Tetrahedron Letters,Vol.30,No.25,pp 3349-3350,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

AN UNUSUAL HYDROXYL INVERSION MEDIATED BY DAST

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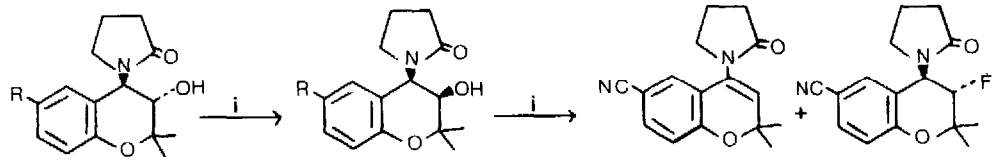
Summary Trans-3-hydroxy-4-(2-oxopyrrolidin-1-yl) benzopyrans have been shown to undergo inversion to cis-3-hydroxy-4-(2-oxopyrrolidin-1-yl) benzopyrans in moderate yield on treatment with diethylaminosulphur trifluoride (DAST).

Cromakalim (1) is a potent smooth muscle relaxant which exerts its activity by opening cellular potassium channels with subsequent hyperpolarisation of the cellular membrane. As a result of this action cromakalim has been shown to have potential in the treatment of hypertension [1] and asthma [2].

During the course of studies aimed at introducing a fluorine atom in place of the 3-hydroxyl group in (1) the reaction of (1) with diethylaminosulphur trifluoride (DAST) [3] was investigated. Rather than the expected 3-fluoride the sole benzopyran product isolated was the C-3 epimeric cis-amido-alcohol (3)* in 28% yield (Scheme 1). A similar reaction of the cis-amido-alcohol (3) with DAST afforded the chromene (5) in 44% yield together with trace amounts of the trans-3-fluoride (6), 3% .

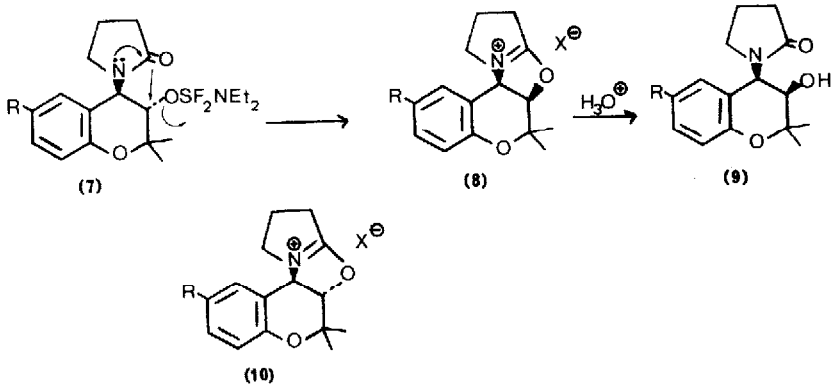


i) DAST, 1.1 equiv, CH_2Cl_2, R.T., 16 hr

Scheme 1

The divergent reaction profiles of (1) and (3) suggest that when the trans-amido-alcohol (1) is reacted with DAST the cis-amido-alcohol (3) is not present in the reaction mixture and is only formed during isolation. In similar fashion, the trans-amido-alcohol (2) was also observed to undergo the unusual epimerisation reaction, the formyl group being unaffected by the conditions 3

Epimerisation of the 3-hydroxyl is all the more surprising when one considers that it is neopentylic. It seems likely that the inversion proceeds via an intermediate (7) (Scheme 2) produced by an intramolecular displacement of the C-3 leaving group. Subsequent hydrolysis of the intermediate (8) would yield the cis-amido-alcohol (9). Presumably the cis-amido-alcohol (3) cannot give rise to an intermediate (10) analogous to (8) since this would involve the formation of an unfavourable trans-fused 5,6-ring system. In this instance fluoride mediated elimination of the DAST ester is the primary reaction. However, one cannot totally discount the formation of (10) and its subsequent fluoride induced elimination to chromene (5).



SCHEME 2

Participation of neighbouring groups have previously been evoked to explain DAST induced migrations[4] and epimerisation of 2-(acetoxymethyl)myoinositol through anchimeric assistance of an ester group has been observed[5].

We would like to thank Dr. D.R. Buckle and Dr. D.G. Smith for their encouragement during the course of this work.

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* All compounds are racemic of which one isomer is shown; all new compounds exhibited satisfactory microanalytical and/or spectroscopic properties.

(Received in UK 15 May 1989)