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Thermal Rearrangements of C-(4-Oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone-a Route to Novel Quinolino[2,3-*b*]chroman-12-ones

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Abstract:

C-(4-Oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrones (**1a-c**) undergo facile rearrangements on refluxing in benzene, yielding 2-(*N*-phenylamino)-4-oxo-4*H*[1]-benzopyran-3-carboxaldehydes (**2a-c**,70%) and 3-(phenyliminomethylene)-chroman-2,4-diones (**3a-c**, 25%). **2a-c** undergo cyclization on refluxing with anhydrous $AlCl_3$ in dry CCl_4 followed by treatment with sulfuric acid, to give novel quinolino[2,3-*b*]chroman-12-ones(**4a-c**) in 90% yield.

Keywords: Chromone, Nitrone, Rearrangement, Cyclisation.

The use of 3-formylchromone and its derivatives in the syntheses of heterocyclic systems of medicinal importance is well known.[1] Condensation of phenylhydroxylamine with 3-formylchromone yields C-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (**1**)[2] quantitatively. Contrary to the reported[2a] thermal stability of **1** under refluxing conditions (benzene), we report here that nitrone (**1a**) and its 6-chloro and 6-methyl analogues (**1b,c**) undergo facile novel rearrangements even at room temperature. The rearranged products **2a-c** have been cyclized to yield novel heterocyclic systems i.e., quinolino[2,3-*b*]- chroman-12-ones(**4a-c**), in 90% yield.

Nitrones (**1a-c**) were obtained by condensing the corresponding 3-formylchromones with phenylhydroxylamine in dry ethanol. Refluxing a solution of a nitrone (**1a-c**, 1.50 mmol.) in dry benzene (25ml) for 8 hr and column chromatographic resolution (silica gel, 60-120 mesh) of the residue gave **2a-c** (70%) and **3a-c** (25%). However, when a solution of nitrone (**1a-c**) in dry chloroform was allowed to stand at room temperature for a week and then resolved chromatographically, rearrangement products (**2a-c**) were obtained in 90% yield along with **3a-c** (5-6%). The assigned structures are based on detailed spectroscopic analysis.

That **2a-c** are derived, respectively, from **1a-c** without any loss or gain of mass was indicated by mass spectra and microanalytical data.[3] UV and IR spectra of **2a-c** alluded to an intact chromone nucleus,[4] which was also supported by ^{1}H nmr spectra.[3] In the ^{1}H nmr spectrum of **2a** the C5-H appeared as a split doublet at δ 8.22 (1H, *J*=7.26 & 1.84 Hz); the spectrum also revealed a broad resonance (1H) at δ 12.51(exchanged with

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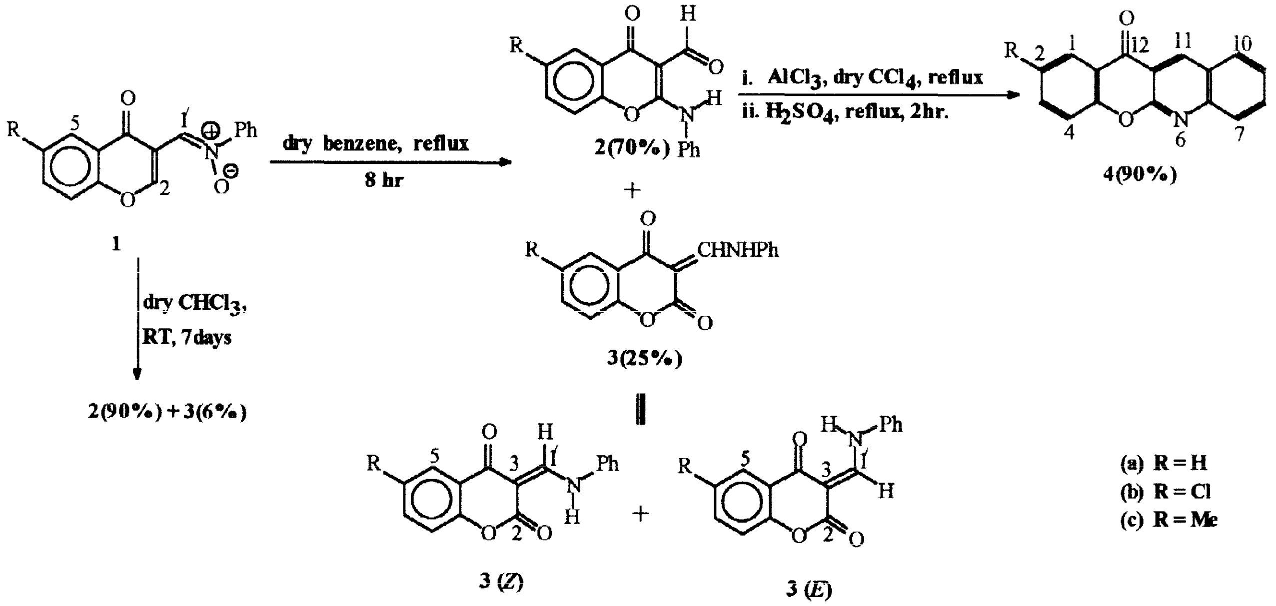
deuterium, NH) and an aldehydic proton singlet at δ 10.28. The presence of aldehyde function was also corroborated by IR and ^{13}C nmr spectra.[3] The aldoxime of **2a** has been prepared and characterized spectroscopically.[3]

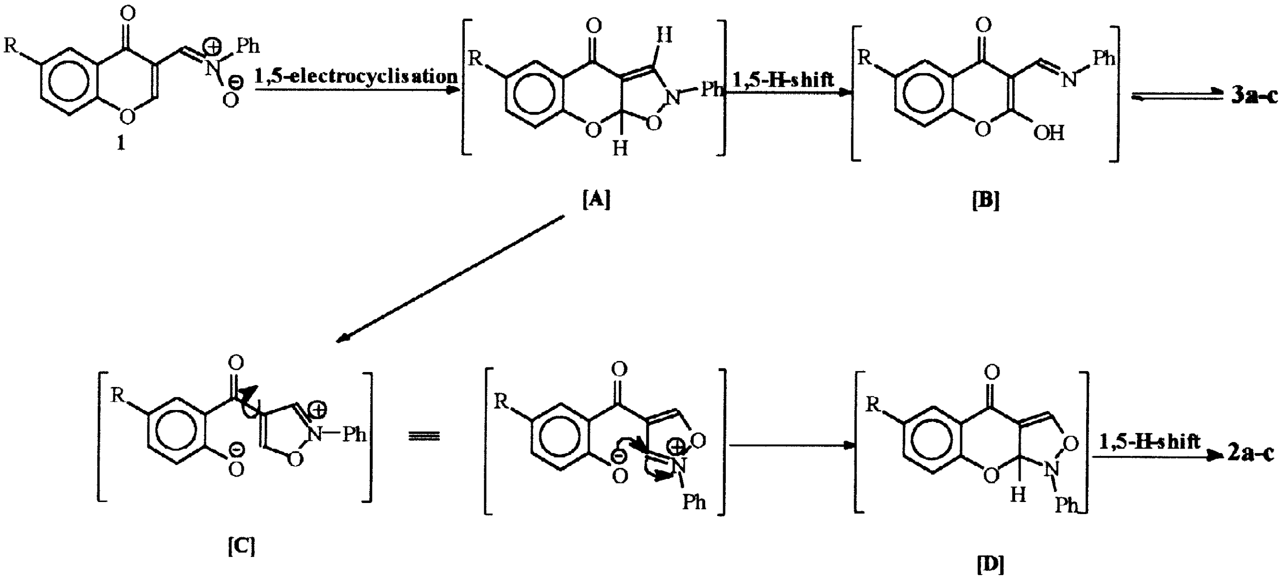
3a-c were also found to have the same molecular mass and elemental composition as the corresponding nitrones. The presence of geometric isomers involving the exocyclic double bond was revealed by their ^1H nmr spectra, however, these gave single spot on tlc and could not be resolved; repeated crystallizations led to some variations in relative amounts of the isomers. In its ^1H nmr spectrum **3a** revealed[5] broad resonances at δ 13.64 and 11.94 (together 1H) which alluded to a hydrogen bonded -NH proton. Shaking with a drop of D_2O led to suppression of these broad (NH) resonances with concomitant collapsing of two doublets at δ 9.04 and 8.98(J = 14.00 Hz) to singlets; the latter doublets are attributed to C1'-H in isomeric structures (**3a**, Z & E). It should be mentioned here that some compounds related to **3** (geometry at exocyclic double bond not assigned) have been obtained earlier[6] by MnO_2 oxidation of 3-(aryliminomethyl)chromones and the reported data[6] compare favorably with the presently obtained data as far as gross structural features are concerned.



For the cyclization of **2a-c**, a few drops of sulfuric acid were added to their refluxing solutions (0.40 mmol, in dry CCl_4, 10 ml), containing anhydrous $AlCl_3$ (1.0 eqv.) and the contents were further refluxed with fast stirring for two hours. The cooled reaction mixtures were poured into water and $CHCl_3$ (20 ml) was added to them. After shaking, the organic layers were separated, washed with H_2O, dried over anhydrous Na_2SO_4, and the solvents were evaporated. The obtained products (**4a-c**, >90%) were crystallized from $CHCl_3$ - pet. ether and re-crystallized from benzene-pet. ether.

The structures of compounds (**4a-c**) are again based on rigorous spectral analysis. The loss of elements of water during conversion of **2a-c** to **4a-c** was inferred on the basis of mass spectra and corroborated by microanalytical data.[7] The assigned structures are based on absence of NH and aldehyde functions as evidenced by IR and ^1H nmr spectra of **4a-c**; involvement of the aldehydic-carbonyl in the cyclization was also confirmed by^{13}C nmr spectra. The ^{13}C nmr further revealed nine methine (CH) carbons in the downfield (aromatic/olefinic) region in case of **4a**[7] and eight in case of **4b,c**. Some of the critical ^{1}H and ^{13}C nmr assignments in case of **4a** are included.[7]

Mechanistically, the formation of the rearranged products from the nitrones (**1**) can be rationalized in terms of an initial 1,5-electrocyclization, precedented in the case of conjugated nitrones,[8] resulting in the formation of the intermediate **A** which undergoes a 1,5-H shift leading, through **B**, to **3a-c**. Alternatively, the rearrangement of **A** may involve its conversion to the chromone ring opened intermediate **C** which, after recyclization followed by a 1,5-H shift, yields products **2a-c**.



At present work is in progress to investigate the effects of varying the *N*-aryl group of the nitrone on the above transformations together with cycloadditions of the rearranged products.

References and Notes

1. (a) Fitton, A.O.; Frost,J.R. and Suschitzky, H.; *Synthesis*, **1977**, 133.
   (b) Sabitha, G.; *Aldrichimica Acta*, **1996**, 29, 15.
   (c) Ghosh,C.K. and Ghosh, C.; *Indian J. Chem.*, **1997**, 36B, 968.

2. (a) Baruah,A.K.; Prajapati,D. and Sandhu,J.S.; *J.Chem. Soc., Perkin Trans I*, **1987**, 1995.
   (b) **1a**: yellow needles, mp. 138°; λ_{max}(MeOH): 389, 361, 317, 278 , 235 nm; ν_{max}(KBr): 1645, 1600, 1590, 1563, 1460, 1260, 1210, 1180 cm^{-1}; ^{1}H NMR(CDCl$_3$): δ 10.63(s , 1H, -CH=N$^+$), 8.46 (s, 1H, C2-H), 8.28(dd, 1H, J = 8.2 & 1.5 Hz, C5-H), 7.82-7.39(m, 8H); ^{13}C NMR (CDCl$_3$): δ175.0(C4), 157.8 (C2), 155.8(C8a), 148.0(C1'), 134.4, 130.1, 129.3, 126.3, 125.9, 125.7 , 123.1(C4a), 121.4, 118.6(C8), 117.0(C3); Mass: m/z 266(16, M$^+$+1), 265(100, M$^+$), 264(37), 249(5), 237(35), 236(70), 173(72), 162(35), 144(15), 121(50), 117(60), 104(82), 91(27), 77(78).

3. **2a**:Yellow needles(chloroform-pet. ether), mp. 156-158°; λ_{max}(MeOH): 368, 337, 275, 220 nm; ν_{max}(KBr): 3350(NH), 1660(HC=O), 1625(C=O), 1602, 1580; ^{1}H nmr(CDCl$_3$): δ 12.51 bs, 1H exchanged with deuterium, NH), 10.28(s,1H, C1'-H), 8.22(sp d,1H, J = 7.26 & 1.84 Hz, C5-H), 7.66-7.27(m,8H); ^{13}C nmr(CDCl$_3$): δ189.6(CH=O), 175.3(C4), 162.0(C2), 153.1(C8a), 134.8(quat.), 133.5, 129.3, 126.3, 125.8, 125.7, 123.0(C4a), 122.8, 116.6(C8), 99.6(C3); Mass m/z: 267(M$^+$+2), 266(25, M$^+$+1), 265(80, M$^+$), 263(95), 237(50), 235(98), 220(10), 180(18), 144(20), 121(48), 117(88), 93(20), 92(18), 77(100); Analysis: Calculated (for $C_{16}H_{11}NO_3$) C 72.45, H 4.15, N 5.28%; Found C 72.62, H 4.42, N 5.22%. Aldoxime of **2a**, colorless crystals(methanol-chloroform); mp. 227-228°; ν_{max} (KBr): 3400(broad), 1655, 1620, 1597, 1578, 1460, 1440, 1385, 1352, 1230, 1210 cm^{-1}; ^{1}H NMR (acetone-d$_6$): δ11.16(br, 1H, NH), 10.32(1H, OH), 8.70 (s, 1H, CH=N), 8.13(dd, 1H, J = 6.9 & 1.6 Hz, C5-H), 7.70 (split t, 1H), 7.52(m, 6H), 7.28(t, 1H); ^{13}C NMR(acetone-d$_6$): δ 175.51(C4), 158.26(C2), 152.47(C8a), 143.30(quat.), 132.49, 131.48, 128.48, 124.96, 124.65, 124.42, 121.53, 121.02(C4a),115.91(C8), 92.39 (C3); Mass: m/z 262(55, M$^+$-H$_2$O), 149(25); Analysis: Calculated (for $C_{16}H_{12}O_3N_2$) C 68.57, H 4.28, N 10.00%; Found C 68.87, H 4.41, N 10.25%.

4. (a) Griffiths,P.J.F. and Ellis,G.P.; *Spectrochim. Acta*, **1972**, 28A, 707.
   (b) Nohara,A.; Umetani,T. and Sanno,Y., *Tetrahedron*, **1974**, 30, 3553.

5. **3a**: Off-white fluffy solid(chloroform- pet. ether), mp. varies with isomeric composition from 194 to 236°; λ_{max} (MeOH): 364.2, 310, 285 nm; ν_{max}(KBr): 3300 & 3250 (NH), 1688 (O-C=O), 1655 (C4=O), 1610, 1590, 1580; ^{1}H nmr(CDCl$_3$): δ 13.64 & 11.94 (b singlets, together 1H, NH in isomeric structures), 9.04(d, J = 14.0Hz, C1'-H), 8.98(d, J = 14.0 Hz, C1'-H in isomeric structure), 8.05(Overlapping dds, 1H, J = 1.70 & 7.62 Hz, C5-H), 7.68-7.26(m, 8H); Mass: m/z 267(M$^+$+2), 266(61,M$^+$+1), 265(95,M$^+$), 173 (25), 172(95), 145(35), 144(41), 121(82), 120(19), 117(100), 93(20), 92(22), 90(39), 89(30), 77(61); Analysis: Calculated (for $C_{16}H_{11}NO_3$) C 72.45, H 4.15, N 5.28%; Found C 72.71, H 4.38, N 5.41%.

6. Fitton,A.O.; Frost,J.R.; Houghton,P.G. and Suschitzky,H.; *J. Chem. Soc., Perkin Trans I*, **1979**, 1691.

7. Spectral data of **4a**: colorless crystals (benzene: pet. ether, 90%), mp 210-211°; λ_{max}(CHCl$_3$): 381, 367, 350 (sh), 327, 281, 255nm; ν_{max}(KBr): 1668 (C=O), 1632 (sh), 1601, 1500, 1468 cm^{-1} ; ^{1}H nmr (CDCl$_3$): δ 9.26(s,1H, C11-H), 8.34(dd, 1H, C1-H, J = & 7.95 1.46 Hz), 8.10(dd, 2H, J=2.1 & 7.34 Hz), 7.90(m,1H), 7.78(dd, 1H, J = 1.66 & 7.00 Hz), 7.63(dd, 2H, J=1.03 & 8.42 Hz), 7.43(sp t, 1H, J=1.10 & 7.49 Hz); ^{13}C nmr(CDCl$_3$): δ 177.5(C12), 165.26(C5a), 152.89(C4a), 147.99(6a), 140.07(C11), 136.07, 133.49, 129.65, 128.38, 127.19, 126.45, 126.25(C10a), 124.43, 122.02(C12a), 118.57(C4), 117.12 (C11a) ; Mass m/z: 249(10, M$^+$+2), 248(20, M$^+$+1), 247(100, M$^+$), 219(30), 190(20); Analysis: Calculated for $C_{16}H_9O_2N$ C 77.73, H 3.64, N 5.66; Found C 77.84, H 3.78, N 5.73.

8. Singh,N. and Mohan,S.; *J. Chem. Soc., Chem. Commun.*, **1968**, 787 and references cited therein.