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Synthesis of tetrazolo[1,5-*a*]quinoxaline derivatives

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Abstract- Displacement reaction of 2,3-dichloroquinoxaline with secondary amines in boiling ethanol afforded it`s mono aminoquinoxaline derivatives. Further reaction of the latter compounds with sodium azide in warm dimethylsulfoxide achieved a group of 4-amino tetrazolo[1,5-*a*]quinoxaline derivatives. 1HNMR spectra of these compounds are discussed.

Keywords: 2,3-dichloroquinoxaline, sodium azide, tetrazolo[1,5-*a*]quinoxaline.

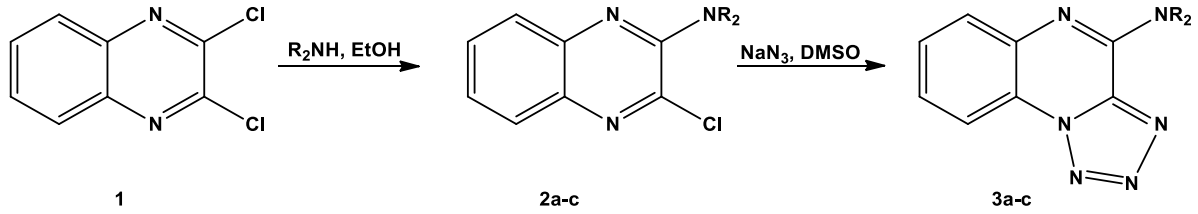
INTRODUCTION

Starting from biological considerations and due to our interest in the synthesis of polycyclic N-heterocycles, [1-6] it was decided to synthesize fused quinoxaline derivatives. Fused quinoxaline systems have been described as privileged compounds as variety biologically active compounds, including antimicrobials, agrochemicals, antineoplastics etc. A group of these class of heterocycles are tetrazolo[1,5-*a*]quinoxaline derivatives, which have been described as potent anticonvulsants [7] and antiphytopathogens agents [8]. Despite their importance from pharmacological and synthetic point of views, comparatively few methods for their preparation have been reported. These methods include, the sequential reaction of 2-chloro-3-methylquinoxaline with sodium azide and aldehydes [7] and cyclocondensation reaction of a-cyano-2-nitroacetanilide [8]. In the present research we exhibit a general rout for the preparation of tetrazolo[1,5-*a*]quinoxaline-4-amine derivatives.

RESULTS AND DISCUSSION

As shown in **Scheme I**, our synthesis started from the 2, 3-dichloroqinoxaline **1**, which was prepared according to the previous procedure [9]. This compound easily reacted with secondary amines to achieve quinoxaline derivatives **2a-c** in high yields. ^{1}HNMR spectra of products **2a-c** showed the expected signals regarding to the methylen moieties due to precursors as well as

aromatic protons belonging to the 2, 3-dichloroqinoxaline **1**. These results were amplified by observation of a 3 to 1 ratio for M and M+2 molecular ions respectively in the mass spectra of the products **2a-c**, confirming the replacement of a chlorine atom of 2, 3-dichloroqinoxaline **1** during the reaction. Microanalytical data of these compounds showed no significant difference with their expected values. For example, ^{1}HNMR spectrum of product of the reaction of 2, 3-dichloroqinoxaline **1** with morpholine showed three signals in δ 3.5, 3.8 and 7.8-8.2 ppm valued for 4H, 4H and 4H easily assignable to $N(CH_2)_2$, $O(CH_2)_2$, and aromatic hydrogens respectively. Mass spectrum of this product showed two signals in m/z 249 and 251 with the ratio 3 to 1 respectively. Elemental analysis of this compound, C, 57.54%; H, 4.92%; N, 16.58% has no significant difference with its expected analysis, C, 57.72%; H, 4.84%; N, 16.83% verifying the molecular formula $C_{12}H_{12}ClN_3O$. These findings strongly supported the structure **2a** for this product.



Scheme I

Substitution of the chlorine atom of compounds **2a-c**, easily carried out by their reaction with sodium azide in warm dimethylsulfoxide to furnish novel 4-amino tetrazolo[1,5-*a*]quinoxaline derivatives **3a-c**. The structural assignments of compounds **3a-c** was based upon the spectral and microanalytical data. The IR spectra did not exhibited stretching vibration bands at 2000- 2200 cm^{-1} as expected for an azido group, which confirmed the closure of tetrazolo ring by the participation of this group and the nitrogen atom of quinoxaline ring. This result was strongly verified by the ^{1}HNMR spectra, which showed a signal in δ 8.5 ppm easily assignable to the H atom in position number 9 of the tetrazolo[1,5-*a*]quinoxaline ring, strongly affected by the anisotropic current of both benzene and tetrazole rings. Microanalytical data of these compounds showed no significant difference with their expected values.

CONCLUSION

In Conclusion, the sequential treatment of 2, 3-dichloroqinoxaline with amines and sodium azide

Is an efficient access to tetrazolo[1,5-*a*]quinoxaline derivatives.

EXPERIMENTAL

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}HNMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer.

General procedure for the reaction of 2, 3-dichloroqinoxaline with amines

2, 3-Dichloroqinoxaline **1** (2gr, 10mmol) in ethanol (25mL) was heated under reflux with either morpholine (2.0gr), pyrrolidine (1.8gr) or piperidine (2gr) for 4 hours. Then water (20mL) was added and the solution was kept overnight, the precipitate was filtered off and Washed with warm water and dried at 80^{0}C to give **2a-c**.

2-Chloro-3-(morpholin-4-yl)quinoxaline 2a:

This compound was obtained as a green powder in 70% yield, mp 120-122 ^{o}C, IR: 800, 2900, 2940 cm-^{1} ; ^{1}HNMR: ($CDCl_3$) δ, 3.5 (t, 4H, $N(CH_2)_2$), 3.8 (t, 4H, $O(CH_2)_2$) and 7.8-8.2 (m, 4H, aromatic); ms: m/z , 249 (60), 251(20).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: C, 57.72; H, 4.84; N, 16.83. Found: C, 57.54; H, 4.92; N, 16.58.

2-Chloro-3-(pyrrolidin-1-yl)quinoxaline 2b:

This compound was obtained as a green powder in 75% yield, mp 112-115 ^{o}C, IR: 750, 2940, 2960 cm-^{1} ; ^{1}HNMR: ($CDCl_3$) δ, 1.5 (t, 4H, $(CH_2)_2$), 3.5 (t, 4H, $N(CH_2)_2$) and 7.8-8.2 (m, 4H, aromatic); ms: m/z , 233 (60), 235 (20).

Anal. Calcd. for $C_{12}H_{12}ClN_3$: C, 61.67; H, 5.18; N, 17.98. Found: C, 61.44; H, 4.95; N, 17.69.

2-Chloro-3-(piperidin-1-yl)quinoxaline 2c:

This compound was obtained as a green powder in 85% yield, mp 102-104 ^{o}C, IR: 780, 2920, 2960 cm-^{1} ; ^{1}HNMR: ($CDCl_3$) δ, 1-1.5 (m, 6H, $(CH_2)_3$), 3.5 (t, 4H, $N(CH_2)_2$) and 7.8-8.2 (m, 4H, aromatic); ms: m/z , 247 (50), 249 (16).

Anal. Calcd. for $C_{13}H_{14}ClN_3$: C, 63.03; H, 5.70; N, 16.96. Found: C, 62.86; H, 5.94; N, 17.12.

General procedure for the reaction of 2-aminosubstituted- 3-chloroqinoxaline sodium azide

Either compounds 2a-c (10mmol) in dimethylsulfoxide (15mL) was heated under reflux with sodium azide (1gr) for 3 hours. Then water (20mL) was added and the precipitate was filtered off, washed with warm water and dried at 80^{0}C to give **3a-c**.

4-(Morpholin-4-yl)tetrazolo[1,5-*a*]quinoxaline 3a:

This compound was obtained as a green powder in 85% yield, mp 141-143 ^{o}C, IR: 2900, 2940 cm-^{1} ; ^{1}HNMR: ($CDCl_3$) δ, 3.8 (m, 8H, O&N $(CH_2)_2$), 8-8.2 (m, 3H, aromatic) and 8.55 (dd, 1H, Aromatic); ms: m/z , 256.

Anal. Calcd. for $C_{12}H_{12}N_6O$: C, 56.24; H, 4.72; N, 32.79. Found: C, 56.41; H, 4.94; N, 32.61.

4-(Pyrrolidin-1-yl)tetrazolo[1,5-*a*]quinoxaline 3b:

This compound was obtained as a green powder in 90% yield, mp 151-154^{o}C, IR: 2930, 2970 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 1.7 (t, 4H, $(CH_2)_2$), 3.9 (t, 4H, $N(CH_2)_2$), 8-8.2 (m, 3H, aromatic) and 8.55 (dd, 1H, Aromatic); ms: m/z , 240.

Anal. Calcd. for $C_{12}H_{12}N_6$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.31; H, 4.92; N, 34.72.

4-(Piperidin-1-yl)tetrazolo[1,5-*a*]quinoxaline 3c:

This compound was obtained as a green powder in 90% yield, mp 139-142^{o}C, IR: 2900, 2950 cm-^{1} ; ^{1}HNMR: ($CDCl_3$) δ, 1-1.6 (m, 6H, $(CH_2)_3$), 3.9 (t, 4H, $N(CH_2)_2$), 8-8.2 (m, 3H, aromatic) and 8.55 (dd, 1H, Aromatic); ms: m/z , 254.

Anal. Calcd. for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.22; H, 5.67; N, 32.85.

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