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Aminative rearrangement of 2-alkoxy-3,4-dihydro-2*H*-pyrans: a novel stereocontrolled route to substituted pyrrolidines†

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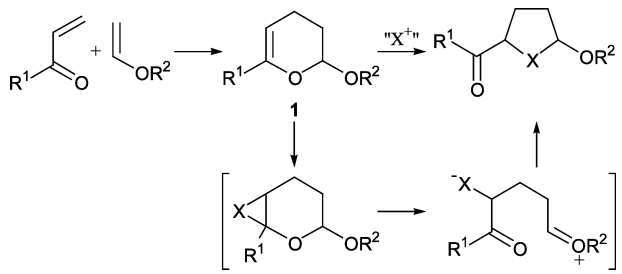
Aziridination of 2-alkoxy-3,4-dihydro-2*H*-pyrans leads to rearrangement and stereocontrolled formation of 5-alkoxypyrrolidines which may be reduced to pyrrolidines or allylated stereoselectively.

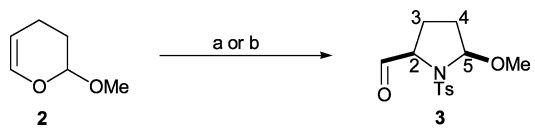
The widespread occurrence of the substituted pyrrolidine motif amongst biologically significant natural products and pharmaceuticals has stimulated great interest in methods for its synthesis.[1] As part of a total synthesis programme, we became aware that epoxidation of 2-alkoxy-3,4-dihydro-2*H*-pyrans **1** leads to ring contraction, resulting in formation of a tetrahydrofuran product[2] (Scheme 1, X = O). We reasoned that performing aziridination rather than epoxidation might in an analogous fashion result in the valuable pyrrolidine ring system (X = N). Because the substrates **1** may be readily prepared by a hetero-Diels–Alder reaction between an enol ether and an α,β-unsaturated carbonyl compound,[3] the overall synthesis would represent a novel and versatile strategy towards such a target. Here we report the successful realisation of this concept, including preliminary results on scope and stereocontrol in the reaction.

Our initial experiments employed the commercially available dihydropyran **2**. Pleasingly, we were able to establish that this substrate did indeed undergo the desired rearrangement under two different sets of aziridination conditions: the Cu-catalyzed process using PhINTs as the nitrogen source,[4] and Sudalai's modification of the "redox-aziridination" reaction of Sharpless employing Chloramine-T (TsNClNa) in conjunction with *N*-bromosuccinimide (NBS)[5] (Scheme 2). The alkoxypyrrolidine **3** was obtained as predominantly the 2,5-*cis*-isomer, presumably the thermodynamic product following epimerization on silica.

Having established the feasibility of the process, we set about exploring its scope and limitations. We first explored substrate **4** since we believed this would address the important issue of relative stereochemistry at C2 and C3 in the product pyrrolidine. We anticipated that the distinctly different mechanistic pathways for the two aziridination procedures would have important stereochemical consequences.[6] The Cu–nitrene reagent system would be expected to effect aziridination of **4** on the less hindered face, *trans*- to the isopropyl substituent, leading to the formation of the *cis*-disubstituted pyrrolidine. On the other hand, the redox-aziridination would be expected to commence with bromination on the less hindered face followed by nucleophilic attack on the bromonium intermediate by the TsNClNa, with inversion of configuration leading to eventual formation of the *trans*-substituted pyrrolidine. Pleasingly, this was found to be the case. As shown in Scheme 3, aziridination of **4** with the TsNClNa/NBS system followed by reduction with $Et_3SiH/BF_3{\cdot}Et_2O$ to remove the complication of the aminal stereocentre afforded the *trans*-pyrrolidine **5** with > 9 : 1 selectivity. The corresponding *cis*-isomer **6** was formed with similar selectivity when the Cu(I)/PhINTs reagents were used, and its configuration was established by X-ray crystallography.‡ The ability to obtain complementary stereochemical outcomes is a powerful feature of this approach to pyrrolidine synthesis.



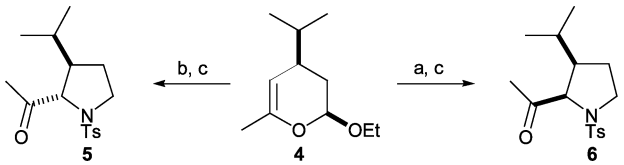
Scheme 1



Scheme 2 *Reagents and conditions*: (a) $Cu(MeCN)_4PF_6$ (10 mol%), PhI=NTs (1.05 equiv.), MeCN, 0 °C, 0.5 h, 48%; (b) NBS (10 mol%), TsNClNa (1.1 equiv.), MeCN, rt, 1 h, 79%.

A further five substrates were subjected to the same conditions, with results shown in Table 1. An unproductive background reaction exists in Br^+-catalysed reactions for substrates where $R^1 = CH_3$, and so in these cases 3 equiv. of Chloramine-T was used. In all cases where there was the potential for a 2,3-*cis*/*trans* relationship, the copper catalyst afforded preferentially the *cis* product and the Br^+ catalyst the *trans* (albeit with lower selectivity). Mixtures of anomers at the aminal centre were sometimes observed, and in some examples hydrolysis occurred; in such cases direct reduction of the crude product was preferred. These issues are fully detailed in the Supplementary Information. The examples in Table 1 illustrate that the method will tolerate the presence of a benzyl ether (entry 1) and that the dihydropyrans may be aziridinated in the presence of an isolated alkene (entry 2). Formation of a quaternary centre at C2 (entry 3) or incorporation of an existing one at C3 (entry 4) is possible. Although the simplest substrate **2** (comparable to **7**, $R^1 = R^2 = R^3 = R^4 = H$) undergoes successful transformation, substrates **7** in which $R^1 = R^2 = H$ but which have a substituent at C4 have thus far proved incompatible (entry 5).

An attractive feature of this pyrrolidine synthesis is that the initial products contain two functional groups (carbonyl and aminal) with rich possibilities for further manipulation. We have briefly explored alternative reactions of the aminal unit rather than



Scheme 3 *Reagents and conditions*: (a) $Cu(MeCN)_4PF_6$ (10 mol%), PhI=NTs (1.1 equiv.), MeCN, 0 °C, 0.5 h, 52%; (b) NBS (20 mol%), TsNClNa (3 equiv.), MeCN, rt, 1 h, 64%; (c) Et_3SiH (3 equiv.), $BF_3{\cdot}Et_2O$ (2 equiv.), −78 to 0 °C, 2 h, > 90%.

† Electronic supplementary information (ESI) available: experimental details and characterisation data for all new compounds. See http://www.rsc.org/suppdata/cc/b3/b316554j/

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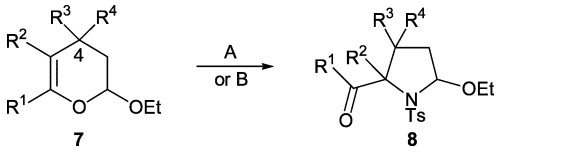
Table 1 Amination of 2-alkoxy-3,4-dihydro-2*H*-pyrans



7 8

Entry	R^1	R^2	R^3	R^4	Method[a]	Yield[b] (%)	Ratio[e]
1	Me	H	CH_2OBn	H	A	53[c]	3.8 : 1
					B	51[c]	1 : 2.2
2	Me	H	*Z*-$(CH_2)_4CHCHEt$	H	A	46[d]	3 : 1
					B	44[d]	1 : 1.6
3	H	nBu	H	H	A	42	—
					B	43	—
4	Me	H	Me	Me	A	47[d]	—
					B	72	—
5	H	H	CH_2OBn	H	A	0	—
					B	0	—

[a] Method A: $Cu(MeCN)_4PF_6$ (10 mol%), PhI=NTs (1–1.25 equiv.), MeCN, 0 °C, 0.5–1 h; Method B: NBS (20 mol%), TsNClNa (1.2–3 equiv.), MeCN, rt, 1 h.§ [b] Isolated yield following chromatography. [c] Combined yield of separated isomers. [d] Isolated yield (of inseparable 2,3-*cis*/*trans* mixture for entry 2) following reduction of crude product with $BF_3{\cdot}Et_2O/Et_3SiH$. [e] 2,3-*cis*/*trans* ratio.

the simple reduction hitherto employed. While stereoselective intermolecular attack on iminium ions generated from *N*-acylpyrrolidines is well precedented,[7] there are far fewer examples with *N*-sulfonylpyrrolidines.[8] We have demonstrated highly diastereoselective allylation of selected products (Fig. 1). In the case of the 2,3-*trans* substrates, the 2,5-*cis* products **9** were generated, with no 2,5-*trans* isomers visible by ^1H NMR. This was also the case for the C3-dimethyl product **10**. For the 2,3-*cis* substrates, analogous reaction provided the 2,5-*trans* products **11**. The stereochemistry of the allylated products was determined by NOESY interactions (see Supplementary Information for details).

These allylations appear to fit with a model proposed by Woerpel *et al.*[9] for the allylation of 5-membered cyclic oxonium ions, based on 'inside attack' on the oxonium in an envelope conformation to form a staggered product. However, this model does not take account of the developing pyramidal configuration at nitrogen and so is incomplete in our case.

In conclusion, we have developed a novel, stereoselective synthesis of functionalised pyrrolidines with wide potential for further modifications. Depending on the choice of aziridination conditions, both the 2,3-*cis* and -*trans* isomers can be prepared selectively. The ease of substrate synthesis means that a variety of pyrrolidine 'building blocks' could be rapidly prepared, including proline derivatives for incorporation into non-natural peptides. From the point of view of enantioselective synthesis, it is noteworthy that Jacobsen *et al.* have recently demonstrated[10] the enantioselective reaction of α,β-unsaturated aldehydes with ethyl vinyl ether at room temperature using a Cr(III) catalyst to produce highly enantioenriched 2-alkoxydihydropyrans. Ongoing work is aimed at improving the scope of the reaction by using alternative aziridination reagent systems, including investigation of alternative nitrogen protecting groups.[11] Possible applications to target synthesis are also evident.

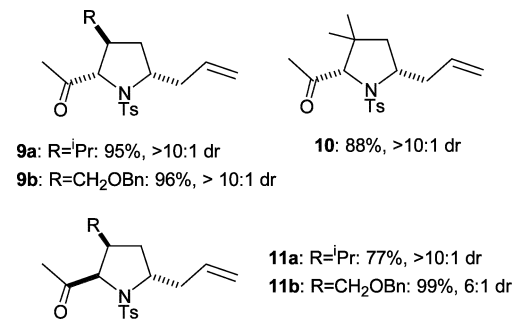


Fig. 1 Allylation of *N*-tosyliminium ions with allyltrimethylsilane/$BF_3{\cdot}Et_2O$.

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Notes and references

‡ CCDC 227678. See http://www.rsc.org/suppdata/cc/b3/b316554j/ for crystallographic data in .cif or other electronic format.

§ Copper-catalysed amination procedure (Method A): To a stirred mixture of PhI=NTs (1.0–1.25 equiv.) and 4 Å molecular sieves (0.3 g $mmol^{-1}$) in MeCN (3 ml $mmol^{-1}$) at 0 °C was added $Cu(MeCN)_4PF_6$ (0.1 equiv.), followed by a solution of the substrate in MeCN (2 ml $mmol^{-1}$). Following consumption of PhI=NTs (0.5–1 h), the green mixture was passed through a 2.5 cm plug of Et_3N-washed silica, flushing with EtOAc (100 ml). The solution was concentrated and the product isolated by chromatography on Et_3N-washed silica or the crude mixture reduced directly with $BF_3{\cdot}Et_2O/Et_3SiH$ in CH_2Cl_2.

Typical NBS-catalysed amination procedure (Method B): To a stirred solution of the dihydropyran in MeCN (20 ml $mmol^{-1}$) at room temperature was added NBS (0.2 equiv.) and Chloramine-T (dried to constant mass at 80 °C under reduced pressure, 1.2–3 equiv.). After 1 h the heterogeneous reaction mixture was treated as in Method A above.

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