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Studies on chromone derivatives: Microwave assisted 1,3-dipolar cycloaddition reactions of 4-oxo-1-benzopyran-3-carboxaldehyde imine oxides

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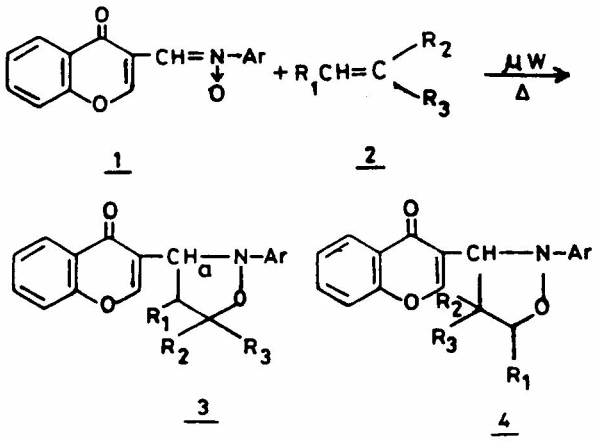
1,3-Dipolar cycloaddition reactions of chromone nitrones **1** have been carried out successfully under microwave irradiation. The reaction of nitrone **1** and alkene **2** proceeds regiospecifically at atmospheric pressure and the corresponding chromone linked isoxazolidines **3** are obtained in high yields.

There has been considerable interest in the 4*H*-1-benzopyran-4-one (chromone) ring system, both with regard to natural product chemistry (it forms the basis for the flavanoid family), and the pharmacological activity of several of its derivatives[1]. Prominent in the latter area is the bis-chromone disodium 5,5′-(2-hydroxypyropane-1,3-diyl)bis-(4-oxo -4*H* -1-benzopyran-2-carboxylate), well known for its prophylactic activity against bronchial asthma[2]. Synthesis of substituted chromones is limited by the resistance of the parent ring system to electrophilic attack (due to pyrilium salt formation) and by the susceptibility of the γ-pyrone ring to undergo attack and cleavage with a variety of nucleophiles[3]. This dual reactivity has led both to some controversy[4] and difficulties in the synthesis of pure compounds. In our earlier report[5] we have prepared successfully imine oxides by reacting 3-formylchromone with phenyl- and methyl-hydroxylamines in good yields without by-products arising from 1,5-electrocyclisation. This is in contrast with reports[6] both of chromone ring rupture upon attack by nitrogen nucleophiles and instantaneous 1,5-electrocyclisation by conjugated nitrones. Herein we wish to report the first example of 1,3-dipolar cycloaddition reactions of chromone nitrones with typical unactivated alkenes under microwave irradiation[7]. The reaction proceeds efficiently in high yields at ambient pressure within few minutes time and in the absence of a solvent.

Nitrones and in particular chromone nitrones are somewhat unreactive dipoles because of considerable charge delocalisation. Recently several cycloadditions of nitrones with various dipolarophiles have been reported[8], but these reactions require very drastic conditions, high pressure or long reaction periods at high temperature to obtain the corresponding cycloadducts. Therefore we chose to study chromone nitrones and unactivated alkenes which require long reaction periods and drastic thermolytic conditions before they undergo cycloaddition. The chromone nitrones were prepared as reported earlier[5] and their thermolytic reactions under refluxing conditions with alkenes were repeated. The same reactions under microwave activations were successfully completed more rapidly (within 2-15 min.) than the thermolytic reactions[5]. All reactions were performed in a commercial microwave oven operating at 2450 MHz frequency. In a typical case, equimolar quantities of chromone nitrone **1a** (10 mmoles) and methyl acrylate (10 mmoles) were mixed together without solvent in an Erlenmeyer flask and placed in the microwave oven and irradiated for 6 min. After usual work-up, the chromone linked isoxazolidine **3a** (Table I, entry 1) was obtained in 85% yield, m.p. 236°, without the formation of any rearranged amide or oxime-*O*-ether[9] or diastereoisomers. The formation of regioisomer **4** can be easily ruled out from the spectral data, since H_a and H_d (R_2=H_d) appeared as quartets at δ 5.40 and 4.45, a spectral result possible only if they are separated by H_b and H_c (R_1=H_b). So structure **3** is favoured over the regioisomer **4** where neither H_a nor H_d can appear as quartets. The characteristic data of other cycloadducts are recorded in the Experimental Section.



	Ar	R_1	R_2	R_3
a	C_6H_4Br-p	H	H	COOMe
b	C_6H_4Br-p	H	Me	COOMe
c	C_6H_4Br-p	H	H	CH_2Br
d	C_6H_4Br-p	H	H	CN
e	C_6H_4Cl-p	H	H	COOMe
f	C_6H_4Cl-p	H	Me	COOMe
g	C_6H_4Cl-p	H	H	CH_2Br
h	C_6H_4Me-p	H	H	COOMe
i	C_6H_4Me-p	H	Me	COOMe
j	C_6H_4Me-p	H	H	CH_2Br
k	C_6H_5	H	H	CN

This reaction is not equally effective when carried out thermally in refluxing toluene (it takes about 48 hrs to complete the reaction in 50% yield). Similarly methyl acrylate, allyl bromide and acrylo-nitrile were reacted with chromone nitrone and the products **3b-k** were isolated in high yields. The reaction periods and yields for thermal and microwave reactions are recorded in Table I.

In conclusion, it is noteworthy to mention that this simple and easily reproducible technique in solid state, affords various isoxazolidines in just one-pot in a shorter reaction period and with higher yields than the classical or sonochemical reactions in solvents. Moreover, the reaction takes place at ambient pressure and in the absence of a solvent thereby reducing the risk of hazardous explosion when the reaction was conducted in a closed vessel.

Experimental Section

General. Melting points were determined using a Buchi melting point apparatus and are uncorrected.

Table I — Comparison of microwave and thermal reactions of chromone nitrones with dipolarophiles

Entry	Product	Thermal		Microwave		m.p °C
		Reaction period (hr)	Yield[a] (%)	Reaction period (min)	Yield (%)	
1	**3a**	36	50	6	85	236
2	**3b**	28	55	8	80	223
3	**3c**	17	60	2	75	230
4	**3d**	20	45	6	50	254
5	**3e**	32	62	8	70	246
6	**3f**	24	60	6	75	235
7	**3g**	14	55	2	60	220
8	**3h**	48	58	15	70	159
9	**3i**	48	65	12	90	105
10	**3j**	24	60	10	65	144
11	**3k**	12	60	2	70	149

[a]Yields refer to the yield of pure isolated products.

IR spectra were recorded in KBr discs on a Perkin-Elmer 237B IR spectrophotometer. Microanalyses were performed on a Perkin-Elmer 240C analyser. 90MHz ^1H NMR spectra were recorded at RSIC, Shillong. Mass spectra were recorded on AEIMS 30 instrument by the electron impact method. Solvents were dried following the standard procedures. Light petroleum is the fraction with boiling point 60-80°C. All reagents were of commercial quality from freshly opened containers and were purchased from Aldrich Chemical Co. and used without further purification.

Preparation of chromone nitrones 1. 3-Formyl-chromone was added to a solution of 4-bromo-phenylhydroxylamine in dry benzene (1:1 molar ratio) with occasional stirring to give an immediate reaction and separation of light yellow crystals of nitrone **1a** (Ar=4-bromophenyl) in 65% yield. The crystals were filtered and recrystallised from benzene-light petroleum ether (1:1), m.p. 187-88°. Similarly 4-methyl- and 4-chlorophenylhydroxyl-amines were reacted with 3-formylchromone and the corresponding nitrones were isolated in 70-75% yields.

Preparation of chromone linked isoxazolidines 3a-j. Chromone nitrone **1a** (10 mmoles) and methyl acrylate were mixed together without a solvent in an Erlenmeyer flask and placed in a commercial micro-

wave oven operating at 2450 MHz frequency and irradiated for 6 min. The reaction mixture was allowed to reach room temperature and extracted with chloroform. After removal of the solvent the residue afforded the isoxazolidine **3a** (Table I, entry 1), m.p. 236°, in 85% yields without the formation of any side products. ^{1}H NMR ($CDCl_3$): δ 3.10 (3H, s, COOMe), 2.20 and 3.40 (2H, both dt), 4.45 (1H, q), 5.40 (1H, q, and 7.30-8.30 (9H, m, 8H, ArH and 1H, chromone); MS: m/z 430 (M^+); Anal. Found: C, 55.70; H, 3.83; N, 3.30. Calcd for $C_{20}H_{16}O_5NBr$: C, 55.81; H, 3.72; N, 3.26%.

Similarly methyl methacrylate, allyl bromide, and acrylonitrile were reacted with chromone nitrone and the corresponding isoxazolidines were obtained in high yields. The characterization data of the products are recorded below:

3b: ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, Me), 3.02 (s, 3H, COOMe), 2.30-2.85 (m, 2H), 5.35 (q, 1H), 7.35-8.25 (m, 9H, 8H, ArH and 1H, chromone), 2.25 and 3.45 (2H, both dt), 4.10 (m, 1H), 4.50 (q, 1H); MS: m/z 444 (M^+); Anal. Found : C, 56.83; H, 4.16; N, 3.09. Calcd for $C_{21}H_{18}NO_5Br$:C, 56.76; H, 4.05; N, 3.15%.

3c: ^{1}H NMR ($CDCl_3$): δ5.40 (q, 1H), 7.30-8.30 (m, 9H, 8H, ArH and 1H, chromone); MS: m/z 465 (M^+); Anal. Found C, 49.20; H, 3.36; N, 3.06. Calcd for $C_{19}H_{15}NO_3Br_2$: C, 49.03; H, 3.23; N, 3.01%.

3d: ^{1}H NMR ($CDCl_3$): δ2.35-3.05 (m, 2H), 4.50 (q, 1H), 5.20 (q, 1H), 7.10-8.20 (m, 9H, 8H, ArH and 1H, chromone), MS: m/z 397 (M^+); Anal. Found: C, 57.49; H, 3.11; N, 7.13. Calcd for $C_{19}H_{13}N_2O_3Br$:C, 57.43; H, 3.27; N, 7.05%.

3e: ^{1}H NMR ($CDCl_3$): δ0-3.10 (s, 3H, COOMe), 2.15 and 3.45 (2H, both dt), 4.50 (q, 1H), 5.44(q, 1H), and 7.20-8.25 (m, 9H, 8H, ArH and 1H, chromone); MS: m/z 385 (M^+); Anal. Found: C, 62.36; H, 4.06; N, 3.69. Calcd for $C_{20}H_{16}NO_5Cl$: C, 62.25; H, 4.15; N, 3.63%.

3f: ^{1}H NMR ($CDCl_3$): δ2.10 (s, 3H, Me), 3.05 (s, 3H, COOMe), 2.30 and 2.90 (2H, both dt), 5.40 (q, 1H), 7.20-8.10 (m, 9H, 8H, ArH and 1H, chromone), MS: m/z 399 (M^+); Anal. Found: C, 63.11; H, 4.46; N, 3.39. Calcd for $C_{21}H_{18}NO_5Cl$: C, 63.07; H, 4. 5; N, 3.5%.

3g: ^{1}H NMR ($CDCl_3$): δ2.25 and 3.50 (2H, both, dt), 4.10 (m, 2H),4.52 (q, 1H), 5.35 (q, 1H), 7.15-8.20 (m, 9H, 8H, ArH and 1H, chromone); MS: m/z 420 (M^+). Anal. Found: C, 54.36; H, 3.61; N, 3.42 Calcd for $C_{19}H_{15}NO_3ClBr$: C, 54.22; H, 3.56; N, 3.32%.

3h: ^{1}H NMR ($CDCl_3$): δ1.75 (s, 3H, Me), 3.10 (s, 3H, COOMe), 2.20 and 3.45 (2H, both, dt), 4.50 (q, 1H),5.40 (q, 1H), 7.25-8.30 (m, 9H, 8H, ArH and 1H, chromone); MS: m/z 365 (M^+). Anal. Found: C, 69.12; H, 5.19; N, 3.96. Calcd for $C_{21}H_{19}NO_5$: C, 69.04; H, 5.2; N, 3.83%.

3i: ^{1}H NMR ($CDCl_3$): δ1.60 (s, 3H, Me), 2.02 (s, 3H, Me), 3.10 (s, 3H, COOMe), 2.35 and 2.95 (2H, both dt), 5.40 (q, 1H), 7.30-8.20 (m, 9H, 8H, ArH and 1H, chromone); MS: m/z 379 (M^+). Anal. Found: C, 69.76; H, 5.63; N, 3.75. Calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.54; N, 3.69%.

3j: ^{1}H NMR ($CDCl_3$): δ1.70 (s, 3H, Me), 2.30 and 3.35(2H, both dt), 4.08 (m, 2H),4.55 (q, 1H),5.40 (q, 1H), 7.20-8.25 (m, 9H, 8H, ArH and 1H, chromone); MS: m/z 400 (M^+); Anal. Found: C, 60.09; H, 4.53; N, 3.61. Calcd for $C_{20}H_{18}NO_3Br$: C, 60.00; H, 4.5; N, 3.5%.

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