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THE ACTION OF DIETHYLAMINOSULPHUR TRIFLUORIDE (DAST) ON TRANS-4-AMIDO-3-CHROMANOLS: PREPARATION OF CIS-AMIDOALCOHOLS VIA OXAZOLINES

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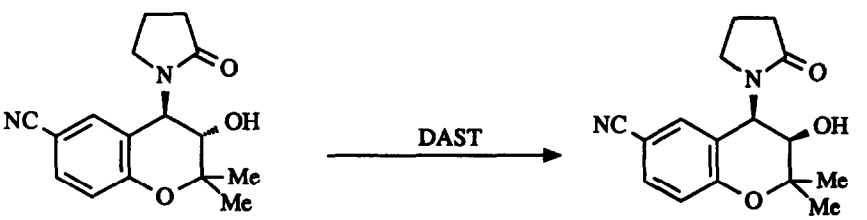
Abstract. Treatment of a variety of trans-4-amido-3-chromanols (3) with DAST gives oxazolines (4) which can be hydrolysed to give the corresponding cis-amido-alcohols (5). Similar treatment of the trans-4-ureido-3-chromanol (8) gave the unexpected 4-fluoro-3-ureidochromanol (9) as the major product.

Following a recent report[1] that treatment of the novel antihypertensive 4-amido-3-chromanol, cromakalim[2] (1), with diethylaminosulphur trifluoride (DAST)[3] resulted in unexpected epimerisation at the 3-hydroxyl centre (Scheme 1), we present the extension of this reaction to the trans - cis isomerisation of some related 4-amido-3-chromanols, and the isolation of oxazoline intermediates.

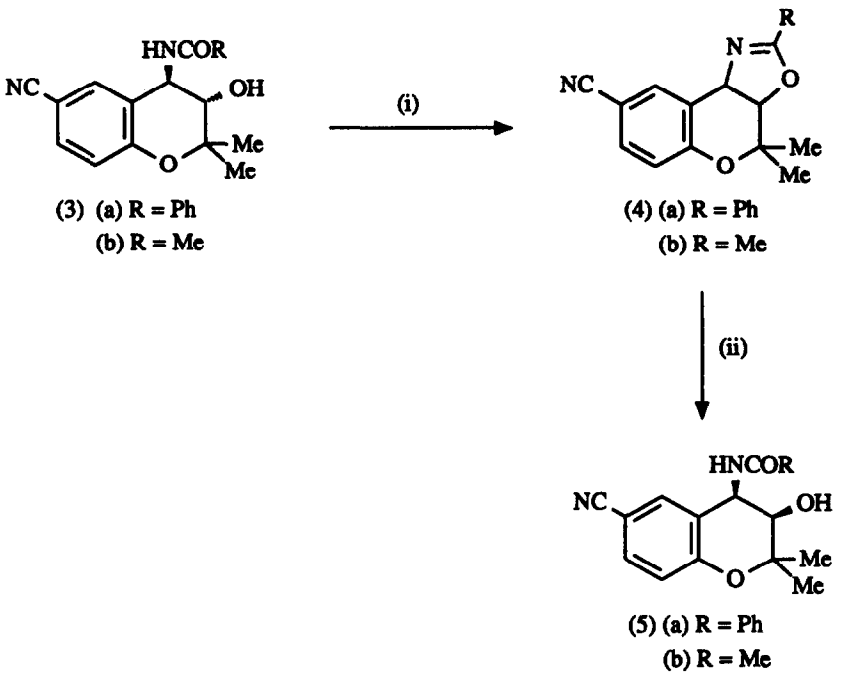
Scheme 1.



cromakalim (1) (2)

In a typical experiment, the trans-amido-alcohols (3) were treated with DAST as in Scheme 2. Removal of solvent, followed by chromatography (silica gel, ethyl acetate as eluant) gave the oxazolines (4). Hydrolysis of (4) with aqueous acid gave the cis-amidochromanols (5). The cis configuration of (5) was established by a coupling constant of 4 Hz between the protons at C-3 and C-4.

Scheme 2.



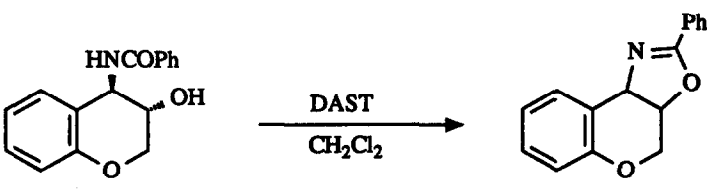
(3) (a) R = Ph
(b) R = Me

(4) (a) R = Ph
(b) R = Me

(5) (a) R = Ph
(b) R = Me

Reagents (i) 1.1 equiv DAST, CH_2Cl_2, 20 °C, 16h.
(ii) 0.1 N H_2SO_4, aqueous dioxan, 20 °C, 16h.

We considered that formation of the oxazolines (4) could be due to steric hindrance at C-3 caused by the presence of a gem-dimethyl group at C-2 in these compounds preventing the expected replacement of the 3-hydroxyl group by fluorine. However, treatment of (6) with DAST under identical conditions gave the oxazoline (7), thus indicating the generality of the reaction for the trans - cis isomerisation of amido-alcohols.

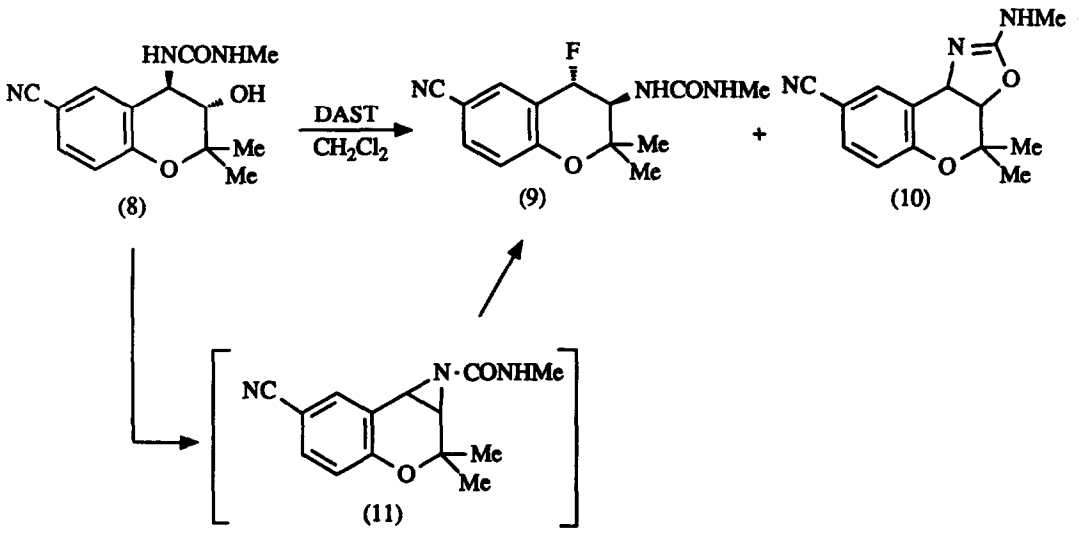


(6) (7)

Interestingly, when the 4-ureidochromanol (8) was treated with DAST under the above conditions, the

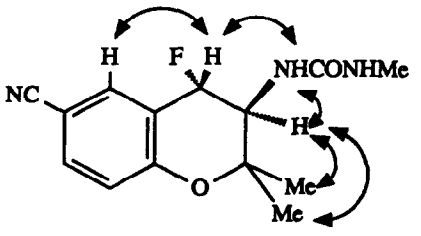
expected methylamino oxazoline (10) was obtained only in low yield. The major product was the rearranged 4-fluoro-3-ureidochroman (9), which is presumably formed *via* the attack of fluoride ion on the intermediate aziridine (11) (Scheme 3).

Scheme 3.



The positions of the fluoro and ureido substituents in (9) were deduced from nuclear Overhauser effects in the proton NMR spectrum, as shown in Figure 1. The coupling constant observed between the C-3 and C-4 protons, 5.2 Hz, is much smaller than expected for the trans configuration with the substituents pseudoequatorial, but formation of the corresponding cis compound seems unlikely on mechanistic grounds. We have therefore assigned a trans-pseudodiaxial configuration to (9), consistent with the approximately equal n.O.e.'s observed between the C-3 proton and both gem-dimethyl groups.

Figure 1. Principal n.O.e.'s for compound (9).



The isolation of oxazolines from the reaction of DAST with trans-4-amido-3-chromanols strongly

supports the mechanism proposed for the epimerisation of the C-3 hydroxyl of cromakalim[1]. Furthermore, the formation of oxazoline (7) from (6) demonstrates that this reaction is not dependent on steric hindrance at C-3 and that treatment with DAST could provide an efficient and general procedure for the conversion of trans-amido-alcohols into their corresponding cis-analogues[4].

References and Notes

1. C.S.V. Houge-Frydrych and I.L. Pinto, Tet. Letts., **30**, 3349, 1989.

2. V.A. Ashwood, R.E. Buckingham, F. Cassidy, J.M. Evans, E.A. Faruk, T.C. Hamilton, D.J. Nash, G. Stemp, K. Willcocks, J. Med. Chem., **29**, 2194, 1986.

3. (a) S.S. Yang and T.R. Beattie, J. Org. Chem., **46**, 1718, 1981.

(b) J. Mann, Chem. Soc. Rev., **16**, 381, 1987.

4. Reactions with DAST were performed on scales of between 1 and 10 mmoles of amidochromanols (3), (6) and (8).

Yields of compounds, (4a) R=Ph, 68%, m.pt. 127-30 °C (EtOAc/pentane); (4b) R=Me, 58%, gum; (5a) R=Ph, 62%, m.pt. 158-9 °C (EtOAc); (5b) R=Me, 68%, m.pt. 192-3 °C (EtOAc); (7) 88%, m.pt. 137-9 °C (EtOAc/pentane); (9) 21%, m.pt. 220-1 °C (EtOAc/60-80 °C petrol); (10) 11%, m.pt. 172-4 °C (EtOAc/60-80 °C petrol), were not optimised and are for recrystallised material with the exception of (4b) which was converted into (5b) on attempted recrystallisation. All new compounds gave satisfactory analytical and/or mass spectral data.

Compound (4a) : ^{1}H NMR ($CDCl_3$); δ 1.39 (s, 3H), 1.58 (s, 3H), 4.78 (d, J=9 Hz, 1H), 5.31 (d, J=9 Hz, 1H), 6.90 (d, J=8 Hz, 1H), 7.36 - 7.53 (m, 4H), 7.83 (d, J=2 Hz, 1H), 7.94 (m, 2H).

Compound (5a) : ^{1}H NMR ($CDCl_3$); δ 1.38 (s, 3H), 1.53 (s, 3H), 2.46 (m, 1H, collapsing to d, J=4 Hz on D_2O shake), 5.60 (q, J=8, 4 Hz, 1H), 6.92 (d, J=9 Hz, 1H), 7.05 (d, J=8 Hz, 1H), 7.33 - 8.05 (m, 7H).

Compound (9) : ^{1}H NMR (DMSO-d_6); δ 1.32 (s, 3H), 1.36 (d, J=1 Hz, 3H), 2.58 (d, J=5 Hz, 3H), 4.16 (ddd, J=13, 9, 5 Hz, 1H), 5.39 (dd, J=51, 5 Hz, 1H), 5.78 (q, J=5 Hz, 1H), 6.30 (d, J=9 Hz, 1H), 7.07 (d, J=9 Hz, 1H), 7.78 (d, J=9 Hz, 1H), 7.99 (s, 1H).

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