Efficient Synthesis of Cyclopropane Fused Heterocycles with Bromoethylsulfonium Salt


The 3-azabicyclo[3.1.0]hexane is a common motif in natural products.[1-6] Furthermore this rigid framework represents a privileged class of pharmacologically active compounds, often showing enhanced binding affinities with their targets (Figure 1).[7] These bicycles also represent conformationally restricted analogues of piperidines (e.g. trovafloxacin).[8] When substituted with a carboxylic acid moiety, they resemble conformationally restricted analogues of glutamate, gamma-amino butyric acid (GABA) or α/β-proline analogues (Figure 2).[9]

Numerous methods have been developed for the construction of azabicyclo[3.1.0]hexanes.[10] These include the Kulinkovich/de Meijere reaction,[11,12] cyclisation of tethered amines with metals (Pd,[13] Ru,[14] Rh,[15] Ag,[16]), cyclisation of tethered cyclopropanes,[17] and the Simmons-Smith/[18]/Corey-Chaykovsky/[19]/sulfur ylide-Au[cyclopropanations. These methods are usually only effective in the synthesis of one specific type of scaffold.

We were keen to develop a general strategy that could deliver 3-azabicyclo[3.1.0]hexanes with a range of functional groups in a range of positions. Our design plan for the synthesis of the scaffold was to effect a tandem process initiated by conjugate addition of an unsaturated amine 1 to vinyl sulfonium salt 2, generated in situ from the stable and crystalline salt 3 (Scheme 1). The intermediate sulfur ylide 4 would undergo intramolecular addition to the Michael acceptor to give a sulfonium enolate 5 which would ring close to the cyclopropane 6.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200(will be filled in by editorial staff).

Figure 1. Selected examples of important bicyclo[3.1.0]hexanes.

Figure 2. Conformationally restricted scaffolds discussed in this work.

This tandem process is related to the previously described reactions that bear aldehydes or imines in place of Michael acceptors, giving fused bicyclic epoxides and aziridines respectively.[21,22] However, the more complex reaction with...
Our studies began with the preparation of a diverse array of allylic amines. The allylic amines 1a-g were prepared in one step using either cross-metathesis[24] or Wittig chemistry. Similarly, 1h-j were synthesized in two steps from commercially available amino acid-derived methyl esters through a DIBAL-H reduction/Wittig reaction sequence. Allylic amines 1k, and 1l with the appropriate protecting groups required several steps[25] whilst 1m was available in one step from reaction of dihydropinnonamaldehyde with a vinlychromium nucleophile[26] (see SI for details).

The reaction of unsaturated amide 1a with the stable and crystalline salt 3 was initially tested. After optimisation of the process (see supporting information) a set of conditions were established (method A), that led to moderate-high yields of the [3.1.0] bicycles with complete diastereoselectivity (Table 1).[27]

For example, unsaturated amide 1a gave the cyclopropane 6a in 62% yield as a single diastereomer. The Michael acceptors tested bore a range of electron-withdrawing groups, including Me and Bu esters, ketones, amides and nitriles (6a-6e). Furthermore, in the case of the unsubstituted allylic amide, the N-Cbz carbamate 1f[24] could also be employed in place of the tosyl protecting group leading to the pyrroline 6f. The piperidine 6g was also accessible using the same process and again was formed with complete diastereoselectivity.

The methodology readily lent itself to the preparation of enantioenriched products, as illustrated with 6k, 6l, since the α-substituted allylic amines are easily obtained from chiral amino acids (serine in this case).

Expanding this methodology further, we were able to utilise easily accessible aza-Morita-Baylis-Hillman adducts 7a-7c[29] (one step from the acrylate), as starting materials for the cyclisation. These reactions now lead to the formation of β-proline-derived fused cyclopropanes 8a-8c (Table 2).[30]

Whilst unsaturated esters 7a and 7b worked well, giving the corresponding adducts 8a and 8b, respectively, in high yield and very high diastereoselectivity, unsaturated ketone (7c) behaved differently. In this case the major product was the epoxide annulation adduct 9. Evidently, after 1,4-addition of the amide 7c to the vinyl sulfinium salt 1, the ylide intermediate reacts in a more favoured 6-exo-trig mode with the ketone moiety, rather than the desired 6-endo-trig mode with the alkene. Nevertheless, the pyrroline 8c was formed with high diastereoselectivity as before. The methodology readily lends itself to asymmetric synthesis, since the aza-Morita-Baylis-Hillman adducts 7a, 7b are obtainable using asymmetric organocatalysis[31] This was illustrated in the use of (+)-7a (82% ee), which gave the [3.1.0] bicycle (+)-8a without measurable racemization, which was increased to >99% ee after recrystallization.

Michael acceptors (leading to products with additional stereogenic centers) has not been previously reported.[23] The potential for a very rapid increase in molecular complexity from simple starting materials was an additional attractive feature of the chemistry. In this paper, we report the successful realisation of this strategy and the formation of azabicyclo[3.1.0]hexanes with surprisingly high diastereoselectivity.

All yields are isolated yields and dr is determined by 1H NMR of the crude: [a] Yield of TBS deprotected product including an in situ deprotection with TBAP (5 equiv) added after 15 h; [b] reaction at 0 °C, if run at rt yield is 75% and d.r. is 7:1; [c] minor traces of other diastereomer visible in 1H NMR.

Table 1: Scope of the transformation.
Table 2: Reactivity of (aza)-Morita-Baylis-Hillman adducts.

![Chemical structure](image)

All yields are isolated yields and dr is determined by 1H NMR of the crude; [a] The ee was determined by chiral SFC, see SI for full details.

The relative stereochemistry of cyclopropanes 6g, 6i, and 8a were determined by X-ray analysis and related compounds were assigned by analogy (see Supporting information for details). It is believed that the steps prior to ring closure are reversible and that the selectivity is determined in the non-reversible ring closure step which forms the cyclopropane. The origin of selectivity of the two classes of substrates 1 and 7 can be rationalised by considering the non-bonded steric interactions in the TSs where the less hindered X1 and Y1 are favoured over X2 and Y2, which subsequently leads to the preferred formation of trans (6h-6m) and cis (8a-8c) isomers (Scheme 2).

![Scheme 2. Model for diastereoselectivity in the formation of 6 and 8](image)

The cyclopropyl-annulation reaction was further extended to include the medicinally important CF3 group. Thus, reaction of 1a with the CF3-substituted vinyl sulfonium salt 10 gave the CF3-substituted [3.1.0] pyrrolidine 11, again with essentially complete diastereoselectivity (Scheme 3).

![Scheme 3. Formation of 11 with β-CF3 vinylsulfonium salt 10](image)

Finally, pyrrolidine 6f was converted into 6-amino-3-azabicyclo[3.1.0]hexan-3-ium chloride 16, an intermediate used in the synthesis of trovafloxacin, a potent antibiotic. Thus, saponification of the ester 6f, followed by the Schmidt reaction with diphenyl phosphoryl azide (DPPA) gave pyrrolidine 15. Finally, hydrogenolysis gave amino pyrrolidine 16 in just a few synthetic steps (Scheme 6).

![Scheme 6. Formal synthesis of the trovafloxacin precursor 16](image)

In conclusion we have developed a novel, efficient and versatile route for the formation of cyclopropane-fused heterocycles from easily available starting materials. In comparison to previous methods, this protocol enables the synthesis of a more diverse range of substituted and functionalized [3.1.0] scaffolds with very high diastereoselectivity. There is considerable interest in exploring this class of bioactive compounds, which should now be enabled by the methodology described herein.

**Experimental Section**

A stirred solution of amine or alcohol 1 (1.0 equiv.) and diphenyl bromoethyl sulfonium salt 3 (1.25 equiv.) in anhydrous solvent (0.1 M) at room temperature under inert atmosphere was treated with base (3.5 equiv.) and stirred for the indicated time (until complete consumption of starting material was detected by
HPLC or TLC). The reaction mixture was then quenched with 10% aqueous citric acid solution (15 mL/mmol) and the aqueous was extracted with CH2Cl2 (3 × 30 mL/mmol). The combined organic layers were washed with brine (30 mL/mmol), dried (MgSO4) and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography, eluting with either EtOAc/Incomplete-pentane or EtO/Incomplete-pentane to give the desired product.

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Keywords: heterocycles • cyclopropanes • sulfur ylides • amino acids • Baylis-Hillman

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*S. P. Fritz, J. V. Matlock, E. M. McGarrigle, * V. K. Aggarwal*

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**Efficient Synthesis of Cyclopropane Fused Heterocycles with Bromoethylsulfonium Salt**

**Lord of the Rings**: [3.1.0] Bicyclic ring systems were synthesized using bromoethylsulfonium triflate and easily available, amino acid/aza-Morita-Baylis-Hillman derived allylic amines. The simple transformation displays a very high degree of diastereoselectivity and enables access to a diverse range of densely substituted pyrrolidine-based bicycles, a class of biologically important scaffolds.

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