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SYNTHESIS AND PROPERTIES OF 1,3-DIARYL-5,6-DIHYDRO-8H-IMIDAZO-[2,1-*c*]-1,4-OXAZINIUM BROMIDES

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It has been established that the condensation of 3-(4-methoxyphenylamino)-5,6-dihydro-2H-1,4-oxazine with substituted phenacyl bromides occurs at the exocyclic nitrogen atom with formation of 3-aryl-3-hydroxy-1-(4-methoxyphenyl)-2,5,6,8-tetrahydro-3H-imidazo[2,1-c]-1,4-oxazinium bromides. By treatment of the latter with acetic anhydride 3-aryl-1-(4-methoxyphenyl)-5,6-dihydro-8H-imidazo[2,1-c]-1,4-oxazinium bromides are formed. The structures of the compounds synthesized were determined via ^{1}H NMR spectroscopy and X-ray diffraction.

Keywords: heterocyclic amidines, 3-(4-methoxyphenylimino)-5,6-dihydro-2H-1,4-oxazine, substituted phenacyl bromides, 3-ethoxy-5,6-dihydro-2H-1,4-oxazine, exocyclic nitrogen atom, alkylation.

In a continuation of our work on the properties of heterocyclic N-aryl(alkyl)amidines [1,4], we have studied the alkylation of 3-(4-methoxyphenylamino)-5,6-dihydro-2H-1,4-oxazine (**1**) with substituted phenacyl bromides. The initial products of the reaction are the salts **2a-e** in 48-78% yield (Table 1). 3-Aryl-1-(4-methoxyphenyl)-5,6-dihydro-8H-imidazo[2,1-*c*]-1,4-oxazinium bromides **3a-e** are obtained when the initial salts are refluxed with acetic anhydride. The structures of the reaction products **2a-e** were investigated by IR and ^{1}H NMR spectroscopy. For example the stretching bands of the CO group in the range 1650-1750 cm^{-1} and of the NH group in the 3300-3500 cm^{-1} are absent from the IR spectra of products **2a-e**, while the characteristic absorption bands of the associated OH group appear in the range 3060-3100 cm^{-1}. In the ^{1}H NMR spectra of DMSO-d$_6$ solutions, the signals of the methylene group of the oxazine ring occur in the range 3.01-4.48 ppm. The two-proton singlet of the 8-CH$_2$ group is found in the 4.38-4.48 ppm region. The signals of the methoxy groups are recorded at 3.81-3.84 ppm. As a result of the presence of an asymmetric carbon atom in compounds **2**, the methylene groups in the second position in the systems appear as characteristic AB systems in the 4.46-4.95 ppm (J = 16.8-17.4 Hz). The one-proton singlet of the OH group is observed in the 8.11-8.30 ppm region (this assignment is confirmed by disappearance of this signal when the spectra are recorded for a second time in the presence of a small amount of D$_2$O) (Table 2). Thus compounds **2a-e** are 1,3-diaryl-2,5,6,8-tetrahydro-3H-imidazo[2,1-*c*]-1,4-oxazinium bromides. It is interesting to note that these salts dissolve well in chloroform as well as in polar solvents.

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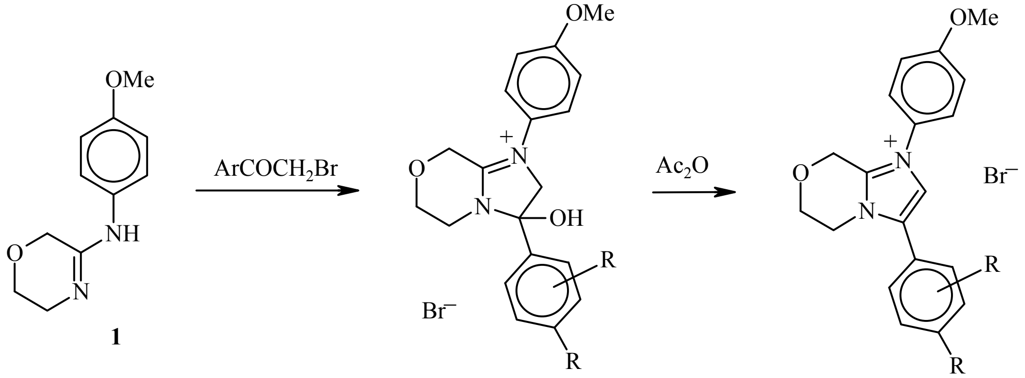

1 **2a–c** **3a–c**

2, **3** **a** R = 4-Me; **b** R = 4-Br; **c** R = 2-F,4-OMe; **d** R = 3,4-OCH_2CH_2O; **e** R = 4-Ph

Compounds **3a-e** were obtained by refluxing salts **2a-e** in Ac_2O. The structures of the imidazolinium salts obtained were also determined by ^1H NMR spectroscopy. The disappearance of the asymmetric center on going from compounds **2** to products **3** led to a considerable simplification of the proton spectra of the latter. For example the methylene groups of the oxazine ring appear as two triplets and a singlet at 4.18, 4.33, and 5.1 ppm.

It should be noted that the data from the spectral studies do not determine unambiguously which of the nitrogen atoms is alkylated. Therefore an X-ray crystallographic of compound **3a** was carried out which showed that alkylation occurred at the exocyclic nitrogen atom to give 3-aryl-3-hydroxy-1-(4-methoxyphenyl)-2,5,6,8-tetrahydro-3H-imidazo[2,1-*c*]-1,4-oxazinium bromides, **3a-e**.

TABLE 1. Characteristics of Compounds **1, 2a-e,** and **3a-e**

Compound	Empirical formula	Found N, % / Calculated N, %	mp, °C	Yield, %
1	$C_{11}H_{14}N_2O_2\cdot HBr$	9.98 / 9.76	173-174	78
2a	$C_{20}H_{23}N_2O_3\cdot Br$	6.50 / 6.68	206-207	65
2b	$C_{19}H_{20}BrN_2O_3\cdot Br$	5.84 / 5.79	206-207	75
2c	$C_{20}H_{22}FN_2O_4\cdot Br$	6.03 / 6.18	202-203	68
2d	$C_{21}H_{23}N_2O_5\cdot Br$	5.96 / 6.05	176-177	64
2e	$C_{25}H_{25}N_2O_3\cdot Br$	5.97 / 5.82	213-215	78
3a	$C_{20}H_{21}N_2O_2\cdot Br$	6.72 / 6.98	213-214	50
3b	$C_{19}H_{18}BrN_2O_2\cdot Br$	5.76 / 6.01	230-231	62
3c	$C_{20}H_{20}FN_2O_3\cdot Br$	6.26 / 6.44	209-210	48
3d	$C_{21}H_{21}N_2O_4\cdot Br$	6.51 / 6.29	212-213	53
3e	$C_{25}H_{23}N_2O_2\cdot Br$	5.88 / 6.05	241-242	62

TABLE 2. IR and ^{1}H NMR Spectra of Compounds **1**, **2a-e**, and **3a-e**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectra, δ, ppm (*J*, Hz)						
		MeO (s)	OCH_2 (s)	$OCH_2–\underline{CH_2}N$	$O\underline{CH_2}–CH_2N$	OH (s)	H_{Ar} (m)	Other signals
1		3.80	4.68	3.33 (t, *J* = 5.1)	3.95 (t, *J* = 5.1)		7.06-7.28 (4H)	9.58 (s, 1H, NH)
2a	1630; 3060-3070	3.81	4.42	3.01-3.42 (m)	3.97 (m)	8.16	7.10-7.72 (8H)	2.36 (s, 3H, CH_3); 4.69 and 4.87 (dd, *J* = 17.4, 2H, CH_2N)
2b	1620; 3060-3070	3.81	4.43	3.05-3.43 (m)	4.00 (m)	8.30	7.09-7.32 (8H)	4.46 and 4.86 (dd, *J* = 16.8, 2H, CH_2N)
2c	1635; 3080-3090	3.84	4.44	3.07-3.69 (m)	4.08-4.39 (m)	8.24	6.68-7.86 (7H)	3.86 (s, 3H, OCH_3); 4.58 and 4.82 (dd, *J* = 17.1, 2H, CH_2N)
2d	1630; 3090	3.81	4.38	3.05-3.42 (m)	3.98 (m)	8.11	6.95-7.58 (7H)	4.29 (s, 4H, OCH_2CH_2O); 4.67 and 4.83 (dd, *J* = 17.1, 2H, CH_2N)
2e	1620; 3090-3100	3.82	4.48	3.08-3.50 (m)	4.03 (m)	8.27	7.09-7.85 (13H)	4.75 and 4.95 (dd, *J* = 17.1, 2H, CH_2N)
3a	1620	3.82	5.09	4.18 (t, *J* = 4.5)	4.30 (t, *J* = 4.5)		7.19-7.71 (8H)	2.41 (s, 3H, CH_3); 8.24 (s, 1H, CHN)
3b	1620	3.86	5.09	4.18 (t, *J* = 4.2)	4.33 (t, *J* = 4.2)		7.19-7.82 (8H)	8.32 (s, 1H, CHN)
3c	1640	3.85	5.12	4.19 (t, *J* = 4.5)	4.33 (t, *J* = 4.5)		6.85-8.02 (7H)	3.86 (s, 3H, OCH_3); 8.31 (s, 1H, CHN)
3d	1610	3.84	5.21	4.18 (t, *J* = 4.5)	4.36 (t, *J* = 4.5)		7.02-7.75 (7H)	4.27 (s, 4H, OCH_2CH_2O); 8.22 (s, 1H, CHN)
3e	1610	3.86	5.13	4.20 (t, *J* = 4.8)	4.42 (t, *J* = 4.8)		7.21-7.95 (13H)	8.37 (s, 1H, CHN)

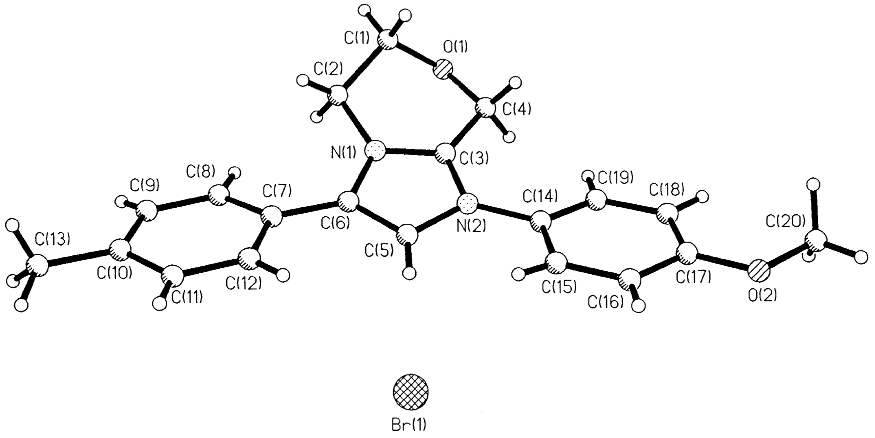

Fig. 1. General view of the molecule of 3-(4-methylphenyl)-1-(4-methoxyphenyl)-5,6-dihydro-8H-imidazo[2,1-*c*]-1,4-oxazinium bromide (**3a**).

The overall shape of molecule **3a** is shown in Fig.1, and its basic geometric parameters are shown in Table 3. The central five-membered ring $N_{(1)}C_{(3)}N_{(2)}C_{(5)}C_{(6)}$ is planar withing limits of 0.010 A, while atoms $C_{(2)}$, $C_{(4)}$, $C_{(7)}$, and $C_{(14)}$ are displaced from this plane by 0.212, -0.022, -0.015, and 0.130 A respectively. Distribution of bond lengths in this ring indicate significant delocalization of electron density which is a characteristic trait of the structure of similar systems [2]. The benzene rings $C_{(7-12)}$ and $C_{(14-19)}$ are twisted in the same direction relative to the five membered ring, forming bifacial angles of 17.8 and 17.3° with it. The torsion angles in the six-membered ring $O_{(1)}C_{(1)}C_{(2)}N_{(1)}C_{(3)}C_{(4)}$ ($O_{(1)}C_{(1)}C_{(2)}N_{(1)}$ 54.4(5), $C_{(1)}C_{(2)}N_{(1)}C_{(3)}$ -16.3 (5), $C_{(2)}N_{(1)}C_{(3)}C_{(4)}$ -9.0(5), $N_{(1)}C_{(3)}C_{(4)}O_{(1)}$ -4.2(5), $C_{(3)}C_{(4)}O_{(1)}C_{(1)}$ 44.4(4), $C_{(4)}O_{(1)}C_{(1)}C_{(2)}$ -72.0(4)°) indicate considerable nonplanarity. Calculated Kremer–Pople modification parameters [5] (S 0.85, θ 43.1°, ψ 20.9°) show that this heterocycle has a somewhat distorted *half-chair* conformation.

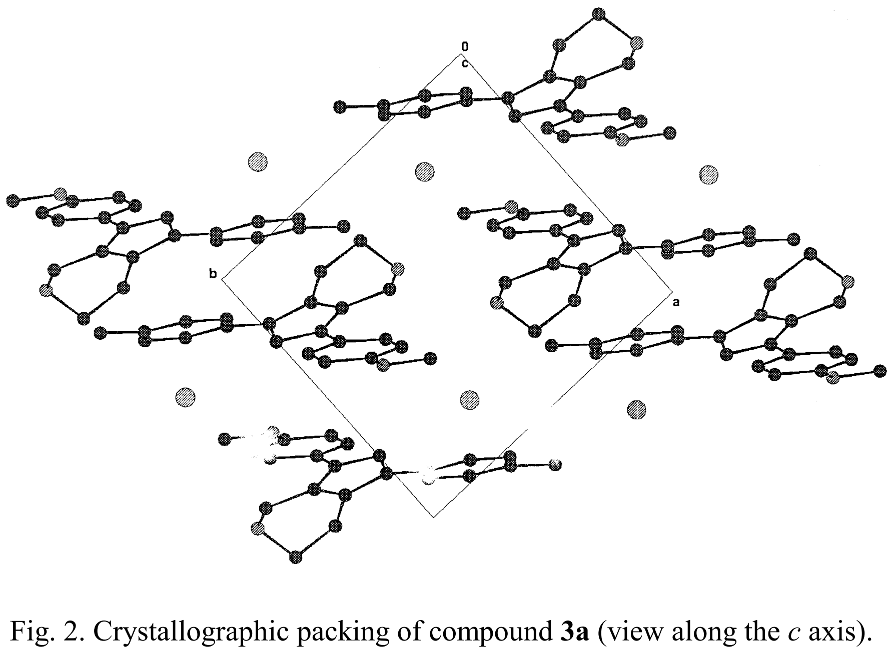

Fig. 2. Crystallographic packing of compound **3a** (view along the *c* axis).

TABLE 3. Basic Bond Lengths (*d*) and Bond Angles (ω) in the Cation of Compound **3a**

Bond	*d*, Å	Angle	ω, deg.
$O_{(1)}-C_{(4)}$	1.398(4)	$C_{(4)}-O_{(1)}-C_{(1)}$	111.8(3)
$O_{(1)}-C_{(1)}$	1.423(5)	$C_{(17)}-O_{(2)}-C_{(20)}$	117.1(3)
$O_{(2)}-C_{(17)}$	1.356(4)	$C_{(3)}-N_{(1)}-C_{(6)}$	109.2(3)
$O_{(2)}-C_{(20)}$	1.433(5)	$C_{(3)}-N_{(1)}-C_{(2)}$	121.4(3)
$N_{(1)}-C_{(3)}$	1.335(4)	$C_{(6)}-N_{(1)}-C_{(2)}$	128.8(3)
$N_{(1)}-C_{(6)}$	1.400(4)	$C_{(3)}-N_{(2)}-C_{(5)}$	107.7(3)
$N_{(1)}-C_{(2)}$	1.475(5)	$C_{(3)}-N_{(2)}-C_{(14)}$	128.0(3)
$N_{(2)}-C_{(3)}$	1.342(4)	$C_{(5)}-N_{(2)}-C_{(14)}$	124.1(3)
$N_{(2)}-C_{(5)}$	1.384(4)	$O_{(1)}-C_{(1)}-C_{(2)}$	108.2(3)
$N_{(2)}-C_{(14)}$	1.443(4)	$N_{(1)}-C_{(2)}-C_{(1)}$	108.2(3)
$C_{(1)}-C_{(2)}$	1.501(5)	$N_{(1)}-C_{(3)}-N_{(2)}$	108.3(3)
$C_{(3)}-C_{(4)}$	1.497(5)	$N_{(1)}-C_{(3)}-C_{(4)}$	121.6(3)
$C_{(5)}-C_{(6)}$	1.342(5)	$N_{(2)}-C_{(3)}-C_{(4)}$	130.0(3)
$C_{(6)}-C_{(7)}$	1.468(5)	$O_{(1)}-C_{(4)}-C_{(3)}$	111.5(3)
		$C_{(6)}-C_{(5)}-N_{(2)}$	109.0(3)
		$C_{(5)}-C_{(6)}-N_{(1)}$	105.7(3)
		$C_{(5)}-C_{(6)}-C_{(7)}$	128.5(3)
		$N_{(1)}-C_{(6)}-C_{(7)}$	125.9(3)

In the crystal of compound **3a** the cations are associated in centrosymmetric dimeric pairs with the aromatic systems $N_{(1)}C_{(3)}N_{(2)}C_{(5\text{-}12)}$ placed in parallel at a distance of 3.434(5) A in a head to tail arrangement (Fig. 2). These cationic dimers are organized in layers separated by layers of anions. No short contacts were observed between cations and anions.

EXPERIMENTAL

IR spectra of KBr disks were taken on a UR-20 instrument. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Bruker instrument (300 MHz). Constants, yields, and elemental analyses of new compounds are given in Tables 1 and 2.

The X-ray Structural Analysis of Compound 3a was carried out at room temperature on an automatic four circle Enraf-Nonius CAD-4 diffractometer (λMoKα radiation, relative rate of scanning $\omega/2\theta = 1.2$, $\theta_{max} = 24°$, segment of sphere $0 \leq h \leq 11$, $-11 \leq k \leq 11$, $-10 \leq l \leq 11$). To determine the parameters of the elementary cell and the orientation matrix for a monocrystal of compound **3a** with linear dimensions 0.22 × 0.38 × 0.47 mm, 22 reflexions with $12 < \theta < 13°$ were used. A total of 2850 reflexions were collected, of which 2667 were symmetrically independent (average *R* factor 0.020). Crystals of compound **3a** are triclinic, $a = 9.652(2)$, $b = 9.690(1)$, $c = 9.847(1)$ Å; $\alpha = 79.42(1)$, $\beta = 73.08(1)$, $\gamma = 85.09(1)°$; $V = 863.2(2)$ Å^3; $Z = 2$; $d_{calc} = 1.544$ g/cm^3; $\mu = 2.397$ mm^{-1}; $F(000) = 412$; space group *P*1 (No.2). The structure was solved by direct methods and refined by least squares in the full-matric anisotropic approximation using the SHELXS and SHEXL 93 programs [6, 7]. For the refinement 2304 reflexions with $I > 2\sigma(I)$ were used (310 parameters were refined, with number of reflexions per parameter 7.43; the weighting used was $\omega = 1/[\sigma^2(F\sigma^2) + (0.060P)^2 + 0.217P]$, where $P = (F\sigma^2 + 2Fc^2)/3$, ratio of maximum/mean shift to error in the last cycle 0.013/0.001). Corrections for anomalous dispersion were introduced , but errors for absorption were not taken into account. All hydrogen atoms were revealed objectively in the electron density difference syntheses and were refined isotropically. The final values of the residual factors were $R1(F) = 0.0387$, $R_w(F^2) = 0.0933$, *GOOF* 1.065. The residual electron densities from the Fourier difference series were 0.69 and -0.64 e/A^3. The complete set of X-ray structural data has been deposited in the Cambridge Structural Data Bank (register No. 145573).

3-(4-Methoxyphenylamino)-5,6-dihydro-2H-oxazine-1,4 (1). 3-Ethoxy-5,6-dihydro-2H-1,4-oxazine [8] (14.2 g, 0.11 mol) was added to anisidinium chloride (16 g, 0.1 mol) at 20°C. The reaction mixture was kept at room temperature for 24 h, after which the residue was triturated with ether, filtered, and sissolved in water (20 ml). 50% Sodium hydroxide solution (10 ml) was added to the solution. The oily layer was extracted with chloroform, the chloroform was evaporated in vacuum, the residue was ground with a minimum amount of ether, filtered, washed with hexane, and used in further syntheses.

3-Aryl-3-hydroxy-1-(4-methoxyphenyl)-2,5,6,8-tetrahydro-3H-imidazo[2,1-*c*]-1,4-oxazinium Bromides (2a-e). Morpholinimine (**1**) (2.06 g, 0.01 mol) was added to a solution of an α-halo ketone (0.01 mol) in ethyl acetate (30 ml). The mixture was refluxed until a precipitate began to form (1-2 h). The mixture was then cooled, the precipitate was filtered off, washed with ether, and crystallized from ethanol.

3-Aryl-1-(4-methoxyphenyl)-5,6-dihydro-8H-imidazo[2,1-*c*]-1,4-oxazinium Bromides (3a-e). Acetic anhydride (30 ml) was added to a bromide **2a-e** (0.01 mol) and the mixture was refluxed for 5 h. The Ac_2O was then evaporated in vacuum, the oily residue was ground with acetone, filtered, and crystallized from 2-propanol.

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