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HETEROARYLATION OF ACETONITRILES.

3.* HETEROARYLATION OF PYRIDIN-2-YL AND QUINOLIN-2-YLACETONITRILES BY CHLOROQUINOXALINES

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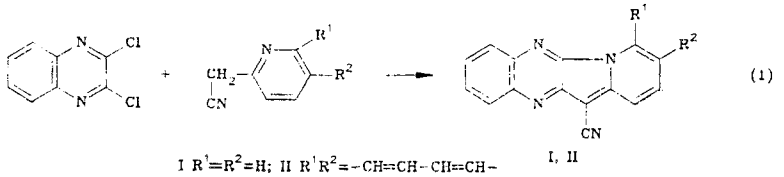
It has been shown that α-chloroquinoxalines heteroarylate pyridin-2-yl and quinolin-2-ylacetonitriles primarily at the methylene group. A method has been developed for synthesizing 1-R-2-amino-3-heteroarylpyrrolo[2,3-b]quinoxalines permitting the preparation of compounds containing the pyridine and quinoline nuclei.

We have previously shown that ambident carbanions formed from benzimidazol-2-yl, benzothiazol-2-yl, and 4-methylthiazol-2-yl-acetonitriles are heteroarylated by 2,3-dichloroquinoxaline in the presence of potassium carbonate at the methylene group carbon [1, 2]. In a similar reaction, pyridin-2-ylacetonitrile forms the product of heteroarylation at both nucleophilic centers, i.e., the methylene group and the exocyclic nitrogen atom [3].

As in the pyridine case, quinolin-2-ylacetonitrile reacts with 2,3-dichloroquinoxaline at both nucleophilic centers (I) in spite of the substantial steric hindrance to nucleophilic attack at the quinoline ring nitrogen atom arising from the hydrogen at position 8 [4].



(1)

I $R^1=R^2=H$; II $R^1R^2=-CH=CH-CH=CH-$ I, II

Heteroarylation of I by 2-chloro-3-methylquinoxaline (2) leads to the product of reaction at the methylene group in high yield, as shown by the presence of an exchangeable NH proton signal at 17 ppm in the NMR spectrum. The presence of a strong C≡N stretching vibration at 2200 cm^{-1} in the infrared spectrum indicates that it is conjugated to the double bond. Hence both in solution and in the solid state, compound III exists in one of the tautomeric forms IIIb or IIIc or as a mixture of these forms.

Thus reaction of α-chloroquinoxalines with ambident carbanions initially forms products of C-heteroarylation. This has allowed us to develop a new synthesis of 1-R-2-amino-3-heteroarylpyrrolo[2,3-b]quinoxalines containing the pyridine and quinoline rings and unavailable by the use of previously reported methods [1, 2].

The benzimidazole, benzothiazole, and thiazole derivatives made in this way were identical to previously reported compounds [1, 2] according to elemental analytical and spectroscopic data and melting points.

The IR and PMR data for the pyridines and quinolines given in the experimental section confirm their proposed structures.

EXPERIMENTAL

PMR Spectra were recorded on a Bruker WP-100SY spectrometer using TMS as internal standard and IR spectra on a Pye-Unicam SP3-300 in KBr tablets. Melting points are uncorrected.

*For Communication 2, see [1].

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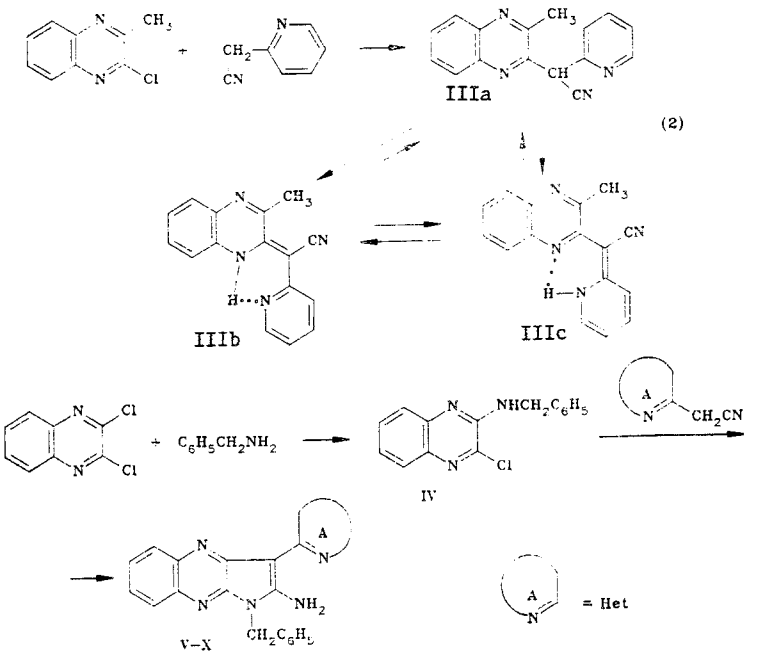

(2)

V Het=benzimidazole VI Het=1-methylbenzimidazole VII Het=benzothiazole VIII Het=4-methylthiazole IX Het=pyridine X Het=quinoline

Pyridin-2-yl, quinolin-2-ylacetonitrile, and 2-chloro-3-methylquinoxaline were obtained by [5-7], respectively. Elemental analytical data for C, H, and N agreed with those calculated.

Indolizino[2,3-b]quinoxalin-12-carbonitrile (I, $C_{15}H_8N_4$). Anhydrous finely powdered potassium carbonate (1.38 g, 10 mmole) was added to a solution of pyridin-2-ylacetonitrile (1.18 g, 10 mmole) and 2,3-dichloroquinoxaline (1.99 g, 10 mmole) in DMF (15 ml) and refluxed for 30 min. After cooling of the reaction mixture, water (50 ml) and acetic acid (2 ml) were added and the red precipitate filtered off and dried in air to give 2.12 g (87%) with mp 281-282°C (from toluene). IR spectrum: 1625 (C=N), 2200 cm^{-1} (C≡N). PMR spectrum (DMSO-D_6): 9.24 (1H, d, $^3J_{43}$ = 7 Hz, 4-H); 8.27 (2H, m, 1-H and 2-H); 7.92 (4H, m, 7-, 8-, 9-, and 10-H); 7.21 ppm (1H, m, 3-H).

Quino[1',2':1,5]pyrrolo[2,3-b]quinoxalin-7-carbonitrile (II , $C_{19}H_{10}N_3$). Anhydrous finely divided potassium carbonate (1.38 g, 10 mmole) was added to a solution of quinolin-2-ylacetonitrile (1.68 g, 10 mmole) and 2,3-dichloroquinoxaline (1.99 g, 10 mmole) in DMF (15 ml) and refluxed for 1 h. Nitrile II was isolated (2.81 g, 96%) using previously described method as an orange fibrous material with mp > 300°C (toluene), IR spectrum: 1590 (C=N), 2170 cm^{-1}, (C≡N). PMR spectrum ($CDCl_3$): 10.21 (1H, d, $^3J_{12}$ = 8 Hz, 1-H); 8.5-7.4 ppm (9H, m).

α-(Pyridin-2-yl)-α-(30methylquinoxalin-2-yl)acetonitrile (III, $C_{16}H_{12}N_4$). A mixture of 2-chloro-3-methylquinoxaline (0.36 g, 2 mmole), pyridin-2-ylacetonitrile (0.24 g, 2 mmole), finely divided potassium carbonate (0.28 g, 2 mmole), and DMF (27 ml) were refluxed for 30 min. The product was cooled, diluted with water (30 ml), neutralized with acetic acid, and the precipitated solid filtered off, washed with water, and dried in air to give 0.41 g (79%) of fibrous, orange-brown crystalline product with mp 210-211°C (from aqueous DMF). IR spectrum: 1610 (C=N), 2200 cm^{-1} (C≡N), PMR spectrum:(DMSO-D_6): 17.12 (1H, s, NH); 8.57 (1H, d, $^3J_{65}$ = 4.5 Hz, 6-H pyridine); 8.1-7.3 (6H, m); 7.18 (1H, dd, $^3J_{56}$ = 4.5, J_{54} = 8 Hz, 5-H pyridine); 2.94 ppm (3H, s, CH_3).

2-Benzylamino-3-chloroquinoxaline (IV, $C_{15}H_{12}ClN_3$). Benzylamine (3.3 ml, 30 mmole) was added to a solution of 2,3-dichloroquinoxaline (1.99 g, 10 mmole) in dioxane (25 ml) which had been heated to 60°C and the whole was refluxed for 1 h. The reaction mixture was cooled, diluted with water (150 ml), and acidified with acetic acid. The precipitate was filtered, washed with water and dried in air to give 2.4 g (89%) of colorless microcrystalline powder with mp 78°C (from dioxane). IR spectrum: 1570 (C=N), 3260 cm^{-1} (N-H). PMR spectrum ($CDCl_3$): 7.9-7.2 (9H, m);1 5.83 (1H, br.s, NH); 4.80 ppm (2H, d, ^4J = 6 Hz, CH_2).

2-Amino-1-benzyl-3-heteroarylpyrrolo[2,3-b]quinoxalines. Anhydrous finely powdered potassium carbonate (0.55 g, 4 mmole) was added to a solution of 2-benzylamino-3-chloroquinoxaline (0.54 g, 2 mmole) and the corresponding heteroarylacetonitrile (2 mmole) in DMF (15 ml). The reaction mixture was cooled, diluted with water (50 ml), acidified with acetic acid and the precipitate was filtered, washed with water, and dried in air.

2-Amino-1-benzyl-3-(benzimidazol-2-yl)pyrrolo[2,3-b]quinoxaline (V), yield 0.71 g (93%); 2-amino-1-benzyl-3-(1-methylbenzimidazol-2-yl)pyrrolo[2,3-b]quinoxaline (VI), yield 0.75 g (94%); 2-amino-1-benzyl-3-(benzothiazol-2-yl)pyrrolo[2,3-b]quinoxaline (VII), yield 0.75 g (94%); 2-amino-1-benzyl-3-(4-methylthiazol-2-yl)pyrrolo[2,3-b]quinoxaline (VIII), yield 0.70 g (95%).

2-Amino-1-benzyl-3-(pyridin-2-yl)pyrrolo[2,3-b]quinoxaline (IX, $C_{22}H_{18}N_5$). Yield 0.62 g (89%) as a yellow microcrystalline powder with mp 212-213°C (from aqueous DMF), IR spectrum 1595 (C=N), 3290 cm^{-1} (N-H). PMR spectrum (DMSO-D_6): 9.1 (2H, br.s, NH_2); 8.94 (1H,d, $^3J_{34}$ = 8 Hz, 3-H pyridine); 8.1-7.2 (9H, m), including 7.28 (5H, s, arom. benzyl protons); 7.08 (1H, dd, $^3J_{H5,H6}$ = 4.5, $^3J_{54}$ = 7 Hz, 5-H pyridine); 5.58 ppm (2H, s, CH_2); 2-amino-1-benzyl-3-(quinolin-2-yl)pyrrolo[2,3-b]quinoxaline (X, $C_{26}H_{19}N_5$). Yield 0.79 g (95%) as a yellow microcrystalline powder with mp 246-247°C (aqueous DMF). IR spectrum: 1600 (C=N), 3195 cm^{-1} (N-H). PMR spectrum:(DMSO-D_6): 9.5 (2H, br.s, NH^2); 9.20 (1H, d, $^3J_{34}$ = 9 Hz, 3-H quinoline); 8.36 (1H, d, $^3J_{43}$ = 9 Hz, 4-H quinoline); 8.2-7.2 (13H, m), including 7.31 (5H, s, arom. benzyl protons); 5. 63 ppm (2H, s, CH_2).

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SYNTHESIS AND PROPERTIES OF AZOLES AND THEIR DERIVATIVES.

23.* ELECTRON IMPACT MASS SPECTROMETRY OF REGIO- AND STEREOISOMERIC DIARYLNITRO-Δ^2-ISOXAZOLINES

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It was shown that the general paths of dissociation of molecular ions of 3-phenyl-4(5)-aryl-5(4) nitro-Δ^2-isoxazolines involve the primary elimination of the $NO_2^{\cdot}$, HNO_2, and $OCHNO_2$ particles, and also the formation of the $C_6H_5CN^{+\cdot}$, $C_6H_5^+$, ions and substituted tropylium cations. The 3,5- and 3,4-diaryl isomers differ most sharply in the probability of formation of $[RC_6H_4C{\equiv}O]^+$ ions, the peaks of which are maximal in the first case. The mass spectra of cis- and trans-isomers in the 3,5-diarylisoxazoline series differ little quantitatively.

Derivatives of nitro-Δ^2-isoxazolines have lately attracted increased interest in connection with their structural features [2], the possibility of using them as intermediates in the synthesis of other heterocyclic compounds [2-8], and also in relation to examination

*For Communication 22, see [1].

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