A One-Step Synthesis of 3-Nitroflavanones and their Conversion to 3-Nitroflavones

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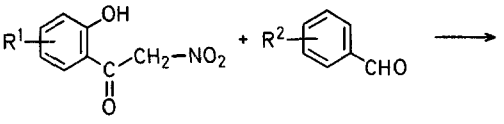
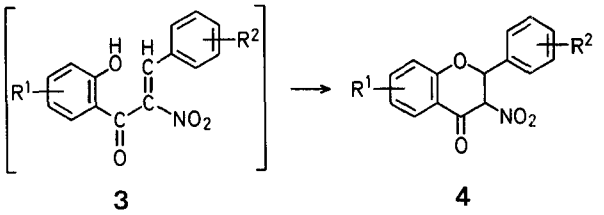
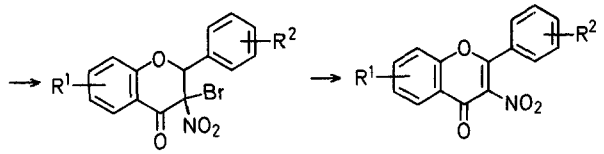
We report here a facile one-step synthesis of 3-nitroflavanones **4** by the cyclocondensation of 2′-hydroxy-2-nitroacetophenones **1** with arylaldehydes **2** and their subsequent conversion to the corresponding flavones **6**. The only compound reported so far is 3-nitroflavanone[1] obtained by the nitrosation of flavanone and its subsequent oxidation which requires, as starting material, flavanones which are not easily accessible in pure form. No other flavanones with an electron-withdrawing substituent in the 3-position have been prepared by analogous cyclocondensation reactions.



1 **2**



3 **4**



5 **6**

3-6	R^1	R^2
a	H	H
b	6-H_3C	H
c	6-H_3C	4″-H_3CO

2′-Hydroxy-ω-nitroacetophenone (**1**; R^1 = H) on reaction with benzaldehyde (**2**; R^2 = H) in glacial acetic acid with a trace of ammonium acetate yielded a yellow solid, identical in structure to 3-nitroflavanone (**3a**) previously reported[1]. Ammonium acetate has not been used so far in the synthesis of flavanones by the cyclocondensation reactions. Other conventional basic reagents used in the synthesis of chalcones or flavanones are not suitable in the present reaction as oximinocoumaranones[2] are formed under these conditions. Probably ammonium acetate helps in the initial formation of chalcone **3** which subsequently cyclises to the flavanone **4** in presence of the acid.

Compound **4a** on bromination in boiling bromine/acetic acid gave 3-bromo-3-nitroflavanone (**5a**; $R^1 = R^2 = H$). From ^{1}H-N.M.R. studies, Michalska[3] surmised that in **5a** the bromo group occupies the equatorial position while the nitro group occupies the axial position at C-3 in a half-chair conformation. Compound **5a** undergoes dehydrobromination when refluxed in pyridine to give 3-nitroflavone (**6a**). Probably pyridine facilitates the isomerisation of **5** to its isomer with bromine in the axial position which then easily undergoes 1,2-elimination.

This method has been extended to the synthesis of differently substituted 3-nitroflavanones **4** and the yields are uniformly good (Table). However, bromination of 4′-methoxy-6-methyl-3-nitroflavanone (**4c**) gave the 3,3′-dibromo derivative (**5′c**) which, on dehydrobromination in boiling pyridine, gave the corresponding 3′-bromo-4′-methoxy-6-methyl-3-nitroflavone (**6′c**) as is evident from mass spectral data.

0039-7881/81/0332-0236 $ 03.00

Table. Compounds **4**, **5**, and **6** Prepared

Product	Yield [%]	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr)[b] ν [cm^{-1}] C=O	asym-NO_2	sym-NO_2	U.V. (CH_3OH)[c] λ [nm]	^{1}H-N.M.R. ($CDCl_3$/TMS)[d] δ [ppm]	M.S.[e] *m/e* (relative intensity, %)
4a	60	137°	136–138°[1]	1710	1565	1340	380, 324, 260	5.90 (s, 2H); 7.1–8.2 (m, 9H_{arom})	269 (M^+, 15); 237 (15); 223 (14); 222 (22); 121 (43); 120 (100); 92 (22); 77 (51)
4b	55	168°	$C_{16}H_{13}NO_4$ (283.3)	1710	1525	1345	392, 335, 265	2.16 (s, 3H, CH_3); 5.65 (s, 2H); 6.8–8.0 (m, 8H_{arom})	—
4c	66	145°	$C_{17}H_{15}NO_5$ (313.3)	1711	1535	1350	390, 345, 264	—	313 (M^+, 23); 267 (97); 237 (18); 224 (19); 165 (12); 135 (75); 134 (100); 106 (15.2); 77 (52)
5a	65	111°	111°[1]	1710	1560	1325	310, 262	6.11 (s, 1H); 7.1–8.2 (m, 9H_{arom})	349 (7); 347 (M^+, 7); 301 (8); 221 (100); 120 (80); 105 (19); 92 (25); 77 (19)
5b	65	248°	$C_{16}H_{12}BrNO_4$ (362.2)	1712	1545	1345	315, 268	2.31 (s, 3H, CH_3); 5.85 (s, 1H); 6.8–8.3 (m, 8H_{arom})	—
5c[f]	70	180°	$C_{17}H_{13}Br_2NO_5$ (471.1)	1710	1550	1345	320, 232	—	475 (22), 473 (38), 471 (M^+, 65); 427 (52); 330 (43); 266 (55); 135 (75); 28 (100)
6a	50	139°	140.5°[1]	1670	1540	1350	344, 281, 226	7.3–8.4 (m, 9H_{arom})	267 (M^+, 19); 239 (19); 235 (41); 221 (2); 121 (14); 120 (39); 81 (100); 77 (55)
6b	50	195°	$C_{16}H_{11}NO_4$ (281.3)	1680	1545	1350	330, 266, 236	—	—
6c[g]	55	233°	$C_{17}H_{12}BrNO_5$ (390.3)	1680	1545	1340	335, 272, 232	—	393 (14), 391 (85), 389 (M^+, 86); 359 (73); 345 (15); 310 (100); 135 (25); 134 (50); 77 (45)

[a] Satisfactory microanalyses obtained: C ±0.11, H ±0.06, N ±0.09.
[b] Measured on Perkin-Elmer I.R. 337 spectrophotometer.
[c] Measured on Hilger and Watts instrument.
[d] Recorded on a Varian A-60/90 D-spectrometer.
[e] Recorded on Perkin-Elmer Hitachi RMU 6 L instrument.
[f] 3,3′-Dibromo derivative.
[g] 3′-Bromo derivative.

3-Nitroflavanones 4a–c; General Procedure:
2′-Hydroxy-ω-nitroacetophenone **1** (5 mmol) is dissolved in glacial acetic acid (15 ml). Freshly distilled arylaldehyde **2** (5 mmol) is then added. Ammonium acetate (0.5 g) is added to the above mixture which is then heated under reflux for about 10 min, as indicated by the change of the colour of the solution from pale yellow to brown. The reaction mixture is then cooled and poured on to crushed ice (100 g) with stirring. The yellow crystalline solid which separates is filtered and recrystallised from methanol using animal-charcoal to give the product **4** as pale yellow needles.

3-Bromo-3-nitroflavanones 5a–c; General Procedure:
The 3-nitroflavanone **4** (0.5 g) is dissolved in glacial acetic acid (10 ml). 10% Bromine in acetic acid (1.75 ml) is added to the above solution which is then heated over a low flame for 0.5 h. The contents are cooled and poured on to crushed ice (100 g) with stirring. The colorless solid that separates is filtered and recrystallised from methanol to give the product **5** as a white amorphous powder.

3-Nitroflavones 6a–c; General Procedure:
The 3-bromo-3-nitroflavanone **5** (0.5 g) is taken in dry pyridine (10 ml) and the solution heated under reflux for ~30 min. The contents are allowed to stand overnight. The crystalline solid that separates is filtered, washed with a small amount of acetic acid and recrystallised from chloroform or acetic acid to give the product **6** as pale yellow rectangular plates. If no solid separates on standing, the reaction mixture is poured on to crushed ice (100 g) and the solid which separates is filtered, dried, and recrystallised to afford the pure 3-nitroflavone **6**.

One of the authors (CPR) gratefully acknowledges the Head, Department of Chemistry (O. U.) for providing facilities and the Management of Dharmavant College of Science and Commerce, Hyderabad for due encouragement. Our thanks are due to Dr. Sidhu, Director, R. R. L., Hyderabad for providing mass spectra.

Received: April 1, 1980
(Revised form: June 16, 1980)

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