Benzopyrans. Part 45[1]. Reactions of monobrominated 3-acetyl-2-methyl-1-benzopyran-4-one with some binucleophiles

Chandra Kanta Ghosh*[a], Chandreyi Ghosh[a], Sumit Kumar Karak[a] and Ajit Kumar Chakravarty[b]

[a]*Organic Chemistry Laboratory, Department of Biochemistry, Calcutta University, Kolkata – 700 019, India*

[b]*Medicinal Chemistry Division, Indian Institute of Chemical Biology, Kolkata – 700 032, India*

The chromone **5**, obtained by bromination of 3-acetyl-2-methylchromone (**3**), gives [1]benzoxepino[4,3-*d*]isoxazole (**10**) and [1]benzoxepino[3,4-*c*]pyrazole (**11**), respectively, with hydroxylamine and phenylhydrazine, pyrrolo[3,4-*b*][1]benzopyran (**18**) with thiourea, thiazole **19** with thioacetamide, and quinoxaline **21** with *o*-phenylenediamine.

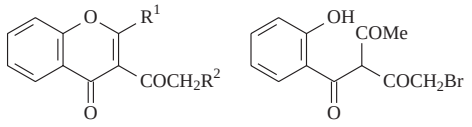
Keywords: 1-benzopyran-4-ones, fused [1]benzoxepins, isoxazoles, pyrazoles, pyrroles, benzopyrans, quinoxalines

3-Acetyl-1-benzopyran-4-one (3-acetylchromone, **1**) on treatment with bromine in chloroform gives 3-bromoacetylchromone (**2**).[2] The methyl group of 3-unsubstituted 2-methylchromone is reactive towards iodine[3] and dimethylformamide dimethyl acetal (DMFDMA)[4] in the presence of pyridine. The 2-Me group of 3-acetyl-2-methylchromone (**3**) is more active than its acetyl methyl towards DMFDMA, even in the absence of added base.[5] So monobromination of **3** may give either or both of **4** and **5**. Both the isomers **4** and **5**, being related to the same pyran ring opened form **6**, may be 'chemically equivalent' towards nucleophiles under certain conditions.

Bromination of 3-acetyl-6-chloro-2-methylchromone with bromine in acetic acid has been reported, without any convincing proof, to give the corresponding 3-bromoacetyl compound.[6] The compound **3**, having 2.52 and 2.64 as δ_H values for its methyl and acetyl groups, on bromination in carbon tetrachloride gave a compound (m.p. 114 °C) showing two-proton and three-proton singlets respectively at δ 4.84 and 2.62 ppm; these ^{1}H NMR data indicate monobromination of **3** but fail to distinguish between structures **4** and **5**. Its ^{13}C NMR spectrum shows a methylene and a methyl carbon respectively at δ 36.4 and 20.1 ppm, apart from six singlets and four doublets. The 2-methyl carbon of 2-methyl- and 3-acetyl-2-methylchromone appears at δ 18–20, whereas the acetyl methyl carbon of 2-unsubstituted and 2-methyl-3-acetylchromone appears around δ 32 ppm.[4,7] Furthermore, the methylene carbons of 3-bromoacetylchromone (**2**) and 3-benzoyl-2-bromomethylchromone appear respectively at 36.9 and 25.2 ppm.[8] Comparison of these ^{13}C NMR spectral data convincingly demonstrates that the said monobromo derivative of **3** should be assigned the structure of 3-bromoacetyl-2-methylchromone (**5**). The reactions of the chromone **5** with some binucleophiles are described in this paper.

Nucleophilic 1,4-addition to 3-bromoacetylchromone (**2**)[2,9] as well as 3-acetyl-2-methylchromone (**3**)[10,11] is well known. So a nucleophile such as hydroxylamine **7** (X = O) is likely to undergo 1,4-addition to the α,β-unsaturated carbonyl functionality of **5** with concomitant opening of the pyran ring and the resultant intermediate **8** (Scheme 1) may give rise to the fused isoxazole **10** via **9** (path *a*) or oxazine **13** via **12** (R = Me) (path *b*). The formation of the intermediate **9** from **5** and **7** is analogous to the base-catalysed ring-enlarging rearrangement of 3-bromoacetylchromone (**2**) to 2,3-dihydro-3-oxo-5-hydroxy-1-benzoxepin-4-carboxaldehyde.[2,9]

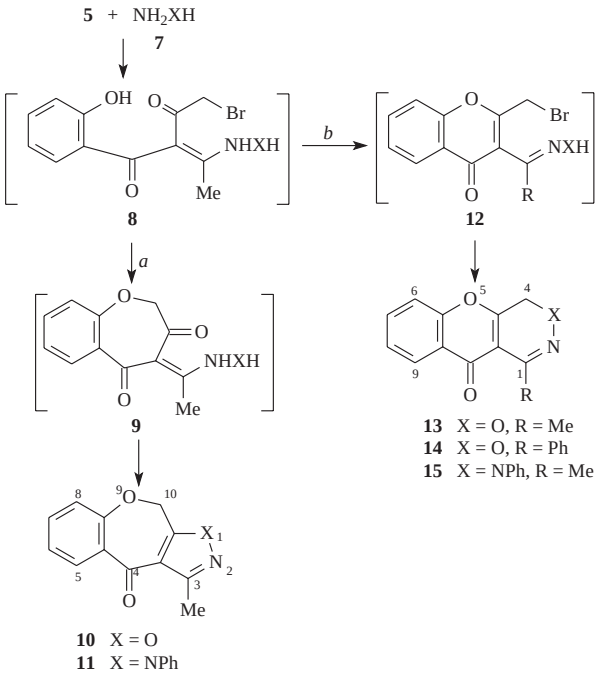
The structure **10** or **13** is indeed assignable to the product isolated from the reaction mixture of the chromone **5** and hydroxylamine. Its ^{1}H NMR spectrum fails to distinguish between these two isomeric structures. The product is, however, assigned the structure **10** on the basis of its ^{13}C NMR spectrum,



	R^1	R^2
1	H	H
2	H	Br
3	Me	H
4	CH_2Br	H
5	Me	Br

6

the peak at δ 190.4 being attributable to the carbonyl carbon of its 2*H*-1-benzoxepin-5-one system[12] and the peak positions for its isoxazole ring carbons tallying with those of 4-acyl-3,5-dialkylisoxazoles.[13] Had this product been the oxazine **13**, its carbonyl carbon being a part of the 1-benzopyran-4-one system[4,14] would have appeared around δ 180 ppm. The oxazine **14**, analogous to **13**, was prepared by reacting 3-benzoyl-2-bromomethylchromone[8] with hydroxylamine, the formation of the product involving the derivatisation of the carbonyl group of the substrate with hydroxylamine (forming **12**, X = O, R = Ph) followed by cyclisation. ^{13}C NMR spectrum of **14** indeed exhibits a peak at δ 180.6 ppm ascribable to the carbonyl carbon of its 1-benzopyran-4-one moiety. The chromone **5** with phenylhydrazine gave the fused pyrazole **11** in exclusion of the pyridazine **15**.

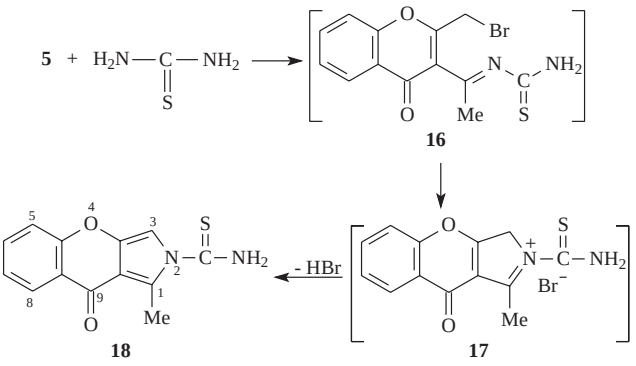


10 X = O
11 X = NPh

13 X = O, R = Me
14 X = O, R = Ph
15 X = NPh, R = Me

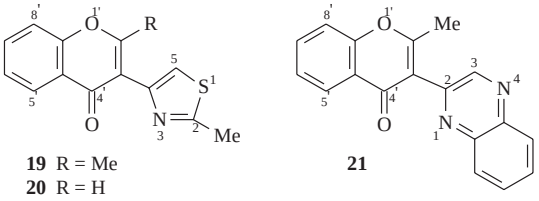
Scheme 1

* Correspondence. E-mail: chandrakantaghosh@rediffmail.com



Scheme 2

The chromone **5** with thiourea gave the pyrrolopyran **18**. Here thiourea with **5** forms the intermediate **16,** through a mechanism similar to the one as depicted in Scheme 1 path *b*, that on cyclisation by an intramolecular substitution reaction (forming the intermediate **17**) and subsequent elimination of hydrogen bromide leads to the pyrrole-*N*-thiocarbamide **18** (Scheme 2). The pyrrole **18** shows in its mass spectrum the molecular ion peak as the base peak and the ion obtained therefrom after elimination of the neutral C(=NH)S species has also a high relative stability.



19 R = Me
20 R = H

21

The chromone **5** behaved as a halocarbonyl compound in condensing with thioacetamide (Hantzsch's synthesis)[6,15] to give the disubstituted thiazole **19**. The 2-unsubstituted analogue of **5** also behaved similarly towards thioacetamide in giving the thiazole **20**. Condensation of *o*-phenylenediamine with the α-bromoketone functionality of **5** followed by air oxidation gave the quinoxaline **21**. The latter reaction is analogous to the formation of pyrazines from β-ketosulfoxides and a 1,2-diamino-alkene or -arene.[16]

Experimental

Yields and uncorrected melting points of the crystallised products are reported and no attempt was made to optimize the yield. NMR spectra were recorded for the compounds dissolved in $CDCl_3$ unless stated otherwise; *J*-values are given in Hz. Light petroleum refers to the fraction with distillation range 40–60 °C.

3-Bromoacetyl-2-methyl-1-benzopyran-4-one (**5**): To a warmed solution of 3-acetyl-2-methylchromone **3** (4.04 g, 20 mmol) in carbon tetrachloride (200 ml) was added dropwise bromine (1.0 ml, ~ 20 mmol). The reaction started after some time and hydrogen bromide started to evolve. After the addition was over, the reaction mixture was warmed for 10–15 min. in order to complete the reaction and remove HBr as far as possible. It was then concentrated and diluted with light petroleum, the deposited solid was collected by filtration and crystallised from chloroform (charcoal)–light petroleum to yield **5** as colourless crystals (4.30 g, 77 %), m.p. 114 °C (Found: C, 51.0; H, 2.9. $C_{12}H_9BrO_3$ requires C 51.3; H, 3.2 %); δ_H 8.26 (1H, dd, *J* 8.0, 2.0, 5-H), 7.88–7.32 (3H, m, other Ph H), 4.84 (2H, s, CH_2) and 2.62 (3H, s, Me); δ_C 193.1 (exocyclic CO), 175.3 (4-C), 171.1 (2-C), 155.2 (8a-C), 134.2 (7-C), 125.7 (5-, 6-C), 123.2 (4a-C), 120.3 (3-C), 117.7 (8-C), 36.4 (CH_2) and 20.1 (Me); *m/z* 282, 280 (M^+, 3 %), 201 (M – Br, 4), 187 (M – CH_2Br, 6), 173 (201 – CO, 3) and 92 (C_6H_4O, 100).

General procedure for treatment of the chromone **5** *with hydroxylamine, thiourea and o-phenylenediamine*: The chromone **5** (280 mg, 1 mmol) was refluxed separately with each of hydroxylamine hydrochloride, thiourea and *o*-phenylenediamine (1 mmol) in ethanol (75 ml) containing sodium acetate (~ 500 mg). The progress of the reaction was monitored by TLC. Though the substrate **5** ceased to exist generally after 3 h, the reaction went to completion in about 5 h. The reaction mixture was then concentrated and diluted with water and the precipitated solid was filtered off. The filtrate was extracted with chloroform. No pure compound could be obtained from this organic extract, even by elaborate column chromatography. The solid material was dried and crystallised from chloroform–light petroleum to give the product, the characterisation data of which are given below.

3-Methyl-[1]benzoxepino[4,3-d]isoxazol-4(10H)-one (**10**): From **5** and **7** (X = O) as colourless crystals (30 %), m.p. 114 °C (Found : C, 67.2; H, 4.5; N 6.2. $C_{12}H_9NO_3$ requires C, 67.0; H, 4.2; N, 6.5 %); ν_{max} ($CHCl_3$) / cm^{-1} 1650 (CO) and 1600 (C=C); δ_H 8.08 (1H, dd, *J* 8.0, 2.0, 5-H), 7.65–7.12 (3H, m, 6-, 7-, 8-H), 5.28 (2H, s, CH_2) and 2.60 (3H, s, Me); δ_C 190.4 (4-C), 169.1 (3-C), 160.2 (10a-C), 157.1 (8a-C), 133.6 (7-C), 127.7 (5-C), 124.9 (6-C), 121.6 (8-C), 119.2 (4a-C), 114.9 (3a-C), 77.2 (CH_2) and 11.4 (Me); *m/z* 215 (M^+, 100 %), 186 (M–CO–H, 8), 173 (M–MeCN–H, 29), 159 (M–MeCNO + H, 16), 144 (173–CO–H, 37) and 121 (HOC_6H_4CO, 56).

1-Methyl-9-oxo-2,9-dihydro[1]benzopyrano[2,3-c]pyrrole-2-thiocarbamide (**18**): From **5** and thiourea as yellowish brown crystals (23 %), m.p. 230–232 °C (Found : C, 60.2; H, 4.1; N, 10.8. $C_{13}H_{10}N_2O_2S$ requires C, 60.4; H, 3.9; N, 10.8 %); ν_{max} (KBr) / cm^{-1} 3330, 3122 (NH_2) and 1623 (CO); δ_H (DMSO-d_6) 8.05 (1H, dd, *J* 7.9, 1.5, 8-H), 7.77 (1H, ddd, *J* 8.4, 7.2, 1.5, 6-H), 7.59 (1H, d, *J* 8.4, 5-H), 7.45 (1H, m, 7-H), 6.96 (2H, s, NH_2), 6.77 (1H, s, 3-H) and 2.49 (3H, s, Me); δ_C (DMSO-d_6) 175.0 (9-C), 167.0 (C=S), 165.1 (3a-C), 154.9 (4a-C), 141.5 (1-C), 133.8 (6-C), 125.3 (8-C), 125.1 (7-C), 122.6 (8a-C), 117.8 (5-C), 117.7 (9a-C), 107.5 (3-C) and 19.8 (Me); *m/z* 258 (M^+, 100 %), 241 (M–NH_2–H, 42), 199 [M–C(=NH)S, 88] and 183 (30).

2-(2-Methyl-4-oxo-4H-1-benzopyran-3-yl)quinoxaline (**21**): From **5** and *o*-phenylenediamine as white solid (25 %), m.p. 192 °C (chloroform–light petroleum) (Found : C, 75.2; H, 3.9; N, 9.5. $C_{18}H_{12}N_2O_2$ requires C, 75.0; H, 4.2; N, 9.7 %); δ_H 9.08 (1H, s, 3-H), 8.36–7.36 (8H, m, ArH) and 2.52 (3H, s, Me); *m/z* 288 (M^+, 100 %), 186 (M–C_6H_5NC + H, 12) and 168 (M–$C_7H_4O_2$, 35).

1-Phenyl-[1]benzopyrano[3,2-d][1,2]oxazin-10(4H)-one (**14**): 3-Benzoyl-2-bromomethyl-chromone[8] (343 mg, 1 mmol) on treatment with hydroxylamine hydrochloride (70 mg, 1 mmol) and sodium acetate (~ 500 mg) by the previously described procedure yielded the oxazine **14** as colourless crystals (90 mg, 32 %), m.p. 166 °C (Found : C, 73.7; H, 4.1; N, 5.3. $C_{17}H_{11}NO_3$ requires C, 73.6; H, 4.0; N, 5.1 %); δ_H 8.00 (3H, m, 9-H + 2 PhH *ortho* to –C=N), 7.72-7.16 (6H, m, other ArH), 5.30 (2H, s, CH_2); δ_C 180.6 (10-C), 161.7 (4a-C), 159.4 (5a-C), 135.2 (7-C), 131.9 (9-C), 129.6 (3'-,5'-C), 128.5 (1-C), 126.4 (2'-,4'-,6'-C), 124.3 (9a-c), 122.8 (8-C), 120.3 (6-C), 66.2 (CH_2), 10a-C and 1'-C not detected; *m/z* 277 (M^+, 77 %), 105 (C_6H_5CO, 100) and 77 (C_6H_5, 76).

3-Methyl-1-phenyl-1,10-dihydro-4H-[1]benzoxepino[3,4-c]pyrazol-4-one (**11**): The chromone **5** (1 mmol) was treated with phenylhydrazine hydrochloride (144 mg, 1 mmol) in the presence of sodium acetate (~ 500 mg) similarly as described for the treatment of **5** with hydroxylamine hydrochloride. The reaction was monitored by TLC and found to be complete in about 5 h. The reaction mixture on usual work-up did not produce any solid material. It was extracted with chloroform and the concentrated organic extract was chromatographed over silica gel. The material eluted out with ethyl acetate–light petroleum (1:6) afforded the pyrazole **11** (67 mg, 22 %), m.p. 162 °C (chloroform–light petroleum) (Found : C, 74.8; H, 5.2; N, 10.0. $C_{18}H_{14}N_2O_2$ requires C, 74.5; H, 4.9; N, 9.7 %); ν_{max} ($CHCl_3$) / cm^{-1} 1665 (CO); δ_H 7.62-6.80 (9H, m, Ph H), 4.60 (2H, s, CH_2) and 2.60 (3H, s, Me); δ_C 194.3 (4-C), 157.3 (8a-C), 151.9 (3-C), 140.8 (10a-C), 139.9 (Ph C linked to N), 131.1 (7-C), 129.7 (5-C), 129.2 (Ph C *meta* to N), 128.4 (6-C), 125.8 (Ph C *ortho* to N), 124.2 (Ph C *para* to N), 122.0 (8-C), 121.8 (4a-C), 118.2 (3a-C), 79.3 (CH_2) and 13.8 (Me); *m/z* 290 (M^+, 100 %), 261 (M–CO–H, 25), 220 (261–MeCN, 25), 190 (220–CH_2O, 21), 157 (M–CO–Ph N_2, 21) and 118 (220–PhNC + H, 43).

Treatment of 3-bromoacetylchromone with thioacetamide: Each of the chromones **2** and **5** (1 mmol) was heated under reflux in ethanol (75 ml) containing thioacetamide (75 mg, 1 mmol) and sodium carbonate (~ 150 mg) for 4 h. The reaction mixture was concentrated by distilling out most of ethanol. It was then diluted with water and made acidic by addition of acetic acid. The deposited solid was collected by filtration, dried and crystallised from chloroform–light petroleum to afford the following thiazoles.

2-Methyl-4-(2-methyl-4-oxo-4H-1-benzopyran-3-yl)thiazole (**19**): From **5** and thioacetamide, yield 52 %; m.p. 124 °C (Found : C, 6.51; H, 3.9; N, 5.1. $C_{14}H_{11}NO_2S$ requires C, 65.4; H, 4.3; N, 5.4 %);

δ_H 8.26 (1H, dd, *J* 8.0, 2.0, 5'-H), 7.76-7.24 (4H, m, 3 Ph H + thiazole-H), 2.64 (3H, s, Me) and 2.56 (3H, s, Me); *m/z* 257 (M^+, 100 %), 216 (M – MeCN, 23), 199 (M – CH_2CS, 27), 183 (M – MeCNS, 45), 155 (183 – CO, 10) and 121 (HOC_6H_4CO, 28).

2-Methyl-4-(4-oxo-4H-1-benzopyran-3-yl)thiazole (**20**): From **2** and thioacetamide, yield 33 %; m.p. 174 °C (Found: C, 63.9; H, 3.8; N, 6.1. $C_{13}H_9NO_2S$ requres C, 64.2; H, 3.7; N, 5.8 %); δ_H 9.08 (1H, s, 5-H), 8.42 (1H, s, 2'-H), 8.38 (1H, dd, *J* 8.0, 2.0, 5'-H), 7.82–7.40 (3H, m other Ph H) and 2.76 (3H, s, Me); δ_C 175.6 (4'-C), 164.4 (2-C), 157.7 (2'-, 8'a-C), 145.4 (4-C), 133.3 (7'-C), 126.0 (5'-C), 125.1 (6'-C), 124.3 (4'a-C), 118.6 (3'-C), 118.0 (8'-C), 117.6 (5-C) and 19.0 (Me).

Financial assistance from CSIR, New Delhi is duly acknowledged.

Received 14 August 2003; accepted 6 January 2004
Paper 03/2054

References

1 Part 44: C.K. Ghosh, S.K. Karak and A. Patra, *Heterocycles*, 2003, **60**, 825.
2 S. Klutchko and M. von Strandtmann, *Synthesis*, 1977, 61.
3 J. Schmutz, R. Hirt and H. Lauener, *Helv. Chim. Acta*, 1952, **35**, 1168.
4 C.K. Ghosh, S. Bhattacharyya, C. Ghosh and A. Patra, *J. Chem. Soc., Perkin Trans. 1*, 1995, 3005.
5 C.K. Ghosh, C. Pal, J. Maiti and M. Sarkar, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1489.
6 R.P. Kapoor, M.K. Rastogi, R. Khanna and C.P. Garg, *Ind. J. Chem*., 1984, **23B**, 390.
7 G.P. Ellis and J.M. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2557.
8 C.K. Ghosh, unpublished results.
9 S. Klutchko and M. von Strandtmann, US Patent, 4, 001, 224; *Chem. Abstr*., 1977, **87**, 3914.
10 C.K. Ghosh, C. Pal and A. Bhattacharyya, *Ind. J. Chem*., 1985, **24B**, 914.
11 C.K. Ghosh, S. Sahana and A. Patra, *Tetrahedron*, 1993, **49**, 4127.
12 J.K. Holroyle, A.F. Orr and V. Thaller, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1490.
13 C.M. Buchan and A.B. Turner, *J. Chem. Soc., Perkins Trans. 1*, 1975, 2115.
14 I.W.J. Still, N. Plavac, D.M. McKinnon and M.S. Chauhan, *Can. J. Chem*., 1976, **54**, 280.
15 J.V. Metzger in *Comprehensive Heterocyclic Chemistry* A.R. Katritzky and C.W. Rees eds, Pergamon Press, 1984, vol. 6, part 4B, p. 294.
16 S. Kano, Y. Takahagi and S. Shibuya, *Synthesis*, 1978, 372.