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A NOVEL SYNTHESIS OF IMIDAZO[1,2-*a*]QUINOXALINES

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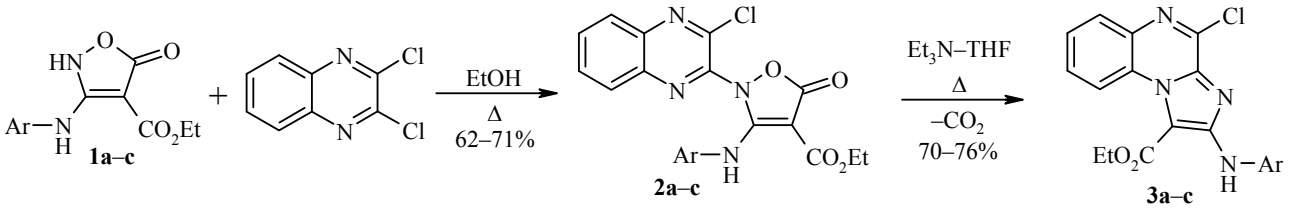
Several new derivatives of imidazo[1,2-a]quinoxalines have been synthesized in good to excellent yields starting from arylaminoisoxazol-5(2H)-ones and 2,3-dichloroquinoxaline through a rearrangement under mild base-catalyzed conditions.

Keywords: arylaminoisoxazol-5(2*H*)-ones, 2,3-dichloroquinoxaline, imidazo[1,2-*a*]quinoxalines, *N*-quinoxalinylisoxazolones, basic catalysis.

Quinoxaline derivatives are an important class of benzoheterocycles, which have received much attention in recent years owing both to their biological properties and pharmaceutical applications. These derivatives are particularly interesting since some of them have shown antimicrobial [1, 2], anticancer [3–5], antimalarial [6], anti-inflammatory [7], antinociceptive [8], antitubercular [9], anthelmintic [10], antidiabetic [11], and antiepileptic [12] properties.

We reported earlier the syntheses of imidazoles [13], imidazopyridines [14-17], imidazobenzothiazoles [18], indoles [19], imidazopyrimidine [20], and pyrimidoquinolines [21-23] starting from isoxazol-5(2*H*)-ones. Here we report the synthesis of a series of novel imidazo[1,2-*a*]quinoxalines in good to excellent yields by rearrangement of new *N*-quinoxalinylisoxazolones under mild base-catalyzed conditions.

The *N*-quinoxalinylisoxazolones **2a-c** were prepared by the reaction of the corresponding arylaminoisoxazolone **1a-c** with 2,3-dichloroquinoxaline in good yields in EtOH under reflux for 24 h. The obtained compounds **2a-c** were rearranged to the new imidazo[1,2-*a*]quinoxaline derivatives **3a-c** in good yields by refluxing with triethylamine in THF.



a Ar = 3-MeC_6H_4, **b** X = 4-BrC_6H_4, **c** X = 4-$O_2NC_6H_4$

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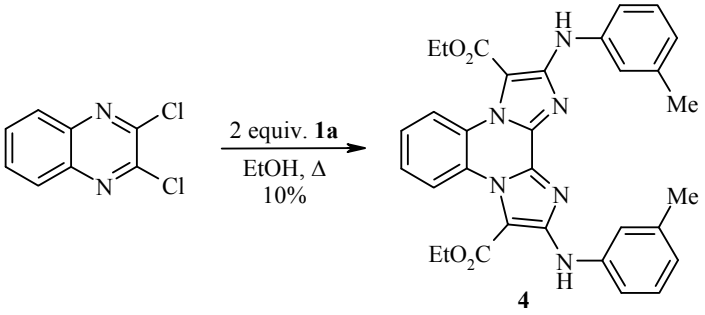
Also, when 2 equivalents of the isoxazolone **1a** was reacted with 2,3-dichloroquinoxaline under the above-described conditions in the absence of base, the rearranged bisimidazoquinoxaline product **4** was precipitated from the reaction mixture in 10% yield. Reaction of compounds **1b**,**c** with 2,3-dichloroquinoxaline under the same conditions failed to produce the corresponding bis-imidazoquinoxalines, which may reflect relatively low susceptibility of the quinoxaline ring to nucleophilic substitution.



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The structure of the obtained products was confirmed by the appropriate spectroscopic methods. The ring system of the derivatives **3a**-**c** and **4** appears to be novel and the synthesis reported here has the advantage of being straightforward.

In conclusion, the work reported herein provides a facile and highly effective method for the synthesis of imidazoquinoxalines with functional groups capable of further elaboration, potentially being of interest in medicinal chemistry.

EXPERIMENTAL

FT-IR spectra were recorded in KBr disks on a Thermo Nicolet (Nexus 670) FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 FT-NMR spectrometer (300 and 75 MHz, respectively) in DMSO-d_6 (compound **4**) or in $CDCl_3$ (remaining compounds) using TMS as internal standard. Mass spectra (EI, 70 eV) were recorded on a Varian Matt 311 spectrometer. Elemental analyses were performed on a Leco Analyzer 932. Melting points were determined on a digital melting point apparatus (Electrothermal) and remain uncorrected. Freshly distilled solvents were used throughout, anhydrous solvents were obtained according to Perrin and Armarego [24]. Starting isoxazoles **1a**-**c** were prepared according to literature methods [16] (for compounds **1a**,**c**) and [19] (for compound **1b**).

Ethyl 3-(arylamino)-2-(3-chloroquinoxalin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylates 2a-c (General Method). Ethyl 3-(arylamino)-5-oxo-2,5-dihydroisoxazole-4-carboxylates **1a-c** (0.38 mmol) and 2,3-dichloroquinoxaline (76 mg, 0.38 mmol) were refluxed in EtOH (20 ml) for 24 h. Removal of the solvent and recrystallization of the precipitate from EtOH gave the desired compound.

Ethyl 2-(3-chloroquinoxalin-2-yl)-5-oxo-3-(*m*-tolylamino)-2,5-dihydroisoxazole-4-carboxylate (2a). Yield 110 mg (68%). Yellow crystals, mp 174-176°C. FT-IR spectrum, ν, cm^{-1}: 3291 (NH), 2981, 1777, 1678, 1616, 1604, 1584, 1487, 1291, 1102, 963, 798. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$); 2.02 (3H, s, $ArCH_3$); 4.47 (2H, q, *J* = 6.9, $C\underline{H}_2CH_3$); 6.57 (1H, d, *J* = 6.6, H Ar); 6.78-6.83 (2H, m, H Ar); 6.93 (1H, s, H Ar); 7.72-7.86 (3H, m, H Ar); 7.93 (1H, d, *J* = 7.8, H Ar); 9.81 (1H, s, NH, exchanged by D_2O addition). ^{13}C NMR spectrum, δ, ppm: 14.5; 20.8; 60.9; 120.1; 123.6; 127.5; 128.1; 128.8; 129.1; 131.2; 131.5; 132.6; 135.4; 139.0; 139.5; 141.6; 142.7; 144.5; 164.4; 165.4; 166.0. Mass spectrum, *m/z* (I_{rel}, %): 426 $[M+2]^+$ (4), 424 $[M]^+$ (12), 390 (11), 380 (62), 334 (94), 305 (18), 271 (25), 256 (32), 230 (100), 158 (80), 102 (60), 91 (94), 65 (40), 44 (20). Found, %: C 59.47; H 3.98; N 13.22. $C_{21}H_{17}ClN_4O_4$. Calculated, %: C 59.37; H 4.03; N 13.19.

Ethyl 3-(4-bromophenylamino)-2-(3-chloroquinoxalin-2-yl)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2b). Yield 133 mg (71%). White crystals, mp 170-172°C. FT-IR spectrum, ν, cm^{-1}: 3290 (NH), 3090, 2987, 1778, 1660, 1621, 1485, 1296, 794, 762. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 4.47 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.00 (2H, d, *J* = 8.7, H Ar); 7.12 (2H, d, *J* = 8.7, H Ar); 7.75-7.89 (3H, m, H Ar); 7.99 (1H, d, *J* = 8.7, H Ar); 9.86 (1H, s, NH, exchanged by D_2O addition). ^{13}C NMR spectrum, δ, ppm: 14.5; 61.2; 120.0; 124.0; 124.2; 128.3; 128.6; 131.5; 132.1; 132.4; 132.9; 134.8; 138.9; 141.7; 142.4; 144.1; 165.3; 165.7. Mass spectrum, *m/z* (I_{rel}, %): 492 $[M+4]^+$ (1), 490 $[M+2]^+$ (4), 488 $[M]^+$ (3), 446 $[M+2\text{-}CO_2]^+$ (27), 444 $[M\text{-}CO_2]^+$ (22), 319 (92), 294 (24), 224 (20), 222 (20), 163 (29), 129 (20), 103 (100), 90 (29), 76 (43), 63 (19), 45 (28). Found, %: C 49.15; H 2.71; N 11.51. $C_{20}H_{14}BrClN_4O_4$. Calculated, %: C 49.05; H 2.88; N 11.44.

Ethyl 2-(3-chloroquinoxalin-2-yl)-3-(4-nitrophenylamino)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (2c). Yield 107 mg (62%). Yellow crystals, mp 178-180°C. FT-IR spectrum, ν, cm^{-1}: 3227, 2935, 1782, 1673, 1626, 1588, 1345, 1298, 960. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 4.49 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.30 (2H, d, *J* = 9.0, H Ar); 7.76–7.86 (3H, m, H Ar); 7.94 (2H, d, *J* = 9.0, H Ar); 8.00 (1H, d, *J* = 8.4, H Ar); 10.28 (1H, s, NH, exchanged by D_2O addition). ^{13}C NMR spectrum, δ, ppm: 14.4; 61.6; 121.1; 121.2; 124.9; 125.1; 128.5; 131.8; 133.1; 138.7; 141.5; 141.8; 142.4; 143.7; 144.7; 163.6; 165.0; 165.1. Mass spectrum, *m/z* (I_{rel}, %): 457 $[M+2]^+$ (2), 455 $[M]^+$ (6), 411 $[M\text{-}CO_2]^+$ (25), 380 (14), 365 (10), 334 (22), 319 (32), 293 (63), 256 (88), 247 (100), 189 (55), 171 (65), 102 (84), 90 (60), 76 (68), 63 (66), 44 (58). Found, %: C 52.88; H 3.01; N 15.22. $C_{20}H_{14}ClN_5O_6$. Calculated, %: C 52.70; H 3.10; N 15.36.

Ethyl 2-(arylamino)-4-chloroimidazo[1,2-*a*]quinoxaline-1-carboxylates 3a–c (General Method). The isoxazolone **2a–c** (0.24 mmol) was refluxed in THF (20 ml) with Et_3N (0.5 ml, 0.36 g, 3.56 mmol) for 6 h. The solvent was removed under reduced pressure to give a yellow oil, which was crystallized from EtOH.

Ethyl 4-chloro-2-(*m*-tolylamino)imidazo[1,2-*a*]quinoxaline-1-carboxylate (3a). Yield 64 mg (71%). Yellow needles, mp 154-155°C. FT-IR spectrum, ν, cm^{-1}: 3410, 3131, 2983, 1705, 1606, 1573, 1495, 1457, 756. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.41 (3H, s, $ArCH_3$); 4.57 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 6.89 (1H, d, *J* = 7.5, H Ar); 7.26-7.31 (1H, m, H Ar); 7.55 (1H, s, H Ar); 7.58-7.68 (3H, m, H Ar); 8.04 (1H, dd, *J* = 9.0, *J* = 1.8, H Ar); 8.55 (1H, s, NH, exchanged by D_2O addition); 8.64 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 14.5; 21.7; 61.6; 103.8; 115.2; 118.8; 118.9; 119.3; 123.2; 126.9; 127.6; 128.5; 129.1; 129.8; 136.1; 139.0; 139.8; 141.6; 154.7; 160.7. Mass spectrum, *m/z* (I_{rel}, %): 382 $[M+2]^+$ (21), 380 $[M]^+$ (80), 337 (10), 336 (42), 335 (33), 334 (100), 305 (20), 271 (18), 102 (40), 91 (26), 77 (12), 65 (18). Found, %: C 63.25; H 4.39; N 14.62. $C_{20}H_{17}ClN_4O_2$. Calculated, %: C 63.08; H 4.50; N 14.71.

Ethyl 2-(4-bromophenylamino)-4-chloroimidazo[1,2-*a*]quinoxaline-1-carboxylate (3b). Yield 69 mg (76%). Pale-yellow solid, mp 180-182°C. FT-IR spectrum, ν, cm^{-1}: 3404, 3064, 2975, 1799, 1695, 1647, 1594, 1492, 1455, 1178, 764. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 4.04 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.48 (2H, d, *J* = 8.4, H Ar); 7.47-7.62 (1H, m, H Ar); 7.78 (2H, d, *J* = 8.4, H Ar); 8.00 (1H, d, *J* = 8.4, H Ar); 8.11 (1H, d, *J* = 8.4, H Ar); 8.13 (1H, s, NH, exchanged by D_2O addition); 8.64 (1H, d, *J* = 7.5, H Ar). ^{13}C NMR spectrum, δ, ppm: 14.0; 60.7; 119.3; 119.7; 127.1; 128.3; 128.5; 128.6; 129.2; 129.9; 132.1; 132.6; 138.4; 138.8; 153.3; 159.9; 164.6. Mass spectrum, *m/z* (I_{rel}, %): 448 $[M+4]^+$ (10), 446 $[M+2]^+$ (40), 444 $[M]^+$ (32), 319 (100), 291 (24), 257 (22), 128 (22), 102 (86), 90 (29), 75 (36), 63 (14), 50 (16). Found, %: C 51.29; H 3.01; N 12.66. $C_{19}H_{14}BrClN_4O_2$. Calculated, %: C 51.20; H 3.17; N 12.57.

Ethyl 4-chloro-2-(4-nitrophenylamino)imidazo[1,2-*a*]quinoxaline-1-carboxylate (3c). Yield 63 mg (70%). Pale-yellow solid, mp 201°C (decomp.). FT-IR spectrum, ν, cm^{-1}: 3392, 2929, 1677, 1604, 1575, 1506, 1329, 1264, 1187, 1110, 750. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 4.62 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.61-7.69 (2H, m, H Ar); 7.96 (2H, d, *J* = 8.7, H Ar); 8.10 (1H, d, *J* = 7.0, H Ar); 8.30 (2H, d, *J* = 8.7, H Ar); 8.66 (1H, d, *J* = 7.5, H Ar); 9.12 (1H, s, NH, exchanged by D_2O addition). ^{13}C NMR spectrum, δ, ppm: 14.5; 62.2; 105.1; 117.2; 119.2; 124.9; 125.4; 125.6; 127.5; 128.3; 128.8; 130.0; 136.3; 141.9; 145.7; 153.1; 160.6. Mass spectrum, *m/z* (I_{rel}, %): 413 $[M+2]^+$ (39), 412 $[M+1]^+$ (36), 411 $[M]^+$ (100), 365 (34), 319 (78), 291 (24), 256 (10), 163 (10), 102 (30), 76 (13). Found, %: C 55.52; H 3.31; N 17.18. $C_{19}H_{14}ClN_5O_4$. Calculated, %: C 55.42; H 3.43; N 17.01.

Diethyl 2,11-bis(*m*-tolylamino)diimidazo[1,2-*a*:2',1'-*c*]quinoxaline-3,10-dicarboxylate (4). Isoxazolone **1a** [16] (100 mg, 0.38 mmol) and 2,3-dichloroquinoxaline (38 mg, 0.19 mmol) were refluxed in EtOH (20 ml) for 48 h. Compound **4** precipitated out during this time as yellow crystals (11 mg, 10%), mp 156°C. FT-IR spectrum, ν, cm^{-1}: 3408, 2971, 2922, 1689, 1647, 1605, 1471, 1432, 1381, 1079, 764. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (6H, t, *J* = 6.9, $2CH_2C\underline{H}_3$); 2.35 (6H, s, $2ArCH_3$); 4.45 (4H, q, *J* = 6.9, $2C\underline{H}_2CH_3$); 6.84 (2H, d, *J* = 8.4, H Ar); 7.20-7.58 (6H, m, H Ar); 7.77 (2H, s, H Ar); 8.21 (2H, d, *J* = 9.0, H Ar); 8.73 (2H, s, 2NH, exchanged by D_2O addition). ^{13}C NMR spectrum, δ, ppm: 14.7; 21.7; 61.3; 102.0; 116.1; 119.3; 121.4; 123.0; 125.1; 126.1; 129.2; 137.1; 138.5; 140.7; 155.3; 160.6. Found, %: C 68.22; H 5.49; N 14.88. $C_{32}H_{30}N_6O_4$. Calculated, %: C 68.31; H 5.37; N 14.94.

The filtrate was concentrated by removal of ethanol to give a yellow solid (45 mg, 55%) identified as compound **2a** by its spectral data.

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