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STUDIES IN CHROMONE DERIVATIVES:CYCLOADDITION REACTIONS OF 4-OXO 4H-1-BENZOPYRAN-3-CARBOXALDEHYDE IMINES WITH BENZONITRILE OXIDE AND NITRILIMINE OF 4-OXO-4H-1-BENZOPYRAN-3-CARBOXALDEHYDE WITH ALKENES

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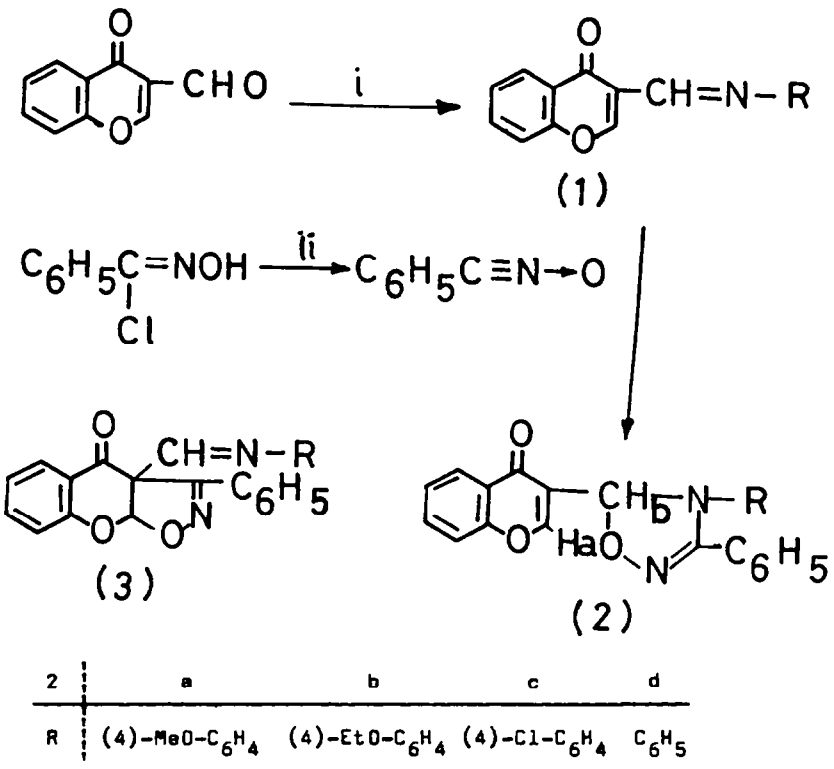
Abstract - The chromone imings 1 and benzonitrile oxide reacted regiospecifically to yield Δ^2-1,2,4 oxadiazolinyl chromones 2 in good yields. Also the preparation of a novel dipole 6 derived from 3-formylchromone and its cycloaddition reactions with a variety of alkenes which gave pyrazolinyl chromones 7 is described.

Flavones and chromones are unique molecules because of the availability of their structural framework in a variety of natural products, biologically active molecules and the challanges involved in the synthesis of these structures and related molecules[1-3]. Natural product Khellin[4] provided lead to a totally synthetic drug disodium cromoglycate[5] and stimulated interest in the synthesis of novel heterocyclic linked chromones[6-10] as the possible superior antiallergy and anti-viral drugs.

The imines 1 have been very attractive synthons to prepare chromones bearing heterocyclic ring systems, which in turn can be readily obtained from 4-oxo-4H-1-benzopyran-3-carboxaldehyde (trivial name 3-formylchromone) by reacting with primary amines. The 3-formylchromone being a very reactive molecule responding to Michael type of additions as well as reactions at the carbonyl site, controversial claims are reported for the synthesis of 4-Oxo-4H-1-benzopyran-3-carboxaldehyde imines[11]. We describe here our success in preparing imines 1a-d in good yields and their 1,3 dipolar cycloaddition reactions to afford us a novel class of chromone linked Δ^2-1,2,4-oxadiazolines 2.

The imines 1 were readily obtained by reacting 3-formylchromone with aromatic amines in refluxing benzene and removing the water eliminated azeotropically (Dean-Stark apparatus) and using a catalytic amount of toluene-p-sulfonic acid. These imines 1 were prepared in good yields without the formation of any side products arising from Michael type of additions onto carbon-carbon double bond of chromone moiety[12] or the rupture of chromone unit itself. Benzonitrile oxide (BNO) was produced from the corresponding benzhydroxamoyl chloride using triethylamine as the base[13]. Reaction of equimolar quantities of chromone imines 1 and BNO (generated in situ) in anhydrous chloroform when stirred at 0°C for 5h, on removal of solvent and crystallisation of the residue from light petroleum (b.p. 40-60°C) gave cycloadducts 2 in good yields. The characteristics of these cycloadducts are given in the Table-1. It was quite interesting to observe the

site selectivity followed by the dipole[14] and cycleaddition occurring only across the azomethine function leaving chromone double bond intact. This site selectivity seems to be a remarkable contrast in view of the reactivity of chromone double bond towards a variety of nucleophiles and typical 1,3 dipole diazomethane reacting at this site which is well documented[15]. The structural assignment of



2	a	b	c	d
R	(4)-MeO-C_6H_4	(4)-EtO-C_6H_4	(4)-Cl-C_6H_4	C_6H_5

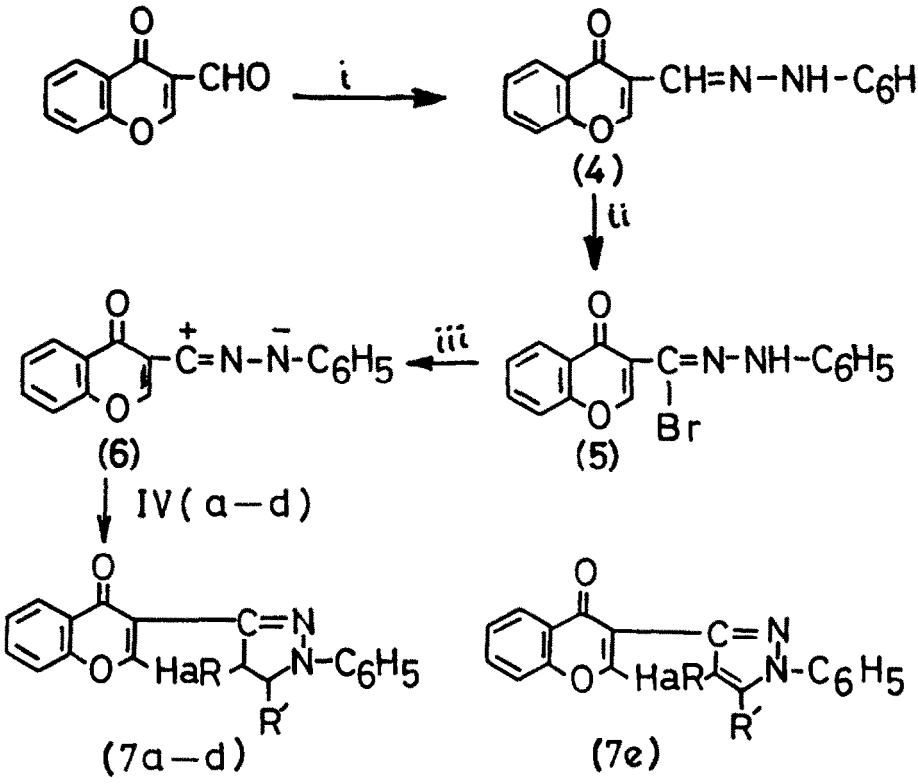
Reagents: i, RNH_2 in dry benzene; ii, Et_3N in anhydrous $CHCl_3$

Scheme 1.

cycloadducts 2 mainly rests on elemental as well as spectral analyses.

The ^1H NMR (60 MHz, $CDCl_3$) of 2a δ : 3.60 (s, 3 H, OCH_3), 6.35 (s, 1 H, 1 Hb), 6.50-7.60 (13 H, complex multiplet), 7.85 (s, 1 H, 1 Ha). The diagnostic signal for azomethine proton which showed at δ 8.30 was absent in the cycloadduct. The mass spectrum showed the molecular ion at m/z (M^+) at 398 and other major fragments showed at 279, 145, 119. The cycloaddition at the azomethine site is finally supported by the upfield shift of azomethine proton Hb from δ 8.30 to δ 6.35 which also clearly ruled out the posibility of any product formation of the type 3 scheme - 1.

To achieve the production of nitrilimine 6 we had three possible options before us; in view of the already published reports for the generation of this type of 1,3 dipoles. Accordingly one could attempt the generation of this dipole via thermolysis of the suitably functionalised tetrazole which is well precedented in case of diarylnitrilimines[16] or by preparing the chromone-3-carboxylic acid chloride followed by acylation of phenylhydrazine with this acid chloride[17]. Keeping in view the pros and cons of these methods we prefered to start with more attractive and straightforward procedure starting from 3-formylchromone, which was converted to the corresponding phenylhydrazone 4 in good yield. We could



7	a	b	c	d	e
R	CH_2Br	$COCH_3$	CN	C_6H_5	$COOCH_3$
R'	H	H	H	H	$COOCH_3$

Reagents: i, $C_6H_5NHNH_2HCl$-CH_3COONa; ii, NBS in CCl_4; iii, Et_3N in dry benzene; iva, allylbromide; ivb, methyl vinyl ketone; ivc, acrylonitrile; ivd, styrene ; ive, dimethylacetylene dicarboxylate.

Scheme 2.

efficiently prepare corresponding α-bromo phenylhydrazone 5 by using N-bromo-succinimide. The chromone nitrilimine 6 was generated in situ using triethylamine as the base. This novel dipole 6 reacted readily regiospecifically affording us a novel class of chromone linked pyrazolines 7.

Reaction of chromone nitrilimine 6 with various alkenes (scheme 2) for example allylbromide were carried out by dissolving their equimolar quantities in dry benzene and stirring the reaction mixture for 2h at room temperature. The removal of solvent gave a residue which was soluble in dry benzene and the precipitated triethylamine hydrobromide was filtered off. The filtrate on concentration and purification by column chromatography using benzene-ethylacetate (4:1) as the eluent gave 7a m.p. 102-103°C in 55% yield. The assignment of structure 7a to this product rests on elemental as well as spectral data. The mass spectrum (CIMS) showed the molecular ion at m/z, (M^+) at 384 and other prominent fragments at 383, 305, 266, 265, 171, 145 and 121. Similarly were prepared pyrazolines 7b-d and their characteristics are recorded in the Table - 1 and 2.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. Mass spectra were recorded on AEIMS 30 instrument by electron impact method and CIMS and 400 MHz ^{1}H NMR spectra were recorded from CDRI Lucknow. The 60 MHz ^{1}H NMR spectra were recorded at Varian T-60 machine using tetramethyl silane (TMS) as the internal standard. The chemical shifts are recorded in δ units (parts per million).

3-(Aryliminomethyl)chromones 1a-d : To a solution of 1.74 g of 3-formylchromone (10 mmol) and 1.23 g p-anisidine (10 mmol) in dry benzene (80 ml), 10 mg of toluene-p-sulphonic acid was added. The resulting mixture was than heated under reflux using Dean-Stark water trap for 30 min. The solvent was distilled under reduced pressure and the product 1a thus obtained was purified by recrystallisation from benzene-petroleum ether mixture.

Preparation of Benzhydroxamoyl chloride : Method A. In a 500 ml flask α-benzaldoxime (10 g) was dissolved in 8.3 N hydrochloric acid (60 ml). This solution was cooled to 0°C in an ice-salt bath, and through this solution pure chlorine gas prepared from potassium permanganate and hydrochloric acid was passed very slowly for 10 to 15 min. After this, the product was extracted with ether. The ether layer was dried over anhydrous magnesium sulphate and then removed under vacuum below 40°C. Benzhydroxamoyl chloride was obtained as a liquid which on excessive cooling solidified (5.5 gm, 55%) m.p. 42-46°C.
Method B. α-Benzaldoxime (10 g) was taken in pure chloroform and cooled in an ice-salt bath at 0°C and dry chlorine gas was bubled very slowly for a period of 3h. After this the excess chloroform was removed under reduced pressure and the product was allowed to cool in a refrigerator overnight. Benzhydroxamoyl chloride precipitated as light yellow coloured compound m.p. 42-46°C. The yield of the product is 56% (5 - 6 g approximately).

Reaction of 3-(aryliminomethyl)chromone with Benzonitrile oxides : Dry triethylamine (10 mmol) in anhydrous chloroform was added dropwise to a well stirred solution of benzhydroxamoyl chloride and the chromone imine 1a (10 mmol) in anhydrous chloroform (40 ml) over a period of 1h at 0°C. The mixture was further stirred for 5h. After removal of the solvent, the residue was taken up in benzene (20 ml). The precipitated triethylamine hydrochloride was filtered off and the filtrate thus obtained was distilled under vacuum. The product 2a was purified by column chromatography and recrystallised from light petroleum ether (b.p. 40-60°C). Similarly other cycloadducts 2b-d were prepared and their characteristics are given in Table - 1 and 2.

Preparation of Phenylhydrazone of 3-formylchromone : Phenylhydrazine hydrochloride (0.72 g, 5 mmol) and sodium acetate (0.49 g, 6 mmol) were dissolved in 5 ml of water by slightly warming. The solution thus obtained was then added to 3-formylchromone (0.87 g, 5 mmol) dissolved in ethanol after sometime yellow coloured hydrazone 4 was separated out. The solid crystalline hydrazone thus separated was filtered and was further purified by recrystallisation from absolute ethanol m.p. 210°C in 90% yield (literature m.p. 213°C)[18].

Bromination of Hydrazone 4 with N-bromosuccinimide : A mixture of hydrazone (1.32 g, 5 mmol) and N-bromosuccinimide (0.89 g, 5 mmol) in 1:1 molar proportions in carbontetrachloride (50 ml) were heated at 50 - 55°C for 2h. The reaction mixture was then filtered and the filtrate was concentrated to obtain the α-bromo phenylhydrazone of chromone 5 which was used as such in the further reaction without purification. IR (KBr): $\bar{\nu}$ = 3350 Cm^{-1} (NH). The ^{1}H NMR of the crude product also showed the presence of a proton exchangeable on D_2O addition.

General Procedure for the Reaction of Chromone nitrilimine with Various Alkenes : Allylbromide (0.605 g, 5 mmol) and α-bromo phenylhydrazone (1.72 g, 5 mmol) of chromone 4 (prepared as above) in equimolar proportions were taken in dry benzene (50 ml) and stirred magnetically at room temperature. To this well stirred reaction mixture was added dry triethylamine (10 mmol, excess) in benzene (5 ml) dropwise over a period of 30 min and the stirring was continued for further 1h. Generation of nitrilimine was indicated by the precipitation of triethylamine hydrobromide salt which was filtered off. The filtrate thus obtained was concentrated and the residue was purified by column chromatography using benzene-ethylacetate (4:1) as the eluent. The yellow product thus obtained was crystallised from benzene-petroleum ether (60-80) (1:4) mixture to obtain pyrazoline 7a m.p. 103-104°C in 55% yield. The other cycloadducts 7b-e were obtained similarly following the above procedure and their characteristics are recorded in Table - 1 and 2.

Table - 1: Physical Characteristics and Micro Analytical Data of 2a-d and 7a-e

Compound	Yield (%)	M.p. (°C)	Molecular formula	Analysis Calculated C	H	(Found) N
2a	70	115-116	$C_{24}H_{18}N_2O_4$	72.36	4.52	7.03
				(72.22	4.63	6.82)
2b	65	135-136	$C_{25}H_{20}N_2O_4$	72.81	4.85	6.79
				(72.92	4.93	6.66)
2c	60	129-130	$C_{23}H_{15}N_2O_3Cl$	68.57	3.72	6.95
				(68.67	3.86	7.02)
2d	60	130-131	$C_{23}H_{16}N_2O_3$	75.00	4.35	7.61
				(75.21	4.46	7.48)
7a	55	103-104	$C_{19}H_{15}N_2O_2Br$	59.53	3.92	7.31
				(59.40	3.76	7.19)
7b	60	153-154	$C_{20}H_{16}N_2O_3$	72.29	4.82	8.43
				(72.40	4.96	8.29)
7c	61	145-146	$C_{19}H_{13}N_3O_2$	72.38	4.13	13.33
				(72.26	4.01	13.46)
7d	50	181-182	$C_{24}H_{18}N_2O_2$	78.69	4.92	7.65
				(78.80	4.79	7.76)
7e	65	143-144	$C_{22}H_{16}N_2O_6$	65.35	3.96	6.93
				(65.24	3.79	6.80).

Table - 2 : Spectroscopic Data of Product 2a-d and 7a-e.

Compound	M^+	^1H N.M.R. δ (ppm)
2a	398,279,173, 145,119	3.60 (s, 3 H, OCH_3); 6.35 (s, 1 H, 1 Hb); 6.50-7.65 (13 H, complex multiplet); 7.85 (s, 1 H, 1 Ha).
2b	412,293,173, 145,119	1.10 (t, 3 H, CH_3); 3.80-4.22 (q, 2 H, OCH_2); 6.42 (s, 1 H, 1 Hb); 6.72-7.65 (13 H, complex multiplet); 7.85 (s, 1 H, 1 Ha).
2c	402,283,172, 119	6.30 (s, 1 H, 1 Hb); 6.65-7.60 (13 H, complex multiplet); 7.85 (s, 1 H, 1 Ha).
2d	368,249,173, 119	6.41 (s, 1 H, 1 Hb); 6.65-7.75 (s, 15 H, 1 Ha).
7a	384,383,171, 145,121	3.65 (dd, 2 H, $-CH_2$); 3.38 (m, 2 H, $-CH_2$); 3.85 (m, 1 H, -CH); 6.95 - 8.20 (9 H, complex multiplet); 8.55 (s, 1 H, Ha).
7b	333,332,331, 289,171,145	2.20 (s, 3 H, CH_3); 3.50-3.91 (m, 2 H, $-CH_2$); 4.45-4.75 (dd, 1 H, -CH); 6.70 - 8.35 (9 H, complex multiplet); 8.60 (s, 1 H, Ha).
7c	315,288,171, 265	3.65-4.00 (m, 2 H, $-CH_2$); 4.60-4.85 (dd, 1 H, -CH); 6.80-7.60 (9 H, complex multiplet); 8.25 (s, 1 H, Ha).
7d	366,264,263, 262,171	3.55-3.95 (m, 2 H, $-CH_2$); 4.55-4.85 (dd, 1 H, -CH); 6.60-7.80 (14 H, complex multiplet); 8.35 (s, 1 H, Ha).
7e	404,264,171 145,142	3.75 (s, 3 H, $-CH_3$); 3.85 (s, 3 H, $-CH_3$); 7.20-7.85 (9 H, complex multiplet); 8.25 (s, 1 H, Ha).

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