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NOVEL APPROACH TO SYNTHESIS OF IMIDAZO[2,1-*b*][1,3]BENZOXAZINES

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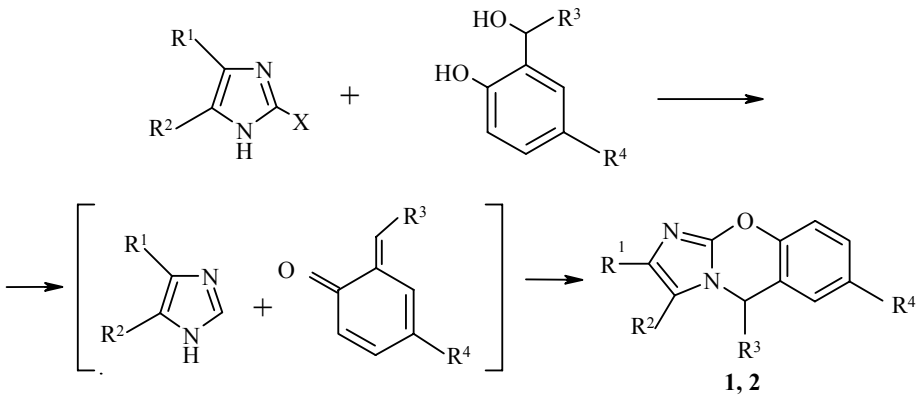
There are isolated instructions in the literature for synthesis of compounds containing a condensed imidazo[2,1-*b*][1,3]benzoxazine system [1, 2]. At the same time, such compounds have significant biological activity, in particular anti-inflammatory and antihelminthic activity [3, 4].

We propose a simple one-step method for obtaining substituted imidazo[2,1-*b*][1,3]benzoxazines **1** and benzimidazo[2,1-*b*][1,3]benzoxazines **2**, including reaction of 2-haloimidazoles or 2-halobenzimidazoles with 2-hydroxybenzyl alcohols in the melt.



1, 2

1 $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = Br$; **2** $R^1 + R^2 = (CH)_4$, $R^3 = Me$, $R^4 = NO_2$; X = Br, Cl

The reaction probably occurs through a step of intermediate formation of *o*-methylenequinone (*o*-quinone methide), which attacks the azole molecule to form the end product.

7-Bromo-2,3-diphenyl-5H-imidazo[2,1-*b*][1,3]benzoxazine (1). A mixture of 2-bromo-4,5-diphenylimidazole (1.5 g, 5 mmol) and 5-bromo-2-hydroxybenzyl alcohol (1.17 g, 5.75 mmol) was heated at 160-165°C with rapid stirring for 20 min until liberation of water stopped. The mixture was cooled and dissolved in methanol; then a saturated NaOH solution in methanol (7 ml) was added and it was poured into water. The precipitate formed was filtered out and crystallized from ethanol. We obtained 1.83 g (91%) of product as colorless crystals with mp 198-200°C. IR spectrum (KBr), ν, cm^{-1}: 3059 (CH arom.), 2924, 2866 (CH_2), 1547, 1508, 1485, 1474 (C=C / C=N), 1269 (C–O–C), 1242, 775, 706 (CH arom.). ^1H NMR spectrum (DMSO-d_6, 400 MHz), δ, ppm (*J*, Hz): 4.99 (2H, s, CH_2); 7.14 (1H, d, *J* = 8.7, H-9); 7.22 (2H, t, *J* = 7.5, C_6H_5);

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7.26 (1H, d, J = 8.7, H-8); 7.40 (2H, d, J = 7.8, C_6H_5); 7.49-7.56 (6H, m, C_6H_5); 7.63 (1H, s, H-6). Mass spectrum (electron impact, 70 eV, for the ^{79}Br isotope), m/z (I_{rel}, %): 402 $[M]^+$ (100), 401 $[M - H]^+$ (21), 323 $[M - Br]^+$ (18), 165 (51), 89 (83), 77 $[C_6H_5]^+$ (30). Found, %: C 65.72; H 3.66; N 6.78. $C_{22}H_{15}BrN_2O$. Calculated, %: 65.51; H 3.72; N 6.95.

12-Methyl-2-nitro-12H-benzimidazo[2,1-*b*][1,3]benzoxazine (2) was obtained as for compound **1** from 2-chlorobenzimidazole and 2-(1-hydroxyethyl)-4-nitrophenol as light yellow crystals with mp 191-192°C (EtOH), yield 85%. IR spectrum (KBr), ν, cm^{-1}: 3047 (CH arom.), 2928, 2858 (CH_3), 1624, 1589 (C=C / C=N), 1524 (NO_2), 1493, 1481, 1443, 1350 (NO_2), 1273 (C–O–C), 1223, 744 (CH arom.). ^{1}H NMR spectrum (DMSO-d_6, 400 MHz), δ, ppm (J, Hz): 1.77 (3H, d, J = 7.9, CH_3); 6.01 (1H, q, J = 7.5, H-12); 7.25-7.56 (5H, m, H-7,8,9,10); 8.25 (1H, d, J = 8.1, H-3); 8.48 (1H, s, H-1). Mass spectrum (electron impact, 70 eV), m/z (I_{rel}, %): 281 $[M]^+$ (83), 266 $[M - Me]^+$ (100), 220 $[M - Me - NO_2]^+$ (80), 131 (38), 84 (39), 82 (57). Found, %: C 64.26; H 6.01; N 24.36. $C_{15}H_{11}N_3O_3$. Calculated, %: C 64.06; H 6.11; N 23.33.

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