JCRS

Journal of Chemical Reactivity and Synthesis 2022: 12(2) 110-117

Research Article

# Synthesis of novel [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives

Sara Abarkar and Mohsen Nikpour*

Department of Chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran

ARTICLE INFO:

Received:
14 March 2022

Accepted:
27 May 2022

Available online:
12 June 2022

✉: M. Nikpour
nikpour@iauahvaz.ac.ir

**ABSTRACT**

Reaction of 2, 3- dichlroquinoxaline with hydrazine in methanol at room temperature gave 1-(2-chloroquinoxalin-3-yl) hydrazine and after 24 hours. Condensation of 1-(2-chloroquinoxalin-3-yl) hydrazine with ethylorthoesters on their boiling carboxylic acids for 8 hours afforded a group of 4-Chloro- [1,2,4] triazolo[4, 3-a]quinoxaline derivatives. Stirring of 4-Chloro- [1,2,4]triazolo[4, 3-*a*]quinoxaline derivatives with amines for 2 hours in ethanol at room temperature afforded a group of 4-Amino- [1,2,4]triazolo[4, 3-a]quinoxaline derivatives. Solvent effect of methanol and chloroform on this reaction and the spectral data is discussed.

***Keywords:*** 2,3- dichloroquinoxaline; [1,2,4]triazolo[4, 3-*a*]quinoxaline; orthoesters

## 1. Introduction

Fused quinoxalines are a well-known class of heterocycles. In the recent decades, these class of heterocycles attract attention of chemists for the new biologically active structures [1-5]. Moreover, triazoles and especially fused triazoles are an important class of heterocyclic compounds with varied activities including; antifungal [6], bactericidal [6,7], anxiolytic [8,9], anticonvulsant [10], herbicidal [11], antidepressants [12] and Antiproliferative [13]. Keeping

this in view, we decide to prepare a group of new [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives.

## 2. Experimental

### *2.1. Materials and instruments*

The melting points were recorded on an Electro thermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The $^{1}$HNMR (300MHz) spectra were recorded on a Bruker AC 300 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 micro analyzer. The purity of all new compounds synthesized was tested by TLC using chloroform as mobile phase. Precursors 2 was prepared according to an earlier procedure [14].

### *2.2.General Procedure for Preparation of 4-Chloro-[1,2,4]triazolo[4,3-a]quinoxalines 3a-c.*

A mixture of 2-chloro-3-hydrazinyl quinoxaline 2 (0.39 gr, 2 mmol) and either (triethyorthoformate, triethyorthoacetate or triethyorthopropionate, 1.5 ml) in appropriate carboxylic acid (formic acid, acetic acid or propionic acid) (10 ml) heated under reflux condition for 8 hours. The resulting mixture dried by heating and recrystallized from ethanol to achieve novel 4-chloro- [1,2,4] triazolo[4, 3- *a*]quinoxaline derivatives 3a-c.

***4-Chloro-[1,2,4]triazolo[4,3-a]quinoxaline 3a:***

Yield (72%), red powder, mp 152-153 °C. IR spectrum, ν, cm$^{-1}$: 1570 (C=N). $^{1}$HNMR (d$^{6}$-DMSO) ppm: 8.05 (dd, 2H, $C_7H$ & $C_8H$); 8.32 (dd, 2H, $C_6H$ & $C_9H$); 9.8 (s, 1H, $C_1H$). Mass spectrum, m/z: 204 $[M]^+$, 206 [M+2]+. Anal. Calcd. for $C_9H_5ClN_4$: C, 52.83; H, 2.46; N, 27.38 Found: C, 53.05; H, 2.49; N, 27.31.

***4-Chloro-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline 3b:***

Yield (83%), yellow powder, mp 161-163 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N); 2910, 2940 ($CH_3$). $^1$HNMR ($d^6$-DMSO) ppm: 2.37 (s, 3H, $CH_3$), 8.05 (dd, 2H, $C_7H$ & $C_8H$); 8.32 (dd, 2H, $C_6H$ & $C_9H$). Mass spectrum, m/z: 218 [M]+, 220 [M+2]+. Anal. Calcd. for $C_{10}H_7ClN_4$: C, 54.93; H, 3.23; N, 25.62 Found: C, 54.82; H, 3.29; N, 25.78.

***4-Chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline 3c:***

Yield (85%), yellow powder, mp 146-148 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N); 2910, 2960 ($CH_3$). $^1$HNMR ($d^6$-DMSO) ppm: 0.97 (t, 3H, $CH_3$), 2.65 (q, 3H, $CH_2$), 8.05 (dd, 2H, $C_7H$ & $C_8H$); 8.32 (dd, 2H, $C_6H$ & $C_9H$). Mass spectrum, m/z: 232 [M]+, 234 [M+2]+. Anal. Calcd. for $C_{11}H_9ClN_4$: C, 56.78; H, 3.90; N, 24.08 Found: C, 56.59; H, 3.96; N, 21.18; S, 24.19.

***2.3. General Procedure for Preparation of 4-amino-[1,2,4]triazolo[4,3-a]quinoxalines 4a-f.***

A mixture of foregoing products 3a-c (1 mmol) and either (morpholine or pyrrolidine 1 ml) in ethanol (5 ml) stirred at room temperature for 2 hours. To the resulting mixture water (10 ml) added after cooling and the precipitant recrystallized from ethanol to achieve novel 4-amino- [1,2,4] triazolo[4, 3- *a*]quinoxaline derivatives 4a-f.

***4-(Morpholin-4-yl)- [1,2,4]triazolo[4,3-a]quinoxaline 4a:***

Yield (80%), red powder, mp 171-172 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N) 2910, 2960 ($CH_2$). $^1$HNMR ($CDCl_3$) ppm: 3.65 (t, 4H, $N(CH_2)_2$), 3.91 (t, 4H, $O(CH_2)_2$), 7.96 (dd, 2H, $C_7H$ & $C_8H$); 8.15 (dd, 2H, $C_6H$ & $C_9H$); 9.7 (s, 1H, $C_1H$). Mass spectrum, m/z: 255 [M]+. Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43 Found: C, 61.34; H, 5.18; N, 27.31.

***4-(Pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-a]quinoxaline 4b:***

Yield (80%), red powder, mp 185-186 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N) 2910, 2960 ($CH_2$). $^1$HNMR ($CDCl_3$) ppm: 2.05 (t, 4H, $(CH_2)_2$), 3.62 (t, 4H, $N(CH_2)_2$), 7.96 (dd, 2H, $C_7H$ & $C_8H$); 8.15 (dd, 2H, $C_6H$ & $C_9H$); 9.7 (s, 1H, $C_1H$). Mass spectrum, m/z: 239 [M]+. Anal. Calcd. for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27 Found: C, 65.14; H, 5.41; N, 29.39.

***1-Methyl- 4-(morpholin-4-yl)- [1,2,4]triazolo[4,3-a]quinoxaline 4c:***

Yield (70%), red powder, mp 116-117 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N) 2910, 2960 ($CH_2$). $^1$HNMR ($CDCl_3$) ppm: 2.41 (s, 3H, $CH_3$), 3.65 (t, 4H, $N(CH_2)_2$), 3.91 (t, 4H, $O(CH_2)_2$), 7.96 (dd, 2H, $C_7H$ & $C_8H$); 8.15 (dd, 2H, $C_6H$ & $C_9H$). Mass spectrum, m/z: 269 [M]+. Anal. Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01 Found: C, 62.32; H, 5.69; N, 25.87.

***1- Methyl- 4-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-a]quinoxaline 4d:***

Yield (68%), red powder, mp 124-125 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N) 2910, 2960 ($CH_2$). $^1$HNMR ($CDCl_3$) ppm: 2.05 (t, 4H, $(CH_2)_2$), 2.41 (s, 3H, $CH_3$), 3.62 (t, 4H, $N(CH_2)_2$), 7.96 (dd, 2H, $C_7H$ & $C_8H$); 8.15 (dd, 2H, $C_6H$ & $C_9H$). Mass spectrum, m/z: 253 [M]+. Anal. Calcd. for $C_{14}H_{15}N_5$: C, 66.38; H, 5.97; N, 27.65 Found: C, 66.45; H, 6.06; N, 27.52.

***1-Ethyl- 4-(morpholin-4-yl)- [1,2,4]triazolo[4,3-a]quinoxaline 4e:***

Yield (70%), red powder, mp 191-192 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N) 2910, 2960 ($CH_2$). $^1$HNMR ($CDCl_3$) ppm: ١,٠٢ (t, 3H, $CH_3$), 2.٧٥ (q, 3H, $CH_2$), 3.65 (t, 4H, $N(CH_2)_2$), 3.91 (t, 4H, $O(CH_2)_2$), 7.96 (dd, 2H, $C_7H$ & $C_8H$); 8.15 (dd, 2H, $C_6H$ & $C_9H$). Mass spectrum, m/z: 283 [M]+. Anal. Calcd. for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72 Found: C, 63.68; H, 6.16; N, 24.59.

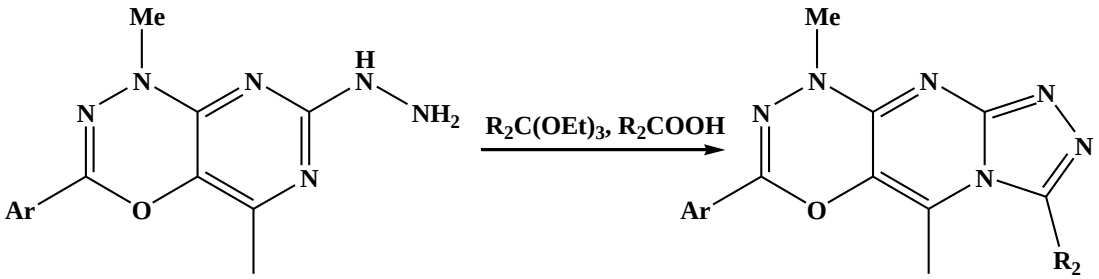
***1-Ethyl- 4-(pyrrolidin-1-yl)-[1,2,4]triazolo[4,3-a]quinoxaline 4f:***

Yield (70%), red powder, mp 185-186 °C. IR spectrum, ν, $cm^{-1}$: 1570 (C=N) 2910, 2960 ($CH_2$). $^1$HNMR ($CDCl_3$) ppm: ١,٠٢ (t, 3H, $CH_3$), 2.05 (t, 4H, $(CH_2)_2$), 2.٧٥ (q, 3H, $CH_2$), 3.62 (t, 4H, $N(CH_2)_2$), 7.96 (dd, 2H, $C_7H$ & $C_8H$); 8.15 (dd, 2H, $C_6H$ & $C_9H$). Mass spectrum, m/z: 267 [M]+. Anal. Calcd. for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20 Found: C, 67.54; H, 6.48; N, 26.09.

## 3. Results and Discussion

In a previous report; treatment of 1-(1,5-dimethyl-3-aryl-1H-pyrimido[4,5-e][1,3,4]oxadiazin-7-yl)hydrazine with orthoesters in their carboxylic acids exhibited as a

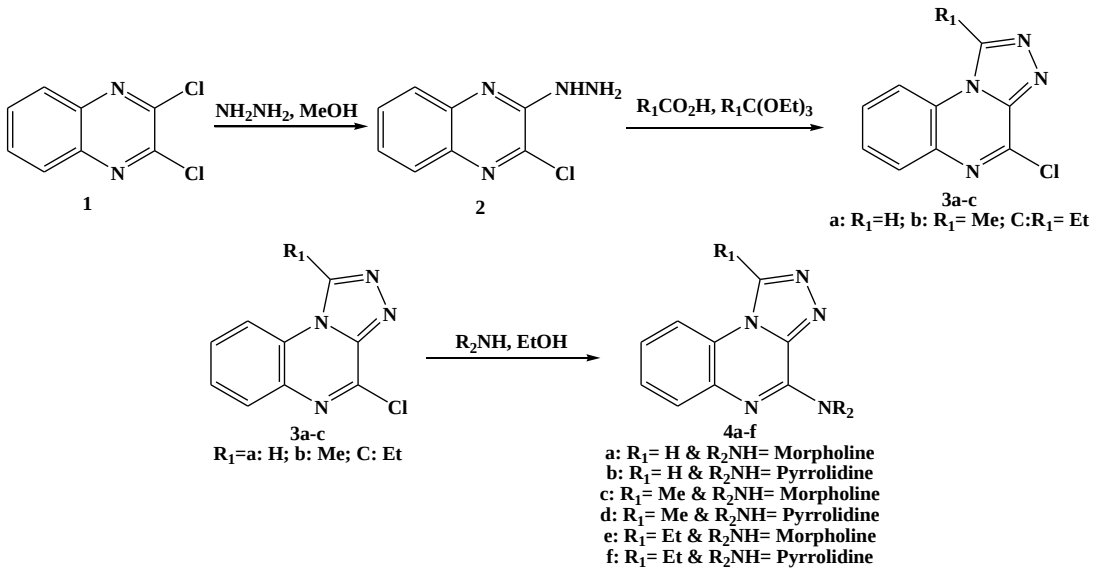
convenient rout for the synthesis of 3-Aryl-1,5-dimethyl-1H- [1,2,4]triazolo[4`,3`:1,2]pyrimido[4,5-*e*][1,3,4]oxadiazines derivatives [13] as shown in Scheme 1.




***Scheme 1***

**Scheme 1.** synthesis of 3-Aryl-1,5-dimethyl-1H- [1,2,4]triazolo[4`,3`:1,2]pyrimido[4,5-*e*][1,3,4]oxadiazines derivatives

In this study, we extend the foregoing rout for the synthesis of our target compounds. For this purpose; 2,3-dichloroquinoxaline 1 reacted with hydrazine to produce 2-chloro-3-hydrazinyl quinoxaline 2 in ethanol at room temperature according to an earlier procedure [14], which condensed with ethyorthoesters in their boiling carboxylic acids to achieve 4-chloro- [1,2,4] triazolo[4, 3- *a*]quinoxaline derivatives 3a-c. The latter compounds easily reacted with amines in room temperature to produce appropriate 4-amino derivatives 4a-f as shown in *Scheme 2*.




*Scheme 2*

**Scheme 2.**synthesis route for achieve 4-chloro- [1,2,4] triazolo[4, 3- *a*]quinoxaline derivatives

The structure of novel derivatives 3a-c and 4a-f were strongly confirmed by their spectral and micro analytical data. The IR spectra did not show the stretching vibration bands at 3450 and 3300 cm-1 (broad, $NH_2$) belonging to precursor 2 but appeared new bands around 2900 $cm^{-1}$ belonging to $CH_2$ & $CH_3$ groups. Mass spectra of compounds 4a-f devoid the isotopic effect of chlorin atom of precursor's 3a-c in the molecular ion region and confirm its replacement by amines. $^1$HNMR spectra of products 3a-c lacked the broad $NH_2$ and NH signals at δ 4.2 & 6.5 ppm respectively belonging to precursor 2 but showed new signals at δ 9.8 ppm for 3a and δ 1-2.7 ppm for 3b-c. $^1$HNMR spectra of products 4a-f showed new multiple signals due to amino moieties. Microanalytical data of all products showed no significant difference with the calculated values. These results strongly confirms the formation of [1,2,4] triazolo[4, 3- *a*]quinoxaline derivatives.

## 4. Conclusion

In conclusion, sequential treatment of 1-(quinoxalin-3-yl)hydrazine with orthoesters in boiling carboxylic acids and amines in ethanol at room temperature is a new, convenient and general access to [1,2,4] triazolo[4, 3- *a*]quinoxaline derivatives.

## Acknowledgment

This study concerns to the MSc thesis of Mrs Sara Abarkar and its support by Ahvaz Branch, Islamic Azad University is gratefully acknowledged.

## References:

[1] Y. A. Ammar, I. M. Ismail, A. M. El- Sharief, Y. A. Mohamed and R. M. Amer, *J. Ind. Chem. Soc.* 66(1989) 124.

[2] V. G. Baklykov, V. N. Charushin, O. N. Chupakhin and V. N. Droazd; *Khim. Getrosikl. Soedin.* 4(1987) 557-561.

[3] D. S. Yufit, Yu. T. Strachkov, V. N. Droazd, V. N. Charushin, V. G. Baklykov and O. N. Chupakhin, *Khim. Getrosikl. Soedin*, 5(1987) 701-706.

[4] A. J. Elliot and M. S. Gibson; *J. Org. Chem*. 45(1980) 3677-3681.

[5] M. Bakavoli, M. Nikpour and M. Rahimizadeh; *Phosphorus, Sulfur Silicon Relat. Elem.* 180 (2005) 2265-2268.

[6] S. A.El-Hawash, N. S.Habib, N. H. Fanaki, *Pharmazie*. 54(1999) 808.

[7] D. J.Brown, Y. Iwai, *Aust J Chem*,32 (1997) 2727.

[8] G.Tarzia, E.Ocelli, E.Toja, D.Barone, N.Corsico, L.Gallico, F.Luzzani, *J Med Chem*, 31 (1988) 1115.

[9] R. I.Trust, J. D. Albright, *U.S. Pat*.4,242,515, (**1980**) (R. I.Trust, J. D. Albright, *Chem Abstr*, 94 (1981)139815d).

[10] G.Tarzia, E.Ocelli, D.Barone, *Farmaco*, 44 (1989) 3.

[11] (a) R.Peignier, A.Chene, R.Cantregril, J. Mortier, *Eur. Pat.* 441718 ,1991,; *Chem Abstr*, 115 (1991) 208000; (b) R.Cantegril, A.Chene, J.Mortier, R.Peignier, *Eur. Pat.* 483027,1992,; *Chem Abstr*, 117(1992)131214.

[12] S.Sarges, H. R.Howard, R. G.Browne, L. A.Lebel, P. A.Seymour, B. K. Koe, *J Med Chem*, 33(1990) 2240.

[13] M.Bakavoli, M.Rahimizadeh, A,Shiri, M.Akbarzadeh, S. H.Mousavi, Z. Tayarani-Najaran, H. Atapour-Mashhad, M.Nikpour, *J Heterocycl Chem*, 48(2011) 183.

[14] R. Sarges, H. R. Howard, R. G. Browne, L. A. Lebel, P. A. Seymour, B. K. Koe; *J. Med. Chem.* 33(1990) 2240.