An Unexpected Aromatic S_N2' Substitution of a 4-Bromobenzopyran

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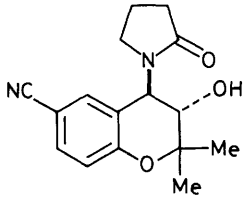
Reaction of 4-bromo-6-cyano-3,4-dihydro-2,2-dimethyl-3,3-ethylenedioxy-2*H*-1-benzopyran (**2**) with secondary amide anions provides C-5 substituted products in moderate yields.

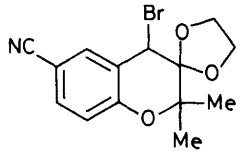
Cromakalim (**1**) is a potent smooth muscle relaxant which has potential use in the treatment of hypertension[1] and asthma.[2] As part of a synthetic programme to investigate the biological activity of novel 4-amidobenzopyran-3-ones we have examined the reaction of the benzylic bromide (**2**) with nitrogen nucleophiles (Table 1).

The reaction of (**2**) with the anions of *N*-methylacetamide and pyrrolidinone was found not to yield the expected 4-amidobenzopyrans but to result in a novel aromatic attack at C-5 to give the 5-amidobenzopyrans (**3**)† and (**4**), isolated in 25 and 65% yields respectively.‡ These observations suggest that with hindered disubstituted amide nucleophiles, direct attack at the C-4 neopentylic centre is sterically difficult and a C-5 conjugate substitution occurs *via* an aromatic S_N2' attack followed by a 1,3-hydride shift to restore aromaticity. It is probable that the presence of the electron-withdrawing 6-cyano group facilitates addition to the aromatic ring.

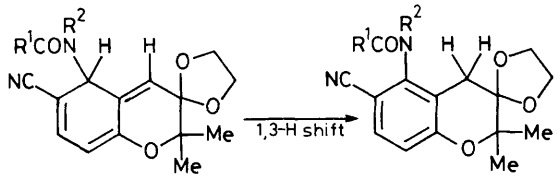
In order to investigate further the proposed mechanism, the use of smaller nucleophiles was examined (Table 1). Treatment of (**2**) with acetamido anion resulted in oxygen attack to



(±)-(**1**)

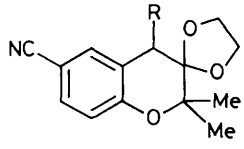


(**2**)



(**3**) $R^1 = R^2 = Me$

(**4**) $R^1R^2 = -(CH_2)_3-$



(**5**) R = OH

(**6**) R = —O—C(=NH)Me

(**7**) R = N_3

† All new compounds exhibited satisfactory microanalytical and/or spectroscopic properties.

‡ Compound (**3**) exists as two rotamers A and B (1:7): n.m.r. ($CDCl_3$) δ 1.33 (s, 3H, A), 1.37 (s, 3H, B), 1.38 (s, 3H, B), 1.47 (s, 3H, A), 1.82 (s, 3H, B), 2.32 (s, 3H, A), 2.70 (AB system, *J* 19.5 Hz, 2H, A + B), 3.22 (s, 3H, B), 3.37 (s, 3H, A), 4.20—4.00 (m, 4H, A + B), 6.88 (d, *J* 8.5 Hz, 1H, A), 6.96 (d, *J* 8.8 Hz, 1H, B), 7.45 (d, *J* 8.5 Hz, 1H, A), 7.51 (d, *J* 8.8 Hz, 1H, B). A variable temperature n.m.r. experiment showed that when heated to 170 °C in $(CD_3)_2SO$ the double resonances present at room temperature coalesced.

Compound (**4**): n.m.r. ($CDCl_3$) δ 1.35 (s, 3H), 1.38 (s, 3H), 2.75—2.20 (m, 4H), 2.49 (d, *J* 17 Hz, 1H), 2.95 (d, *J* 17 Hz, 1H), 3.6 (m, 1H), 4.15—4.00 (m, 5H), 6.90 (d, *J* 8.5 Hz, 1H), 7.46 (d, *J* 8.5 Hz, 1H).

Compound (**5**): n.m.r. ($CDCl_3$) δ 1.34 (s, 3H), 1.42 (s, 3H), 2,44 (d, *J* 10 Hz, 1H), 4.40—4.05 (m, 4H), 4.77 (d, *J* 10 Hz, 1H), 6.86 (d, *J* 8.5 Hz, 1H), 7.44 (dd, *J* 2 and 8.5 Hz, 1H), 7.81 (d, *J* 2 Hz, 1H).

Compound (**7**): n.m.r. ($CDCl_3$) δ 1.40 (s, 3H), 1.52 (s, 3H), 4.48—4.12 (m, 4H), 4.6 (s, 1H), 6.98 (d, *J* 9 Hz, 1H), 7.58 (dd, *J* 2 and 9 Hz, 1H), 7.78 (d, *J* 2 Hz, 1H).

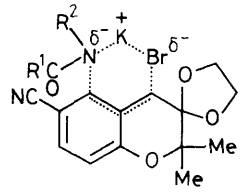
Table 1. Reaction of (2) with nitrogen nucleophiles.

Nucleophile	Product
MeCONMe $K^{+a,b}$	(3)
$\overline{CH_2CH_2CH_2\bar{N}C{=}O}\ K^{+a,c}$	(4)
$MeCO\bar{N}H\ K^{+a,b}$	(5) [(6)]
$NaN_3{}^{d}$	(7)

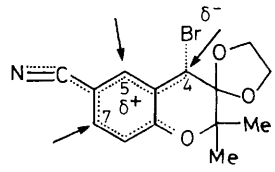
[a] Reaction was performed in the corresponding amide as solvent using 1.0—1.1 equiv. of $KOBu^t$. [b] 17 h, 80 °C. [c] 4 h, 100 °C. [d] Reaction was performed in dioxane–water using 11.5 equiv. of sodium azide at reflux for 25 h.

give the alcohol (5)‡ in 54% yield after hydrolysis of the putative intermediate acetimidate (6). Reaction of (2) with sodium azide afforded the expected 4-azido compound (7) in 65% yield.‡

Although the S_N2' reaction of allylic halides is well documented,[3] to our knowledge no similar substitutions involving the aromatic ring of benzylic halides have been reported. Surprisingly, only the C-5 regioisomers (3) and (4) have been isolated, although substitution at C-7 is also feasible. This regioselectivity could be due to co-ordination of the potassium cation to the nitrogen nucleophile and the bromide leaving group§ (8). An alternative explanation involves the oxygen lone pair of the benzopyran ring. Thus, departure of the bromide ion could be assisted by delocalisation of the oxygen lone pair which would spread the partial positive charge through the transition state (9). Three electron deficient sites, namely C-4, C-5, and C-7, are therefore available to the nucleophilic species. When large nucleophiles are used the 3,3-disubstitution sterically retards the substitution at C-4 resulting in attack at C-5 thereby maintaining the greatest conjugated system.



(8)



(9)

The use of this novel aromatic substitution as a route to otherwise difficultly accessible C-5 substituted benzopyrans is being evaluated and the results will be reported in due course.

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§ Reaction of pyrrolidinone anion with (2) in the presence of 18-crown-6- resulted mainly in the formation of (4) (64%), although the 7-pyrrolidino regioisomer was isolated in 4% yield.

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