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Diversity-oriented approach to novel spirocycles via 1,2,4,5-tetrakis(bromomethyl)benzene under operationally simple reaction conditions

Sambasivarao Kotha *, Rashid Ali

Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai 400076, India

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ABSTRACT

Here, we have established a simple and an efficient methodology for the synthesis of spirocyclic α-amino acids as well as spirosulfones starting with readily available active methylene compounds (AMCs). The key di-bromo building blocks were assembled by reacting various active methylene compounds with 1,2,4,5-tetrakis(bromomethyl)benzene in one step. We have also expanded this strategy to generate a variety of bis-spirocycles by treating the di-bromo intermediates with different AMCs under operationally simple reaction conditions.

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1. Introduction

In recent years, spirocycles have elevated the chemical and pharmacological space to a higher level. There are also some other reasons that render them unique, for example, they are the integral parts of several natural as well as non-natural products[1] and also valuable building blocks in thermotropic liquid crystals, which in turn are useful for optical display device.[2] Due to the unique structural and reactivity pattern a great deal of attention has been paid to spirocycles and simple methodologies to these targets are in high demand. Generally, design and synthesis of spirocycles is a difficult task in preparative organic chemistry because of the formation of a spiro-ring junction.[3]

Synthesis of conformationally constrained α-amino acid (AAA) derivatives are in great demand because they are useful for drug discovery and development.[4] Replacement of proteinogenic AAAs by cyclic α-imino acid derivatives or cyclic AAAs is considered to be a useful tactic for the design of peptidomimetics with diverse pharmacological profiles. Recently, usage of peptide drugs have been expanded to a higher level.[5] However, sometimes their applicability is restricted due to various factors such as instability towards proteolytic degradation, poor absorption after oral ingestion, rapid excretion through liver and kidneys, non-selectivity and undesirable side effects because of the interaction of conformational flexibility of peptide(s) with a receptor.[6] To address this problem, incorporation of cyclic AAAs into a given peptide chain alter the conformational rigidity and thus modulate the pharmacological properties.[7] The structures of some interesting constrained AAAs synthesized in our laboratory are shown in Fig. 1.[8]

The sulfone functional group is often present in 'drug-like' small molecules and they are also valuable synthons for the construction of C–C bonds.[9] In addition, they are latent resource of conjugated dienes useful for the Diels–Alder (DA) chemistry.[10] The α-methylene groups in sulfones can be alkylated with various electrophiles due to the electron withdrawing nature of the sulfone moiety and this aspect in combination with the ease of desulfonylation has been explored in the numerous instances for assembling various biologically interesting targets.[11] Furthermore, α-halogenated sulfones are useful precursors suitable for the Ramberg–Bäcklund reaction for the generation of C–C double bonds.[12]

Here, we have demonstrated new strategies to various spirocyclic AAAs, spirosulfone derivatives and architecturally intricate bis-spirocyclic frameworks. Although, several methods are available for synthesis of AAAs and sulfone derivatives, most of them involve multi-step synthetic sequences.[13] Limited number of methods are available for the synthesis of spirocyclic AAAs and spirosulfone derivatives.[14] The importance of spirocycles, cyclic

* Corresponding author. Tel.: +91 22 2576 7160; fax: +91 22 2572 7152; e-mail address: srk@chem.iitb.ac.in (S. Kotha).

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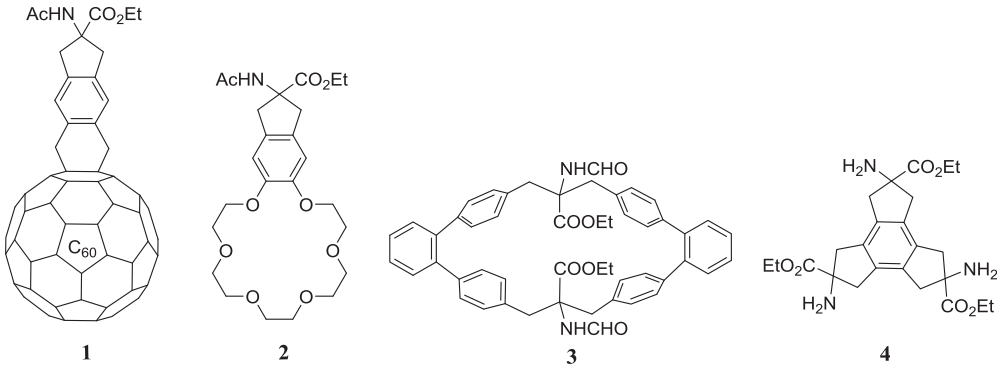

Fig. 1. Some interesting constrained AAAs synthesized in our laboratory.

AAAs as well as sulfone derivatives (Fig. 2)[15] and the documented difficulties in their synthesis prompted us to develop operationally simple methods from the readily available starting materials. To this end, we now report a simple route to spirocyclic AAAs and spirosulfone derivatives including some interesting bis-spirocyclic scaffolds. Here, the key di-bromo intermediates have been assembled by partial alkylation of 1,2,4,5-tetrakis(bromomethyl)benzene with a variety of AMCs. The structures of the AMCs used in our strategy are shown in Fig. 3.

10a–**j** under mild reaction conditions appears to be a good option (Scheme 2).

To achieve this goal, we started our journey with the preparation of 1,2,4,5-tetrakis(bromomethyl)benzene **16** by using the known procedure.[17] Having the tetra-bromo derivative **16** in hand, it was treated with various AMCs (Fig. 3) to assemble the corresponding di-bromo building blocks in a single step. To this end, the compound **10a** on treatment with tetra-bromide **16** gave the desired di-bromo building block **14a** (39%) along with the dimeric

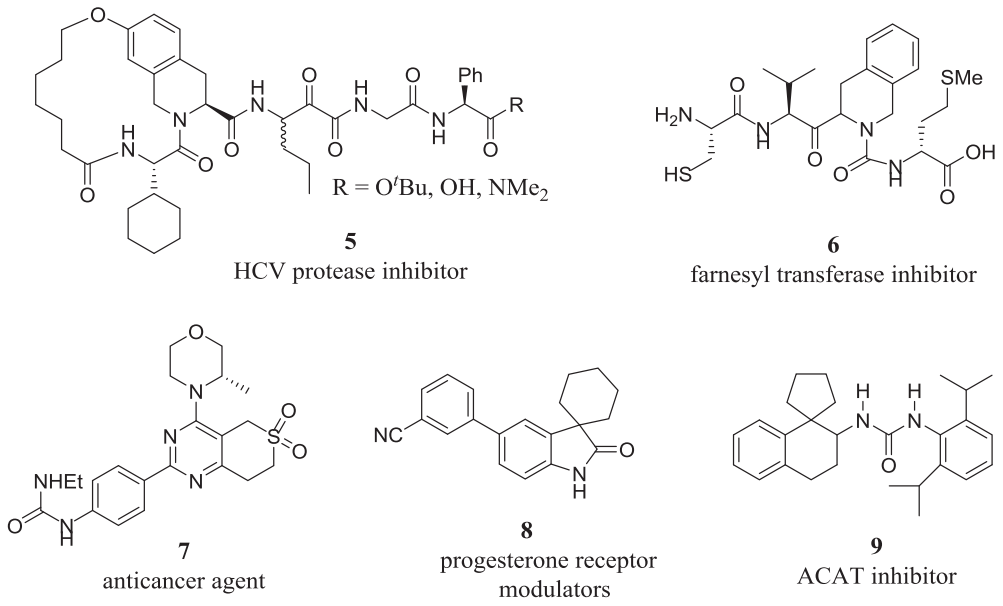

Fig. 2. Structures of some important bioactive AAAs, sulfones and a spirocyclic system.

2. Results and discussion

In view of our interest to generate new methodologies to spirocycles, here we report short and operationally simple strategies. In our earlier report,[16] we have assembled various di-bromo building blocks **14a**–**j** involving three steps: (i) propargylation of AMCs **10a**–**j**; (ii) [2+2+2] cycloaddition reaction of di-propargylated building blocks **11a**–**j** with 2-butyne-1,4-diol **12**; (iii) conversion of diols **13a**–**j** into the di-bromo building blocks **14a**–**j** via PBr_3 reaction (Scheme 1). In this context, conversion of diols into the di-bromo derivatives seems to be problem with sensitive substrates. This aspect forced us to look for an alternate approach. Therefore, it occurred to us that selective one side alkylation of 1,2,4,5-tetrakis(bromomethyl)benzene **16** with AMCs products **17a** (25%) (Scheme 2, Fig. 4 and Fig. 5). Surprisingly, when we treated the tetra-bromide **16** with indane-1,3-dione **10b**, we isolated the desired di-bromo product **14b** in low yield (8%) along with the *C* and *O*-alkylated compounds **14b**′ and **17b** in 30% and 18% yields, respectively (Figs. 4 and 5).

On the other hand, we were pleased to observe that when the tetra-bromo compound **16** was treated with 1,3-dimethylbarbituric acid **10c** the expected product **14c** was obtained in respectable yield (Fig. 4). Along similar lines, treatment of tetra-bromide **16** with 1-indanone **10d** or various tetralone derivatives **10e**–**g** delivered the desired products **14d**–**g** in satisfactory yields (Fig. 4). Later, this strategy has also been extended to some interesting fluorene derivatives. To this end, the compounds **10h**–**j** were treated with tetra-bromide **16** to yield the fluorene-based di-bromo building

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