulate a biological target is likely to result in more efficient complementary interaction between the two. This, in turn, leads to higher affinity of the future drug to its target, better efficacy (lower dose required to achieve therapeutic effect) and lower toxicity (off-target) profile.[3] Being more saturated (i.e. containing a higher fraction of sp^3-hybridized atoms or F_{sp3}), compared to flat aromatic scaffolds, spirocycles are also more attractive from a drug development perspective. This has to do not only with the higher solubility of compounds based

on high-sp^3 cores (due to the absence of π-π crystal packing). The number of aromatic rings in the molecule was also shown to correlate with a compound's advanced properties, including serum albumin binding, cytochrome P450 and hERG channel inhibition.[4] Collectively, these are likely reasons explaining the tendency of compounds to become more saturated as they progress through the development cycle (according to a statistical analysis published by Wyeth).[5]

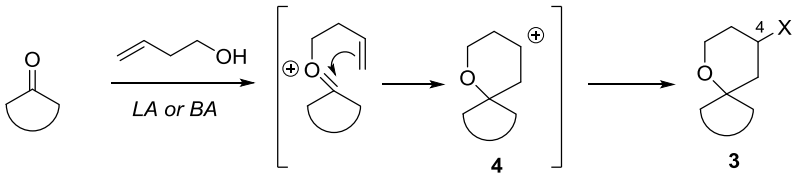
Our recent interest in designing new antidiabetic agonists of free fatty acid receptor 1 (FFA1 or GPR40)[6] led us to consider one of Eli Lilly's advanced compounds, LY2881835 (**1**)[7] as a lead for a new series (**2**), containing a similar spirocyclic amine periphery (Figure 1) with potential affinity to the receptor.

Figure 1. FFA1 agonist series **2** containing a basic scaffold and a spirocyclic periphery inspired by LY2881835 (**1**).



Lewis (LA) or Brønsted (BA) acid-promoted Prins cyclization of cyclic ketones with homoallyl alcohol conveniently delivers spirocyclic tetrahydropyrans **3**. In the latter, the substituent in position 4 of the tetrahydropyran ring results from interception of intermediate carbocation **4** by the acidic catalyst's counterion (X = I,[8] Br,[9] F,[10] OMs[11]) or water (X = OH).[12] Alternatively, carbocation **4** can be trapped in an intermolecular fashion by a nucleophilic nitrile molecule[13] or an electron-rich arene[14] *via* Ritter and Friedel-Crafts reactions, respectively (Scheme 1).

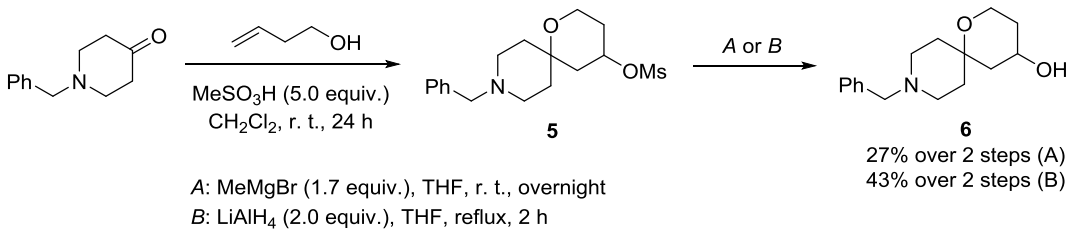
Scheme 1. The Prins cyclization of cyclic ketones and homoallyl alcohol.



Intramolecular interception of the cationic center in **4** by a judiciously positioned nucleophilic moiety such as hydroxyalkyl,[15] aryl,[16] alkenyl[17] or arylsulfonylamino[18] leads to rapid buildup of the product's molecular complexity. However, the trapping of carbocation **4** sometimes competes with E1-type elimination leading to a mixture of olefinic products, which complicates the isolation of the desired functionalized spirocycle **4**.[12f, 11a]

We reasoned that if a suitably protected amine functionality was positioned within the structure of a cyclic ketone, the Prins cyclization with homoallylic alcohol would furnish the desired spirocyclic framework while the additional functionality handle (X) could be used for fine-tuning the GPR40 agonist activity and lipophilicity profile[19] during a medicinal chemistry optimization. Among the possible variants of X, the hydroxyl group was viewed as the most suitable functionality as it could be conveniently used for introducing further modifications either directly or *via* oxidation to the respective ketone (a similar strategy was exploited to optimize spirocyclic μ opioid receptor ligands, also amenable by Prins chemistry).[12a] However, examples of using azacycloalkanones in Prins cyclization were scarce in the literature and appeared to be limited to those synthesized in the form of their respective mesylates (X = OMs) by Ghosh and co-workers *via* methanesulfonic acid-promoted reaction in dichloromethane.[11a] The literature protocol was found to be scalable to tens of grams of the starting material (ESI) and the mesyl group could in principle be removed either with MeMgBr or LAH as demonstrated for *N*-benzyl-4-piperidone-derived product **5** (Scheme 2). However, the modest overall yield of alcohol **6** and the inconvenience associated with the use of the metal-based reagents encouraged us to seek methods to directly prepare spirocyclic amino alcohols akin to **6**.

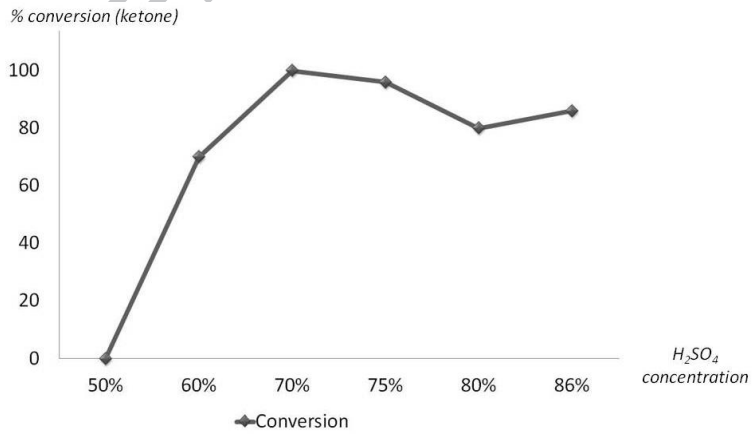
Scheme 2. Preparation of mesylate **5** according to Ghosh and co-workers[11a] and subsequent removal of the mesyl group.



The direct literature protocols toward spirocyclic 4-hydroxytetrahydropyrans included the use of 75% sulfuric acid,[12a-b] phosphomolybdic acid,[12c] cellulose-sulfonic acid,[12d] and indium(III)[12e] or mercury(II)[12f] triflates. Among these, the method employing inexpensive sulfuric acid appeared to be the most convenient and environmentally friendly. However, the presence of a basic nitrogen atom in our starting material initially made us skeptical about the prospects of applying the strong mineral acid-based method toward azacycloalkanones.

To our delight, when we tested the reaction of *N*-benzyl-4-piperidone with homoallyllic alcohol in sulfuric acid of varying concentration, we found the reaction to work quite well at concentrations above 60%, with the best conversion achieved in 70% H_2SO_4. These conditions were not optimized further and were used for all Prins-type spirocyclizations described below. Interestingly, reducing the H_2SO_4 concentration to 50% led to no conversion (Figure 2), as determined by the unchanged presence of the characteristic signals in the ^{1}H NMR spectrum of the reaction, ascribed to the piperidone starting material.

Figure 2. Conversions[a] for the reaction of *N*-benzyl-4-piperidone with homoallylic alcohol using various concentrations of sulfuric acid.



[a] Determined by integration of the ^{1}H NMR signals relative to the internal standard (DMAP) which was added to the organic phase containing the crude product following reaction workup.

Once our ability to achieve the Prins spirocyclization of azacycloalkanones in a strong mineral acid medium was demonstrated, the same protocol (Scheme 3)[20] was applied to a range of ketones, some of which were not basic in nature, and the respective spirocyclic products were obtained in good yields (Table 1). Gratifyingly, for compounds **11**-**12** the spirocyclization

reaction was completely diastereoselective and only a single diastereomer was obtained. In contrast, compound **14** was obtained as a 1:1 mixture of diastereomers.

Scheme 3. Preparation of spirocyclic 4-hydroxytetrahydropyrans **6-20** from various azacycloalkanones in 70% sulfuric acid.

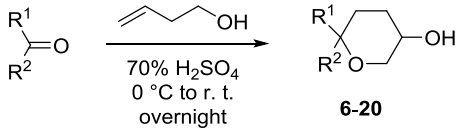
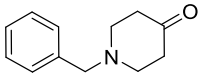
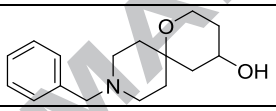
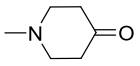
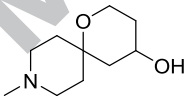
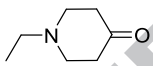
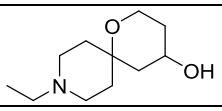
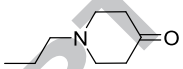
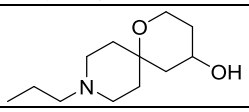
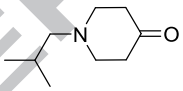
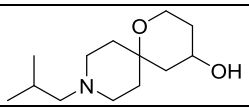
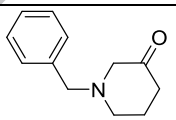
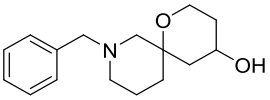
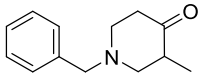
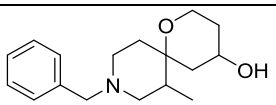
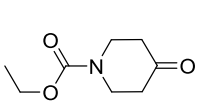
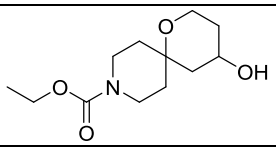
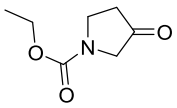
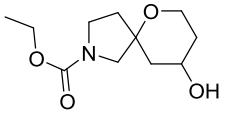
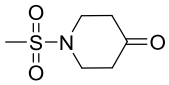
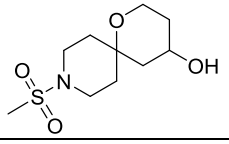
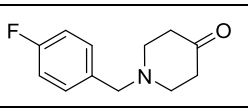
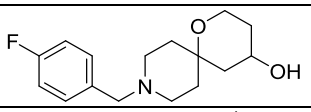
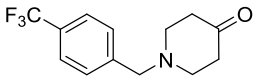
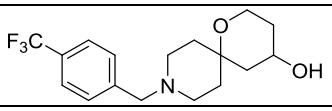
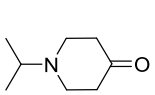
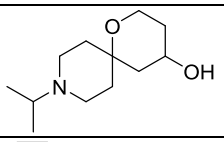
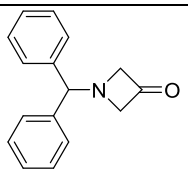
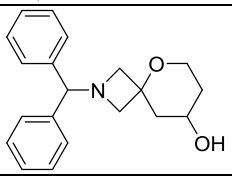
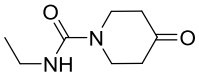
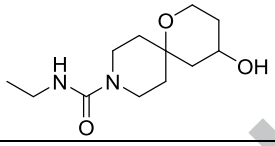


Table 1. 4-Hydroxytetrahydropyrans **6-20** synthesized in this work.

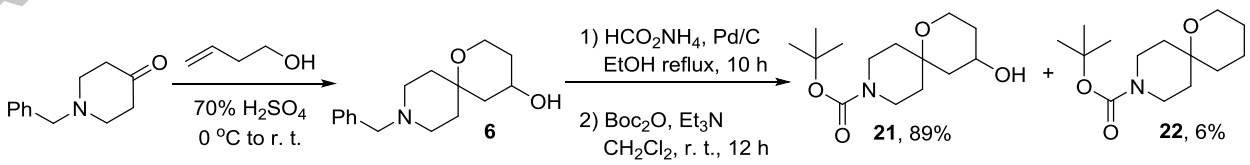
	Product		Isolated yield (%)
		**6**	70
		**7**	65
		**8**	54
		**9**	63
		**10**	63
		**11**	44[a]
		**12**	63[a]
		**13**	61
		**14**	55[b]
		**15**	51

		**16**	57
		**17**	54
		**18**	65
		**19**	65
		**20**	44

[a] One diastereomer isolated.
[b] Diastereomeric mixture (1:1)

Similar to the MsOH-promoted protocol by Ghosh and co-workers (*vide supra*), the developed direct amino alcohol synthesis also worked quite well on a multigram scale and was realized on a 25-gram scale using *N*-benzyl-4-piperidone (ESI). Without further purification, the resulting product (**6**) was debenzylated and the secondary amine Boc-protected to provide, after chromatographic purification, an excellent yield of **21**, along with a small amount of dehydroxylation product **22** (Scheme 4). This building block has been recently used in the preparation of a library of potential GPR40 agonists, as envisioned in Figure 1.[21]

Scheme 4. Three-step, one-purification protocol toward Boc-protected building blocks **21**-**22**.



In summary, we report a convenient and environmentally friendly protocol toward valuable 'high-F_{sp3}' spirocyclic amino alcohol building blocks which was applicable to a range of azacycloalkanones. Considered to be privileged motifs in drug design,[1] these building blocks are

useful for constructing potential agonists of GPR40, an important biological target in type II diabetes mellitus. The results of these studies will be reported in due course.

Acknowledgement

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/xxx.

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20. General procedure for preparation of compounds **6-20**: To a 0 °C vigorously stirred neat mixture of the respective azacycloalkanone (4.42 mmol) and 3-butenol (4.86 mmol) in a 2 mL glass vial was slowly added 70% H_2SO_4 (1.5 mL). The stirring was continued overnight, at which point the mixture was diluted by water (5 mL) and the pH adjusted to 9-10 using a saturated aqueous NaOH solution. The mixture was extracted with ethyl acetate (2 x 10 mL), the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Chromatographic purification of the residue on silica gel using 0→5% MeOH in chloroform as eluent afforded analytically pure products **6-20** in the indicated yields.
21. Lukin, A.; Krasavin, M. Manuscript in preparation.

- Prins-type spirocyclization was conducted in 70% sulfuric acid
- The aqueous protocol was applied to basic substrates for the first time
- The resulting building blocks are useful in antidiabetic drug design