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Benzopyrans: Part 46†—Reactions of 3-benzoyl-2-bromomethyl-1-benzopyran-4-one with some bisnucleophiles

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Phenylhydrazine as well as thiourea, like sodium acetate, brings about substitution of bromine in the title bromomethylpyranone **2**. The pyranone **2** gives the pyrano fused oxazine **9** with hydroxylamine, pyridiazines **10** and **11**, respectively with hydrazine and phenylhydrazine, and thiophene **16** with thioacetamide.

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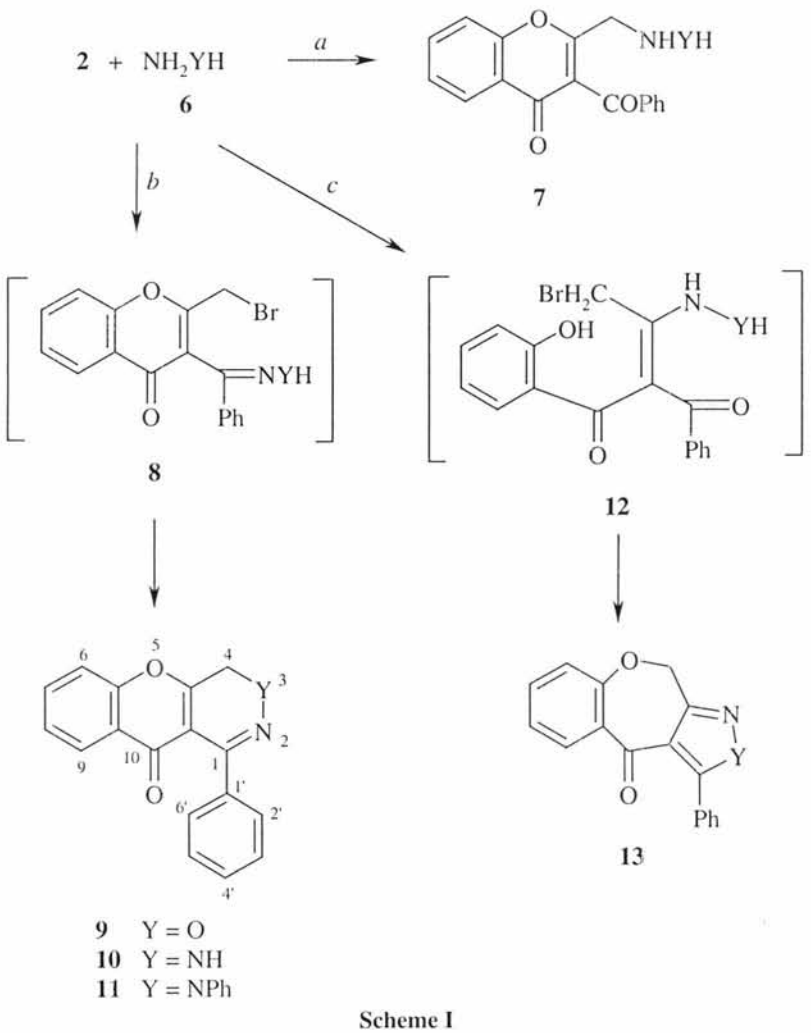
The title benzopyranone **2** (trivial name: 3-benzoyl-2-bromomethylchromone) obtained by bromination of 2-methylchromone **1** has three significant electropositive centres – carbon bonded to bromine, pyran ring carbon at 2-position and exocyclic carbonyl carbon. So the nature of the product obtainable by reacting the title chromone **2** even with a simple mononucleophile will depend on the initial mode of attack by that nucleophile. Reactions of the substrate **2** with some bisnucleophiles, seemingly further complicated and more interesting, were studied and the results are discussed in this paper.

Results and Discussion

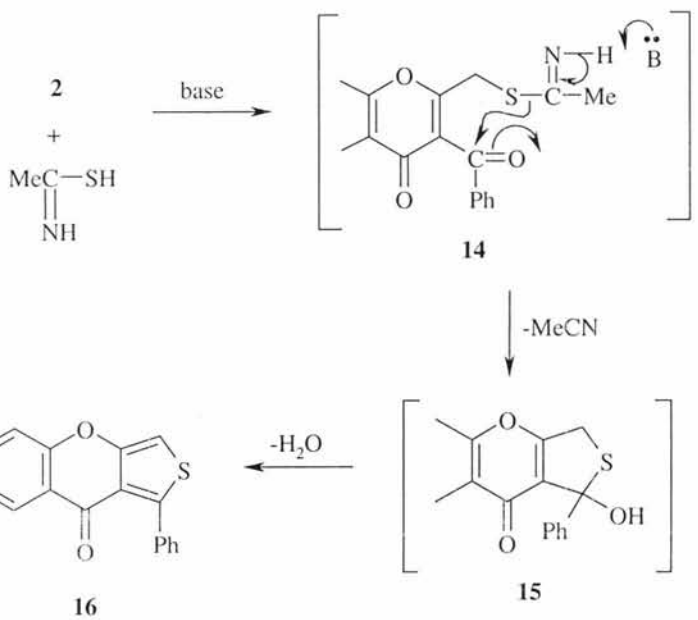
In its reaction with the chromone **2** a bisnucleophile like hydroxylamine (**6**, Y = O) can (i) simply substitute bromine giving **7** (**Scheme I** – path *a*) that can undergo further transformation, (ii) derivatise exocyclic carbonyl group to form **8** that may cyclise to the benzopyrano-oxazine **9** (path *b*), and (iii) attack at pyran 2-position (nucleophilic 1,4-addition to the α,β-unsaturated carbonyl functionality) with concomitant opening of the pyran ring (→ **12**) followed by recyclisation to **13** (Y = O) (path *c*). The isomers **9** and **13** (Y = O) can best be distinguished from their ^{13}C NMR spectra. The appearance of a singlet around δ 190 ppm is a diagnostic feature of the carbonyl carbon of 2*H*-1-benzoxepin-5-one systen[1,2] whereas the carbonyl carbon of γ-pyrone, chromone[3], and 2,3-fused chromones[4] appears at δ 175-180 ppm. Refluxing **2** with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol gave exclusively the fused oxazine **9**. The chromone **2** on similar treatment with hydrazine hydrochloride gave the fused pyridiazine **10**. A mixture of 2-acetoxymethylchromone **3** and the hydrazine **4**, evidently resulting from substitution of bromine respectively with acetate anion and phenylhydrazine (path *a*) was obtained by refluxing **2** with phenylhydrazine hydrochloride in aqueous ethanol containing sodium acetate. The same reaction with sodium carbonate replacing sodium acetate afforded the pyridiazine **11**. All the pyrano fused heterocyles (**9** - **11**) arise from chromone **2** and NH_2YH (Y=O, NH and NPh) through the intermediate **8** by a mechanism as depicted in **Scheme I** (path *b*), the formation of **10** through **7** (Y=NH) (path *a*) being not completely ruled out.

Thiourea brought about substitution reaction in **2** giving **5** that survived heating under reflux even in a high boiling solvent as ethylene glycol. The chromone **2** reacted with thioacetamide in the presence of a base to give the thieno[3,4-*b*][1]benzopyran **16**. Here the intermediate **14**, initially resulting from substitution of bromine by thioacetamide, undergoes base catalysed elimination of acetonitrile and cyclisation to **16** via **15** (**Scheme II**). The proposed mechanism entails that

†For Part 45, see ref. 1



Scheme I



Scheme II

thioacetamide here functions as a source of hydrogen sulfide. It is relevant to mention here that thioacetamide as a source of hydrogen sulfide is indeed utilized in the synthesis of thioamides from the corresponding nitriles under acidic conditions[5].

Conclusion

All the nucleophiles under present study while reacting with 3-acyl-2-bromomethylchromone **2** initially brings about either substitution at bromomethyl carbon (**Scheme I** – path *a* and **Scheme II**) or derivatisation involving exocyclic carbonyl carbon (**Scheme I** – path *b*); the complete exclusion of the reaction course as depicted in **Scheme I** (path *c*) indicates the pyran 2-position of **2** to be less electropositive compared to the aforesaid two carbons.

Though various heterocycles fused with the 2,3-bond of 1-benzopyran-4-one are known[6,7], the 1-phenyl-1-benzopyrano[3,2-*d*][3,2]oxazin-10(4*H*)-one system as **9** is reported for the first time. 1-Benzopyrano[2,3-*d*]pyridiazine system as present in **10** and **11** is also scarce in literature, only synthesis of 1,2-dihydro-2-phenyl-1-benzopyrano[2,3-*d*]pyridiazine-4,10-dione from ethyl 3-bromomethyl-4-oxo-4*H*-1-benzopyran-2-carboxylate and phenylhydrazine having been described[8]. Among thiophenes fused with the 2,3-bond of 1-benzopyran-4-one, only thieno[3,2-*b*][1]benzopyran-9-one system is known[9,10], and the compound **16** reported in the present paper seems to be the first member of the heitherto unknown thieno[3,4-*b*][1]benzopyran-9-one system.

Experimental Section

General. Melting points are uncorrected. Yields of the isolated pure products are recorded. NMR spectra of the compounds dissolved in $CDCl_3$, unless stated otherwise, were recorded at 300 MHz. Light petroleum refers to the fraction, bp 60-80°C.

3-Benzoyl-2-bromomethyl-1-benzopyran-4-one 2. To a warm solution of 3-benzoyl-2-methylchromone **1** (5.3 g, 20 mmoles) in carbon tetrachloride (200 mL) was added dropwise bromine (1.0 mL, ~ 20 mmoles)). 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 possible; it was then concentrated and diluted with light petroleum. The deposited solid collected by filtration was crystallised from chloroform (charcoal) -light petroleum to give the title chromone **2** as colourless crystals (5.5 g, 81%), mp 149-52°C; ^{1}H NMR: δ 8.20 (1H, dd, J = 8.0, 2.0 Hz, benzopyran 5-H), 8.00-7.36 (8H, *m*, other ArH), 4.32 (2H, s, CH_2); ^{13}C NMR: δ 193.2 (benzoyl CO), 176.3 (4-C), 162.1 (2-C), 156 (8a-C), 137.2 (1′-C), 135.1 (7-C), 134 (5-C), 129.9 (3′-, 5′-C), 129.2 (2′-, 6′-C), 126.5 (6- or 6′-C), 126.4 (6′- or 6-C), 123.9 (4a-C), 118.6 (8-C), 25.2 (CH_2), 3-C not detected.

Treatment of the chromone 2 with hydroxylamine hydrochloride, hydrazine hydrochloride and phenylhydrazine hydrochloride in the presence of sodium acetate. The chromone **2** (343 mg, 1 mmole) was refluxed separately with each of the above named hydrochlorides (1 mmole) in ethanol (75 mL) containing sodium acetate (~ 500 mg) for 4-6 hr. The reaction mixture was concentrated and diluted with water. The precipitated solid was filtered off, dried and crystallised from chloroform – light petroleum. By this procedure the chromone **2** gave with hydroxylamine and hydrazine hydrochlorides respectively, the fused oxazine **9** and pyridiazine **10** but with phenylhydrazine hydrochloride, a mixture of the acetate **3** and hydrazine **4** which were separated by fractional crystallisation from chloroform, the latter **4** first crystallising out. The characterization data of the products are given below.

2-Acetoxymethyl-3-benzoyl-1-benzopyran-4-one 3: White solid (12%), mp 167°C; ^{1}H NMR: δ 8.18 (1H, dd, J = 7.8, 1.2 Hz, 5-H), 7.92 (2H, dd, J = 7.2, 1.2 Hz, 2′-, 6′-H), 7.74 (1H, m, 7-H), 7.60-7.43 (5H, m, other ArH), 5.06 (2H, s, CH_2), 1.83 (3H, s, Me); ^{13}C NMR: δ 192.9 (benzoyl CO), 176.3 (4-C), 170.2 (acetoxy CO), 161.5 (2-C), 156.2 (8a-C), 137.3 (1′-C), 134.9 (7-C), 134.7 (4′-C), 129.8 (2′-, 6′-C), 129.1 (3′-, 5′-C), 126.5 (5-C), 126.3 (6-C), 124.1 (4a-C), 124.0 (3-C), 118.5 (8-C), 61.3 (CH_2), 20.4 (Me).

3-Benzoyl-2-(2-phenylhydrazinomethyl)-1-benzopyran-4-one 4: Yellowish shining crystals (18%), mp 126°C; Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.6; H, 5.0; N, 7.6. Found: C, 75.0; H, 4.7; N, 7.8%; ^{1}H NMR: δ 8.18 (1H, dd, J = 7.9, 1.5 Hz, 5-H), 7.92 (2H, m, PhH *ortho* to CO), 7.70-7.14 (11H, m, other ArH), 4.47 (2H, s, CH_2), 2.38 (1H, ArNH).

1-Phenyl-4*H*-1-benzopyrano[3, 2-*d*][3,2]oxazin-10-one 9: Colourless crystals (32%), mp 166°C. Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.6; H, 4.0; N, 5.1. Found: C, 73.7; H, 4.1; N, 5.3%; ^{1}H NMR: δ 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); ^{13}C NMR: δ 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; Mass: m/z 277 (M^+, 77%), 105 (C_6H_5CO, 100), 77 (C_6H_5, 76).

3,4-Dihydro-1-phenyl-1-benzopyrano[2,3-*d*]pyridiazin-10-one 10: White shining crystals (54%), mp 134°C. Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.9; H, 4.4; N 10.1. Found: C, 74.2; H, 4.0; N, 10.3%; ^{1}H NMR: δ 8.17 (1H, dd, J = 8.0, 1.5 Hz, 9-H), 7.92 (2H, dd, J = 7.1, 1.4 Hz, 2′-, 6′-H), 7.70 (1H, ddd, J = 7.4, 7.0, 1.5 Hz, 7-H), 7.64-7.44 (5H, m, other ArH), 4.67 (2H, s, CH_2); ^{13}C NMR: δ 175.9 (10-C), 161.2 (4a-C), 155.9 (5a-C), 136.8 (1′-C), 134.7 (7-C), 134.2 (9-C), 129.5 (3′, 5′-C), 128.8 (2′, 6′-C), 126.1 (4′-C), 126.0 (8-C), 123.5 (10a-C), 118.2 (6-C), 1-C and 9a-C not being detected.

(3-Benzoyl-4-oxo-4*H*-1-benzopyran-2-methyl)-thiourea 5. Bromomethylchromone **2** (686 mg, 2 mmoles) and thiourea (152 mg, 2 mmoles) were refluxed together in ethanol for 6 hr. The reaction mixture was concentrated, cooled and diluted with water but no solid compound precipitated out. So the organic matter in the reaction mixture was extracted with chloroform, the chloroform extract dried and concentrated to give the substituted thiourea **5** as a yellow solid (340 mg, 50%), mp 250°C (chloroform); Anal. Calcd for $C_{18}H_{14}N_2SO_3$: C, 63.9; H, 4.2; N, 8.3. Found: C, 64.0; H, 4.0; N, 8.5%; ^{1}H NMR (DMSO-d_6): δ 8.16-7.40 (9H, m, ArH), 6.88 (2H, brs, NH_2), 6.42 (1H, brs, NH), 3.32 (2H, s, CH_2).

3,4-Dihydro-1,3-diphenyl-1-benzopyrano[2,3-*d*]-pyridazin-10-one 11. A mixture of **2** (343 mg, 1 mmole), phenylhydrazine hydrochloride (150 mg, 1 mmole) and sodium carbonate (~ 400 mg) was refluxed in a mixture of ethanol (50 mL) and water (10 mL) for 8 hr. On usual work-up of the reaction mixture was obtained as solid material. This was dried, dissolved in chloroform, the concentrated solution charged over a silica gel column and the column eluted with a mixture of ethyl acetate-light petroleum (1:6). The fractions 4-11 (each fraction measuring ~ 15 mL) were combined and concentrated to yield the title pyridiazinone **11** (67 mg, 19%), mp 154°C; Anal. Calcd for $C_{23}H_{16}N_2O_2$: C, 78.4; H, 4.6; N, 8.0. Found: C, 78.1; H, 4.8; N, 8.2%; ^{1}H NMR: δ 8.20 (1H, dd, J = 8.0, 2.0 Hz, 9-H), 7.68-7.08 (13H, m, other ArH), 5.34 (2H, s, CH_2). This compound does not show any peak in the lower field beyond δ 176 ppm in its ^{13}C NMR spectrum.

1-Phenylthieno[3,4-*b*][1]benzopyran-9-one 16. The chromone **2** (343 mg, 1 mmole) and thioacetamide (75 mg, 1 mmole) were refluxed together in ethanol (50 mL) containing sodium acetate (~ 500 mg) for 6 hr. On usual work-up of the reaction mixture as described for the preparation of **9** and **10** was obtained the fused thiophene **16** as yellow needle shaped crystals (162 mg, 58%), mp 158°C (chloroform-light petroleum); Anal. Calcd for $C_{17}H_{10}SO_2$: C, 73.4; H, 3.6. Found: C, 73.2; H, 3.8%; IR (KBr): 1659 (CO) cm^{-1}; ^{1}H NMR: δ 8.23 (1H, dd, J = 8.1, 1.5 Hz, 8-H), 7.74 (2H, dd, J = 7.5, 2.1 Hz, 2′-, 6′-H), 7.64 (1H, ddd, J = 8.5, 7.5, 1.5 Hz, 6-H), 7.48-7.24 (5H, m, other PhH), 7.01 (1H, s, 3-H); ^{13}C NMR: δ 175.1 (9-C), 156.7 (4a-C), 153.4 (3a-C), 149.3 (1-C), 135.3 (6-C), 133.4 (1′-C), 130.3 (2′-, 6′-C), 129.6 (4′-C), 128.5 (3′-, 5′-C), 127.7 (8-C), 123.7 (7-C), 121.9 (8a-C), 121.6 (9a-C), 117.7 (5-C), 102.9 (3-C); Mass: m/z 278 (M^+, 100%), 277 (M-1, 100).

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