Benzopyrans: Part 47†—Reactions of 3-(β-dimethylaminoacryloyl)-1-benzopyran-4-one with some nitrogen nucleophiles

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The title pyranone 1 gives a mixture of pyridines 4 and 7 with ammonia, pyridine 5 and pyrazole 10 with phenylhydrazine, and pyridine N-oxide 8 with hydroxylamine.

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Nucleophiles generally undergo 1,4-addition to α,β-unsaturated ketones including 3-acetylchromone2,3. The title 1-benzopyran-4-one (chromone) 1, derived from 3-acetylchromone and dimethylformamide dimethyl acetal, contains two α,β-unsaturated carbonyl functionalities, one endocyclic and the other exocyclic. The presence of two electron withdrawing carbonyl groups at C-3 makes C-2 of the pyran 2,3-olefinic bond of 1 more electrophilic than the β-carbon of its exocyclic α,β-unsaturated carbonyl functionality. So 1,4-addition of a nucleophile to the said endocyclic functionality is likely to predominate over that to the exocyclic enamino moiety. Whatever may be the mode of initial addition of the nucleophile as NH₂ (2, Y = H, NHPh, OH) to the substrate 1, the resultant intermediate depending on the nature of its Y group would undergo further transformation. This aspect has been dealt in this paper.

Refluxing an ethanolic solution of 1 with ammonium acetate afforded the pyridone 4 and 2-aza-xanthone 7 together with other unidentified compounds. Here ammonia attacks at pyran 2-position (nucleophilic 1,4-addition to the endocyclic α,β-unsaturated carbonyl functionality) with concomitant opening of the pyran ring (Scheme I); the resultant dienaminone 3 (Y = H) gives 4 by an intramolecular nucleophilic 1,4-addition followed by dimethylamine elimination (path - a) and recyclises to 6 (Y = H) which by electrocyclisation and subsequent elimination of dimethylamine gives 7 (path - b). The formation of 4 through the intermediate 9 (Y = H) arising by 1,4-addition of ammonia to the enamino moiety of 1 with subsequent elimination of dimethylamine (Scheme II – path a) cannot be completely ruled out. Phenylhydrazine gives with 1 the pyridone 5 and the pyrazole 10, the former arising through path – a of either or both of the Schemes I and II whereas the latter by cyclisation of the intermediate 9 (Y = NHPh) (Scheme II – path b). From the reaction mixture of 1 and hydroxylamine could be isolated only the fused pyridine N-oxide 8 evidently arising through the intermediacy of 3 and 6 (Y = OH). The azaxanthones 7 and 8 are also formed by treating 3-formyl-2-(2-dimethylaminovinyl)chromone (6, CHO in place of CH=NY) with ammonia and hydroxylamine, respectively; these are, of course, formed not through the intermediacy of the aldehyde-derivatives 6 (Y = H or OH) but through a nucleophilic 1,6-addition, dimethylamine elimination and cyclisation sequence3.

Appearance of three broad singlets at δ 10.81, 9.89 and 9.72 in the PMR spectrum in DMSO-d₆ of the pyridone derived from 1a and ammonia indicates that 4a is in tautomeric equilibrium with 4'a; peaks at δ 10.81 and 9.72 are attributable respectively to OH and NH of pyridone 4a and that at 9.89 to two hydroxy protons of 4'a. Measurement of these peak areas
Scheme I

shows the population 4a and 4'a in their tautomeric equilibrium in the ratio of 15:1. PMR spectrum of the analogous pyridone resulting from 1b and ammonia shows, in addition to three low field (δ 10.76-9.64) broad singlets, two sharp singlets at δ 2.30 and 2.45 attributable to methyl groups of 4b and 4'b, respectively. Population of the equilibrating tautomers 4b and 4'b as 23:1 is calculated by measuring the peak areas of the latter two singlets.

In 13C NMR spectra 1-C and 3-C being α to nitrogen atom in 2-azaxanthone 7 are deshielded respectively to the extent of nearly 30 and 15 ppm relative to the corresponding carbons of xanthone and deshielding of the said carbons by N-oxidation of 7 (→8) follows the expected general trend.

Experimental Section

Uncorrected melting points and yields of isolated pure products are reported. Optimisation of yield was not attempted. All the new compounds gave satisfactory C, H, N analyses. IR spectra in KBr pellet and NMR spectra in CDCl₃ solution, unless stated otherwise, were recorded on Perkin-Elmer 782 and Bruker AM 300L spectrophotometers, respectively. Light petroleum refers to the fraction, b.p. 40-60°C.

3-(β-Dimethylaminoacryloyl)-1-benzopyran-4-one 1. Dimethylformamide dimethyl acetal (2.5 mL, ~30 mmoles) was added to 6-unsubstituted or 6-methyl-3-acetylchromone (20 mmoles) dissolved in dry benzene (100 mL). The reaction mixture assuming a red colour was heated under reflux for 3 hr, concentrated and cooled. The deposited solid was filtered off and crystallised from chloroform-light petroleum to give the title compound as crystals in 70-80% yield. Characterisation data of the individual members of 1 are given below.

3-(β-Dimethylaminoacryloyl)-1-benzopyran-4-one 1a: m.p. 153°C; ¹H NMR: δ 8.63 (s, 1H, 2-H),
The mixture was refluxed for 6 h. The chromone 1 (2 mmol) and ammonium acetate (1.0 g) were dissolved together in alcohol (100 mL). The mixture was refluxed for 6-8 h, concentrated, diluted with water and cooled. The precipitated solid was separated by filtration and crystallized from dimethylformamide-water to yield the pyridone 4. The filtrate was extracted with chloroform, the organic extract was dried, concentrated and chromatographed over silica gel, a mixture of ethyl acetate and light petroleum (1:8) being the eluent. Fractions 9-12 (each fraction measuring ~ 20 mL) were combined and concentrated to give [1]benzopyran[3,2-c]pyridine 7. The characterization data of the products 4 and 7 are given below.

3-Salicyloylpyridin-4(1H)-one 4a \(\rightleftharpoons\) 4-hydroxy-3-salicyloylpyridine 4a

Yield 37%; m.p. 234°C; \(^1\)H NMR (DMSO-d\(_6\)); \(\delta\) 10.81 (brs, OH of 4a), 9.89 (brs, 2 OH of 4a), 8.46-8.21 (m, pyridine H), 7.87, 7.58, 7.24 (m, other PhH).

4-Pyridone 4b \(\rightleftharpoons\) 4-hydroxy pyridine 4b

Yield 27%; m.p. 232°C; \(^1\)H NMR (DMSO-d\(_6\)); \(\delta\) 10.76 (brs, OH of 4b), 9.85 (brs, 2 OH of 4b), 9.70 (brs, NH of 4b), 9.44-8.36 (m, pyridine H), 8.31-8.22 (m, pyridine H), 7.65 (ill split doublet, PhH ortho to CO), 7.40 (m, PhH ortho Me), 7.13 (m, PhH ortho to OH), 2.45 (s, Me of 4b), 2.30 (s, Me of 4b).

1-Benzopyran[3,2-c]pyridin-10-one 7a

Yield 15%; m.p. 184°C (lit. m.p. 185°C); \(^1\)H NMR: \(\delta\) 8.54 (s, 1H, 1-H), 7.99 (d, \(J = 2.1\) Hz, 1H, 5-H), 7.84 (d, \(J = 12.5\) Hz, 1H, CHNMe\(_2\)), 7.22 (dd, \(J = 8.5\) and 2.1 Hz, 1H, 7-H), 6.39 (d, \(J = 12.5\) Hz, 1H, CH=CHNMe\(_2\)), 6.27 (d, \(J = 8.5\) Hz, 1H, 8-H), 3.10 (s, 3H, NMe), 2.91 (s, 3H, NMe), 2.40 (s, 3H, 6-Me); \(^{13}\)C NMR: \(\delta\) 182.9 (exocyclic CO), 175.8 (4-C), 160.7 (CHNMe\(_2\)), 155.8 (8a-C), 153.9 (2-C), 133.5 (7-C), 126.3 (5-C), 125.4 (6-C), 123.6 (4a-C), 118.0 (8-C), 96.6 (CH=CHNMe\(_2\)), 44.8 (Me), 37.4 (Me), 3-C not detected.

3-(\(\beta\)-Dimethylaminoacryloyl)-6-methyl-1-benzopyran-4-one 1b

Yield 15%; m.p. 184°C; \(^1\)H NMR: \(\delta\) 8.64 (s, 1H, 1-H), 7.99 (d, \(J = 2.1\) Hz, 1H, 5-H), 7.84 (d, \(J = 12.5\) Hz, 1H, CHNMe\(_2\)), 7.22 (dd, \(J = 8.5\) and 2.1 Hz, 1H, 7-H), 6.39 (d, \(J = 12.5\) Hz, 1H, CH=CHNMe\(_2\)), 6.27 (d, \(J = 8.5\) Hz, 1H, 8-H), 3.10 (s, 3H, NMe), 2.91 (s, 3H, NMe), 2.40 (s, 3H, 6-Me); \(^{13}\)C NMR: \(\delta\) 183.2 (exocyclic CO), 175.8 (4-C), 160.7 (CHNMe\(_2\)), 154.1 (8a-C), 153.9 (2-C), 135.5 (6-C), 134.7 (7-C), 125.7 (5-C), 125.1 (3-C), 123.5 (4a-C), 117.8 (8-C), 96.7 (CH=CHNMe\(_2\)), 44.7 (NMe), 37.4 (NMe), 20.8 (6-Me).

Treatment of the chromone 1 with ammonia.

The chromone 1 (2 mmol) and ammonium acetate (1.0 g) were dissolved together in alcohol (100 mL). The mixture was refluxed for 6-8 h, concentrated, diluted with water and cooled. The precipitated solid was separated by filtration and crystallized from dimethylformamide-water to yield the pyridone 4. The filtrate was extracted with chloroform, the organic extract was dried, concentrated and chromatographed over silica gel, a mixture of ethyl acetate and light petroleum (1:8) being the eluent. Fractions 9-12 (each fraction measuring ~ 20 mL) were combined and concentrated to give [1]benzopyran[3,2-c]pyridine 7. The characterization data of the products 4 and 7 are given below.

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4-Pyridone 4b \(\rightleftharpoons\) 4-hydroxy pyridine 4b

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1-Benzopyran[3,2-c]pyridin-10-one 7a

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Treatment of the chromone 1 with ammonia.

The chromone 1 (2 mmol) and ammonium acetate (1.0 g) were dissolved together in alcohol (100 mL). The mixture was refluxed for 6-8 h, concentrated, diluted with water and cooled. The precipitated solid was separated by filtration, dried and digested in boiling chloroform.

The insoluble solid was crystallized from methanol to afford the title pyridone 5 as faintly yellow shining crystals. The chloroform solution was concentrated and subjected to column chromatography over silica gel. The pyrazole 10a (14%) could be obtained as yellowish crystals from the reaction from 1a whereas...
attempt to get 10b similarly from 1b and phenylhydrazine was unsuccessful.

1-Phenylamino-3-salicyloylpyridin-4-(1H)-one 5a: Yield 38%; m.p. 200°C; 1H NMR (DMSO-d6): δ 11.24 (brs, 1H, NH), 9.62 (brs, 1H, NH), 8.01 (dd, J = 7.8 and 2.5 Hz, 1H, 2-H), 7.78 (dd, J = 7.8 and 2.5 Hz, 1H, 6-H), 7.49 (dd, J = 7.9 and 1.1 Hz, 1H, PhH $\text{ortho}$ to CO), 7.47-6.71 (m, 8H), 6.29 (d, J = 7.8 Hz, 1H, 5-H); 13C NMR (DMSO-d6): δ 197.3 (salicyloyl CO), 174.4 (4-C), 158.8 (2'-C), 147.7 (1-C), 140.5 (PhC $\text{ortho}$ to N), 144.3 (3-C), 137.2 (1-C), 136.5 (1-C), 136.1 (7-C), 126.7 (9-C), 125.4 (8-C), 121.6 (9a-C), 119.8 (10a-C), 118.2 (4-C), 116.3 (6-C).

8-Methyl-10-oxo-1-benzopyrano[3',2'-c]pyridine 2-oxide 8a: Yield 27%; m.p. 242°C (lit.3, m.p. 248°C); 1H NMR: δ 9.00 (d, J = 1.4 Hz, 1H, 1-H), 8.39 (dd, J = 7.2 and 1.4 Hz, 1H, 3-H), 8.08 (ill split d, 1H, 9-H), 7.65 (dd, J = 8.5 and 1.9 Hz, 1H, 7-H), 7.43 (d, J = 7.2 Hz, 1H, 4-H), 7.35 (d, J = 8.5 Hz, 1H, 6-H), 2.48 (s, 1H, Me); 13C NMR: δ 173.5 (10-C), 155.8 (5a-C), 152.2 (4a-C), 144.5 (3-C), 136.5 (1-C), 136.1 (7-C), 126.7 (9-C), 125.4 (8-C), 121.6 (9a-C), 119.8 (10a-C), 118.2 (4-C), 116.3 (6-C).

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References