Bioorganic & Medicinal Chemistry xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design and synthesis of 1,1-disubstituted-1-silacycloalkane-based compound libraries

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ARTICLE INFO

Article history:
Received 4 October 2014
Revised 19 December 2014
Accepted 26 January 2015
Available online xxxx

Keywords:
Silicon
Bioisostere
Silacyclohexane
Silacyclopentane
Silacycloalkane

ABSTRACT

The introduction of silicon in biologically-relevant molecules represents an interesting medicinal chemistry tactic. Its use is mainly confined to the fine-tuning of specific molecular properties and organosilicon compounds are underrepresented in typical screening libraries. As part of the European Lead Factory efforts to generate novel, drug discovery-relevant chemical matter, the design and synthesis of 1,1-disubstituted-1-silacycloalkane-based compound libraries is described.

1. Introduction

Screening of compound libraries remains a fundamental approach to drug discovery. Here, the availability of adequate chemical starting points for screening and the ability of medicinal chemists to improve their molecular properties by chemical manipulation are pre-requisite for final success. With a view to apply medicinal chemistry tactics to the generation of novel, relevant chemical matter for screening purposes, we considered the use of silicon bioisosteres for the design of organosilicon compound libraries. Silicon is a classical isostere of carbon, as from the number a valence electrons, but significant differences between the two elements exist when size, electronegativity and lipophilicity are considered.[1,2] Because of these similarities and differences, the use of silicon in medicinal chemistry has attracted significant attention, as periodically reviewed over the last decade,[3–7] and several methodologies have been developed for the synthesis of novel, bioactive, organosilicon compounds.[8–14] Nevertheless, organosilicon compounds and other non-natural atom-containing compounds are underrepresented in typical commercial and proprietary screening libraries. As part of the European Lead Factory[15] initiative to generate novel and biologically-relevant chemical matter, we evaluated the feasibility of producing silicon-containing compound libraries. Inspired by the work of Degrado et al. on silaspirane amines (**1**, Fig. 1) as influenza A virus M2 proton channel inhibitors[16] and the Tacke et al. synthesis of sila-venlafaxine taking advantage of a TMOP (2,4,6-trimethoxyphenyl) protecting group on a silanol intermediate (**2**, Fig. 1),[17] we devised 1,1-disubstituted silacycloalkanes with general structures **3** and **4** as scaffolds for compound libraries (Fig. 1).

2. Results

As shown in Figure 1, the intended library could contain three elements of chemical diversity. The first one is represented by the size of the silacycloalkane scaffold, the second and third ones are given by the arylic–heteroarylic substituent and *N*-substituted aminoethyl side chain, both installed on the silicon atom. Therefore, an initial retrosynthetic study supported by available robust

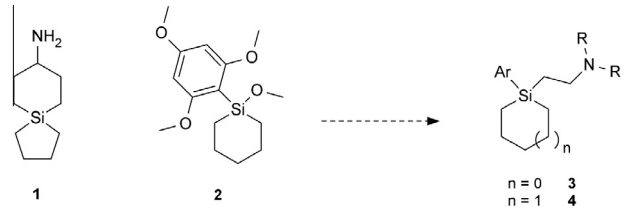

Figure 1. Design of 1,1-disubstituted silacycloalkanes **3** and **4** based on silaspirane amine **1** and TMOP protected silanol derivative **2**.

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http://dx.doi.org/10.1016/j.bmc.2015.01.046
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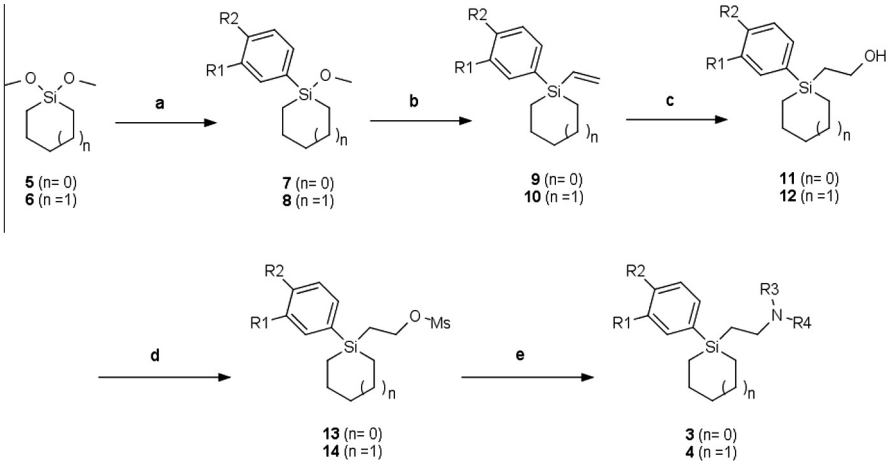

Scheme 1. Reagents and conditions: (a) (R_1R_2)phenylMgBr (1.0–1.2 equiv), THF, rt, N_2 (50–100%); (b) VinylMgCl (1.0 equiv), THF, rt, N_2 (52–100%); (c) 9-BBN (1.5 equiv), THF, 0 °C–rt, N_2, then NaOH, H_2O_2, rt (28–68%); (d) MsCl (1.3 equiv), pyridine, 0 °C, N_2 (66–100)%; (e) R_3R_4NH (3.0 equiv), toluene, 70 °C, N_2 (48–93%).

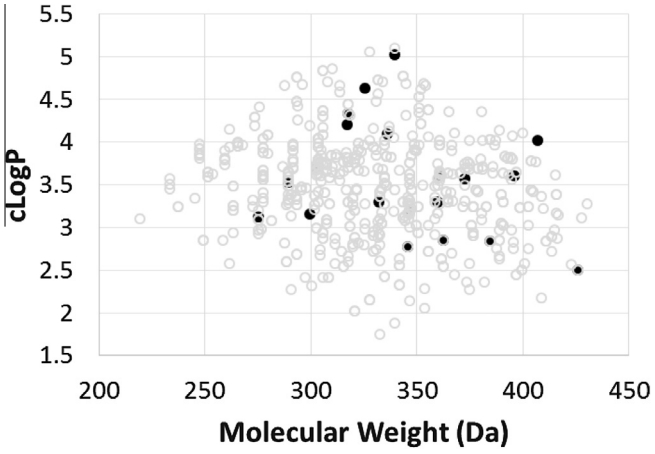

Figure 2. Physicochemical properties (calculated Log*P* (*c*Log*P*) and molecular weight, JChem, ChemAxon 6.3.0) for the theoretical 816 library members (gray circles). Selected compounds (**3a–j**, **4a–j**) synthesized to validate the synthetic approach are marked as black dots.

synthetic methodologies[9,18–20] suggested the use of 1,1-dimethoxy-1-silacyclopentane **5** and 1,1-dimethoxy-1-silacyclohexane **6** as starting materials (Scheme 1). Here, the introduction of further chemical diversity was afforded by aromatic Grignard reagents and primary and secondary amines (Scheme 1). A 8×51 matrix of Grignard and amine reagents was selected to ensure at least 80% of the final compounds would comply with lead-like properties (here defined as molecular weight $\leqslant$400 Da or calculated Log*P* (*c*Log*P*) $\leqslant 4$), yielding a potential collection of 816 compounds (Fig. 2). D-optimal designs as implemented in the R Project for Statistical Computing[21] were then used to select subsets and combinations of those reagents to validate the synthetic approach (Figs. 2 and 3).

Synthesis started from the 1,1-dimethoxy-1-silacyclopentane **5** and 1,1-dimethoxy-1-silacyclohexane **6** scaffolds which were prepared following established procedures.[9,18–20] Controlled substitution of one methoxy group in **5** and **6** with aromatic Grignard reagents[9] yielded compounds **7** and **8**. The methoxy substitution reaction proved to be very reproducible and generally high-yielding without requiring substrate-dependent conditions optimization (Scheme 1). It allowed the introduction of the second diversification point in the compound library using differently decorated and commercially available phenyl magnesium halide derivatives (Fig. 3) to isolate 14 of the 16 potential synthetic intermediates **7a–h** and **8a–f** (Table 1).

Substitution of the second methoxy group was achieved by the reaction with vinyl magnesium chloride to yield the ethylene derivatives **9a–h** and **10a–f** (Scheme 1). Further transformation

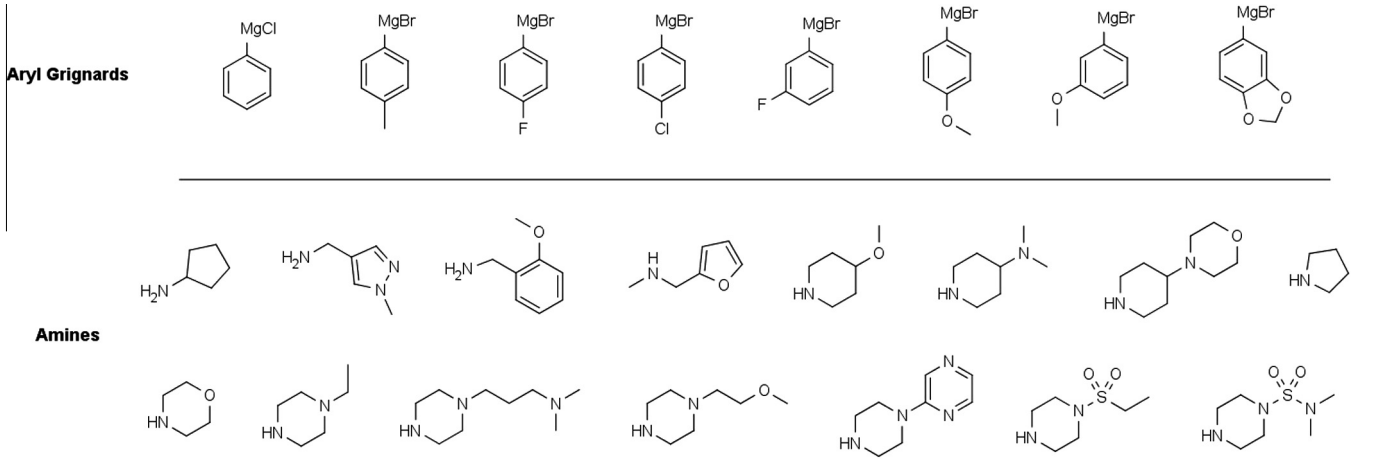

Figure 3. Selection of aryl Grignard and amine reagents used to validate the synthetic approach.