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Lead-oriented synthesis: Investigation of organolithium-mediated routes to 3-D scaffolds and 3-D shape analysis of a virtual lead-like library

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ABSTRACT

Synthetic routes to six 3-D scaffolds containing piperazine, pyrrolidine and piperidine cores have been developed. The synthetic methodology focused on the use of *N*-Boc α-lithiation-trapping chemistry. Notably, suitably protected and/or functionalised medicinal chemistry building blocks were synthesised via concise, connective methodology. This represents a rare example of lead-oriented synthesis. A virtual library of 190 compounds was then enumerated from the six scaffolds. Of these, 92 compounds (48%) fit the lead-like criteria of: (i) $-1 \leqslant A\log P \leqslant 3$; (ii) $14 \leqslant$ number of heavy atoms $\leqslant 26$; (iii) total polar surface area $\geqslant 50$ Å^2. The 3-D shapes of the 190 compounds were analysed using a triangular plot of normalised principal moments of inertia (PMI). From this, 46 compounds were identified which had lead-like properties and possessed 3-D shapes in under-represented areas of pharmaceutical space. Thus, the PMI analysis of the 190 member virtual library showed that whilst scaffolds which may appear on paper to be 3-D in shape, only 24% of the compounds actually had 3-D structures in the more interesting areas of 3-D drug space.

1. Introduction

It is now widely acknowledged that the success of compounds through the drug discovery process is strongly associated with molecular and physical properties.[1–5] In 2012, Nadin et al. at GlaxoSmithKline challenged the synthetic community with the task of developing synthetic methodology that would be better suited to the preparation of lead-like molecules.[6] Their concept, termed 'lead-oriented synthesis', highlighted that 'lead-oriented synthesis must be able to deliver molecules with specific molecular properties with utility in the drug discovery process' and that 'lead-oriented syntheses need to pay particular attention to the physicochemical and functional group properties of the target molecules while also maintaining synthetic efficiency'. With this in mind, and building on Lipinski's rules,[7] lead-oriented synthesis was defined with the following guidelines: (i) lipophilicity should be in the range $-1 \leqslant c\log P \leqslant 3$; (ii) molecular size should be in the range $14 \leqslant$ number of heavy atoms $\leqslant 26$ (corresponding to a molecular weight range of 200–350 Da); (iii) molecules with chemically active, electrophilic or redox active functional groups should be avoided; and (iv) molecules with a lower degree of aromatic character and/or more 3-D shape should be prioritised. Additional recommendations on the associated synthetic chemistry focused, amongst other things, on efficiency, cost, suitability for array synthesis and compatibility with polar functional groups. The lead-oriented synthesis guidelines bring together several aspects that have been highlighted as key to drug discovery. The lead optimisation process generally leads to increases in lipophilicity and molecular complexity (and hence the associated molecular weight).[8,9] Setting lower target ranges for these properties at the outset is thus considered important. Support is also developing for the view that too many aromatic rings adversely affects the lipophilicity of drug compounds[10] (although data analysis is far from straighforward[11]) and that 3-D shape in drug compounds may give a better profile through the drug development process.[12] In this context, Nelson and co-workers have recently reported the lead-oriented synthesis and evaluation of two virtual libraries of lead-like compounds based on a range of drug-relevant scaffolds.[13]

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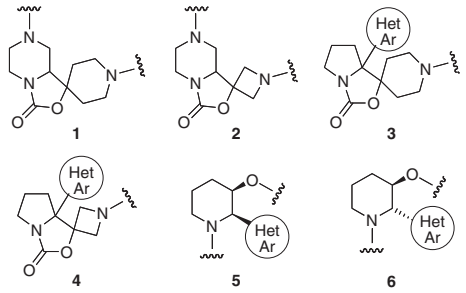
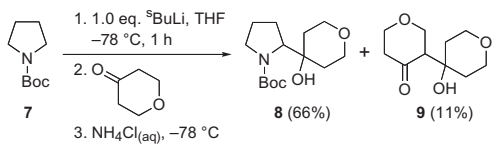
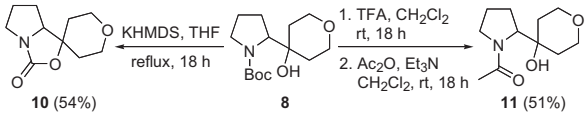


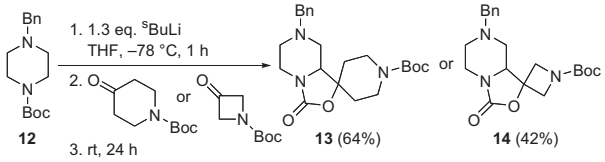
Figure 1. Structures of piperazine-, pyrrolidine- and piperidine-based 3-D scaffolds **1**–**6** with highlighted points of structural diversification (HetAr = heteroaromatic).



Scheme 1. Lithiation of *N*-Boc pyrrolidine **7** and ketone trapping.



Scheme 2. Conversion of **8** into 3-D fragments.



Scheme 3. Lithiation of *N*-Boc piperazine **12** and amino-ketone trapping.

Our long-standing interest in the asymmetric synthesis of saturated nitrogen heterocycles[14–19] and the growing interest in 3-D lead-like[12] and fragment[20,21] compounds led us to consider whether our organolithium-based methodology is suitable for the lead-oriented synthesis of 3-D scaffolds. In this paper, we describe concise, connective synthetic methodology for the construction of suitably protected building blocks which are precursors to 3-D scaffolds **1**–**6** (Fig. 1). These scaffolds incorporate piperazines, pyrrolidines or piperidines which are amongst the most common ring systems found in approved drugs.[22,23] Scaffolds **1**–**6** were specifically selected due to their anticipated 3-D shape (vide infra), the presence of only one (**1**–**4**) or two (**5**–**6**) stereogenic centres, potential ease of synthesis via established organolithium chemistry and the fact that they had two or three points of diversification (different heteroaromatic groups and/or different *O*- and *N*-functionality). Furthermore, by choosing a pyridine group as a representative, electron deficient heteroaromatic substituent, it was felt that lead-like compounds of typical polarity would challenge the methodology. The synthetic approach to scaffolds **1**–**4** involved use of Beak's *N*-Boc α-lithiation methodology,[24] trapping with a heterocyclic ketone and subsequent cyclisation to the carbamate. In contrast, for the synthesis of scaffolds **5** and **6**, an *N*-Boc α-lithiation-ring expansion approach was adopted.[15] Thus, starting from *N*-Boc pyrrolidine, α-lithiation and trapping with an aldehyde would deliver an amino alcohol, which would be ring expanded via an aziridinium ion,[25,26] to give the α-aryl, β-hydroxy piperidine motif.[27]

In addition to the lead-oriented synthetic methodology, we also describe herein the lead-like and 3-D shape analysis of a virtual library of 190 compounds derived from scaffolds **1**–**6**. For the 3-D shape analysis, we elected to use a triangular plot of normalised principal moments of inertia (PMI) as introduced by Sauer and Schwarz.[28] In particular, this analysis allowed us to address the issue of whether scaffolds like **1**–**6** which appear on paper to be 3-D in shape can actually generate compounds with appropriate lipophilicity/molecular size and that occupy new areas of 3-D pharmaceutical space. Herein, we present our results.

2. Results and discussion

2.1. Development of lithiation-trapping methodology for the synthesis of 3-D scaffolds 1–6

The planned synthetic approach to scaffolds **1**–**4** involved the α-lithiation of *N*-Boc heterocycles and trapping with suitable heterocyclic *N*-protected amino-ketones. In order to evaluate this methodology, a model system was explored first. Thus, *N*-Boc pyrrolidine **7** was lithiated α to the nitrogen using our diamine-free protocol[29] (1.0 equiv *s*-BuLi, THF, −78 °C, 1 h) and trapped using tetrahydro-*4H*-pyranone. In this example, the lithium alkoxide intermediate was quenched at −78 °C to prevent cyclisation onto the carbamate. This generated two major products which were isolated after chromatography (Scheme 1): the desired alcohol **8** (66% yield) and the aldol self-condensation by-product **9** (11% yield). It seems likely that enolisation of some of the tetrahydro-*4H*-pyranone by the lithiated *N*-Boc pyrrolidine occurs as a side-reaction. Apparently, there is a fine balance between the basicity and the nucleophilicity of the lithiated *N*-Boc pyrrolidine in reactions with enolisable heterocyclic ketones. There was a slight reduction in yield if 1.3 equiv of *s*-BuLi was used (63% of **8** and 6% of **9**).

Despite the occurrence of the aldol side-reaction to give aldol **9**, we were able to use this connective reaction to generate suitable quantities of alcohol **8** for further synthetic studies. For example, alcohol **8** was converted into two novel, 3-D fragments **10** and **11**. Treatment with KHMDS at reflux led to cyclisation to form carbamate **10** in 54% yield. Alternatively, Boc deprotection using TFA and acylation delivered amide **11** in 51% yield (Scheme 2).

After these successful model studies, our attention switched to the synthesis of piperazine-based scaffolds **1** and **2** starting from *N*-Boc piperazine **12**. Diamine-free lithiation with 1.3 equiv *s*-BuLi was followed by trapping with *N*-Boc piperidin-4-one or *N*-Boc azetidin-4-one. In these cases, in order to differentiate between the two Boc groups in the trapped products, the reaction mixtures were allowed to warm to room temperature and stirred for 24 h. This allowed cyclisation of the alkoxide onto the Boc group and directly gave carbamates **13** (64% yield) and **14** (42% yield), isolated after chromatography (Scheme 3). Aldol self-condensation was also noticed but not quantified in these two reactions. With the preparation of **13** and **14**, a concise synthesis of scaffolds **1** and **2** has been achieved. Notably, variation of the lithiated *N*-Boc heterocycle would allow a wider range of 3-D scaffolds related to **1** and **2** to be generated: the synthesis of **13** and **14** represents proof of concept for this general synthetic approach.

Carbamates **13** and **14** are attractive medicinal chemistry building blocks with orthogonally protected functionality, allowing stepwise functionalisation of each of the amines. To demonstrate the synthetic potential of **13** and **14** for lead-like library synthesis, they were differentially deprotected. Boc deprotection of **13**/**14**