Study of differences in the reactivity of alkyl and aryl nitrones derived from 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde

Tarun Ghosh, Ranjan Patra and Chandrakanta Bandyopadhyay*

Department of Chemistry, R.K. Mission Vivekananda Centenary College, Rahara, Kolkata -700 118, West Bengal, India

On hydrolysis with 70% H_2SO_4, aliphatic nitrones **2a–d** produce the corresponding carboxylic acids **4** but aromatic nitrones **2e, f** give aldehyde **1.** On heating under reflux in dry MeOH, **2a–d** rearrange to **3a–d** but aromatic nitrones **2e, f** remain unchanged.

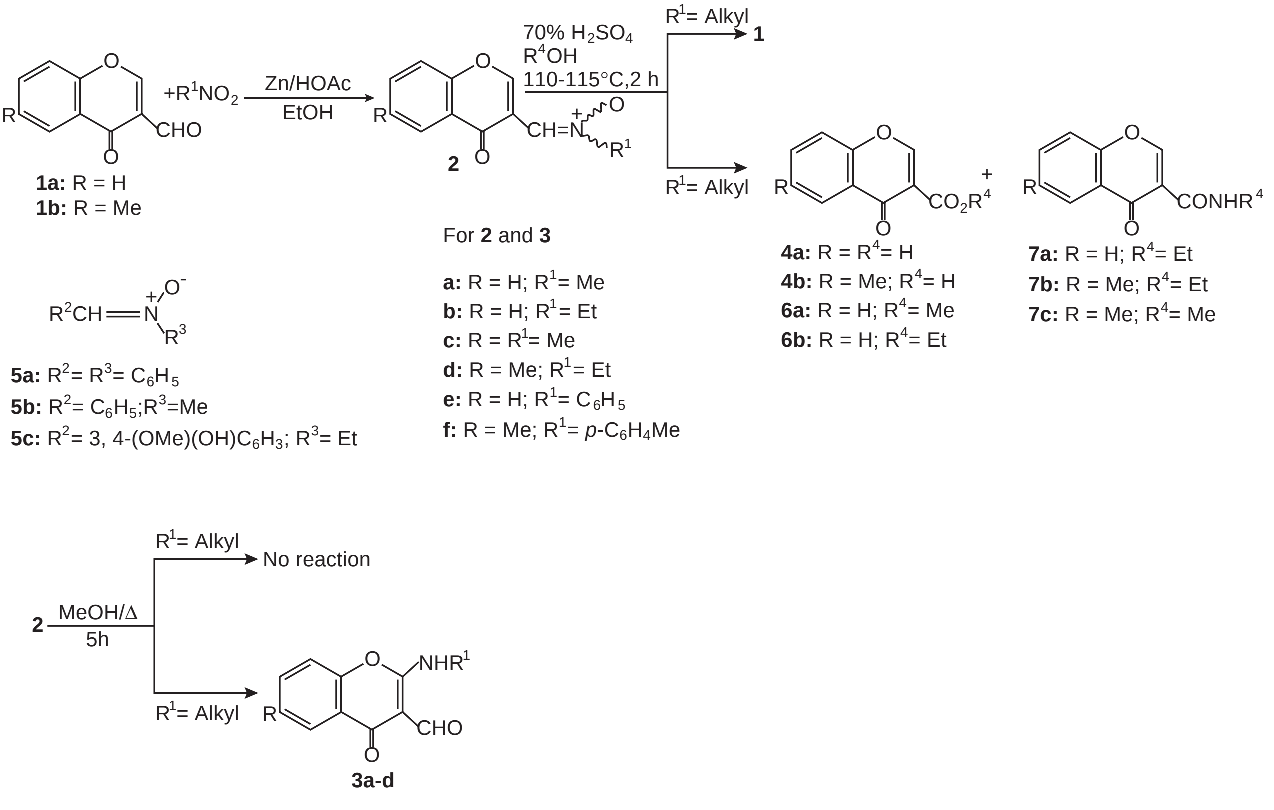
Keywords: 3-formylchromone, nitrone, 1-benzopyran, hydrolysis, rearrangement

Resurgent interest in the chemistry of nitrones is mainly due to their ability to participate in 1, 3-dipolar cycloaddition reactions.[1] Nitrones are also used as radical spin trapping agents.[2] α–Chloronitrone is a good reagent for the insertion of a formyl group.[3] In the synthesis of nonactic acid, a precursor of the macrolide antibiotic nonactin, the formyl group was introduced using α-chloronitrone. The formyl group was oxidised to the carboxylic acid and then esterified.[3] Synthesis of the carbonyl functionality utilizing the Nef reaction is well known.[4] On boiling with concentrated HCl or with 85% H_2SO_4, primary nitro compounds produce the corresponding carboxylic acids whereas secondary nitro compounds produce ketones.[5] We report here a difference in the reactivity of aliphatic and aromatic nitrones derived from aliphatic and aromatic nitro compounds and the title compound 3-formylchromone **1**.

Nitrones **2** were prepared by treatment of **1** and aliphatic or aromatic nitro compounds with zinc in ethanol in the presence of acetic acid under an inert atmosphere.[6] When the reaction was carried out with zinc in THF in the presence of aqueous NH_4Cl, 2-amino-3-formylchromone **3** was isolated along with some nitrone **2**.[7] Generally nitrones are hydrolysed readily forming an aldehyde or ketone and an *N*-substituted hydroxylamine.[8] Aryl nitrones are less susceptible to hydrolysis than alkyl nitrones.[9]

On heating with 70% H_2SO_4 in H_2O at 110–115 °C for 2 h, nitrones **2a–d**, derived from **1** and aliphatic nitro compounds, produced the corresponding carboxylic acid **4a/b** instead of the aldehyde **1** (Scheme 1). By contrast nitrones **2e, f**, derived from **1** and aromatic nitro compounds, produced the corresponding aldehyde **1** under similar reaction conditions.

At first it was considered that the alkyl or aryl group attached to the nitrogen of the nitrones was solely responsible for this differential nature of hydrolysis. To verify this, nitrones **5a–c** were prepared using the same procedure[6] and were heated with 70% H_2SO_4 in H_2O at 110–115 °C for 2 h under an inert atmosphere to avoid air oxidation. In all these cases, the carboxylic acid was not obtained; instead the corresponding aldehyde was produced as the hydrolysed product. So, *N*-alkyl or *N*-aryl groups are not the only factor for their differential behaviour towards hydrolysis but the chromone moiety of nitrone **2** also plays a vital role.



Scheme 1

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

On treatment with 70% H_2SO_4 in MeOH or EtOH, nitrone **2b–d** produced amide **7a–c** along with a trace amount of acid **4a/b.** Formation of ester **6a/b** depending on MeOH or EtOH was also detected from the reaction mixture of **2b**, whereas, the nitrones **2e, f** produced aldehyde **1** under identical reaction conditions. In an endeavour to synthesise ester **6** from nitrones **2**, **2b** was treated with dry MeOH in the presence of *p*-toluene sulfonic acid. Surprisingly, on heating under reflux for 5 h, a rearranged product 2-alkylamino-3-formylchromone **3b**[7, 10] was obtained in excellent yield. Repetition of the above reaction without adding TsOH gave the same result. Other aliphatic nitrones **2** behaved similarly to produce **3,** whereas under the same reaction conditions aromatic nitrones **2e, f** failed to show any change even after heating with dry MeOH under reflux for 15 h.

A plausible mechanism is suggested to explain the effect of the chromone moiety during the acid hydrolysis or alcoholysis of alkyl or aryl nitrones **2** (Scheme 2). The intramolecular substitution of the hydroxyl group in the pyrylium ion **8**, generated from protonation of nitrone **2**, leads to the fused isoxazolium salt **9**. This is then intercepted by water or alcohol to form hemiaminal **10** (R^4 = H) or *N*, *O*-acetal **10**, respectively. Depending on the nature of R^1, the two possibilities are considered. When R^1 = alkyl, acid **4** or amide **7** are formed *via* the imidic ester **11** (path-a). On the other hand, when R^1 = aryl, hydrolysis of hemiaminal **10** (R^4 = H) or *N*, *O*-acetal **10** occur to return to aldehyde **1** *via* **12** and **13** (path-b).

In conclusion, we have reported the differences in the reactivities of *N*-alkyl and *N*-aryl nitrones derived from the title compound **1**. To the best of our knowledge, it is the first example where nitrones have been transformed directly to carboxylic acids or amides.

Table 1 Products from the acid-catalysed solvolysis of **2**

Nitrone	Reagent 70% H_2SO_4 in R^4OH	Product (% Yield)
2a,b	R^4 = H	**4a** (90, 95)
2c, d	R^4 = H	**4b** (92, 90)
2e	R^4 = H	**1a** (85)
2f	R^4 = H	**1b** (80)
2b	R^4 = Me	**7a** (60)
2b	R^4 = Et	**7a** (55)
2c	R^4 = Me	**7c** (72)
2d	R^4 = Me	**7b** (70)

Experimental

Melting points reported are uncorrected. IR spectra were recorded in KBr on a BECKMAN IR-20A Spectrometer and ^1H NMR spectra were recorded in $CDCl_3$ solution with TMS as internal standard on a BRUKER 300 MHz spectrometer. Light petroleum refers to the fraction with boiling point 60–80 °C.

Preparation of nitrones **2a–f**: C-(4-Oxo-4*H*-1-benzopyran-3-yl)-*N*-substituted nitrones **2a–f** were synthesised using the literature procedure.[6]

2a: Light yellow crystalline solid, m.p. 146–148 °C (lit.[11] 144–146 °C).

2b: Light yellow crystalline solid, m.p. 109–110 °C (Found: C, 66.45; H, 5.15; N, 6.50. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.10; N, 6.45%); ν_{max}/cm^{-1} 2920, 1650, 1610, 1515, 1280; δ_H 10.42 (1H, s, CH=N), 8.25 (1H, dd, *J* = 8.0, 1.5 Hz, 5-H), 7.91 (1H, s, 2-H), 7.72 (1H, ddd, *J* = 8.2, 7.8, 1.5 Hz, 7-H), 7.53 (1H, dd, *J* = 8.2, 1.0 Hz, 8-H), 7.45 (1H, ddd, *J* = 8.0, 7.8, 1.0 Hz, 6-H), 4.03 (2H, q, *J* = 7.3 Hz, N-CH_2CH_3), 1.56 (3H, t, *J* = 7.3 Hz, CH_3).

2c: Light yellow crystalline solid, m.p. 145–147 °C (lit.[7] 146 °C).

2d: Light yellow crystalline solid, m.p. 146–148 °C (lit.[7] 148 °C).

2e: Yellow crystalline solid, m.p. 136–138 °C (lit.[7] 138 °C).

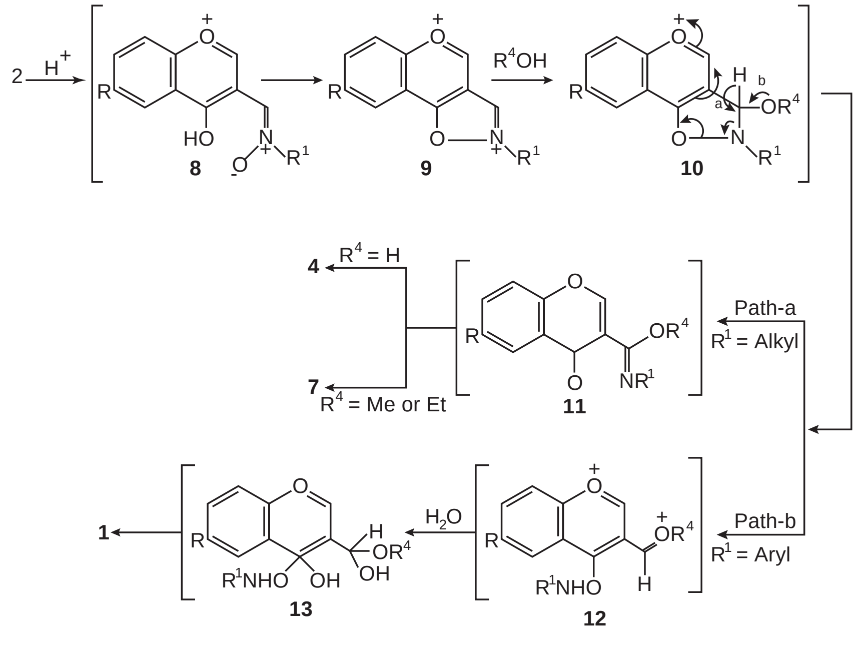
2f: Yellow crystalline solid, m.p. 170–172 °C (lit.[7] 172 °C).

General Procedure for the hydrolysis of nitrones **2**: Nitrone **2** (1 mmol) was dissolved in 70% H_2SO_4 in water (v/v) (3 ml). The resulting reddish solution was heated at 110–115 °C with stirring for 2 h. The reaction mixture was cooled and poured into ice water (50 ml). The deposited solid was filtered, washed and dried in air. Compounds obtained from **2a–d** were crystallised from ethyl acetate using charcoal to afford a white fine crystalline solid and were identified as **4** after comparing with known samples. Compounds obtained from **2e, f** were crystallised either from benzene-light petroleum or ethyl acetate-light petroleum to afford aldehyde **1**.

Similar treatment of **2** with 70% H_2SO_4 in methanol or ethanol instead of water as in the previous case produced amide **7** as the only isolated product. When monitored by TLC, formation of some ester **6** and acid **4** in the reaction mixture was detected by comparing with known samples. Nitrones **2e, f** on similar treatment produced the corresponding aldehyde **1** (Table 1). All the products except **7** were identified by comparing mps, mixed mps and superimposable IR spectra with authentic samples.

7a: White cotton-like solid; m.p. 70–72 °C (Found: C, 66.40; H, 5.12; N, 6.40. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.10; N, 6.45%); ν_{max}/cm^{-1} 3455, 3263, 3097, 1660, 1614, 1562, 1467; δ_H 9.27 (1H, brs, NH), 8.99 (1H, s, 2-H), 8.29 (1H, dd, *J* = 7.9, 1.5 Hz, 5-H), 7.76 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, 7-H), 7.56 (1H, dd, *J* = 8.0, 1.7 Hz, 8-H), 7.50 (1H, ddd, *J* = 7.9, 7.5, 1.7 Hz, 6-H), 3.55–3.45 (2H, m, N-CH_2CH_3), 1.25 (3H, t, *J* = 7.3 Hz, CH_3).

7b: White cotton-like solid; m.p. 127–128 °C (Found: C, 67.49; H, 5.62; N, 6.10. $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06%);



Scheme 2

ν_{max}/cm^{-1} 3450, 3210, 3100, 1670, 1615, 1550, 1470; δ_H 9.29 (1H, brs, NH), 8.95 (1H, s, 2-H), 8.05 (1H, d, J = 2.0 Hz, 5-H), 7.56 (1H, dd, J = 8.5, 2.0 Hz, 7-H), 7.45 (1H, d, J = 8.5 Hz, 8-H), 3.54–3.45 (2H, m, N-CH_2CH_3), 2.49 (3H, s, CH_3), 1.26 (3H, t, J = 7.3 Hz, CH_3).

7c: White cotton-like solid; m.p. 130–132 °C (Found: C, 66.29; H, 5.17; N, 6.35. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.10; N, 6.45%); ν_{max}/cm^{-1} 3440, 3200, 3100, 1660, 1620, 1460; δ_H 9.25 (1H, brs, NH), 8.97 (1H, s, 2-H), 8.05 (1H, d, J = 1.7 Hz, 5-H), 7.56 (1H, dd, J = 8.5, 1.7 Hz, 7-H), 7.45 (1H, d, J = 8.5 Hz, 8-H), 3.01 (3H, d, J = 4.9 Hz, N-CH_3), 2.50 (3H, s, 6-CH_3).

*Rearrangement of nitrone **2** in methanol*: Nitrone **2** (1 mmol) was heated under reflux in dry methanol (10 ml) for 5 h. On concentration, the reaction mixtures from **2a–d** gave yellow solids, which were identified as corresponding **3a–d** by comparison with the authentic samples.[7] Yields of **3a–d** are excellent (90–95%). But nitrones **2e, f** failed to show any change even after heating under reflux for 15 h.

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