A Facile Synthesis of 2-Alkyl(aryl)-6- and -7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines[1]

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2-Substituted 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine derivatives, a class of compounds which possess interesting pharmacological and antimicrobial properties[2,3,4] are usually obtained in two-steps by condensation of *o*-aminophenols with the corresponding α-haloacyl halides or alkyl α-haloacetates followed by cyclisation of the resulting intermediates. However, the above methods suffer from one or more drawbacks such as low overall yields, longer reaction times, and contamination of the end products with by-products. More recently, we have reported[5] a convenient one-step synthesis of some 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines by reaction of the respective *o*-aminophenol with chloroacetyl chloride in refluxing isobutyl methyl ketone in presence of aqueous sodium hydrogen carbonate.

Miller et al.[6,7,8] have recently reported the synthetic utility of potassium fluoride for *C*-, *O*-, and *S*-alkylation in many systems, as well as for intermolecular self-condensation of enolisable ketones[9], and these reactions have been explained on the basis of the strong hydrogen bonding nature of potassium fluoride. Furthermore, the strong basic character of potassium fluoride even in the non-polar solvent medium has been very well documented[10,11]. These observations led us to investigate the utilisation of potassium fluoride for a simple synthesis of the title nitro-substituted benzoxazinones. Thus, we report herein a facile and more convenient one-step synthesis for large scale preparation of 2-substituted 6- and -7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines **3** by potassium fluoride-assisted *O*-alkylation of 4- and 5-nitro-2-aminophenols **1** with

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Table. 2-Substituted 6-(or 7-)-Nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines **3a–j**

Product	Position of NO_2 group	R^1	R^2	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]	I.R. (nujol)[c] $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6)[d] δ [ppm]
3a	7-NO_2	H	H	82	234°	232°[12]	1690	4.75 (s, 2H); 7.10 (d, J=7.5 Hz, 1H); 7.75–9.95 (m, 2H); 11.25 (br. s, 1H)
3b	6-NO_2	H	H	59	235°	233°[12]	1685	4.75 (s, 2H); 7.15 (d, J=7.5 Hz, 1H); 7.7–7.85 (m, 2H); 11.0 (br. s, 1H)
3c	7-NO_2	CH_3	H	87	208°	$C_9H_8N_2O_4$ (208.1)	1685	1.60 (d, J=6 Hz, 3H); 4.80 (q, J=6 Hz, 1H); 7.10 (d, J=7.5 Hz, 1H); 7.75–7.95 (m, 2H); 11.3 (br. s, 1H)
3d	6-NO_2	CH_3	H	63	190°	191°[3]	1680	1.60 (d, J=6 Hz, 3H); 4.70 (q, J=6 Hz, 1H); 7.00 (d, J=7.5 Hz, 1H); 7.8 (m, 2H); 10.7 (br. s, 1H)
3e	7-NO_2	CH_3	CH_3	63	209°	$C_{10}H_{10}N_2O_4$ (223)	1680	1.70 (s, 6H); 7.00 (d, J=7.5 Hz, 1H); 7.9–8.1 (m, 2H); 9.35 (br. s, 1H)
3f	6-NO_2	CH_3	CH_3	61	205°	$C_{10}H_{10}N_2O_4$ (223)	1680	1.50 (s, 6H); 6.90 (d, J=7.5 Hz, 1H); 7.75–7.9 (m, 2H); 10.5 (br. s, 1H)
3g	7-NO_2	C_2H_5	H	72	196°	$C_{10}H_{10}N_2O_4$ (223)	1690	1.15 (t, J=6 Hz, 3H); 1.75–2.15 (m, 2H); 4.55 (t, J=6 Hz, 1H); 7.15 (d, J=7.5 Hz, 1H); 7.8–8.0 (m, 2H)
3h	6-NO_2	C_2H_5	H	54	164°	166°[3]	1690	1.20 (t, J=6 Hz, 3H); 1.85–2.15 (m, 2H); 4.75 (t, J=6 Hz, 1H); 7.50 (d, J=7.5 Hz, 1H); 7.85–8.05 (m, 2H); 9.7 (br. s, 1H)
3i	7-NO_2	C_6H_5	H	67	195°	$C_{14}H_{10}N_2O_4$ (270.2)	1685	5.85 (s, 1H); 6.90 (d, J=6 Hz, 1H); 7.45 (s, 5H); 7.85–8.0 (m, 2H); 9.45 (br. s, 1H)
3j	6-NO_2	C_6H_5	H	45	187°	$C_{14}H_{10}N_2O_4$ (270.2)	1680	5.80 (s, 1H); 7.05 (d, J=7.5 Hz, 1H); 7.45 (s, 5H); 7.75–7.9 (m, 2H)

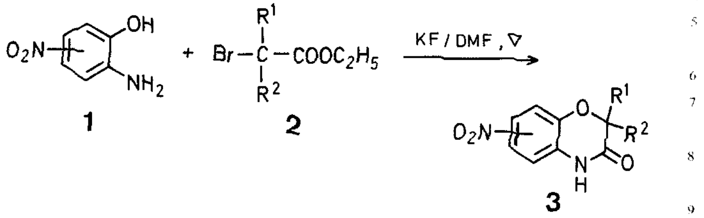
[a] The reported overall yields of **3** are of pure crystallised products.

[b] The microanalyses of the new compounds showed the following deviations from the calculated values: C, ±0.35, H, ±0.45, N, ±0.47.

[c] Recorded on a Perkin-Elmer model 298 spectrometer.

[d] ^{1}H-N.M.R. spectra measured at 90 MHz on a Varian A-90 (EM-390) spectrometer using TMS as an internal standard.

the more easily accessible α-bromoalkanoic acid ethyl esters **2** in dimethylformamide or dimethyl sulfoxide, followed by *in situ* intramolecular cyclisation of the resulting *O*-alkylated aminophenols in presence of excess of fluoride ion.



Six hitherto unreported 2-substituted-6- and -7-nitrobenzoxazinones (**3c**, **3e**, **3f**, **3g**, **3i**, and **3j**) were also prepared by this method in good yields and the results are summarised in the Table. The structures of products **3** were confirmed by microanalyses, and I.R. and ^{1}H-N.M.R. spectrometry.

2-Substituted 6-(or 7-)-Nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazines 3a–j; General Procedure:

To a stirred suspension of potassium fluoride (10 g) in dry dimethylformamide (50 ml) is added the α-bromoalkanoic acid ethyl ester **2** (0.066 mol) and the stirring is continued for 15 min at room temperature. To this mixture is added the nitro-*o*-aminophenol **1** (0.066 mol) and the mixture is stirred for 6 h at 50–60 °C and left overnight at room temperature. It is then poured into ice/water (300 ml), the resulting light yellow solid is filtered, washed with water, and dried. Recrystallisation from ethanol gives pure **3** as yellow shining needles.

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