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Synthesis of Orthogonally Protected 2,6-Diazaspiro[3.5]nonane and 2,6-Diazaspiro[3.4]octane Analogues as Versatile Building Blocks in Medicinal Chemistry

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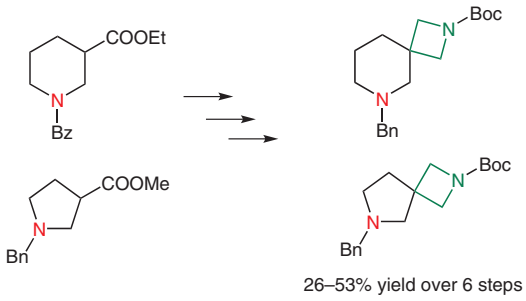

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Abstract A novel and efficient synthesis of orthogonally protected spirocyclic amines is described for the first time.

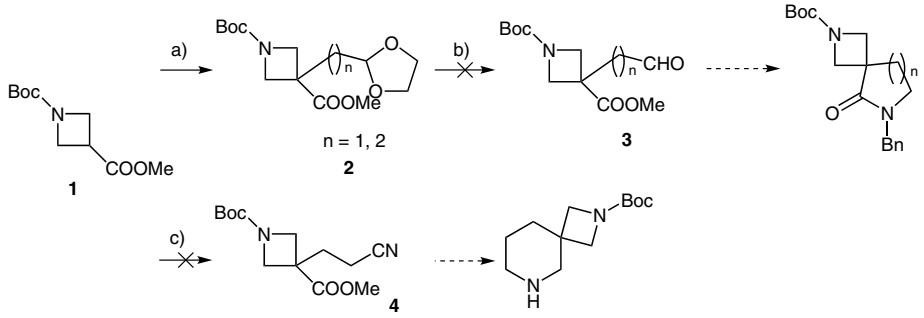
Key words spirocyclic amine, 2,6-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.4]octane, azetidine deprotection, orthogonal protecting groups

Constrained spirocyclic amines are common structural motifs in many natural products and drug molecules such as sanglifehrin, azaspiroacid,[1] and varenicline.[2] They are providing very rigid systems with three-dimensional structures associated with low molecular weights and they are very efficient in terms of atom economy. A vast number of active compounds generated in pharma industry is based on five- and six-membered aliphatic rings that are either fused or linked.[3] In comparison to those, four-membered rings are found less frequently. A number of spirocyclic amino oxetanes,[4] azetidine-thietanes,[4] 2,6-diazaspiro[3.3]heptanes,[4] 1,6-diazaspiro[3.4]octanes,[6] and 2,7-diazaspiro[3.5]nonanes[5,8] are known in medicinal chemistry and their syntheses are described in the literature. In addition, a review compiling multiple syntheses of constrained diamine systems including several spirocycles, for example, 1,6-diazaspiro[3.3]heptane has been published.[7]

For our purposes, we were particularly interested in developing a reliable and efficient synthesis of 2,6-diazaspiro[3.5]nonane and 2,6-diazaspiro[3.4]octane systems orthogonally protected on the respective nitrogen atoms. The synthesis of 2,6-diazaspiro[3.5]nonane was not previously published. The synthesis of 6-benzyl-2,6-diazaspiro[3.4]octane was published before;[9] however, the reported yields were lower than reported herein. It is worth noting that some of the building blocks based on the above-mentioned spirocyclic amines are commercially available at quite expensive price. For our purpose we were interested in developing a reliable synthetic route to obtain gram quantities of these spirocyclic amines. For some of the previously published strategies[6,7] to synthesize similar spirocyclic diamines the reasoning was based on the functionalization of the azetidine building block and then constructing the pyrrolidine or piperidine ring. Thus, we attempted to form the spirocyclic lactam intermediate (Scheme 1) in a sequence of steps starting from azetidine derivative **1**. First, the acetal-protected side chain was introduced via classical deprotonation followed by quenching with an appropriate alkyl bromide to access **2**; however, its deprotection to aldehyde **3** failed (no conversion of **2**). In another approach, similar deprotonation and subsequent alkylation with 3-bromopropionitrile did not provide nitrile **4**, which was expected to be further reduced with Raney nickel to form the desired lactam (Scheme 1). Those approaches via azetidine chemistry were not further pursued since a parallel approach was more promising.

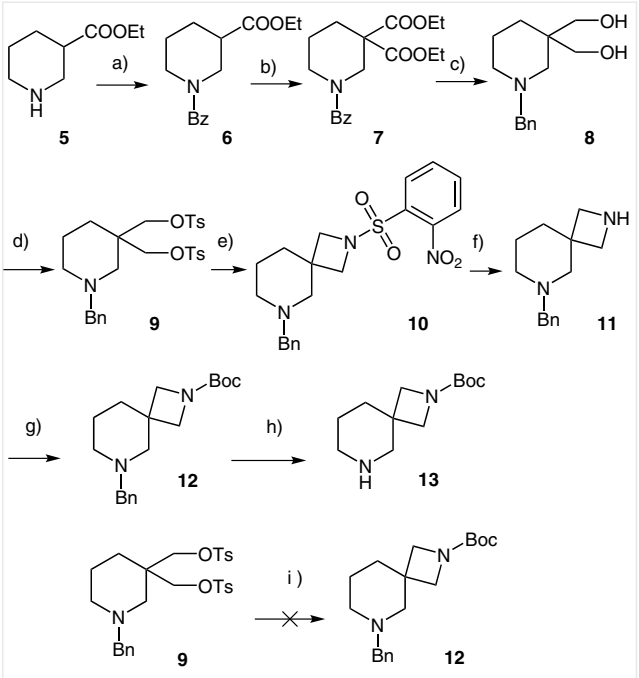
In a parallel synthetic plan, we considered the reverse approach that we thought to be more viable and which would start from readily available and cheap starting materials. First, we pursued the synthesis towards the benzyl-protected 2,6-diazaspiro[3.5]nonane **11** (Scheme 2).

Readily available piperidine ethyl ester **5** was protected as its *N*-benzoyl form leading to **6** in good yield (98%);[10] it is noteworthy to mention that when methyl ester was used, ester hydrolysis was observed during workup. Deprotonation of **6** with in situ formed LDA followed by quenching of the resultant enolate with ethyl chloroformate provided diester **7** in good yield (98%). Reduction of **7** with $LiAlH_4$ solution gave *N*-benzyl protected diol **8** in 91% yield. For the introduction of the nitrogen atom in an elegant way, we envisaged that reaction of the ditosylate **9** (obtained in 87%

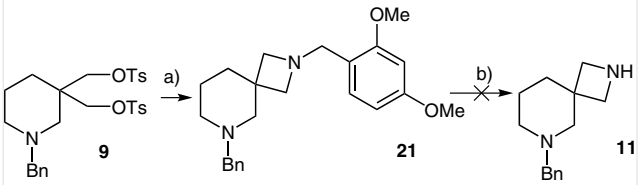


Scheme 1 *Reagents and conditions*: a) LiHMDS, bromoacetal derivative, THF, –70 °C; b) PTSA, acetone–H_2O, 50 °C; c) LDA, –78 °C, 3-bromopropionitrile, THF.

yield) with an appropriately protected nitrogen equivalent would form the azetidine ring. Unfortunately, direct conversion of **9** with *tert*-butyl carbamate proved not to be successful. When reacting ditosylate **9** with 2,4-dimethoxybenzylamine, the spirocyclic intermediate **21** was successfully obtained (Scheme 3). However, deprotection of the azetidine nitrogen to provide intermediate **11** under various conditions did not work. For instance TFA treatment under reflux or microwave irradiation,[11] conversion into the trifluoroacetamide[12] or oxidative cleavage with $K_2S_2O_8$[14] were not successful. Fukuyama reported 2-nitrobenzenesulfonamide[14] as a temporary protecting group for secondary amines that is easily cleavable by treatment with thiophenol. Following this approach, intermediate **10** was obtained (78% yield) by reacting ditosylate **9** with 2-nitrobenzenesulfonamide. Compound **10** was further deprotected with thiophenol in Cs_2CO_3/DMF to give the spirocyclic diamine **11** in an excellent yield (89%) after purification over a short silica plug.[15] It is noteworthy to mention that cyclization works as well with *p*-toluenesulfonamide but deprotection and purification proved to be less efficient. The azetidine moiety in **11** was further Boc-protected using standard conditions (85% yield) to give intermediate **12** that constitutes a versatile building block with orthogonal protecting groups that can be cleaved using standard conditions such as catalytic hydrogenation or HCl/TFA treatment, respectively.



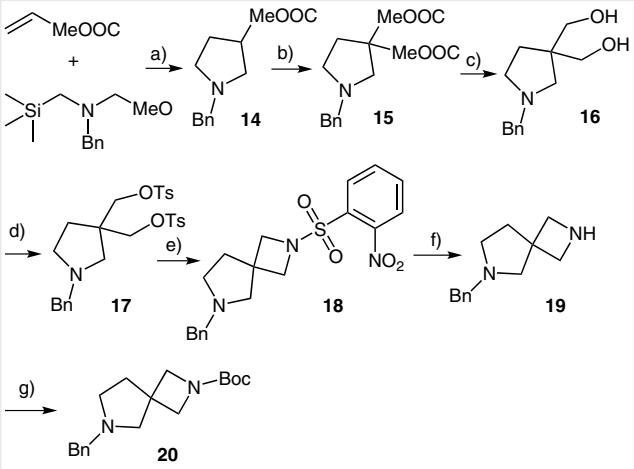
Scheme 2 *Reagents and conditions*: a) BzCl, DIPEA, CH_2Cl_2, r.t. (98%); b) LDA, ClCOOEt, THF, –78 °C to 0 °C (98%); c) $LiAlH_4$, THF, 0 °C to reflux (91%); d) TosCl, Et_3N–DMAP, CH_2Cl_2, r.t. (87%); e) 2-nitrobenzenesulfonamide, K_2CO_3, DMF, 100 °C (78%); f) PhSH, Cs_2CO_3, MeCN, r.t. (89%); g) Boc_2O, $NaHCO_3$, H_2O–dioxane, r.t. (85%); h) H_2 (5 bar), Pd/C, MeOH, r.t. (95%); i), NH_2Boc, K_2CO_3, DMF, 100 °C.



Scheme 3 *Reagents and conditions*: a) 2,4-dimethoxybenzylamine, MeCN, DIPEA, reflux (50%); b) i): TFA, reflux, or MW irradiation; ii) Tf_2O, Et_3N, CH_2Cl_2; iii) $K_2S_2O_8$, MeCN–H_2O.

Benzyl-protected 2,6-diazaspiro[3.4]octane **20** (Scheme 4) was synthesized following the same strategy as for nonane derivative **12**. TFA-catalyzed 1,3-dipolar cycloaddition between *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine and methyl acrylate[16] led to intermediate **14** in good yield (90%) and no ester hydrolysis was observed in this case.

Deprotonation in the α-position of ester **14** with LDA followed by quenching with methyl chloroformate gave diester **15** (84% yield). Reduction to diol **16** with $LiAlH_4$ (91% yield) followed by tosyl protection in a similar fashion to derivative **9** led to ditosyl intermediate **17** (54% yield). For-



Scheme 4 *Reagents and conditions*: a) cat. TFA, CH_2Cl_2, 0 °C to r.t. (90%); b) LDA, ClCOOMe, THF –78 °C to 0 °C (84%); c) $LiAlH_4$, THF, 0 °C to reflux (91%); d) TosCl, Et_3N–DMAP, CH_2Cl_2, r.t. (54%); e) 2-nitrobenzenesulfonamide, K_2CO_3, DMF, 100 °C (95%); f) PhSH, Cs_2CO_3, MeCN, r.t.; g) Boc_2O, Et_3N, CH_2Cl_2, r.t. (60% over two steps).

mation of the nosyl-protected azetidine **18** was high yielding (95%)[17] and subsequent thiophenol-mediated nosyl group removal led to the spirocyclic amine **19** which was Boc-protected giving intermediate **20** in 60% yield over two steps.[18] The orthogonally protected 2,6-diazaspiro[3.5]nonane and 2,6-diazaspiro[3.4]octane building blocks are ideally set up for further functionalizations. The Boc group can be cleaved either with TFA or HCl in dioxane allowing functionalization of the azetidine nitrogen. Then, the benzyl protecting group can be hydrogenolytically cleaved to functionalize the piperidine nitrogen. Alternatively, the order of functionalizations can be interconverted.

In summary, we have reported for the first time the synthesis of the spirocyclic amines 2,6-diazaspiro[3.5]nonane derivative and 2,6-diazaspiro[3.4]octane which are accessible in an excellent overall yield of 53% and 26% over six steps, respectively. The syntheses were optimized on gram scale and are amenable for further scale-up to multigram scale.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378722.

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(15) **Typical Procedure for Nosyl Group Removal**
Cs_2CO_3 (22.64 g, 0.069 mol) and thiophenol (5.21 mL, 0.051 mol) were successively added to a solution of nosyl-protected spiro amine **10** (18.6 g, 0.046 mol) in MeCN (150 mL). The mixture was stirred at r.t. for 16 h. After this time the starting material was consumed as judged by TLC. The reaction mixture was filtered through a short layer of Celite. The cake was washed first with EtOAc (300 mL) and further with CH_2Cl_2–MeOH–NH_3 (7 M in MeOH, 80:18:2, 3 × 100 mL), and the collected organic layer was concentrated to give in total 31.3 g of the crude oil, which was absorbed on the minimum of silica gel and poured into a chromatography column containing a 1 cm layer of silica gel. The elution was carried out with EtOAc to wash off unpolar impurities and then with the system CH_2Cl_2–MeOH–NH_3 (7 M in MeOH, 80:18:2) to give the product **11** (8.8 g, 89% yield) as yellow oil. LCMS (214 nm): t_R = 7.8 min (89.1% content), $[M + H]^+$ = 217.0. TLC analysis: R_f = 0.07 in CH_2Cl_2–MeOH–NH_3 (7 M in MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 7.36–7.19 (m, 5 H), 3.51 (s, 2 H), 3.38–3.33 (m, 4 H), 2.53–2.28

(m, 4 H), 1.65 (s, 2 H), 1.60–1.51 (m, 2 H). ^{13}C NMR (101 MHz, CD_3OD): δ = 137.93, 128.91, 127.92, 126.84, 62.73, 61.32, 55.05, 53.12, 38.27, 33.82, 21.78.

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(17) Intermediate **18** was also obtained from the dimesyl analogue of **17**; however, the isolated yield was lower (51%).

(18) The *p*-toluenesulfonamide derivative of intermediate **18** was obtained, and the deprotection to spirocyclic amine **19** was carried out with Red-Al® in toluene under reflux; however, the isolated yield of was lower.