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Synthesis and differential functionalisation of pyrrolidine and piperidine based spirodiamine scaffolds

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ABSTRACT

The synthesis and differential substitution/protection of a series of spirodiamine scaffolds are described. Methods for selective access to the two mono-*N*-methyl isomers based on 2,7-diazaspiro[4.5]decane are also described. Key precursors associated with this chemistry are prone to rearrangement and methods for circumventing this issue are reported. While direct *mono*-carbamoylation (Boc) was not efficient, selective deprotection of doubly Boc-protected derivatives derived from symmetrical diamines provided mono-Boc variants. N-Arylation, exemplified by a series of monosubstituted spirodiamines incorporating the 2-chloro-5-pyridyl moiety, which is a privileged nicotinic agonist substructure, has also been carried out to provide monoarylated secondary and tertiary spirodiamines variants.

1. Introduction

Nitrogen-based heterocycles based on spirodiamine scaffolds are of significant interest in medicinal chemistry, catalysis and materials chemistry by providing a well defined and comparatively rigid three-dimensional quality to a multisite interaction, be it involving a receptor/enzyme as the target or as the basis of a ligand for a metal-based catalyst. In terms of biologically active molecules,[1a] spiroamines have found application as potential antibacterial[1b] and antitumour drugs,[2] agonists of various protein receptors[3] including neural receptors,[4] and as peptidomimetics.[5] Spiroamine-based scaffolds are also found in Nature, as exemplified by the antimalarial alkaloid manzamine (and related molecules), which are isolated from marine sponges,[6] and have also been identified in a structurally diverse range of natural products derived from plants[7] and fungi.[8] More recently, there has been a significant increase in the awareness of the importance of three dimensionality as a design element within drug candidates.[9] This may involve chirality, but even without explicit consideration of chirality, an increase in the proportion of sp^3 centres, at the expense of more often used sp^2-based structures, can have a profound effect on biological profile that is not just limited to intrinsic activity but will also link to key physicochemical parameters. Consequently, the desirability of sp^3 centres is now recognised as an important critical factor in terms of enhancing a candidate's likelihood of successful translation from laboratory to clinic to market, and new opportunities for chemical methodologies in this area are of value. In this sense, spirodiamines not only offer 'three dimensionality' but, and depending on the specific scaffold, also chirality.

In terms of background, a number of spirodiamine scaffolds **A**–**F** (Fig. 1; based on four-, five- or six-membered rings) are known, and the various methods for the synthesis of each of these scaffolds (as opposed to specific individual examples) are reviewed briefly here. It is important to appreciate that these spirodiamines are not necessarily reported/available in their 'parent' (i.e., unsubstituted on the rings or via N) forms, and we have omitted benzofused variants, as well as comparatively reactive β-lactam derivatives. Aminal (aminoacetal) isomers/variants have been ignored simply because of the susceptibility of such latter systems to isomerisation/ring opening and hence scrambling of the spiro stereocentre.

Several synthetic strategies, including stereoselective approaches, have been applied depending on the structure of the target scaffold, and given the utility of these systems as the basis of more complex structures, it is appropriate to provide a brief overview of the more commonly exploited methods available. A number of these and related spiroamine scaffolds have only been reported or otherwise exploited in the patent literature, but this underscores the potential and perceived importance of these units in drug discovery.

The most common stereoselective approach to pyrrolidine variants has involved the alkylation of L-proline or its derivatives, followed by the cyclisation step to achieve the spirocycle. This

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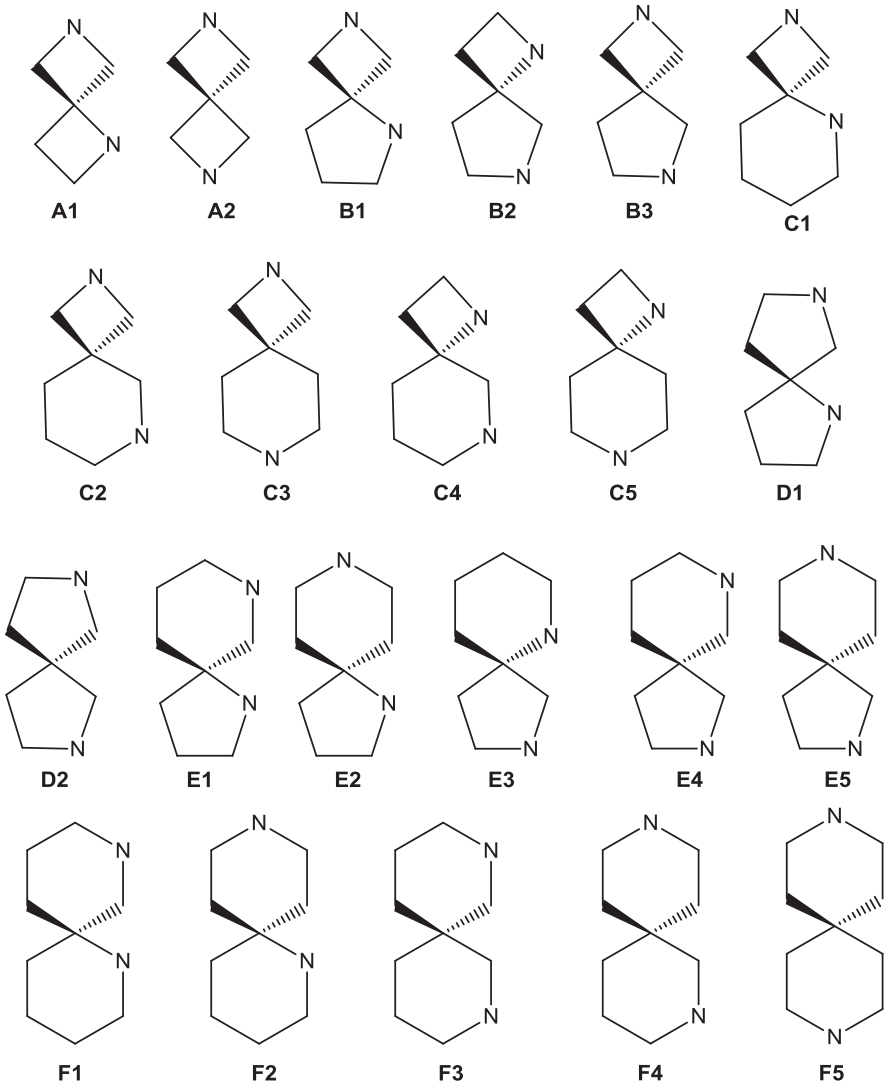

Fig. 1. Azetidine/pyrrolidine/piperidine spirodiamine scaffolds. No absolute stereochemistry should be inferred and scaffolds (i.e., molecular frameworks) are shown without substituents or associated functionality. References to specific examples of structures incorporating each scaffold are included in the text below, but generally β-lactam and benzofused variants have been excluded. Aziridine variants are not shown, given the comparatively high reactivity of these systems, and configurationally labile aminal isomers are also excluded.

provides an entry to pyrrolidine-based scaffolds encompassing 2,5-diazaspiro[3.4]octane **B1**,[5] 1,7-diazaspiro[4.4]nonane **D1**,[10] 1,7-diazaspiro[4.5]decane **E1**[11] and the seven-membered (azepane-based) 1,7-diazaspiro[4.6]undecane (*not shown*),[12] which have been obtained in most cases in enantiopure form.

Other, more varied ways of stereocontrolled construction of diazaspiro systems, often applied in alkaloid synthesis, have included ring-contracting pinacol rearrangements to access 2,7-diazaspiro[4.4]nonane **D2**,[13] synthesis of this same scaffold by electrocyclisation,[14] and synthesis of the core structure of manzamine that contains the 2,7-diazaspiro[4.5]decane **E4** structure via intramolecular stereocontrolled Michael addition to a 2-pyrrolidone derivative.[15]

Spirodiamine skeletons have been obtained via the reaction of geminally disubstituted (i.e., the nascent spiro-centre is already established) azetidine, pyrrolidine or piperidine derivatives with an amine in order to close the second ring, usually involving formation of an amine or an imide. Using this method, 2,6-diazaspiro[3.3]heptane **A2**,[10d,f] 1,6-diazaspiro[3.4]octane **B2**,[10d] 2,6-diazaspiro[3.4]octane **B3**,[10g] 2,5-diazaspiro[3.5]nonane **C1**,[4] 2,5-diazaspiro[3.6]nonane **C2**,[10g] 2,7-diazaspiro[3.5]nonane **C3**,[10e,f] diazaspiro[4.5]decanes **E4**[16] and **E5**,[17] and diazaspiro[5.5]undecanes **F3**,[18] **F4**[19] and **F5**[20] systems have been prepared. One of the geminal substituents can itself already be, e.g., an amine or amide so that the cyclisation step does not necessarily require an external amine, such as in the syntheses of diamine scaffolds **C4**,[4b] **C5**,[21a–d] **D1**,[21e] **E1**,[21e] **E2**,[21f] **E3**[21e] and **E4**[21g] and **F1**.[21e] Both rings of a nascent spiro system can be also closed in the same step, as in the syntheses of the 2,7-diazaspiro[4.4]nonane scaffold **D2**[22] and the 2,8-diazaspiro[5.5]undecane structure **F3**.[1,23] In several cases, the second ring of a diazaspiro scaffold was established via ring closing metathesis, and this process has been applied successfully to generate the 2,6-diazaspiro[4.5]decane **E3**,[24] 1,8-diazaspiro[5.5]undecane **F1**,[24a,25] 1,9-diazaspiro[5.5]undecane **F2**,[24,25c] and analogous systems based on a pyrrolidine and piperidine spirofused to an azepane moiety (not shown in Fig. 1, but included here for completeness), such as 2,7-diazaspiro[4.6]undecane,[24] 3,7-diazaspiro[5.6]dodecane[24] and 3,8-diazaspiro[5.6]dodecane[24] ring systems. One synthesis of the 2,7-diazaspiro[4.4]nonane scaffold **D2** and an example of the 1,6-diazaspiro[3.4]octane **B2** skeleton have been described in which the second heterocyclic ring was constructed via dipolar cycloaddition.[10d,26]

Importantly, a major application of spirodiamines is as spacer units within, for example, medicinal chemistry. Carreira[27a–c] has