# Studies on Chromone Derivatives. Novel 1,3 Dipolar Cycloadditions of 4-Oxo-1-benzopyran-3-carbaldehyde Imines and Imine Oxides

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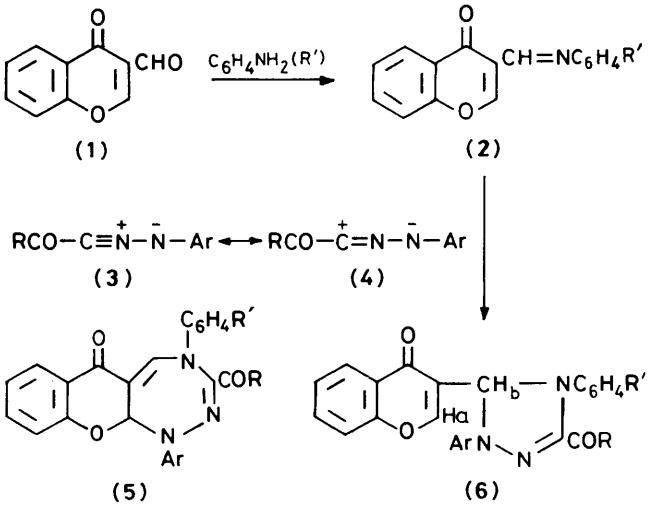
The chromone imines (**2**) and nitrile imines (**4**) reacted smoothly to yield the novel 1,2,4-triazolinyl- and triazepinyl-chromones, (**6**) and (**5**) respectively. The facile preparation of nitrones of chromones and their selected reactions with a variety of alkenes to obtain isoxazolidinylchromones (**12**) is also described.

Benzopyranone analogues occupy a position of considerable significance as a result of their widespread occurrence in plants and their potential as important pharmaceuticals.[2–8] The reactivity of 4-oxo-1-benzopyran-3-carbaldehydes, *i.e.* 3-formylchromones (**1**), has been the focus of much interest, since these compounds undergo both nucleophilic attack at the carbonyl function as well as conjugate additions.[9] Although this dual reactivity has led both to some controversy[10] and difficulties in the synthesis of pure compounds, both imines[11] and imine oxides (nitrones) have been prepared from 3-formylchromone (**1**). The 1,3 dipolar cycloadditions of these synthons have now yielded novel classes of chromone-linked 1,2,4-triazoline and isoxazolidine derivatives respectively. This appears to be the first investigation which employs the principle of 1,3-dipolar cycloaddition in chromone chemistry,[12] a surprising fact in view of the present great interest in such reactions.

3-Formylchromone (**1**) reacted with *p*-anisidine in refluxing benzene with azeotropic removal of water to give the imine (**2a**) in good yield. The *C*-acetyl- and *C*-ethoxy-carbonyl nitrile imines (**4**) were generated *in situ* from the corresponding hydrazonoyl halides[13] in the presence of dry triethylamine in anhydrous chloroform. Reaction of these nitrile imines (**4**) with (*p*-methoxyphenyliminomethyl)chromone (**2a**) in dry chloroform for 2—3 h at 0—5 °C gave upon work-up both types of [2 + 3] and [4 + 3] cycloadducts. The 1,2,4-triazoline [2 + 3] type (**6a**) thus obtained (45%) was further purified.

The structural assignments for (**6**) are fully established on the basis of elemental analysis and spectral results. The yields, m.p.s, and elemental data of these triazolines are given in Table 1 and the microanalytical data in Table 2. The c.i. mass spectrum of (**6a**) gave $M^+$ at *m/z* 456. The diagnostic azomethine proton which was present in imine (**2a**) at δ 8.30 was absent whilst the appearance of the $H_a$ proton at δ 7.65 showed that cycloaddition had occurred at the azomethine function. The formation of (**5**) is also proposed because of the disappearance of the diagnostic azomethine proton as well as the upfield shift of $H_a$ and its submergence with the aromatic protons; this was not so for the products (**6**). The mass spectrum also confirmed this to be a 1:1 adduct.




The mechanistic pathway for the formation of triazolines (**6**) or triazepines (**5**) can be explained by assuming the formation of the zwitterionic transient intermediates (**7**) and (**8**). However, the concerted addition of the dipole (**3**) or (**4**) appears to be more favourable in view of the earlier reports.†

Treatment of the 3-formylchromones, with phenyl- and methyl-hydroxylamine hydrochloride gave the nitrones (**10a**) and (**10b**) in good yields without by-products arising from 1,5 electrocyclisation. This result contrasts with reports[3,10a,14] both of chromone ring rupture upon attack by nitrogen nucleophiles and instantaneous 1,5-electrocyclisation by conjugated nitrones.

The nitrones (**10**) reacted with a number of alkenes (**11**) under a variety of conditions to give novel chromone linked cycloadducts. Thus, although the nitrones (**10a**) and (**10b**) reacted at room temperature with acrylonitrile to give the

† The authors wish to thank a referee for this more plausible suggestion.

**Table 1.** Physical characteristics of 1,2,4-triazolines (**6a**—**f**) and triazepines (**5a**—**f**)

| Substrate | R | R′ | Ar | Reaction time (hrs) | M.p. (°C) (**6**) | Yield (%) (**6**) | M.p. (°C) (**5**) | Yield (%) (**5**) |
|---|---|---|---|---|---|---|---|---|
| **a** | MeCO | OMe | $C_6H_4Me$-*p* | 2—3 | 179—180 | 45 | 88—89 | 15 |
| **b** | $EtO_2C$ | OMe | $C_6H_4Br$-*p* | 3—4 | 148—150 | 40 | 83—84 | 20 |
| **c** | MeCO | OMe | $C_6H_4Br$-*p* | 3—4 | 136—137 | 45 | 96—97 | 10 |
| **d** | $EtO_2C$ | OMe | $C_6H_4Me$-*p* | 2—3 | 135—137 | 45 | 81—82 | 12 |
| **e** | MeCO | OEt | $C_6H_4Me$-*p* | 3—4 | 140—142 | 40 | 96—97 | 10 |
| **f** | $EtO_2C$ | OEt | $C_6H_4Br$-*p* | 2—3 | 150—151 | 45 | 89—90 | 12 |

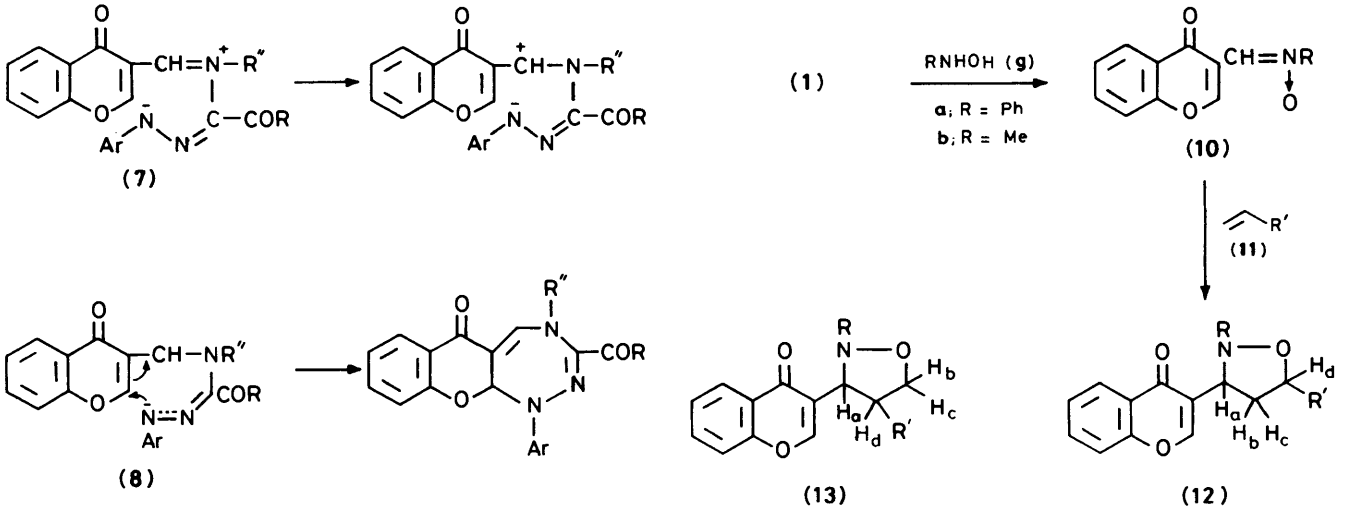
**Table 2.** Microanalytical data for the 1,2,4-triazolines (**6a**—**f**)

| Product | Solvent of crystallisation | Molecular formula | Analysis % Found (Calculated) C | H | N |
|---|---|---|---|---|---|
| (**6a**) | Benzene–light petroleum (b.p. 40—60 °C) (1:3) | $C_{27}H_{23}N_3O_4$ | 71.45 (71.52) | 5.1 5.07 | 9.2 9.27) |
| (**6b**) | Benzene–light petroleum (b.p. 40—60 °C) (1:5) | $C_{27}H_{22}BrN_3O_5$ | 59.0 (59.12) | 4.1 4.01 | 7.6 7.66) |
| (**6c**) | Benzene–hexane (1:7) | $C_{26}H_{20}BrN_3O_4$ | 60.1 (60.23) | 3.7 3.86 | 8.2 8.10) |
| (**6d**) | Benzene–light petroleum (b.p. 60—80 °C) (1:5) | $C_{28}H_{25}N_3O_5$ | 69.4 (69.56) | 5.1 5.17 | 8.7 8.69) |
| (**6e**) | Benzene–light petroleum (b.p. 40—60 °C) (1:8) | $C_{28}H_{25}N_3O_4$ | 71.8 (71.94) | 5.4 5.35 | 8.9 8.99) |
| (**6f**) | Light petroleum (b.p. 40—60 °C) | $C_{28}H_{24}BrN_3O_5$ | 59.8 (59.78) | 4.2 4.27 | 7.5 7.47) |

**Table 3.** $^1$H N.m.r. data of triazolines (**16**—**f**) and triazepines (**5a**—**f**)

| Compd. | δ |
|---|---|
| (**6a**) | 2.20 (3 H, s, Me), 2.50 (3 H, s, Me), 3.65 (3 H, s, Me), 6.20—7.35 (13 H, complex multiplet, 12 H, ArH, 1 Hb, triazoline), and 7.65 (1 H, s, Ha) |
| (**6b**) | 1.25 (3 H, t, Me), 3.50 (3 H, t, OMe), 3.95—4.25 (2 H, q, $OCH_2$), and 6.10—7.85 (14 H, m, 12 H, ArH, 1 H, triazoline, 1 H, chromone) |
| (**6c**) | 2.15 (3 H, s, Me), 3.60 (3 H, s, OMe), 6.15—7.30 (13 H, m, 12 H, ArH, 1 Hb, triazoline), and 7.70 (1 H, s, Ha) |
| (**6d**) | 1.15 (3 H, t, Me), 2.20 (3 H, s, Me), 3.55 (3 H, t, OMe), 4.00—4.30 (2 H, q, $OCH_2$), and 6.15—7.80 (14 H, m, 12 H, ArH, 1 H, triazoline, 1 Hb, chromone) |
| (**6e**) | 1.20 (3 H, t, Me), 2.05 (3 H, s, Me), 3.45—3.85 (2 H, q, $OCH_2$), and 6.80—7.85 (14 H, m, 12 H, ArM, 1 H, triazoline, 1 H, Ha chromone) |
| (**6f**) | 1.25 (6 H, t, Me), 3.95—4.30 (4 H, q, $OCH_2$), and 6.25—7.75 (14 H, m, 12 H, ArH, 1 H, triazoline, 1 H, Hb, chromone) |

| Compd. | δ |
|---|---|
| (**5a**) | 2.15 (3 H, s, Me), 2.45 (3 H, s, Me), 3.60 (3 H, s, OMe), and 6.20—7.20 (14 H, m, 12 H, ArH) |
| (**5b**) | 1.05 (3 H, t, Me), 3.45 (3 H, s, OMe), 3.85—4.25 (2 H, q, $OCH_2$), and 5.85—7.40 (14 H, m, 12 H, ArH) |
| (**5c**) | 2.20 (3 H, s, Me), 3.65 (3 H, s, OMe), and 6.15—7.25 (14 H, m, 12 H, ArH) |
| (**5d**) | 1.10 (3 H, t, Me), 2.15 (3 H, s, Me), 3.50 (3 H, s, OMe), 3.85—4.20 (2 H, q, $OCH_2$), and 6.15—7.90 (14 H, m, 12 H, ArH) |
| (**5e**) | 1.25 (3 H, t, Me), 2.10 (3 H, s, Me), 2.35 (3 H, s, Me), 3.65—3.90 (2 H, q, $OCH_2$), and 5.85—7.00 (14 H, m, 14 H, ArH) |
| (**5f**) | 1.20 (6 H, t, Me), 3.95—4.30 (4 H, q, $OCH_2$), and 6.10—7.25 (14 H, m, 12 H, ArH) |




cycloadducts (**12c** and **d**), similiar reactions with styrene, 4-methylstyrene, and *N*-phenylmaleimide occurred only at high temperature and with prolonged periods of heating. The adduct obtained from the styrene reaction has been assigned structure (**12a**), on the basis of microanalytical and spectral results (see Experimental section). Since $H_a$ and $H_d$ appeared as quartets at δ 5.35 and 4.80, a spectral result possible only if they are separated by $H_b$ and $H_c$, structure (**12a**) is favoured over the regioisomer (**13**) where neither $H_a$ nor $H_d$ can appear as

**Table 4.** Microanalytical data for cycloadducts (**12a—g**)

| Compd. | Dipolarophile | M.p. (°C) | Yield (%) | Molecular formula | Analysis % Found (Calculated) C | H | N |
|---|---|---|---|---|---|---|---|
| (**12a**) | Styrene | 105—106 | 40—45 | $C_{24}H_{19}NO_3$ | 78.1 (78.05 | 5.05 5.15 | 3.9 3.79) |
| (**12b**) | Styrene | 101—103 | 45—50 | $C_{19}H_{17}NO_3$ | 74.4 (74.26 | 5.4 5.53 | 4.7 4.56) |
| (**12c**) | Acrylonitrile | 148—151 | 60—65 | $C_{19}H_{14}N_2O_3$ | 71.8 (71.69 | 4.35 4.40 | 8.7 8.80) |
| (**12d**) | Acrylonitrile | 82—84 | 65—70 | $C_{14}H_{12}N_2O_3$ | 65.5 (65.61 | 4.8 4.68 | 10.8 10.94) |
| (**12e**) | 4-Methylstyrene | 75—76 | 42—45 | $C_{20}H_{19}NO_3$ | 74.8 (74.76 | 5.8 5.92 | 4.2 4.36) |
| (**12f**) | 4-Methylstyrene | 78—79 | 40—42 | $C_{25}H_{21}NO_3$ | 78.2 (78.32 | 5.3 5.48 | 3.7 3.65) |
| (**12g**) | *N*-Phenylmaleimide | 171—172 | 60—65 | $C_{26}H_{18}N_2O_5$ | 71.3 (71.23 | 4.0 4.11 | 6.2 6.39) |

quartets. We observed no regioisomers or diastereoisomers of the type (**13**). The characteristic data of other cycloadducts are recorded in Table 4.

## Experimental

M.p.s were determined in open capillary tubes on a Buchi apparatus and are uncorrected. The 90 MHz $^1H$ n.m.r. spectra were recorded courtesy of Dr. B. J. Wakefield of Salford University, with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. The chemical shift values are recorded in δ units. The i.r. spectra were recorded on a Perkin-Elmer 2378 IR spectrometer for potassium bromide discs. Mass spectra were recorded on AEIMS 30 instrument by the electron impact method and c.i.m.s. were recorded from CDRI Lucknow.

3-(*Aryliminomethyl*)*chromones* (**2a—e**).—Toluene-*p*-sulphonic acid (10 mg) was added to a solution of 3-formylchromone (1.74 g, 10 mmol) and *p*-anisidine (1.23 g, 10 mmol) in dry benzene (80 ml) and the resulting mixture was heated under reflux using a Dean-Stark water trap for 30 min. It was then evaporated under reduced pressure and the product (**2**) recrystallised from benzene–light petroleum.

*Reaction of* 3-(*Aryliminomethyl*)*chromones with Hydrazonoyl Bromides.*—Dry triethylamine (20 mmol) in chloroform was added dropwise, over 20 min, to a solution of 3-(*p*-methoxyphenyliminomethyl)chromone (**2a**) (10 mmol) and *C*-acetylhydrazonoyl bromide (10 mmol) in anhydrous chloroform (30 ml) with magnetic stirring, the temperature being maintained at 0—5 °C. The resulting mixture was stirred for a further 2—3 h after which it was evaporated under reduced pressure; the residue was then taken up in benzene (25 ml). The precipitated triethylamine hydrobromide was filtered off and the filtrate was distilled under reduced pressure. The residue thus obtained was purified by column chromatography (silica gel, benzene–light petroleum, 20:1) to give the [2 + 3] and [4 + 3] type cycloadducts (**6**) and (**5**) in 45 and 15% yield respectively. Other cycloadducts were prepared similarly and their full details are given in Table 1—3.

*Preparation of Nitrones.*—N-*Phenylnitrone* (**10a**). Phenylhydroxylamine was added to a solution of 3-formylchromone in dry benzene (1:1 molar ratio) with occasional stirring to give an immediate reaction and separation of light yellow crystals of (**10a**). These were filtered off and recrystallised from benzene–light petroleum (1:1); yield 75%, m.p. 136—137 °C, *m/z* 265 ($M^+$) (Found: C, 72.6; H, 4.3; N, 5.3. $C_{16}H_{11}NO_3$ requires, C, 72.45; H, 4.15; N, 5.28%).

N-*Methylnitrone* (**10b**). Triethylamine in dry benzene was added to an equimolar mixture of 3-formylchromone and *N*-methylhydroxylamine hydrochloride in dry benzene with magnetic stirring. Stirring was continued for a further 4—6 h after which the mixture was filtered. The filtrate, on evaporation, gave the nitrone as light yellow crystals (**11b**) (80%) which were recrystallised from benzene–light petroleum (1:1), m.p. 144—146 °C; $\delta_H$ (60 MHz, $CDCl_3$) 3.65 (3 H, s, Me), 6.85—7.80 (5 H, m), and 8.45 (1 H, s); *m/z* 203 ($M^+$) (Found: C, 65.15; H, 4.55; N, 6.9. $C_{11}H_9NO_3$ requires C, 65.02; H, 4.43; N, 6.89%).

*Reaction of* N-*Phenylnitrone* (**10a**) *with Styrene.*—Equimolar proportions of the nitrone (**10a**) and styrene were refluxed in dry benzene (70 ml) for 24 h. The refluxing mixture, upon cooling to room temperature, gave light yellow crystals of the cycloadduct which was thoroughly washed with light petroleum (b.p. 60—80 °C), and recrystallised from benzene to give (**12a**) (45%), m.p. 105—106 °C; $\delta_H$ (90 MHz, $CDCl_3$) 2.95 (2 H, m, methylene), 4.80 (1 H, q, Hd), 5.35 (1 H, q, $H_a$), 6.90—7.80 (9 H, m, ArH), and 8.25 (1 H, s); *m/z* 369 ($M^+$).

*Reaction of* N-*Methylnitrone with Styrene.*—Equimolar proportions of the title reactants were refluxed in dry benzene for 36 h. The cycloadduct formed was separated from unchanged nitrone by column chromatography (silica gel) using light petroleum–ethyl acetate (4:1) as the eluant. The crude product was taken up in light petroleum (b.p. 60–80 °C) and the solution cooled to give the cycloadduct as yellow crystals (50%), m.p. 101—103 °C; $\delta_H$ (90 MHz, $CDCl_3$) 2.85 (3 H, s), 2.15 and 3.35 (2 H, both dt), 4.35 (1 H, t), 5.35 (1 H, t), and 7.25—8.25 (10 H, ArH); *m/z* 307 ($M^+$).

*Reaction of* N-*Phenyl- and* N-*Methyl-nitrone with Acrylonitrile.*—The nitrone (**10a**) (1.32 g) and acrylonitrile (0.530 g) were dissolved in dry benzene (50—60 ml) and kept at room temperature overnight. Evaporating of the mixture under reduced pressure gave crude product which was recrystallised from benzene–light petroleum (1:1) to provide the pure product, m.p. 148—151 °C.

The reaction of *N*-methylnitrone (**10b**) with acrylonitrile was similarly carried out in dry benzene, and the adduct formed was separated by column chromatography using ethyl acetate–light

petroleum (1:4) as eluant. The product (**12d**) (55%) had m.p. 82—84 °C. Data for (**12c**), $\delta_H$ (60 MHz, $CDCl_3$) 2.35—2.85 (2 H, m), 4.45—4.95 (2 H, m), and 6.45—7.80 (10 H, m, ArH); $\nu_{max.}$(KBr) 2 130 $cm^{-1}$ (C≡N); *m/z* 318 ($M^+$). For (**13d**), $\delta_H$ (60 MHz, $CDCl_3$) 2.60 (3 H, s), 2.90—3.45 (2 H, m), 3.65—4.70 (2 H, m), and 7.80—8.85 (5 H, m, ArH); $\nu_{max.}$(KBr) 2 135 $cm^{-1}$ (C≡N); *m/z* 256 ($M^+$).

*Reaction of* N-*Methyl- and* N-*Phenyl-nitrone with* 4-*Methyl-Styrene.*—Equimolar proportions of *N*-methylnitron and 4-methylstyrene were refluxed in dry benzene for 24 h and the crude product formed was subjected to column chromatography using light petroleum–ethyl acetate (4:1) as eluant. A solution of the product in light petroleum when cooled gave (**12e**) as white crystalline solid, m.p. 75—76 °C. Similarly *N*-phenyl-nitrone and styrene gave the cycloadduct (**12f**), m.p. 78—79 °C (42%). For (**12a**) $\delta_H$ (60 MHz, $CDCl_3$) 2.05 (6 H, s, Me), 2.45—2.95 (2 H, m), 4.70 (1 H, d), 5.30 (1 H, m), and 6.00—7.75 (9 H, m); *m/z* 321 ($M^+$).

*Reaction of* N-*Methylnitrone with* N-*Phenylmaleimide.*—Equimolar proportions of the reactants were refluxed in dry benzene for 20 h. The reaction mixture, upon cooling to room temperature, gave the adduct as colourless crystals. The solvent was decanted and the product was thoroughly washed with light petroleum and recrystallised from benzene to give (**13g**), m.p. 171—172 °C; $\delta_H$ (60 MHz, TFA), 2.85 (3 H, s, Me), 3.65—4.10 (1 H, m), 4.60 (1 H, m), 5.30 (1 H, m), and 6.25—7.65 (10 H, m, ArH); *m/z* 376 ($M^+$).

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