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Spirocyclic azetidines for drug discovery: novel Boc-protected 7′*H*-spiro[azetidine-3,5′-furo[3,4-*d*]pyrimidines]

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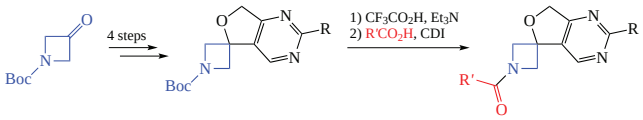
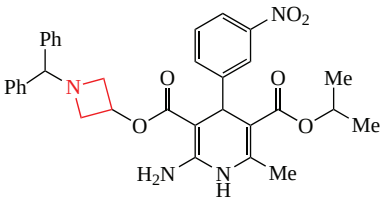
A novel spirocyclic scaffold of 7′*H*-spiro[azetidine-3,5′-furo[3,4-*d*]pyrimidine] chemotype was synthesized in *N*-Boc-protected form. However, the scaffold was revealed to be unstable to storage when deprotected. The solution was found in the brief removal of the Boc protecting group and rapid acylation of the liberated *NH*-azetidine with a carboxylic acid imidazolide.

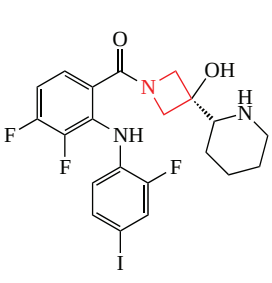


Keywords: azetidines, spirocycles, pyrimidines, instability in deprotected form, privileged scaffold, 5-nitrofuroyl.

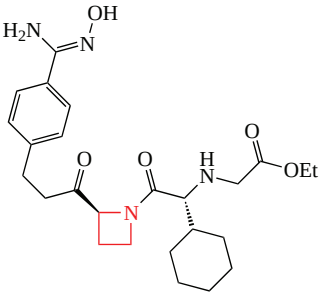
Azetidine is the smallest nitrogen-containing saturated heterocycle possessing reasonable chemical stability. Its inherent lead-likeness[1] and conformational rigidity[2] make azetidines an attractive fragment to build more complex molecular scaffolds around. Azetidine-containing building blocks have been widely used for drug design[3–5] and are part of natural products.[6–8] Among pharmaceutical products, notable examples include antihypertensive calcium channel blocker Azelnidipine,[9] mitogen-activated protein kinase inhibitor Cobimetinib[10] and oral anticoagulant Ximelagatran.[11]



Azelnidipine



Cobimetinib



Ximelagatran

Combining azetidinone motif with such attractive features as spirocyclic arrangement of several rings, a centerpiece of modern drug design[12] as well as very ‘natural-like’ molecular design considering the omnipresence of spirocycles in natural products,[13] appears a very sensible move when the target-agnostic drug design is concenrned.[14] In choosing which spirocycles to construct using the azetidinone motif, a balance should be maintained between the privileged character of the specific spirocyclic motif and the novelty of the scaffold being constructed. For instance, 5-oxa-2-azaspiro[3.4]octane scaffold alone is so omnipresent in Reaxys database (>2000 hits in biomedical area alone) that it can be almost regarded as privileged.[15] However, fusing this oxa/aza spirocycle to a pyrimidine ring (also a privileged heterocycle) produced only a few hits with no biomedical information reported for them (Figure 1). Hence, we set off to synthesize several exemplary Boc-protected 7′*H*-spiro[azetidine-3,5′-furo[3,4-*d*]pyrimidine] building blocks with an intention to use them in drug discovery. Herein, we report our findings in this regard.

The synthesis commenced with commercially available Boc-protected azetidin-3-one **1** which was subjected to the Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate (Scheme 1). The olefinic product **2** was condensed with methyl glycolate and the initial Michael adduct was subjected to intramolecular decarboxylative Claisen condensation to furnish known[16] *tert*-butyl 7-oxo-5-oxa-2-aza-spiro[3.4]octane-2-carboxylate **3**. The latter was condensed with dimethyl formamide dimethyl acetal $Me_2NCH(OMe)_2$ which added to unsymmetrical ketone **3** regiospecifically. Without isolation, the intermediate (dimethylamino)methylene derivative **4** was condensed with various amidine hydrochlorides in the presence of sodium methoxide to afford spirotricyclic products **5a–e**.

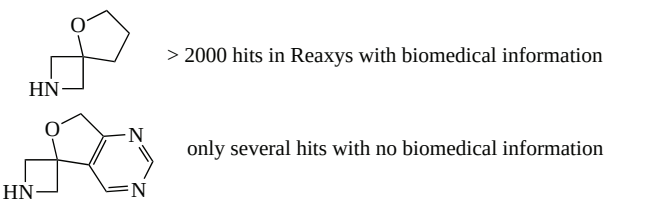
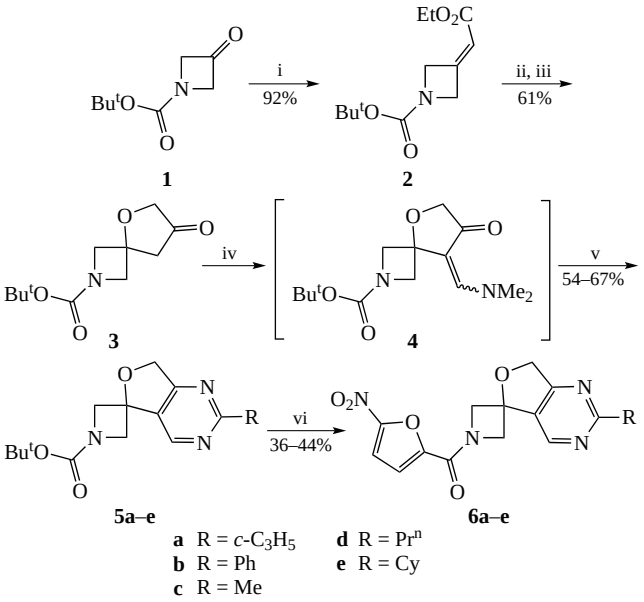


Figure 1 Occurrence of 5-oxa-2-azaspiro[3.4]octane scaffold in the literature.



Scheme 1 *Reagents and conditions*: i, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0→20 °C, 18 h (92%); ii, $HOCH_2CO_2Me$, NaH, Et_2O; iii, DMSO, 0→20 °C, 18 h (61%); iv, $Me_2NCH(OMe)_2$, room temperature, 18 h; v, $RC(=NH)NH_2·HCl$, MeONa, MeOH, 0 °C→reflux, 18 h; vi, CF_3CO_2H, CH_2Cl_2, 0 °C, 1 h, then dissolution in DMF/Et_3N and treatment with CDI-activated (DMF, 0 °C, 1 h) 5-nitrofurancarboxylic acid, room temperature, 18 h.

Compounds **5a–e** represent novel and valuable building blocks for library development. Moreover, they proved rather stable and could be kept at room temperature for extended period of time with no sign of decomposition as checked by ^{1}H NMR. However, removal of the Boc group either with trifluoroacetic acid in dichloromethane or with 4 M HCl in 1,4-dioxane gave substances that, to our disappointment, deteriorated quite rapidly both in the solution or as dry salts.

In order to circumvent this obstacle, we developed a protocol for a rapid swap of the Boc group to other acyl group which, we reasoned, would stabilize the scaffold again. For the model acylating agent, we chose 5-nitrofuran-2-carboxylic acid as a potential source of antibacterial pharmacophore.[17,18] The procedure involved preliminary pre-activation of this carboxylic acid with 1,1′-carbonyldiimidazole (CDI) and separate brief deprotection of compounds **5a–e** with trifluoroacetic acid in dichloromethane at 0 °C followed by treatment with trimethylamine to convert them into free *NH*-bases. The latter solution was rapidly added to the solution of 5-nitrofuran-2-carbonyl imidazolide. This resulted in the formation of *N*-acylated derivatives **6a–e** which proved stable to chromatographic isolation, characterization and subsequent storage at ambient temperature and in ambient atmosphere (see Scheme 1).

In summary, we have designed and synthesized a novel spirocyclic scaffold of 7′*H*-spiro[azetidine-3,5′-furo[3,4-*d*]-pyrimidine] chemotype containing azetidine moiety, in a Boc-protected form. However, the scaffold was found to be unstable when deprotected. The solution was found in the brief removal of the Boc protecting group and rapid acylation of the liberated *NH*-azetidine with a carboxylic acid imidazolide. Once acylated, the compounds were stable to chromatography and subsequent storage in ambient atmosphere and at ambient temperature, which makes them promising for biological testing.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.04.008.

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