

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 AlCl₃ in dry CCl₄ followed by treatment with sulfuric acid, to give novel quinolino[2,3-*b*]chroman-12-ones(**4a-c**) in 90% yield. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Chromone, Nitrone, Rearrangement, Cyclisation.

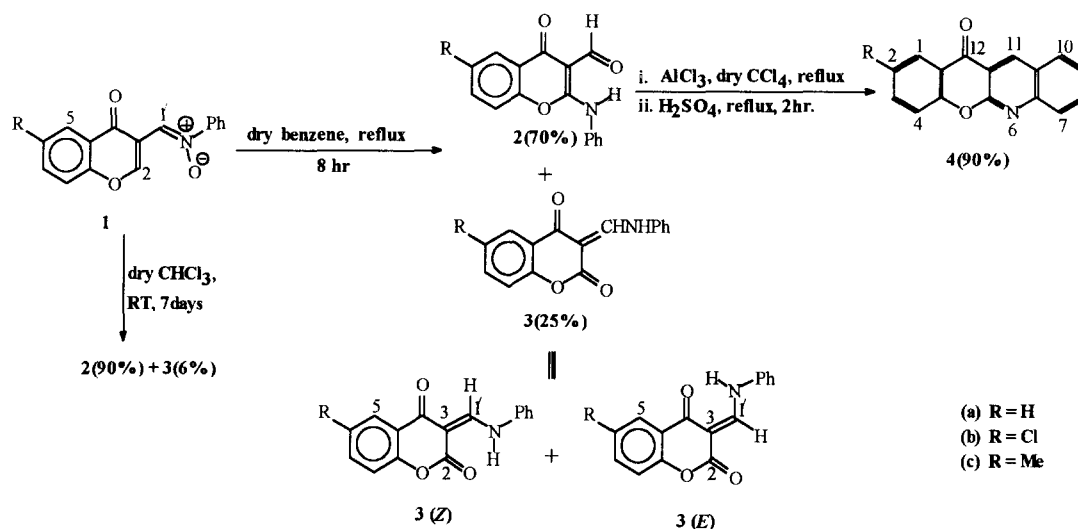
The use of 3-formylchromone and its derivatives in the syntheses of heterocyclic systems of medicinal importance is well known.¹ Condensation of phenylhydroxylamine with 3-formylchromone yields C-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (**1**)² quantitatively. Contrary to the reported^{2a} thermal 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 ¹H nmr spectra.³ In the ¹H 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

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** revealed⁵ 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 earlier⁶ by MnO_2 oxidation of 3-(aryliminomethyl)chromones and the reported data⁶ compare favorably with the presently obtained data as far as gross structural features are concerned.

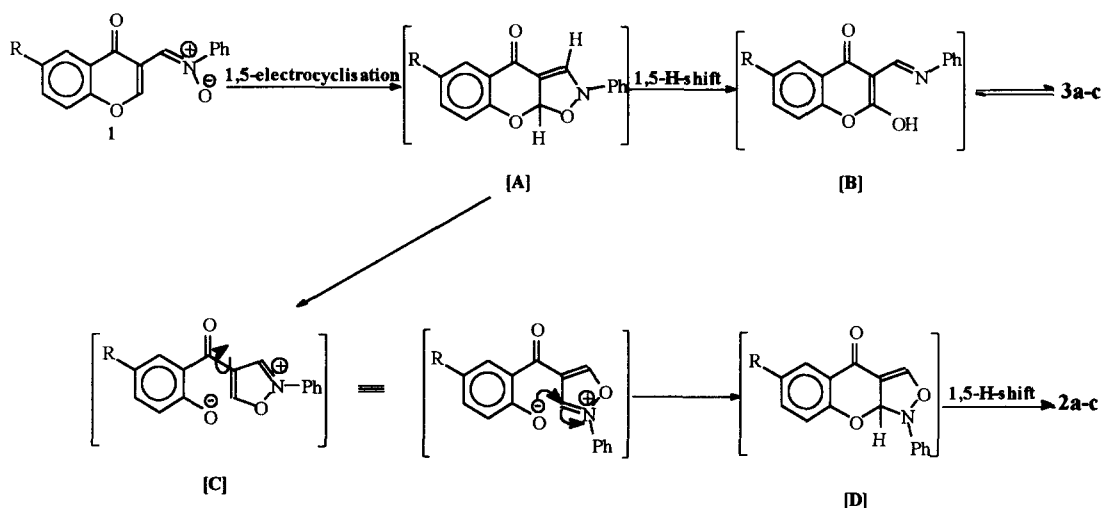


For the cyclization of **2a-c**, a few drops of sulfuric acid were added to their refluxing solutions (0.40 mmol, in dry CCl_4 , 10 ml), containing anhydrous AlCl_3 (1.0 eqv.) and the contents were further refluxed with fast stirring for two hours. The cooled reaction mixtures were poured into water 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 ^1H 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, preceded 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

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 - (b) Sabitha, G.; *Aldrichimica Acta*, **1996**, 29, 15.
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- (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} ; ^1H NMR(CDCl_3): δ 10.63(s, 1H, $-\text{CH}=\text{N}^+$), 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): δ 175.0(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, $\text{M}^+ + 1$), 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°; $\lambda_{\max}(\text{MeOH})$: 368, 337, 275, 220 nm; $\nu_{\max}(\text{KBr})$: 3350(NH), 1660(HC=O), 1625(C=O), 1602, 1580; $^1\text{H nmr}(\text{CDCl}_3)$: 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); $^{13}\text{C nmr}(\text{CDCl}_3)$: δ 189.6(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 $\text{C}_{16}\text{H}_{11}\text{NO}_3$) 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°; $\nu_{\max}(\text{KBr})$: 3400(broad), 1655, 1620, 1597, 1578, 1460, 1440, 1385, 1352, 1230, 1210 cm^{-1} ; $^1\text{H NMR}(\text{acetone-}d_6)$: δ 11.16(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); $^{13}\text{C NMR}(\text{acetone-}d_6)$: 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, $M^+ - \text{H}_2\text{O}$), 149(25); Analysis: Calculated (for $\text{C}_{16}\text{H}_{12}\text{O}_3\text{N}_2$) C 68.57, H 4.28, N 10.00%; Found C 68.87, H 4.41, N 10.25%.
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(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°; $\lambda_{\max}(\text{MeOH})$: 364.2, 310, 285 nm; $\nu_{\max}(\text{KBr})$: 3300 & 3250 (NH), 1688 (O-C=O), 1655 (C4=O), 1610, 1590, 1580; $^1\text{H nmr}(\text{CDCl}_3)$: δ 13.64 & 11.94 (b singlets, together 1H, NH in isomeric structures), 9.04(d, $J = 14.0$ Hz, 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 $\text{C}_{16}\text{H}_{11}\text{NO}_3$) C 72.45, H 4.15, N 5.28%; Found C 72.71, H 4.38, N 5.41%.
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7. Spectral data of **4a**: colorless crystals (benzene: pet. ether, 90%), mp 210-211°; $\lambda_{\max}(\text{CHCl}_3)$: 381, 367, 350 (sh), 327, 281, 255 nm; $\nu_{\max}(\text{KBr})$: 1668 (C=O), 1632 (sh), 1601, 1500, 1468 cm^{-1} ; $^1\text{H nmr}(\text{CDCl}_3)$: 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); $^{13}\text{C nmr}(\text{CDCl}_3)$: 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 $\text{C}_{16}\text{H}_9\text{O}_2\text{N}$ C 77.73, H 3.64, N 5.66; Found C 77.84, H 3.78, N 5.73.
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