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REGIOSELECTIVITY IN THE C-ACYLATION OF 2(3H)-BENZOXAZOLONES

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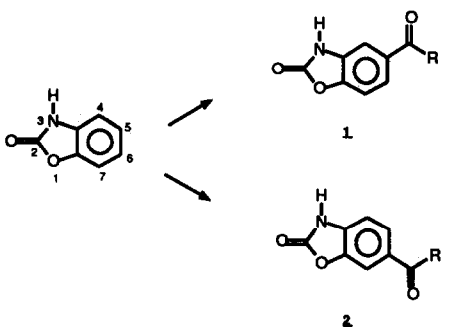
Abstract

Unequivocal synthetic routes towards 5- and 6-acyl-2(3H)-benzoxazolones are described. Comparison of the physico-chemical properties of the compounds obtained by direct acylation under various Friedel-Crafts reaction conditions always leads to the conclusion that 6-acyl derivatives are the only isolated products. This observation contradicts previously published results.

Electrophilic aromatic substitutions of the benzoxalinone ring have been thoroughly investigated. Reactions such as chlorination[1], sulfonation[2], and nitration[3] have long been described. Acylation, however, was found to be more difficult and to occur under peculiar conditions. The reaction readily takes place with aliphatic, aromatic, and arylaliphatic carboxylic acids in the presence of polyphosphoric acid (PPA)[4]. Other conditions are required in the case of dicarboxylic acids, or carboxylic acids containing a halogenoalkyl or heterocyclic moiety. Thus, we recently found that it could be efficiently effected in a mixture of aluminum chloride and dimethylformamide (DMF)[5].



Scheme 1

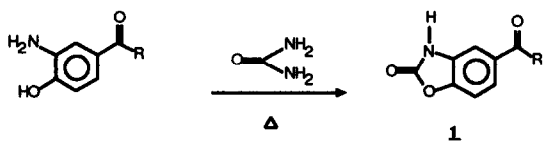
As both the 3-nitrogen and 2-oxygen atoms are electron-donating, both the 5- and 6-position are activated and, therefore, the regioselectivity in the C-acylation of benzoxazolones cannot be easily predicted (Sheme 1). Some authors have claimed 5-acylation products, for example, in the reaction of 2-bromopropionyl bromide with 2(3H)-

benzoxazolone in the presence of aluminum chloride in CS_2, but this report was not substantiated by any spectroscopic data. In our hands, however, acylations using either PPA or $AlCl_3$-DMF always led to 6-acyl derivatives, and these results were supported by different spectroscopic techniques[6] including, in the case of the 6-benzoyl derivative (2d), X-ray single crystal diffraction[7].

In an effort to clarify this situation, we have reproduced the acylation in $AlCl_3$-CS_2[8] and in PPA (which unambiguously leads to 6-acyl-derivatives[6,7]), and found out that the isolated materials had identical physico-chemical and spectroscopic features. The 5-(2-bromopropyl)-2(3H)-benzoxazolone structure claimed by Takeo and Hisashi[8] is therefore incorrect and the product belongs definitively to the 6-acyl series. To settle definitely this question, we report here the synthesis of five 5-acyl representatives and the corresponding 6-isomers along with a comparative study of their physico-chemical and spectroscopic properties.

Preparation of 5-acyl-2(3H)-benzoxazolones

Only a few examples of procedures leading to 5-acylbenzoxalinones have been reported[8-10]; they were characterized only by melting points and micro-analyses, and no spectroscopic data were given. We now report the synthesis of 5-acyl-2(3H)-benzoxazolones by treatment of 4-acyl-2-aminophenols of known structure with urea in the presence of concentrated hydrochloric acid (Scheme 2).



Scheme 2

Preparation of 6-acyl-2(3H)-benzoxazolones

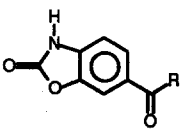
Two methods (A and B) have been used (Scheme 3). Yields are presented in Table 1. Method A uses PPA both as solvent and catalyst and the free carboxylic acids as reagent. Method B uses acid halides or anhydrides in the presence of aluminum chloride and DMF.

Scheme 3

Comparison of the ^{1}H-NMR parameters (chemical shifts (δ, ppm) and coupling constants (^{3}J, Hz), Table 2) permits an easy differentiation of the 5- and 6-series: i) the spectral region corresponding to the aromatic protons extends over a wider range of chemical shifts (7.11-7.92 ppm) in the 6-series; ii) the 4- and 6-protons, which are in the close vicinity of the carbonyl group, are well separated in the 5-series while they overlap in the 6-series.

It is noteworthy that the observed regioselectivity in favour of the 6-position is consistent with energy estimates obtained by molecular mechanics (energy minimization and molecular dynamics) calculations performed on the 5- and 6-benzoylarenium ions (intermediates in the formation of 1d and 2d, respectively) and based on Allinger's MMP2 force field[11-13]. The 6-benzoylarenium ion was indeed found to have a lower potential energy than its corresponding 5-congener (ΔΔE=12.3±1.5 Kcal/mol) while both 5- and 6-benzoxazolinones had quite similar energy (ΔΔE<0.1 Kcal/mol). The same type of calculation was also performed for the thienoyl derivatives and, again, the same results were obtained with an energy difference (ΔΔE=6.8±1.5 Kcal/mol) in favour of the 6-thienoylarenium species and no significant energy difference for the isomeric ketones (1e, 2e). These data are consistent with a kinetic control of the reaction involving an acylium ion and support the higher activation of the 6- over the 5-position in the electrophilic acylation of the 2(3H)-benzoxazolone ring.

An easy access to 5-acyl-2(3H)-benzoxazolones has allowed to study the pharmacology of these compounds, in particular, their analgetic, anti-inflammatory, psychotropic and blood triglyceride-regulating properties[26]; so far, only the 6-series was well-documented[14-24]. Moreover, the 5-acyl compounds are excellent starting materials for the elaboration of pharmacomolecules; recently, some of them have demonstrated interesting analgetic and anti-inflammatory properties[25-26].



2

R	N°	Yields (%)	
		Method A	Method B
CH_3	**2a**	58	68
CH_2 CH_3	**2b**	58	66
CH (Br) CH_3	**2c**	52	65
	**2d**	56	67
	**2e**	25	60

Table 1

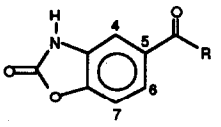
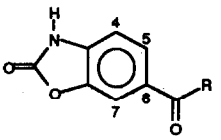
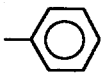
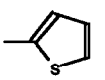
R	 $\delta_{ppm}^{(m)}$; J_{Hz}				 $\delta_{ppm}^{(m)}$; J_{Hz}			
	N°	H - 4	H - 6	H- 7	N°	H - 4	H - 5	H - 7
CH_3	1 a	7.56 (d) ; 1.8	7.77 (dd) ; 1.8 , 8.4	7.36 (d) ; 8.4	2a	7.17 (d) ; 8.6	7.84 (dd) ; 1.6 , 8.6	7.77 (d) ; 1.6
CH_2CH_3	1 b	7.57 (d) ; 1.8	7.77 (dd) ; 1.8 , 8.4	7.36 (d) ; 8.4	2b	7.11 (d) ; 9	7.80 (dd) ; 1.8 , 9	7.73 (d) ; 1.8
$CH(Br)CH_3$	1 c	7.66 (d) ; 1.6	7.86 (dd) ; 1.6 , 8	7.40 (d) ; 8	2c	7.31 (d) ; 9	8.05 (dd) ; 1.8 , 9	8.00 (d) ; 1.8
	1 d	7.48 (m)	7.48 (m)	7.48 (m)	2d	7.21 (d) ; 8.6	7.44 -7.75(m)	7.44 - 7.75 (m)
	1 e	7.49 (d) ; 1.6	7.65 (dd) ; 1.6 , 8.7	7.28 (d) ; 8.7	2e	7.18 (d) ; 9	7.75 (dd) ; 1.8 , 9	7.73 (d) ; 1.8

Table 2

EXPERIMENTAL

Melting points were taken on a Tottoli melting-point apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 177 infrared-spectrometer using potassium bromide pellets. The ^1H NMR spectra were recorded with a Bruker WP80SY spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Elemental analysis were performed by the "Service Central d'Analyses", CNRS, Vernaison, France.

5-Acyl-2(3H)-benzoxazolonesGeneral Procedure

As 4-acyl-2-aminophenols are more stable when the amino group is protected, they were preserved as 4-acyl-2-acetylaminophenols prior use and deprotection was carried out *in situ*. 4-acyl-2-acetylaminophenols[25] (0,03 mole) were suspended in 30 ml of concentrated hydrochloric acid and the mixture was refluxed for 45 min. After cooling and evaporation to dryness under vacuum, the residue was intimately mixed with urea (0.15 mole). Concentrated HCl (7ml) was added and the mixture was kept at 140°C for 1.5 h then 170°C for 2.5 h. After cooling, water (30 ml) were added, and stirring was maintained for 1h. The resulting precipitate was filtered, washed with water and crystallized from the appropriate solvent.

- **5-Acetyl-2(3H)-benzoxazolone** ***1 a***

This compound was obtained as white needles (ethanol) ; 68 % ; mp 231-233°C ;
IR : ν (cm^{-1}) ; 3300 - 3100 (NH), 1785 (CO), 1660 (CO), 1615 (Arom) ; NMR (DMSO-d_6) δ ppm : 2.56 (s, 3H, CH_3), 7.36 (d, 1H, H-7, J = 8.4Hz), 7.56 (d, 1H, H-4, J = 1.8Hz), 7.77 (dd, 1H, H-6, J = 8.4Hz, J = 1.8Hz), 11.68 (s, 1H, NH, exchangeable with D_2O)

Calcd for $C_9H_7NO_3$: C, 61.02 ; H, 3.98 ; N, 7.90
Found : C, 61.22 ; H, 3.95 ; N, 7.76

- **5-Propionyl-2(3H)-benzoxazolone** ***1 b***

This compound was obtained as white needles (ethanol) ; 73 % ; mp 205-206°C ; IR : ν (cm^{-1}) : 3180 (NH), 1810 (CO), 1665 (CO), 1615 (Arom) ; NMR (DMSO - d_6) δ ppm : 1.08 (t, 3H, CH_3), 3.02 (q, 2H, CH_2), 7.36 (d, 1H, H-7, J = 8.4 Hz), 7.57 (d, 1H, H-4, J = 1.8Hz), 7.77 (dd, H-6, J = 8.4Hz, J = 1.8Hz), 11.71 (s, 1H, NH, exchangeable with D_2O)

Calcd for $C_{10}H_9NO_3$: C, 62.82 ; H, 4.75 ; N, 7.33

Found : C, 62.84 ; H, 4.72 ; N, 7.29

- **5-(2-Bromo-propionyl)-2(3H)-benzoxazolone** ***1c***

This compound was obtained as white needles (ethanol) ; 83 % ; mp 149-150°C ; IR : ν (cm^{-1}) : 3140-3040 (NH), 1750 (CO), 1680 (CO), 1620 (Arom) ; NMR (DMSO-d_6) δ ppm : 1.76 (d, 3H, CH_3, J = 6.6Hz), 5.80 (q,1H, CH, J = 6.6 Hz), 7.40 (d, 1H, H-7, J = 8.0Hz) , 7.66 (d, 1H, H-4), 7.86 (dd, 1H, H-6, J = 8.0Hz, J = 1.6Hz), 11,83 (s, 1H, NH, exchangeable with D_2O)

Calcd for $C_{10}H_8NO_3Br$: C, 44.46 ; H, 2.99 ; N, 5.09
Found : C, 44.76 ; H, 3.09 ; N, 5.18

- **5-Benzoyl-2(3H)-benzoxazolone** ***1d***

This compound was obtained as white needles (ethanol) ; 76 % ; mp 169-170°C ; IR : ν (cm^{-1}) : 3260 (NH), 1760 (CO), 1655 (CO), 1620, 1580 (Arom) ; NMR (DMSO-d_6) δ ppm : 7.48 (m, 3H, H-4, H-6, H-7), 7.56-7.74 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 11.70 (s, 1H, NH, exchangeable with D_2O)

Calcd for $C_{14}H_9NO_3$: C, 70.28 ; H, 3.79; N, 5.86
Found : C, 70.43 ; H, 3.73 ; N, 6.01

- **5-(1-Thenoyl)-2(3H)-benzoxazolone** ***1e***

This compound was obtained as a white powder (ethanol/water : 1/4) ; 71 % ; mp 215-217°C ; IR : ν (cm^{-1}) : 3200-3100 (NH), 1780 (CO), 1630 (CO), 1580 (Arom) ; NMR (DMSO-d_6) δ ppm : 7.23-7.46 (m, 2H, H-7, H-3'), 7.49 (d, 1H, H-4, J = 1.6 Hz), 7.65 (dd, 1H, H-6, J = 8.7 Hz, J = 1.6 Hz), 7.74 (d, 1H, H-4', J = 3.9 Hz), 8.08 (d, 1H, H-2', J = 5Hz), 11.60 (s, 1H, NH, exchangeable with D_2O)

Calcd for $C_{12}H_7NO_3S$: C, 58.76 ; H, 2.88 ; N, 5.71
Found : C, 58.60 ; H, 3.05 ; N, 5.79

6-Acyl-2(3H)-benzoxazolones

Method A - General Procedure

To a stirred solution of benzoxazolinone (5,4 g, 40 mmoles) in polyphosphoric acid (80 g) heated at a suitable temperature[4] was slowly added the organic acid (40 mmoles). The mixture was stirred at this temperature for the reported time[4], cooled and poured onto ice. The resulting precipitate was collected by filtration, washed with water, dried and crystallized from the appropriate solvent.

Method B - General Procedure

Dimethyformamide (8.6 ml, 115 mmoles) was slowly added to aluminum chloride (53.3 g, 400 mmoles). This mixture was stirred and maintained at 45°C while benzoxazolinone (5.4 g, 40 mmoles) and the anhydride (60 mmoles 2a - 2b - 2d) or acid chloride (60 mmoles 2c - 2e) were added. The reaction mixture was heated at 75°C under stirring for 2 hours, poured onto ice and the crude product was collected by filtration, air-dried and crystallized.

- **6-Acetyl-2(3H)-benzoxazolone** ***2a***

This compound was obtained as colorless needles (ethanol) ; mp 228°C ; IR : ν (cm^{-1}) : 3180 (NH), 1775 (CO), 1655 (CO) ; NMR (DMSO-d_6) δ ppm : 2.54 (s, 3H, CH_3), 7.17 (d, 1H, H-4, J = 8.6Hz), 7.77 (d, 1H, H-7), 7.84 (dd, 1H, H-5, J = 8.6Hz, J = 1.6Hz), 11.88 (s, 1H, NH, exchangeable with D_20).

Calcd for $C_9H_7NO_3$: C, 61.02 ; H, 3.98; N, 7.90
Found : C, 60.92 ; H, 3.82 ; N, 8.00

- **6-Propionyl-2(3H)-benzoxazolone** ***2b***

This compound was obtained as colorless needles (ethanol) ; mp 205°C ; IR : ν (cm^{-1}) : 3180 (NH), 1770 (CO) , 1655 (CO) ; NMR (DMSO-d_6) δ ppm : 1.08 (t, 3H, CH_3), 3.05 (q, 2H, CH_2), 7.11 (d, 1H, H-4, J = 9Hz), 7.73 (d, 1H, H-7, J = 1.8Hz), 7.80 (dd, 1H, H-5, J = 9Hz, J = 1.8Hz), 11.70 (s, 1H, NH, exchangeable with D_2O).

Calcd for $C_{10}H_9NO_3$: C, 62.82 ; H, 4.75 ; N, 7.33
Found : C, 62.60 ; H, 4.62 ; N, 7.45

- **6-(2-Bromo-propionyl)-2(3H)-benzoxazolone** ***2c***

This compound was obtained as colorless needles (ethanol) ; mp 191-192°C ; IR : ν (cm^{-1}) : 3170 (NH), 1780 (CO), 1660 (CO) ; NMR (DMSO-d_6) δ ppm : 1.85 (d, 3H, CH3, J = 6,5Hz), 5.87 (q, 1H, CH, J = 6.5 Hz), 7.31 (d, 1H, H-4, J = 9Hz), 8.00 (d, 1H, H-7, J = 1.8Hz), 8.05 (dd, 1H, H-5, J = 9.0Hz, J = 1.8Hz), 12.00 (s, 1H, NH, exchangeable with D_20).

Calcd for $C_{10}H_8NO_3Br$: C, 44.46 ; H, 2.99; N, 5.09
Found : C, 44.71 ; H, 3.17 ; N, 5.30

- **6-Benzoyl-2(3H)-benzoxazolone** ***2d***

This compound was obtained as colorless needles (toluene) ; mp 169-170°C ; IR : ν (cm^{-1}) : 3140 (NH), 1780 (CO), 1635 (CO) ; NMR (DMSO-d_6) δ ppm : 7.21 (d, 1H, H-4, J = 8.6Hz), 7.44-7.75 (m, 7H, H-5, H-7, phenyl), 11.97 (s, 1H, NH, exchangeable with D_2O).

Calcd for $C_{14}H_9NO_3$: C, 70.28 ; H, 3.79 ; N, 5.86

Found : C, 70.34 ; H, 3.60 ; N, 6.02

- **6-Thenoyl-2(3H)-benzoxazolone** ***2e***

This compound was obtained as a white powder (ethanol/water : 1/1) mp 187-188°C ; IR : ν (cm^{-1}) : 3240 (NH), 1780 (CO), 1630 (CO) ; NMR (DMSO - d_6) δ ppm : 7.18 (d, 1H, H-4, J = 9 Hz), 7.25 (dd, 1H, H-4', J = 3.8 Hz, J = 4.8 Hz), 7.69 (dd, 1H, H-3', J = 0.9 Hz, J = 3.8 Hz), 7.73 (d, 1H, H-7, J = 1.8 Hz) , 7.75 (dd, 1H, H-5, J = 1.8 Hz, J = 9 Hz), 8.02 (dd, 1H, H-5', J = 0.9 Hz, J = 4.8 Hz), 12.00 (s,1H,NH, exchangeable with D_2O)

Calcd for $C_{12}H_7NO_3S$: C, 58.76 ; H, 2.88 ; N, 5.71

Found : C, 58.39 ; H, 2.91 ; N, 5.71

Molecular Mechanics Calculations.

Energy minimizations were initially carried out on studied compounds (1d, 1e, 2d, 2e and the corresponding arenium ions) using Chem 3D Plus 3.0.1(released in December 1990 by Cambridge Scientific Computing, Inc., Cambridge, Massachusetts). Chem 3D contains a new implementation of Allinger's MM2 force field[11,12] based on work done by Ponder[13]. To test the validity of the parameters used, the energy-minimized structure of 2d was compared to that observed in the crystal[7] and was found nearly identical. In particular, the planes of the benzoxalinone and phenyl moieties were found in both cases equal to 54°. To measure the global potential energy of the various conformers present at the reaction temperature, molecular dynamics studies were performed. using a target temperature of 320°K along with an evolution time of 10-15 psec by dynamic steps of 2 fsec. The heating/cooling rate was 3 Kcal/atom/psec. Potential energy figures were collected during the periods of thermal equilibrium within a range of ±10°K of the target temperature; between 150-300 figures were averaged to provide the final value.

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