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Properties and Reactions of Ring-Deactivated Deuterated Hydroxymethylpyrroles

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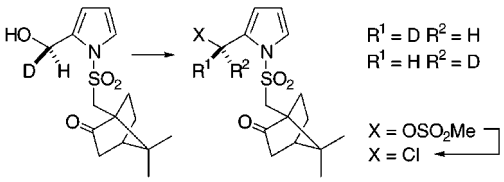
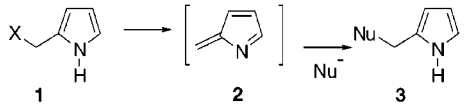
ABSTRACT



Chlorination and mesylation at the hydroxymethyl position of deuterium-labeled *N*-substituted 2-(hydroxymethyl)pyrroles has been shown to occur with some involvement of a highly reactive azafulvenium species. An electron-withdrawing camphorsulfonyl substituent on nitrogen provides a chiral handle for direct analysis of the stereochemical outcome of the reactions by ^{1}H NMR.

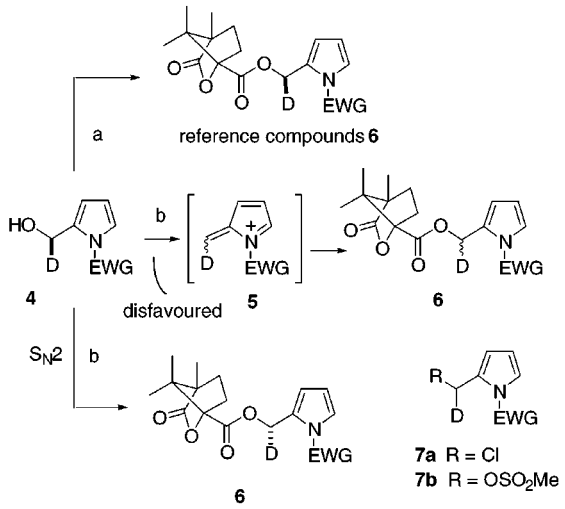
Pyrroles of type **1** are thought to react with a nucleophile (Nu^- in Scheme 1) to give **3** via the intermediacy of the highly reactive azafulvene **2**.[1,2] This chemistry has been used by synthetic chemists to prepare oligomeric pyrrole-based structures (Nu is another pyrrole)[1−3] and also by Nature in the biosynthesis of hydroxymethylbilane and uro′gen III—key intermediates to tetrapyrrolic macrocycles such as porphyrins and corrins.[4] Despite extensive studies there is little direct evidence for the participation of azafulvenes in these synthetic and biosynthetic reactions.[5]

Scheme 1



Our recent work in this area has centered on gaining an insight into the role of azafulvenes in these and related processes. We recently published[1] a method, based on a Mitsunobu[6] displacement at the hydroxymethyl position of deuterium-labeled pyrroles **4** (Scheme 2, conditions b), to

Scheme 2



a. DMAP, diisopropylethylamine, (1S)-(-)-camphanic chloride;
b. Ph_3P, DEAD, (1S)-(-)-camphanic acid (Mitsunobu conditions)

(1) Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Am. Chem. Soc.* **1998**, *120*, 1741. Thompson, A.; Dolphin, D. *Chemtracts-Org. Chem.* **1999**, *12*, 534.

(2) *The Chemistry of Pyrroles*; Jones, A. R., Bean, G. P., Eds.; Academic Press: London, 1977.

(3) Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Org. Chem.* **1998**, *63*, 8163.

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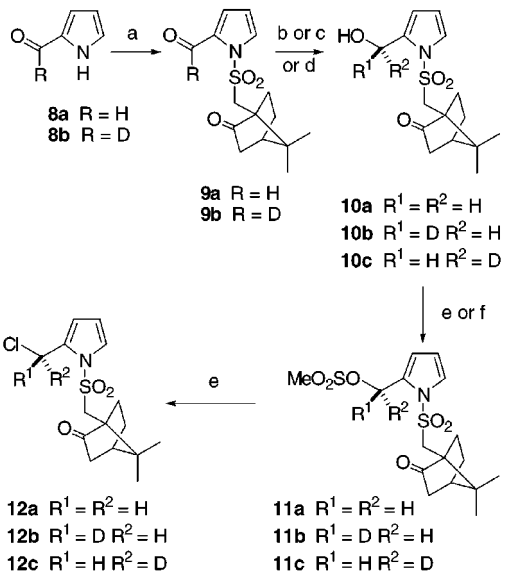
determine the ability of an electron-withdrawing group (EWG) on nitrogen to deactivate the heterocycle and hence suppress the formation of azafulvenium species **5** and the associated deuterium scrambling in product **6**. The ability of a range of substituents to deactivate the pyrrole ring was established by this method. An *N*-triflyl group proved to be the most efficient of those studied, resulting in almost complete inversion of configuration in product **6** (S_N2 mechanism).

In this paper, we address the issue as to whether it is possible to convert *N*-substituted hydroxymethylpyrroles into chloromethyl- and mesylmethylpyrroles (structures **7**, Scheme 2) without the involvement of azafulvenium species **5**. In other words, at what point does the pyrrole's ability to lose its leaving group (R in compounds **7**) negate the ability of the EWG to deactivate the ring such that the azafulvenium species **5** participates in the reaction? The chloromethyl- and mesylmethylpyrroles are also particularly useful synthetic intermediates—we have recently shown that ring-deactivated chloromethylpyrroles of type **7a**, derived from the corresponding hydroxymethylpyrroles **4**, can be coupled to an *N*-magnesio pyrrole salt to give dipyrrylmethanes.[3]

Our earlier work[1] established that deuterated hydroxymethylpyrroles **4** can be prepared, with a high degree of stereochemical purity, by reduction of the corresponding labeled α-formylpyrrole with Alpine borane. Their configurational purity was then determined by the preparation and ^{1}H NMR analysis of the corresponding camphanates **6** (Scheme 2, conditions a). The key to the current study was to convert the labeled hydroxymethylpyrroles **4** into the corresponding chloromethyl- and *O*-mesylmethylpyrroles, **7a** and **7b**, and then determine the resulting configurational purity at the labeled exocyclic methylene position. To achieve this, we incorporated a chiral handle into the EWG to allow direct analysis of the stereochemical outcome of the reaction by ^{1}H NMR spectroscopy. A (1*S*,4*R*)-(+)-10-camphorsulfonyl group was chosen since it was expected to have a similar deactivating ability to that of a methanesulfonyl group, which we had already studied[1] in some detail.

The key deuterium-labeled *N*-camphorsulfonyl hydroxymethylpyrroles **10b** and **10c** (specific examples of **4**) were prepared by initially treating the labeled formylpyrrole **8b** with sodium hydride and reacting the resultant pyrrolyl anion with (1*S*,4*R*)-(+)-10-camphorsulfonyl chloride to give **9b** in 99% yield. Reduction of the deuterated formyl group with either (*S*)- or (*R*)-Alpine borane then gave mixtures of **10b** and **10c** in 70% and 76% yields, respectively (Scheme 3). The ratios of **10b** and **10c** obtained from these (*S*)- and (*R*)-Alpine borane reductions were determined to be 19:1 and 1:19, respectively, by integration of the corresponding pyrrole CHD singlet resonances at δ 4.72 and 4.87. The unlabeled analogue **10a**, which was used as a reference, was similarly

Scheme 3



a. NaH, THF then (1*S*,4*R*)-(+)-10-camphorsulfonyl chloride (**9a**, 95%), (**9b**, 99%); b. $Zn(BH_4)_2$, Et_2O, 0 °C (**10a**, 88%); c. *S*-Alpine borane®, THF, rt (**10b:10c**, 19:1, 70%); d. *R*-Alpine borane®, THF, rt (**10b:10c**, 1:19, 76%); e. $MeSO_2Cl$, iPr_2NEt $CDCl_3$, 0 °C; f. $(MeSO_2)_2O$, iPr_2NEt, $CDCl_3$, -20 °C.

prepared from **9a** using zinc borohydride as the reducing agent (Scheme 3).

Next, we turned our attention to studying the stereochemical course of chloromethylpyrrole formation. Separate samples of **10a** and the above prepared mixtures of **10b** and **10c** (19:1 and 1:19), in $CDCl_3$ at 0 °C, were treated with *N*,*N*-diisopropylethylamine, followed by methanesulfonyl chloride (Scheme 3). The formation of the corresponding chloromethylpyrroles **12a**, **12b**, and **12c** was then monitored by ^{1}H NMR spectroscopy.[7] It was anticipated that the greater the participation of azafulvenium species **5** in these reactions, the greater the deuterium scrambling in the product. The *O*-mesylmethylpyrroles **11** were not detected in these reactions but were presumed to be intermediates. Finally, workup of the reactions with dilute aqueous hydrochloric acid gave the chloromethylpyrroles **12a**, **12b**, and **12c**.

The key point to note from the results of these experiments is that, compared to the configurational purity of the starting deuterated hydroxymethylpyrroles **10b** and **10c** (19:1), only a slight excess of a chloromethylpyrrole isomer resulting from net inversion of configuration[7] was observed by ^{1}H NMR (**12c**:**12b** = ~3:2). This isomeric ratio was, however, in agreement with a ~3:2 ratio previously obtained from the Mitsunobu reaction of deuterium-labeled *N*-mesylhydroxymethylpyrroles with (1*S*,4*R*)-(−)-camphanic acid under conditions known to favor an S_N2 mechanism (Scheme 2,

(4) Battersby, A. R., Leeper, F. J. *Chem. Rev.* **1990**, *90*, 1261. Scott, A. I. In *Advances in Detailed Reaction Mechanisms: Mechanisms of Biological Importance*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1992; pp 189−212.

(5) Barcock, R. A.; Moorcroft, N. A.; Storr, R. C. *Tetrahedron Lett.* **1993**, *34*, 1187.

(6) Mitsunobu, O. *Synthesis* **1981**, 1.

(7) The ratio of (*S*)-**12c** to (*R*)-**12b** was determined by integration of the pyrrole CHD singlets at 4.86 and 5.05 ppm, respectively. It is assumed that the major product from the chlorination reaction is the result of an inversion of configuration at the deuterated center.

EWG = mesyl). Both alkylsulfonyl groups would appear to have a similar ability to deactivate the pyrrole and hence suppress azafulvenium formation. A 3:2 ratio in the current study is, therefore, the maximum value that might be expected from these chlorination experiments. A second point to note is that a ~1:1 mixture of the chloromethylpyrroles **12b** and **12c** was obtained upon workup of the reaction mixtures. This scrambling is presumably the result of subsequent azafulvenium formation. The analysis was repeated using the 1:19 mixture of **10b** and **10c** to give the expected and complementary results.

Having established that chloromethylpyrrole formation proceeded with a degree of scrambling of the deuterium-label at the exocyclic methylene position, we turned our attention to investigating the stereochemical course of *O*-mesylate formation (a proposed reaction intermediate). Consequently, a mixture of labeled *N*-camphorsulfonylpyrroles **10b** and **10c** (19:1 by ^{1}H NMR) and methanesulfonic anhydride and *N*,*N*-diisopropylethylamine, in $CDCl_3$, at −20 °C, was monitored by low-temperature ^{1}H NMR spectroscopy (Scheme 3, reaction conditions f). The *O*-mesylates **11b** and **11c** were observed to form in a ratio of ~4:1 (t = 0 min) with the major isomer assigned as the product of a retention of configuration at the deuterated center.[8] However, a ^{1}H NMR spectrum of the reaction mixture after 30 min, at this temperature, showed a ~1:1 mixture of the two isomers, indicating total scrambling of the deuterium label. This loss of stereochemical integrity at the deuterated methylene center was again attributed to azafulvenium involvement in the reaction sequence. An equivalent experiment using a 1:19 mixture of **10b** and **10c** gave the expected and complementary results. The unlabeled *O*-mesylate **11a** was also prepared from **10a** to give a reference sample.

In conclusion, it is possible to prepare enriched mixtures of the (*R*)- and (*S*)-deuterium-labeled chloromethyl- and mesylmethylpyrroles at low temperatures (0 and −20 °C, respectively). These samples would appear to form an azafulvenium species on warming, or on being left at low temperatures for extended periods. This work provides further insight[1,9] into the role of an azafulvenium species in the generation and reactions of pyrroles of type **1**. The results suggest that there is a delicate balance between the ability of an EWG to suppress azafulvenium formation and the ability of the leaving group to promote its formation. Consequently, the chemistry that these derivatives undergo can be fine-tuned with the correct choice of an EWG on nitrogen. The methods presented in this Letter should be applicable to studying the properties and substitution reactions involving a range of EWG's, leaving groups, and heterocycles.

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Supporting Information Available: General experimental procedure for the reactions shown in Scheme 3. This material is available free of charge via Internet at http://pubs.acs.org.

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(8) The ratio of (*S*)-**11c** to (*R*)-**11b** was determined by integration of the pyrrole-CHD singlets at 5.39 and 5.45 ppm, respectively. It is assumed that the initial *O*-mesylation reaction occurs with retention of configuration.

(9) Abell, A. D.; Litten, J. C.; Nabbs, B. K. *Chem. Commun.* **1998**, 919.