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Synthesis of 1,5-diazaspiro[2.3]hexanes, a novel diazaspirocyclic system

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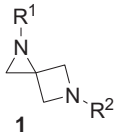
ABSTRACT

The convenient synthesis of 1,5-diazaspiro[2.3]hexanes, as new structurally challenging strained diazaspirocyclic compounds, was developed starting from easily accessible ethyl 2-(bromomethyl)-1-tosylaziridine-2-carboxylate. The key transformations in the developed four-step sequence involved a chemoselective reduction of the functionalized ethyl 1-tosylaziridine-2-carboxylate to the corresponding β-bromo aldehyde and an aza-Payne-type rearrangement of intermediate *N*-tosyl 2-(aminomethyl)aziridines into *N*-alkyl 2-(aminomethyl)aziridines. A final base-mediated cyclization of the formed bromo amines gave efficient access to the new diazaspirocyclic system.

1. Introduction

Recently, there has been a growing interest in the field of spirocyclic chemistry. Spirocycles comprise an interesting class of compounds, both from a chemical and a biological point of view. Azaspiro scaffolds are present in a number of natural products, such as halichlorine,[1] sibirine,[2] nitramine,[3] and families of histrionicotoxins.[4] Heteroatom-containing azaspirocycles, in particular, are considered to be surrogates for other saturated heterocycles, such as piperazines, morpholines, thiomorpholines, and piperidines,[5] in some cases even being stable alternatives of their labile monocyclic analogues[6] with applications as valuable building blocks in the field of drug discovery and for tuning of drugs or drug-like structures.[7] For example, 5-azaspiro[2.4]heptyl substituents were reported to enhance the antibacterial activity of quinolone antibiotics[8] or highly potent oxazolidinone antibacterial agents.[9] 1,6-Diazaspiro[3.4]octanes possess (partial) agonist potencies for nicotinic acetylcholine receptors.[10] 3,9-Diazaspiro[5.5]undecanes,[11] 3-azaspiro[5.5]undecanes,[12] and 2,8-diazaspiro[4.5]decanes[13] were found to be spirocyclic nonpeptide glycoprotein IIb–IIIa antagonists and antiplatelet agents for inhibition of thrombus formation, while several diazaspiro sulfonamides were described as potent Akt inhibitors.[14] Series of potent muscarinic antagonists bear 3,9-diazaspiro[5.5]undecane, 1-oxa-4,9-diazaspiro[5.5]undecane and 2,9-diazaspiro[5.5]undecane moieties.[15] The 2,8-diazaspiro[4.5]decane moiety was used to replace piperidine in a series of soluble, selective neuropeptide Y–Y2 receptor antagonists,[16] while appropriately substituted 2,8-diazaspiro[4.5]decanones were found to be potent and selective T-type calcium channel antagonists.[17] 7-Azaspiro[3.5]nonane and 1-oxa-8-azaspiro[4.5]decane were reported as lead scaffolds for novel spirocyclic inhibitors of fatty acid amide hydrolase.[18] Several 3,9-diazaspiro[5.5]undecanes were disclosed as chemokine receptor antagonists,[19] while 1,7-diazaspiro[4.5]decanes were used as ligands for metal complexation with $ZnCl_2$.[20]

Despite the significant interest and development in this field, some areas of this challenging chemistry are still un- or underexplored. Up to now, 1,5-diazaspiro[2.3]hexanes **1** (Fig. 1) are unknown in the well documented area of spirocyclic diamines, with the exception of some spirocyclic aziridine-azetidinones.[21] In order



1

Fig. 1. General structure of 1,5-diazaspiro[2.3]hexanes **1**.

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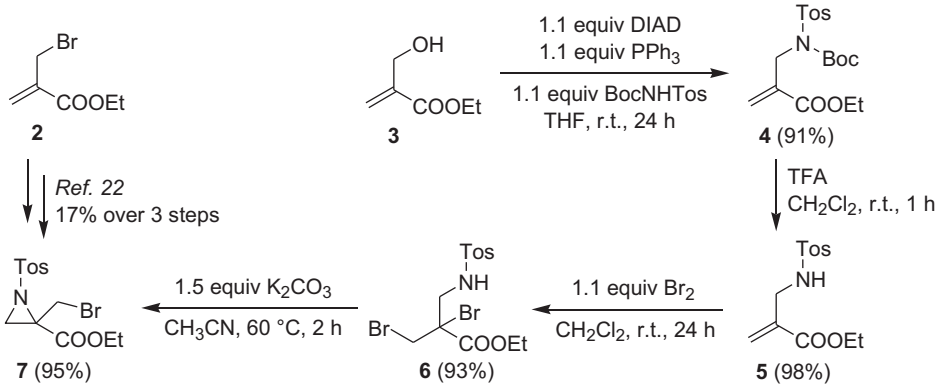
to fill this important gap, the synthesis of 1,5-diazaspiro[2.3]hexanes **1** was investigated starting from previously reported ethyl 2-(bromomethyl)-1-tosylaziridine-2-carboxylate **7**.[22]

2. Results and discussion

In view of the initially reported low yield of aziridine **7** (17% yield over three steps),[22] and the high price of the starting ethyl 2-(bromomethyl)acrylate **2**, a new synthetic pathway for this functionalized aziridine was developed (Scheme 1). As the original synthesis suffered from undesired diallylation in the amination step using *N*-tosylamide, it was envisioned that this side reaction could be avoided if instead of a primary amine, an appropriate secondary amine was used. For this reason, ethyl 2-(hydroxymethyl)acrylate **3** was treated with BocNHTos under Mitsunobu conditions, efficiently affording *N*,*N*-diprotected allylamine **4** in 91% yield. The carbamate function in allylamine **4** was cleaved with TFA in CH_2Cl_2 at room temperature for 1 h, yielding *N*-allyl-*N*-tosylamide **5** in 98% yield. The low yield of 57% of the subsequent bromination, as previously reported,[22] was improved by simply prolonging the reaction time to 24 h (instead of 4.5 h). Thus, after optimizing reaction conditions, and final cyclization of dibromo β-amino ester **6**, ethyl 2-(bromomethyl)-1-tosylaziridine-2-carboxylate **7** was synthesized from commercially available ethyl 2-(hydroxymethyl)acrylate **3** by a four-step procedure in 79% overall yield.

group,[23] a transformation, which was foreseen to provide synthetic access to the structurally challenging 1,5-diazaspiro[2.3]hexanes. All initial attempts to directly form aziridine-2-carboxaldehyde **10** by the use of DIBAL-H,[24] in diethyl ether (−78 °C—reflux) failed as each time no reaction occurred. When $LiAlH_4$ in diethyl ether at 0 °C was used, a mixture of bromo alcohol **8** and alcohol **9** was obtained, in 36% and 41% yield, respectively (Table 1, entry 1). In order to avoid the formation of 2-methylaziridine **9**, as side product resulting from dehalogenation of aziridine **8**, a smaller amount of $LiAlH_4$ was used and the reaction time was shortened to 15 min. However, even under these conditions, dehalogenation could not be avoided (Table 1, entry 2). Surprisingly, when the reaction was performed at −78 °C with 1 mol equiv of $LiAlH_4$ for 1 h, no formation of the corresponding alcohol was observed and instead β-bromo aldehyde **10** was directly obtained in 88% yield (Table 1, entry 3).

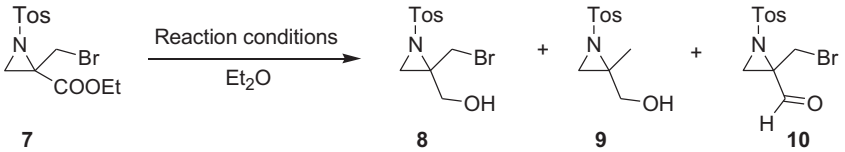
As shown by several groups, halogenated aldehydes[7b,25,26,27] and aldimines[28] can be used as attractive substrates for the synthesis of spiro derivatives. Inspired by these examples, several attempts were made to access the novel class of structurally challenging 1,5-diazaspiro[2.3]hexanes. Initially, it was expected that the reaction of β-bromo aldehyde **10** with an amine and reducing agent would give the corresponding 1,5-diazaspiro[2.3]hexane directly via the intermediate imine.[29] However, even though treatment of bromo aldehyde **10** with benzylamine in the presence of HOAc in methanol at 50 °C for 4 h gave intermediate



Scheme 1. Synthesis of ethyl 2-(bromomethyl)-1-tosylaziridine-2-carboxylate **7**.

It was envisioned that reduction of aziridine **7** with the appropriate reducing agent and, if necessary, subsequent oxidation of the corresponding alcohol **8**, would give β-bromo aldehyde **10**. Aziridine-2-carboxaldehydes have recently proven to be good substrates in reductive aminations for the introduction of an aminomethylene imine **11a**, the addition of 2 equiv of sodium cyanoborohydride did not result in a 4-*exo*-*tet*-cyclization toward the corresponding 1,5-diazaspiro[2.3]hexane. Instead, a ring transformation, similar to an aza-Payne rearrangement, during which activated 2-(hydroxymethyl)aziridines are transformed into the corresponding epoxy

Table 1
Synthesis of 2-bromomethyl-1-tosylaziridine-2-carboxaldehyde **10**



Entry	Reducing agent	Temperature	Reaction time	Result[a,b]
1	1 mol equiv $LiAlH_4$	0 °C	30 min	**8** (36%)+**9** (41%)
2	0.6 mol equiv $LiAlH_4$	0 °C	15 min	**7**/**8**/**9** 2:2:1
3	1 mol equiv $LiAlH_4$	−78 °C	1 h	**10** (88%)

[a] Yields in parentheses indicate isolated yields after flash chromatography.
[b] Ratio of reaction products determined by ^1H NMR analysis of the crude reaction mixture.