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Note

Electrophilic substitution reactions on 3-bromoacetylcoumarins

K Y Anklekar, R A Kusanur & M V Kulkarni*

Department of Chemistry, Karnatak University
Dharwad 580 003, India

E-mail: drmvk274@yahoo.co.in

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Attempted nitration and bromination of 3-bromoacetyl-coumarins result in the formation of racemic 3-ω-bromonitro-acetylcoumarins and 3-ω-dibromoacetylcoumarins.

Keywords: Electrophilic substitution, nitration, bromination, bromoacetylcoumarins

IPC: **Int.Cl.**[7] **C 07 D**

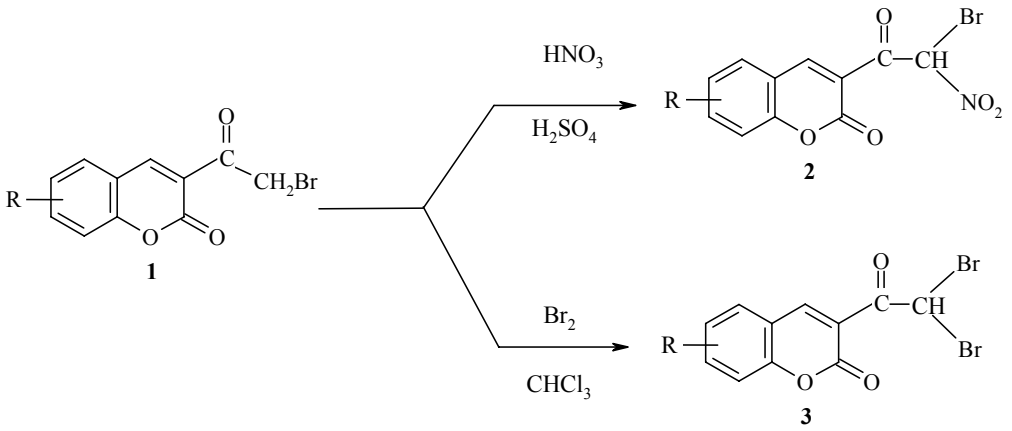
Electrophilic substitution reactions of compounds containing active methylene groups have been of considerable mechanistic interest. Nitration of cyclic ketones[1], alkylpyridines[2], esters[3,4] and isoxazolines[5] have been carried out with a variety of reagents like alkylnitrites, acetone cyanohydrin nitrate and fuming nitric acid. Bromination of diaryl-α-methylene sulphoxides[6] and dialkyl ketones[7] has been found to occur at the active methylene group. In the case of β-ketoester[8] and acetoacetanilides[9] bromination has been found to occur at the methyl group leading to the formation of stable compounds.

In an attempt to synthesise coumarins analogues of chloramphenicol[10] with a nitro group in the benzene ring, nitration of 3-bromoacetylcoumarin **1** was carried out **(Scheme I)**. The resulting compound **2** did not show the presence of methylene protons in the ^{1}H NMR spectrum and hence it was inferred that the nitro group entered the active methylene group. Similarly, bromination also resulted in the formation 3-ω-dibromoacetylcoumarins **3**. The reaction is likely to occur via the enol form because of the enhanced acidity of the methylene protons.

Nitration of various 3-bromoacetylcoumarins[11, 12] was carried out at ice-bath temperatures and the completion of the reaction was ensured by heating the reaction on a water-bath for 2 hr followed by the usual work up. Similarly, addition of liquid bromine was carried out at room temperature and the reaction mixture was heated on a water-bath till the evolution of HBr gas stopped. In both the cases, the yields were in the range of 75-85%.

In the IR spectrum, the racemic 3-ω-bromonitro-acetylcoumarin **2a** exhibited the lactone and C-3 carbonyl stretching bands at 1720 and 1680 cm^{-1}. The ^{1}H NMR spectrum (DMSO-d_6) displayed two singlets at δ 9.15 and 7.25, which have been assigned to C_4-H and $OCHBrNO_2$ protons, respectively. The aromatic multiplet was observed around δ 7.8-8.0. The mass spectrum showed the M-H peak at m/z 310, 312. M-Br and (M-$CHBrNO_2$) peaks were observed at m/z 232 (100%) and 173 (40%), respectively.

The *gem* ω-dibromoacetylcoumarin **3a** exhibited the lactone and the C-3 carbonyl stretching bands at 1739 and 1692 cm^{-1}, respectively. The ^{1}H NMR



R = H, 6-Cl, 6-Br, 8-OMe, 5,6-Benzo

Scheme I

spectrum ($CDCl_3$) showed two singlets at δ 8.6 and 7.1 due to C_4-H and $OCHCHBr_2$ protons, respectively. The aromatic multiplet was observed in the range δ 7.3 to 7.6. In the mass spectra the low intensity molecular ion peak was observed at m/z 344, 346 and 348, respectively. M-Br and M-$CHBr_2$ peaks were observed at m/z 265, 267 (50%) and 173 (100%), respectively. IR and ^{1}H NMR data for all the compounds are given in **Table I**. The structures of all the compounds were consistent with their spectral data and elemental analysis.

X-ray analysis of compound **3e** has shown that this compound exists in the monoclinic crystal system. The conformation in the solid state indicates that the C_3-carbonyl is *cis* to the C_3-C_4 double bond and adopts a *gauche* arrangement when viewed along the OC-$CHBr_2$ bond, the details of which have been published [13].

Experimental Section

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on a Nicolet 410 FTIR spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker 300 MHz FTNMR spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as standard.

3-Bromoacetylcoumarins were prepared according to the earlier literature methods[11, 12].

3-ω-Bromonitroacetylcoumarin 2a. 3-Bromoacetylcoumarin (1.3 g, 0.005*M*) was dissolved in conc. H_2SO_4(2 mL). To this 3 mL of nitrating mixture (1 mL conc. HNO_3+2 mL conc. H_2SO_4) was added with stirring at 0 °C. The reaction mixture was heated to 60-70 °C on water-bath for 2 hr. Then, it was poured into ice water. The separated yellow coloured solid was repeatedly washed with water, dried and recrystallized from acetic acid to get **2a**, yield 1.1g (72%).

Compounds **2b-d** was prepared in the same manner.

3-ω-gem Dibromoacetylcoumarin 3a. Bromine (0.9 g, 0.005*M*) in dry chloroform (10 mL) was added dropwise to 3-bromoacetylcoumarin (1.3 g, 0.005*M*) in dry chloroform (10 mL) with stirring for 5 hr. The reaction mixture was warmed on a water-bath (60-70˚C) to expel HBr gas, cooled and concentrated. The separated solid was crystallized from carbon tetrachloride to get **3a**, yield 1.34g (80%).

Table I — Characterization of compounds **2a-e** and **3a-e**

Compd	R	Yield (%)	m.p. °C	Mol. formula	Found (Calcd) (%) C	H	N	^{1}H NMR
2a	H	72	225-26	$C_{11}H_6NO_5Br$	42.43 (42.34	1.78 1.95	4.63 4.47)	7.25 (s,1H,C-H),9.15 (s,1H,C_4-H) 7.8–8.0 (m,4H,Ar-H)
2b*	6-Cl	86	250-51	$C_{11}H_5NO_5ClBr$	38.28 (38.09	1.63 1.48	4.01 4.06)	*
2c	6-Br	80	270-71	$C_{11}H_5NO_5Br_2$	34.12 (33.76	1.41 1.31	3.43 3.56)	7.67 (s, 1H,C-H), 8.15 (s, 1H, C_5-H), 8.18 (d, 1H, C_7-H, *J* = 9.03 Hz), 7.70 (d, 1H, C_8-H, *J* = 9.04 Hz), 8.64 (s, 1H,C_4-H)
2d	5,6-Benzo	80	256-57	$C_{15}H_8NO_5Br$	48.83 (48.39	2.32 2.17	3.18 3.78)	7.58 (s,1H, C-H), 7.80-9.41 (m, 6H, Ar-H), 9.43 (s, 1H, C_4-H)
3a	H	80	151-52	$C_{11}H_6O_3Br_2$	38.73 (38.17	1.83 1.78	-- -)	7.10 (s,1H,C-H),9.15 (s,1H,C_4-H), 7.80–8.00 (m,4H,Ar-H)
3b	6-Cl	85	209-10	$C_{11}H_5O_3ClBr_2$	34.82 (34.71	1.43 1.38	-- -)	7.38 (s, 1H, C-H), 7.655 (d, 1H, C_8-H, *J* = 8.8 Hz), 7.85 (dd,1H, C_7-H, *Jo* = 8.9 Hz, *Jm* = 2.4 Hz), 8.123 (d, 1H, C_5- H, *Jm* = 2.37 Hz), 8.95 (s,1H,C_4-H)
3c	6-Br	80	210-1	$C_{11}H_5O_3Br_3$	31.05 (31.21	1.23 1.18	-- -)	7.38 (s,1H, C-H),7.515 (d,1H, C_8-H, *J* = 8.75 Hz), 7.955 (dd, 1H, C_7-H, *Jo*=8.58Hz, *Jm* = 2.25 Hz),8.253-(d,1H,C_5H,*Jm* = 2.16Hz) 8.95 (s,1H,C_4-H)
3d	5,6-Benzo	90	212-13	$C_{15}H_8O_3Br_2$	45.25 (45.46	2.13 2.05	-- -)	7.60 (s, 1H,C-H), 7.7-8.7(m, 6H,Ar-H), 9.62(s, 1H, C_4-H).
3e	8-OCH_3	79	175-76	$C_{12}H_8O_4Br_2$	38.19 (38.31	2.23 2.16	-- -)	3.94 (s, 3H,OCH_3),7.36 (s, 1H,C-H), 7.39-7.54 (m, 3H, Ar-H), 8.97 (s, 1H, C_4-H)

* Compound is insoluble in $CDCl_3$ and DMSO-d_6

Compounds **3b-e** were prepared in the same manner.

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