A NOVEL SYNTHESIS OF BENZOPYRANYL ISOXAZOLINES : CYCLOADDITION REACTION OF CHROMONE NITRILE OXIDE

Arpan K Baruah, Dipak Prajapati, and Jagir S Sandhu*
Division of Drugs and Pharmaceutical Chemistry,
Regional Research Laboratory, Jorhat 785 006, India

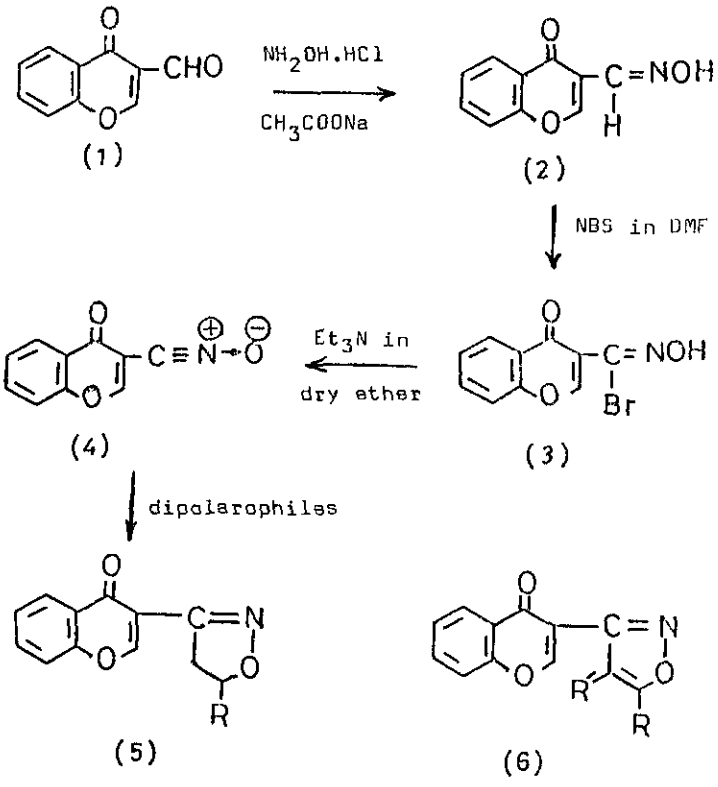
Abstract - A new nitrile oxide successfully prepared from 3-formylchromone is illustrated by reacting it with a variety of alkenes to afford novel benzopyranyl isoxazolines.

Chromone chemistry continues to be an area of intensive investigations because of synthetic complexities[1], natural occurrence[2] and diverse type of biological activity[3] associated with this class of compounds. However the reactions of chromone derivatives with nitrogen nucleophiles are complicated because chromone skeleton provides two potential sites of attack. Reaction of chromone-3-carboxylic acid with hydroxylamine was reported[4] to give oxazepine which has been recently revised[5] to be 5-(2-hydroxyphenyl)isoxazole. Here we report the reaction of hydroxylamine with 3-formylchromone (1) which offers three potential sites of attack, e.g. C-2 position, carbonyl group and the formyl group, and successful production of the aldoxime which afford access to a novel nitrile oxide.

The formation of chromone oxime (2) was facile and could be readily obtained by reacting 3-formylchromone (1) with hydroxylamine hydrochloride and using sodium acetate in ethanol-water in good yield without the formation of any side products or the rupture of the chromone unit itself.

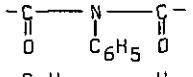
Aromatic nitrile oxides are usually generated in situ via dehydrohalogenation of the corresponding alpha haloaldoximes. The usual three ways of producing alpha haloaldoximes could not be successful in the present case[6]. Bromination with N-bromosuccinimide (NBS) in carbon tetrachloride as the solvent, was neither successful (tlc showed a large number of product formation). The use of NBS in

DMF at low temperature (0 to -10°C) successfully gave us the desired alpha bromoaldoxime (3) which is used in the following cycloaddition reactions for the in situ generation of the nitrile oxide.



(1) (2) (3) (4) (5) (6)

	R
5a	CN
5b	C_6H_5
5c	p-$CH_3C_6H_4$
5d	CH_2Br
5e	$COCH_3$

	R	R'
5f		
6a	C_6H_5	H
6b	C_6H_5	C_6H_5

A mixture of chromone oxime (2) and NBS (2 equiv) in dry DMF was allowed to react at -10°C and then the temperature was allowed to and was kept at this temperature for additional 30 min. The reaction mixture was diluted with dry ether (half the volume of DMF) and solution of acrylonitrile and triethylamine (each in equimolar proportion to 2) in dry ether was added. The reaction was further stirred for additional time at room temperature until acrylonitrile

Table 1 : Microanalytical data of Δ^2-isoxazolines (5a - f) and (6a - b)

Compd.	Dipolarophile R	R'	Yield[a] (%)	Mp[b] (°C)	Molecular[c] formula	Analysis % Calculated C	H	(Found) N
5a	CN		65	168-169	$C_{13}H_8O_3N_2$	65.03 (65.14	3.33 3.45	11.66 11.53)
5b	C_6H_5		68	91-92	$C_{18}H_{13}O_3N$	74.25 (74.32	4.46 4.31	4.80 4.73)
5c	p-$CH_3C_6H_4$		63	82-83	$C_{19}H_{15}O_3N$	74.77 (74.86	4.91 4.79	4.58 4.63)
5d	CH_2Br		70	96-97	$C_{13}H_{10}O_3NBr$	50.69 (50.58	3.25 3.36	4.54 4.63)
5e	$COCH_3$		65	87-89	$C_{14}H_{11}O_4N$	65.40 (65.53	4.28 4.18	5.45 5.56)
5f	N-Phenylmaleimide		72	239-240	$C_{20}H_{12}O_5N_2$	66.69 (66.80	3.33 3.21	7.77 7.63)
6a	C_6H_5	H	63	128-129	$C_{18}H_{11}O_3N$	74.76 (74.87	3.80 3.69	4.84 4.96)
6b	C_6H_5	C_6H_5	62	114-115	$C_{24}H_{15}O_3N$	78.92 (78.81	4.10 4.21	3.83 3.79).

[a] Yield of pure products isolated by silica gel column chromatography.

[b] Uncorrected, measured with a Buchi apparatus in open capillaries.

[c] New compounds ; satisfactory microanalyses obtained.

Table 2 : Spectral data of Δ^2-isoxazolines (5a - f) and (6a - b)

Compd.	I.R. (KBr)[a] (cm^{-1})	MS (M^+)[b] m/z	^1H δ (60 MHz, $CDCl_3$)[c]
5a	2130,1650, 1625,1600	240	3.65-3.80(2H, dd), 4.85-5.05(1H, m), 6.70-7.75(4H, m, aromatic), 7.95(1H, s).
5b	1675,1650, 1610,1575	291	3.60-4.00(2H, dd), 5.50-5.90(1H, m), 7.20-8.20(9H, m, aromatic), 8.50(1H, s).
5c	1670,1650, 1615,1565	305	1.65(3H, s), 3.65-4.05(2H, dd), 5.45-5.85 (1H, m), 7.15-8.15(8H, m, aromatic), 8.45(1H, s).
5d	1655,1630, 1605,1575	308	3.00-3.95(4H, m), 4.90-5.15(1H, m), 7.30-8.35(4H, m, aromatic), 8.55(1H, s).
5e	1650,1625, 1605,1580	257	2.30(3H, s), 3.55-3.90(2H, dd), 4.70-5.20 (1H, m), 7.21-8.20(4H, m), 8.40(1H, s).
5f	1660,1625, 1610,1575	360	5.20-5.90(2H, m), 7.22-8.10(4H, m, aromatic), 8.35(1H, s).
6a	1655,1625, 1600,1575	289	7.20-8.15(10H, m, aromatic and olefinic), 8.40(1H, s).
6b	1650,1620, 1605,1575	365	7.15-8.00(14H, m, aromatic), 8.35(1H, s).

[a] Recorded on Perkin-Elmer 237B Infrared spectrometer.

[b] Recorded on a AEI MS-30 spectrometer.

[c] Recorded on Varian T 60 spectrometer.

was all consumed (checked vide tlc). The hydrotytic work up, extraction with dichloromethane and column chromatography of the concentrated solution over silica gel gave (5a) in 65% yield, mp 168 - 169°C. The reaction of chromone nitrile oxide (4) generated in situ as above with a variety of olefinic dipolarophiles gave the corresponding Δ^2-isoxazolines (5b - f) and (6a - b) in good yields (Scheme 1 and Table 1 and 2). In all the cases reported here the reaction was completely regiospecific and there was no evidence for the formation of any other products arising from dimerisation, 1,5-electrocyclisation or self condensation of the dipole. The structures of these cycloadducts are fully corroborated by the spectral as well as elemental analyses.

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