Tetrahedron 68 (2012) 2107–2112

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of pyrrolo[2,3-*b*]quinoxalines by the Pd/C-catalyzed multicomponent reaction of 1,2-dichloroquinoxaline with hydrazine hydrate, phenylacetylene, and a variety of aldehydes in water

Mohammad Bakherad *, Ali Keivanloo, Saeideh Jajarmi

School of Chemistry, Shahrood University of Technology, Shahrood, Iran

ARTICLE INFO

Article history:
Received 19 November 2011
Received in revised form 1 January 2012
Accepted 16 January 2012
Available online 21 January 2012

Keywords:
Pyrroloquinoxaline
Sonogashira reaction
Palladium catalyzed
Aldehydes

ABSTRACT

The one-pot, Pd/C-catalyzed, multicomponent reaction of 1,2-dichloroquinoxaline with hydrazine hydrate, phenylacetylene, and a variety of aldehydes provides an efficient and direct method for the preparation of *N*-substituted pyrrolo[2,3-*b*]quinoxalines in water at 70 °C.

1. Introduction

Multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because they increase the reaction efficiency by combining several operational steps without isolation of the reaction intermediates or changing the reaction conditions.[1] These approaches allow an overall reduction of the time required to obtain the desired product with an advantageous economy of solvents and an overall reduction of waste production. MCRs have been widely used for the preparation of heterocyclic structures[2] as well as the key steps in the total synthesis of natural products.[3] The quinoxaline nucleus is present in many pharmaceutical agents, exhibiting a broad spectrum of biological activities, such as antitumor,[4] antiviral,[5] antiglucoma,[6] antituberculosis,[7] antiinflammatory,[8,9] and anticancer[10] activities. Furthermore, pyrrolo[1,2-*a*]quinoxalines have been shown to be potent and selective 5-HT3 receptor ligands.[11] There has been growing interest in developing a general and versatile method for the synthesis of pyrrolo[2,3-*b*]quinoxaline derivatives. A number of synthetic approaches to this class of compounds have been introduced in recent years.[12]

Rather surprisingly, palladium catalysis, despite its remarkable versatility and efficiency in the synthesis of heterocyclic compounds,[13] has very rarely been mentioned in this area. Extensive literature search revealed that the Suzuki[14] and Stille[15] cross-coupling reactions have been applied to the synthesis of quinoxaline derivatives from haloquinoxalines, and an intramolecular Heck reaction[16] on aminoquinoxaline scaffolds has been used in the synthesis of 3-substituted pyrrolo[2,3-*b*]quinoxalines.

Our and other recent success in this area encouraged us to examine the possibility of preparing pyrrolo[2,3-*b*]quinoxalines by the palladium/copper-catalyzed alkyne coupling followed by nucleophilic cyclization.

Acardi and co-workers have previously reported an approach for the synthesis of pyrrolo[2,3-*b*]quinoxalines by the reaction of 2-alkynyl-3-trifluoroacetamidoquinoxalines with aryl and vinyl halides or triflates.[17] Unfortunately, the protecting and deprotecting steps required to synthesize alkynylaminoquinoxaline are not particularly attractive, synthetically.

Recently, our group has prepared pyrrolo[2,3-*b*]quinoxaline derivatives by heteroannulation of *N*-alkyl-3-chloroquinoxaline-2-amines with phenylacetylene[18] and propargyl bromide[19] under mild conditions in one-pot reactions catalyzed by Pd–Cu. We attempted to make this overall approach more attractive synthetically by examining the preparation of pyrrolo[2,3-*b*]quinoxalines using MCRs.

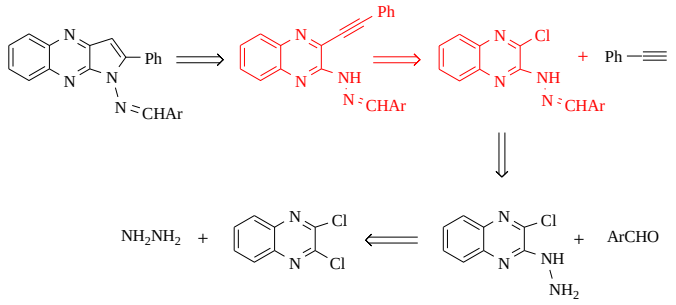
2. Results and discussion

To introduce diversified pyrrolo[2,3-*b*]quinoxaline derivatives, our retrosynthetic analysis implicated the use of 1,2-dichloroquinoxaline, hydrazine, a suitable aldehyde, and phenylacetylene as the starting materials, and palladium-catalyzed

* Corresponding author. E-mail address: m.bakherad@yahoo.com (M. Bakherad).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.01.045

cascade cross coupling-cyclization as the key step, extensively used in the synthesis of indoles (Scheme 1).[20]



Scheme 1. Retrosynthetic analysis of diversified pyrrolo[2,3-*b*]quinoxalines.

The use of Pd/C–CuI as a catalytic system for the efficient Sonogashira coupling of aryl halides with terminal alkynes has also been reported.[21] Compared to the frequently used expensive palladium catalysts [e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, etc.], Pd/C-based methods have an economic advantage, and hence remain attractive in large or industrial scale preparations.

Herein, we describe the Pd/C-catalyzed MCR of 1,2-dichloroquinoxaline, hydrazine, phenylacetylene, and a variety of aldehydes, which provides an efficient route for the synthesis of pyrrolo[2,3-*b*]quinoxalines from simple starting materials.

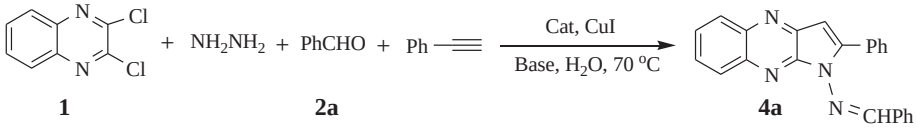
In an initial research work, we found that the reaction of 1,2-dichloroquinoxaline (1 equiv) with hydrazine (1 equiv), benzaldehyde (1 equiv), and phenylacetylene (1 equiv) in the presence of Pd/C (mol %), CuI (10 mol %), and K_2CO_3 (2 equiv) in water at 70 °C provides the desired product **4a** in high yield (Table 1, entry 5).

It was found that while Pd/C, $PdCl_2(PPh_3)_2$, $PdCl_2/PPh_3$, $PdCl_2$, and $Pd(dba)_2$ all catalyze the reaction without the aid of any surfactant, Pd/C turns out to be the best catalyst in terms of yields (entries 1–5). Other parameters, such as the base, catalyst loading, and reaction temperature were also examined. The reaction was influenced significantly by the base employed; it worked very well when inorganic bases, such as K_2CO_3 and Cs_2CO_3 were used (entries 5 and 6), with the best results obtained in the case of potassium carbonate (entry 5). No satisfactory results were obtained with organic bases, such as Et_3N, diisopropylethylamine (DIPEA), pyridine, and piperidine (entries 9–12). When the catalyst loading was decreased to 3 mol %, the yield of *N*-(phenylmethanimine)-2-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline **4a** was 62% (entry 13). Increasing the amount of palladium catalyst did not increase the yield (entry 14). Only a trace amount of the desired product **4a** was obtained when the reaction was carried out without CuI as a co-catalyst (entry 15). Decreasing the temperature to 25 °C caused the yield to decrease to 45% (entry 16).

As indicated in Table 1, the reaction conditions mentioned in entry 5 were used for further examination of the scope of this reaction with various benzaldehydes, 1,2-dichloroquinoxaline, hydrazine, and phenylacetylene. The reactions were carried out under an argon atmosphere, and water was degassed prior to use. The typical results are summarized in Table 2. As shown in this table, nature of the aldehydes used plays a key role in controlling the reaction outcome, the best results being obtained in the presence of electron-withdrawing (entries 2–4) or slightly electron-withdrawing (entries 5–9) substituents. With aldehydes containing electron-neutral (entry 1) or electron-donating (entries 10 and 11) groups, products **4a**, **4j**, and **4k** are isolated in moderate yields, respectively.

Decrease in the reaction yield could be due to the low yield of 2-(arylhydrazino)-3-chloroquinoxaline **3** when aldehydes bearing electron-donating groups are used. Our reason for drawing this conclusion is that when dichloroquinoxaline and hydrazine, in turn, react with 4-methoxybenzaldehyde, 4-methylbenzaldehyde,

Table 1
Effect of base, catalyst, and temperature in heterocyclization during the Sonogashira reaction of 1,2-dichloroquinoxaline **1** with hydrazine hydrate, benzaldehyde, and phenylacetylene[a]

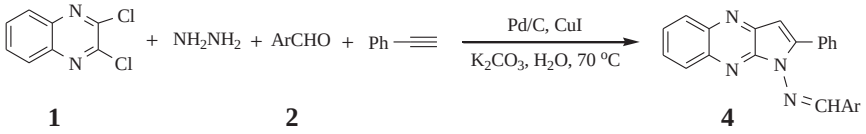


1 **2a** **4a**

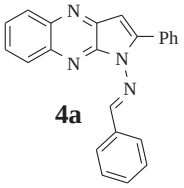
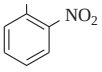
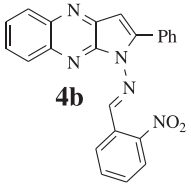
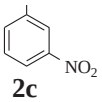
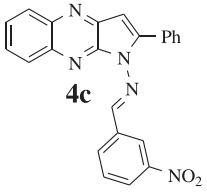
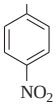
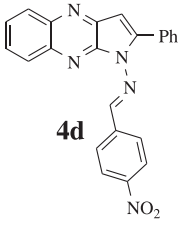
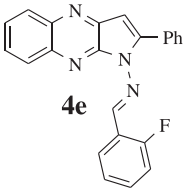
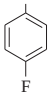
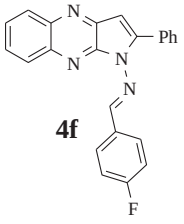
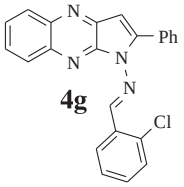
Entry	Catalyst (mol %)	Base	Yield[b] (%)
1	$PdCl_2$ (5)/PPh_3(10)	K_2CO_3	65
2	$PdCl_2(PPh_3)_2$(5)	K_2CO_3	63
3	$Pd(dba)_2$(5)	K_2CO_3	55
4	$PdCl_2$(5)	K_2CO_3	75
5	10% Pd/C (5)	K_2CO_3	80
6	10% Pd/C (5)	Cs_2CO_3	75
7	10% Pd/C (5)	KOH	40
8	10% Pd/C (5)	Na_2CO_3	53
9	10% Pd/C (5)	Et_3N	42
10	10% Pd/C (5)	DIPEA[c]	23
11	10% Pd/C (5)	Pyridine	25
12	10% Pd/C (5)	Piperidine	30
13	10% Pd/C (3)	K_2CO_3	62
14	10% Pd/C (10)	K_2CO_3	80
15[d]	10% Pd/C (5)	K_2CO_3	Trace
16[e]	10% Pd/C (5)	K_2CO_3	45

[a] Reaction conditions: **1** (1.0 mmol), hydrazine hydrate (2.0 mmol), benzaldehyde (1.0 mmol), phenylacetylene (1.0 mmol), K_2CO_3 (2.0 mmol), CuI (10 mol %), at 70 °C for 10 h.
[b] Isolated yields.
[c] Diisopropylethylamine.
[d] Without CuI.
[e] Reaction at 25 °C.

Table 2
Yields of *N*-substituted pyrrolo[2,3-*b*]quinoxalines **4a**–**k**

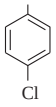
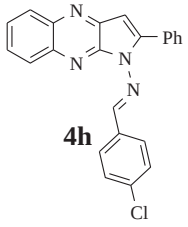
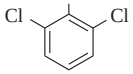
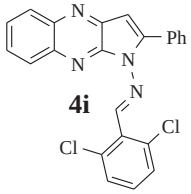
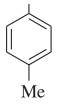
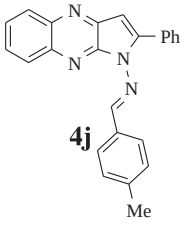
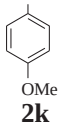
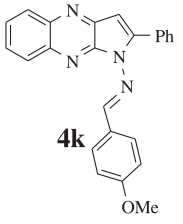


1 **2** **4**

Entry	Ar	Product	Yield[b] (%)
1	 **2a**	 **4a**	80
2	 **2b**	 **4b**	86
3	 **2c**	 **4c**	94
4	 **2d**	 **4d**	95
5	 **2e**	 **4e**	94
6	 **2f**	 **4f**	95
7	 **2g**	 **4g**	91

(*continued on next page*)

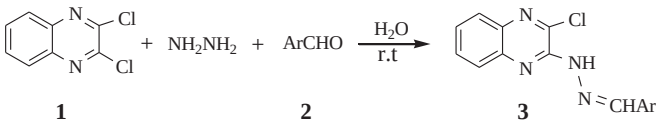
Table 2 (*continued*)

Entry	Ar	Product	Yield[b] (%)
8	 **2h**	 **4h**	94
9	 **2i**	 **4i**	85
10	 **2j**	 **4j**	72
11	 **2k**	 **4k**	66

[a]Reaction conditions: **1** (1.0 mmol), hydrazine hydrate (2.0 mmol), **2a**–**k** (1.0 mmol), phenylacetylene (1.0 mmol), K_2CO_3 (2.0 mmol), 10% Pd/C (5 mol %), CuI (10 mol %), degassed water (5 mL), at 70 °C for 10 h.
[b] Isolated yields.

and 4-nitrobenzaldehyde, the reaction yields for the formation of product **3** are 60, 68, and 95%, respectively (Scheme 2).

A plausible reaction mechanism is depicted in Scheme 3. The Pd(0) species generated in situ from Pd/C catalyzes the coupling of 2-(arylhydrazino)-3-chloroquinoxaline **3** with copper(I) acetylide (generated in situ from phenylacetylene) via intermediate [**A**] leading to 2-(arylhydrazino)-3-alkynylquinoxaline [**B**]. This subsequently affords the corresponding pyrrolo[2,3-*b*]quinoxalines **4** via activation of the triple bond through its complexation with the copper(I) salt followed by intramolecular cyclization[22] with regeneration of the Cu(I) catalyst.[23]



1 **2** **3**

Ar = 4-MeO-C_6H_4-	60%
Ar = 4-Me-C_6H_4-	68%
Ar = 4-NO_2-C_6H_4-	95%

Scheme 2. Synthesis of 2-(arylhydrazino)-3-chloroquinoxaline **3**.

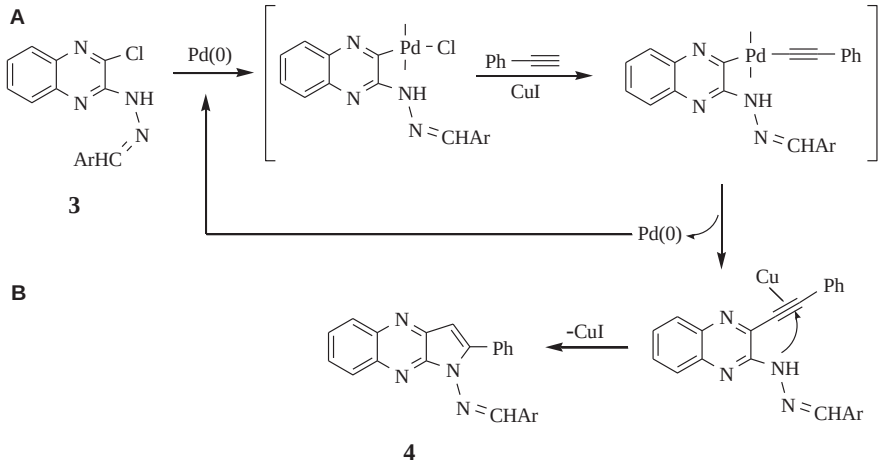
3. Conclusion

In conclusion, we demonstrated a very simple, efficient, clean, and straightforward method for the synthesis of pyrrolo[2,3-*b*]quinoxaline derivatives via the Pd/C-catalyzed reaction of readily available dichloroquinoxaline with hydrazine, phenylacetylene and a variety of aldehydes. This methodology does not involve the use of expensive reagents or catalysts, and thus permits a new and practical access to pyrrolo[2,3-*b*]quinoxalines.

4. Experimental section

4.1. General method

Melting points were uncorrected. The ^{1}H NMR spectra were recorded at 400 MHz, and the ^{13}C NMR spectra were recorded at 100 MHz in DMSO-d_6. The chemical shifts are reported in parts per million (δ), and referenced to the residual proton signal for DMSO-d_6 (δ 2.49). The *J*-coupling constants are reported in hertz. High resolution mass spectrometry was performed on a Bruker micro-TOF instrument using ESI. The reagents used were purchased from commercial suppliers, and used without further purification. Merck silica gel 60 was used for chromatography (230–400 mesh).



Scheme 3. A plausible mechanism for the formation of *N*-substituted pyrrolo[2,3-*b*]quinoxalines **4**.

4.2. Experimental procedures

4.2.1. Synthesis of N-(arylmethamimine)-2-phenyl-1H-pyrrolo[2,3-b] quinoxaline ***4***. A mixture of 1,2-dichloroquinoxaline (199 mg, 1.0 mmol), hydrazine hydrate 99% (0.1 mL, 2.0 mmol), and a suitable aldehyde (1.0 mmol) was stirred in H_2O (5 mL) at room temperature under an argon atmosphere for 30 min. Phenylacetylene (0.11 mL, 1 mmol), 10% Pd/C (53 mg, 0.05 mmol), CuI (19 mg, 0.1 mmol), and K_2CO_3 (276 mg, 2.0 mmol) were added, and the resulting solution was heated in 70 °C for 10 h and cooled to room temperature. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography, eluting with $CHCl_3/CH_3OH$ (50/1) to afford the pure product (Table 2).

4.2.1.1. 2-Phenyl-N-phenylmethylene-1-H-pyrrolo[2,3-b]quinoxaline-1-amine ***4a***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.55; solid; mp=176–178 °C; ν (KBr): 3065, 1595 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.20 (s, 1H), 7.54–7.58 (m, 3H), 7.59–7.63 (m, 3H), 7.76 (d, J=4.8 Hz, 1H), 7.81 (d, J=4.1 Hz, 1H), 7.86–7.89 (m, 3H), 7.97 (dd, J=6.4, 1.6 Hz, 1H), 8.14–8.19 (m, 2H), 10.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 99.9, 128.1, 128.2, 128.7, 128.8, 128.9, 129.2, 129.5, 130.3, 130.4, 131.6, 134.6, 138.4, 140.8, 142.1, 151.5, 155.5. HRMS (ESI): 348.1349; calcd for $C_{23}H_{16}N_4$, 348.1375. Anal. Calcd for $C_{23}H_{16}N_4$: C, 79.29; H, 4.63; N, 16.08. Found: C, 79.05; H, 4.77; N, 16.25.

4.2.1.2. 2-Phenyl-N-[(2-nitrophenyl)methylene]-1-H-pyrrolo[2,3-b]quinoxaline-1-amine ***4b***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.53; solid; mp=262–264 °C; ν (KBr): 3070, 1600, 1545, 1350 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.22 (s, 1H), 7.56–7.63 (m, 3H), 7.73–7.75 (m, 1H), 7.80–7.87 (m, 3H), 7.94 (dd, J=8.0, 2.0 Hz, 2H), 8.05–8.10 (m, 2H), 8.16–8.19 (m, 2H), 11.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 100.9, 125.4, 128.1, 128.5, 128.8, 128.9, 129.0, 129.1, 129.2, 130.2, 130.4, 130.5, 131.9, 134.4, 138.2, 140.9, 141.7, 142.3, 149.1, 149.4, 151.7. HRMS (ESI): 393.1202; calcd for $C_{23}H_{15}N_5O_2$, 393.1226. Anal. Calcd for $C_{23}H_{15}N_5O_2$: C, 70.22; H, 3.84; N, 17.80. Found: C, 70.39; H, 3.97; N, 17.67.

4.2.1.3. 2-Phenyl-N-[(3-nitrophenyl)methylene]-1-H-pyrrolo[2,3-b]quinoxaline-1-amine ***4c***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.52; solid; mp=258–260 °C; ν (KBr): 3070, 1600, 1530, 1355 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.24 (s, 1H), 7.60–7.65 (m, 3H), 7.81–7.86 (m, 3H), 8.17–8.19 (m, 1H), 8.24–8.26 (m, 1H), 8.27–8.29 (m, 1H), 8.35 (dd, J=8.4, 2.4 Hz, 1H), 8.69 (t, J=3.6 Hz, 1H), 10.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 100.6, 122.2, 125.5, 128.4, 128.9, 128.9, 128.9, 129.2, 130.2, 130.4, 130.6, 131.1, 133.9, 136.6, 138.4, 140.9, 141.6, 142.3, 148.7, 151.5, 151.7. HRMS (ESI): 393.1205; calcd for $C_{23}H_{15}N_5O_2$, 393.1226. Anal. Calcd for $C_{23}H_{15}N_5O_2$: C, 70.22; H, 3.84; N, 17.80. Found: C, 70.02; H, 3.69; N, 17.95.

4.2.1.4. 2-Phenyl-N-[(4-nitrophenyl)methylene]-1-H-pyrrolo[2,3-b]quinoxaline-1-amine ***4d***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.54; solid; mp=267–269 °C; ν (KBr): 3060, 1595, 1540, 1350 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.25 (s, 1H), 7.60–7.65 (m, 3H), 7.81–7.84 (m, 2H), 7.97 (dd, J=8.4, 2.0 Hz, 2H), 8.11 (d, J=8.8 Hz, 2H), 8.17–8.19 (m, 1H), 8.21–8.23 (m, 1H), 8.36 (d, J=8.8 Hz, 2H), 10.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 100.9, 124.7, 128.5, 128.9, 128.9, 128.9, 129.0, 129.2, 130.2, 130.4, 130.5, 132.0, 138.3, 140.9, 141.7, 142.4, 148.8, 151.6, 151.6. HRMS (ESI): 393.1208; calcd for $C_{23}H_{15}N_5O_2$, 393.1226. Anal. Calcd for $C_{23}H_{15}N_5O_2$: C, 70.22; H, 3.84; N, 17.80. Found: C, 70.41; H, 3.65; N, 17.62.

4.2.1.5. 2-Phenyl-N-[(2-fluorophenyl)methylene]-1-H-pyrrolo [2,3-b]quinoxaline-1-amine ***4e***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.53; solid; mp=193–195 °C; ν (KBr): 3060, 1595 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.20 (s, 1H), 7.32–7.34 (m, 1H), 7.41–7.44 (m, 1H), 7.56–7.63 (m, 4H), 7.77–7.81 (m, 2H), 7.86–7.88 (m, 1H), 7.90 (dd, J=8.0, 1.6 Hz, 1H), 8.09–8.11 (m, 1H), 8.15–8.17 (m, 1H), 10.67 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 100.3, 116.6, 116.9, 122.2, 122.3, 125.6, 125.6, 125.6, 126.6, 128.3, 128.8, 128.9, 129.2, 130.3, 130.5, 133.5, 133.5, 138.2, 140.8, 141.5, 142.3, 147.2, 147.3, 151.6, 160.4, 162.9. HRMS (ESI): 366.1261; calcd for $C_{23}H_{15}FN_4$, 366.1281. Anal. Calcd for $C_{23}H_{15}FN_4$: C, 75.40; H, 4.13; N, 15.29. Found: C, 75.23; H, 4.22; N, 15.47.

4.2.1.6. 2-Phenyl-N-[(4-fluorophenyl)methylene]-1-H-pyrrolo [2,3-b]quinoxaline-1-amine ***4f***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.54; solid; mp=200–202 °C; ν (KBr): 3060, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.20 (s, 1H), 7.37–7.41 (m, 2H), 7.58–7.63 (m, 3H), 7.78–7.81 (m, 2H), 7.92–7.98 (m, 4H), 8.15–8.19 (m, 2H), 10.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 99.9, 116.6, 116.8, 128.2, 128.7, 128.8, 128.9, 129.2, 130.3, 130.4, 131.2, 131.2, 138.4, 140.8, 141.3, 142.1, 151.5, 154.3, 162.9, 165.4. HRMS (ESI):

366.1259; calcd for $C_{23}H_{15}FN_4$, 366.1281. Anal. Calcd for $C_{23}H_{15}FN_4$: C, 75.40; H, 4.13; N, 15.29. Found: C, 75.62; H, 4.03; N, 15.07.

4.2.1.7. 2-Phenyl-N-[(2-chlorophenyl)methylene]-1-H-pyrrolo [2,3-b]quinoxaline-1-amine ***4g***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.56; solid; mp=190–192 °C; ν (KBr): 3070, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.18 (s, 1H), 7.43 (t, J=7.0 Hz, 1H), 7.50 (t, J=5.2 Hz, 1H), 7.57–7.63 (m, 4H), 7.78–7.81 (m, 2H), 7.90 (dd, J=8.0, 1.6 Hz, 1H), 7.96 (dd, J=8.1, 1.6 Hz, 1H), 8.06–8.08 (m, 1H), 8.12–8.14 (m, 1H), 10.92 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 100.5, 126.8, 128.4, 128.9, 128.9, 129.2, 130.3, 130.6, 132.1, 132.8, 134.7, 138.1, 140.8, 141.5, 142.3, 149.9, 151.6. HRMS (ESI): 382.0966; calcd for $C_{23}H_{15}ClN_4$, 382.0985. Anal. Calcd for $C_{23}H_{15}ClN_4$: C, 72.16; H, 3.95; N, 14.63. Found: C, 72.37; H, 3.73; N, 14.85.

4.2.1.8. 2-Phenyl-N-[(4-chlorophenyl)methylene]-1-H-pyrrolo [2,3-b]quinoxaline-1-amine ***4h***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.57; solid; mp=196–198 °C; ν (KBr): 3075, 1595 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.19 (s, 1H), 7.57–7.62 (m, 5H), 7.72–7.81 (m, 2H), 7.86–7.88 (m, 2H), 7.96 (dd, J=8.0, 1.6 Hz, 2H), 8.15–8.18 (m, 2H), 10.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 100.1, 128.3, 128.8, 128.8, 128.9, 129.2, 129.6, 129.6, 130.3, 130.4, 133.5, 136.0, 138.3, 140.8, 141.4, 142.2, 151.5, 153.7. HRMS (ESI): 382.0962; calcd for $C_{23}H_{15}ClN_4$, 382.0985. Anal. Calcd for $C_{23}H_{15}ClN_4$: C, 72.16; H, 3.95; N, 14.63. Found: C, 72.40; H, 3.84; N, 14.47.

4.2.1.9. 2-Phenyl-N-[(2,6-dichlorophenyl)methylene]-1-H-pyrrolo [2,3-b]quinoxaline-1-amine ***4i***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.52; solid; mp=186–188 °C; ν (KBr): 3070, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 1H), 7.48–7.55 (m, 4H), 7.62–7.64 (m, 2H) 7.79–7.83 (m, 2H), 7.95 (dd, J=7.6, 1.6 Hz, 1H), 8.11–8.13 (m, 1H), 8.15–8.19 (m, 1H), 10.92 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 101.0, 128.6, 128.7, 128.9, 129.0, 129.2, 129.9, 130.1, 130.3, 130.5, 130.7, 132.3, 134.4, 138.2, 140.9, 141.9, 142.9, 142.4, 150.2, 151.9. HRMS (ESI): 416.0577; calcd for $C_{23}H_{14}Cl_2N_4$, 416.0596. Anal. Calcd for $C_{23}H_{14}Cl_2N_4$: C, 66.20; H, 3.38; N, 13.43. Found: C, 66.02; H, 3.50; N, 13.62.

4.2.1.10. 2-Phenyl-N-[(4-methylphenyl)methylene]-1-H-pyrrolo [2,3-b]quinoxaline-1-amine ***4j***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.55; solid; mp=142–144 °C; ν (KBr): 3080, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 3H), 7.21 (s, 1H), 7.36 (d, J=8.0 Hz, 2H), 7.58–7.62 (m, 3H), 7.77–7.82 (m, 4H), 7.97 (dd, J=8.0, 1.6 Hz, 2H), 8.15–8.19 (m, 2H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.6, 99.7, 124.5, 128.1, 128.7, 128.8, 128.9, 129.2, 130.1, 130.3, 130.4, 130.5, 131.8, 138.4, 140.8, 141.3, 141.7, 142.0, 151.5, 155.9. HRMS (ESI): 362.1510; calcd for $C_{24}H_{18}N_4$, 362.1531. Anal. Calcd for $C_{24}H_{18}N_4$: C, 79.54; H, 5.01; N, 15.46. Found: C, 79.71; H, 5.14; N, 15.63.

4.2.1.11. 2-Phenyl-N-[(4-methoxyphenyl)methylene]-1-H-pyrrolo [2,3-b]quinoxaline-1-amine ***4k***. Purification by silica gel column chromatography (chloroform/methanol=50/1): TLC (chloroform/methanol=50/1) R_f=0.53; solid; mp=154–156 °C; ν (KBr): 3050, 1600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.85 (s, 3H), 7.10 (d, J=8.7 Hz, 2H), 7.20 (s, 1H), 7.54–7.66 (m, 3H), 7.68–7.72 (m, 1H), 7.73–7.81 (m, 2H), 7.84 (d, J=8.0 Hz, 2H), 7.97 (dd, J=8.0, 1.6 Hz, 2H), 7.16–8.18 (m, 2H), 10.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.9, 99.4, 115.0, 127.0, 128.0, 128.6, 128.8, 128.9, 129.1, 129.2, 129.9, 130.3, 130.4, 130.6, 132.0, 132.1, 138.4, 140.8, 141.1, 142.0, 151.4, 156.3, 162.4. HRMS (ESI): 378.1460; calcd for $C_{24}H_{18}N_4O$, 378.1481. Anal. Calcd for $C_{24}H_{18}N_4O$: C, 76.17; H, 4.79; N, 14.81. Found: C, 76.37; H, 4.65; N, 14.62.

Acknowledgements

We are grateful to the Research Council of Shahrood University of Technology for the financial support of this work.

Supplementary data

The copies of ^1H NMR and ^{13}C NMR spectra for all products. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.045.

References and notes

1. (a) Zhu, J.; Bienaymé, H. In *Multicomponent Reactions*; Wiley-WCH: Weinheim, 2006; (b) Litvinov, V. P. *Russ. Chem. Rev.* **2003**, *72*, 69–85.
2. (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499; (b) d Souza, D. M.; Müller, T. *J. Chem. Soc. Rev.* **2007**, *36*, 1095–1108; (c) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300–1308.
3. Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486.
4. Hazeldine, S. T.; Polin, L.; Kushner, J.; Paluch, J.; White, K.; Edelstein, M.; Palomino, E.; Corbett, T. H.; Horwitz, J. P. *J. Med. Chem.* **2001**, *44*, 1758–1776.
5. Rong, F.; Chow, S.; Yan, S.; Larson, G.; Hong, Z.; Wu, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1663–1666.
6. David, R. *Exp. Opin. Invest. Drug* **1998**, *7*, 1063–1086.
7. Jaso, A.; Zarranz, B.; Aldana, I.; Monge, A. *J. Med. Chem.* **2005**, *48*, 2019–2025.
8. Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. P. *J. Med. Chem.* **2008**, *51*, 2457–2467.
9. Burguete, A.; Pontiki, E.; Hadjipavlou-Litina, D.; Villar, R.; Vicente, E.; Solano, B.; Ancizu, S.; Perez-Silanes, S.; Aldana, I.; Monge, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6439–6443.
10. Naylor, M. A.; Stephen, M. A.; Nolan, J.; Sutton, B.; Tochcer, J. H.; Fielden, E. M.; Adams, G. E.; Strafford, I. J. *Anticancer Drug Res.* **1993**, *8*, 439–461.
11. (a) Campiani, G.; Cappelli, A.; Nacci, V.; Anzini, M.; Vomero, S.; Hamon, M.; Cagnotto, A.; Fracasso, C.; Uboldi, C.; Caccia, S.; Consolo, S.; Mennini, T. *J. Med. Chem.* **1997**, *40*, 3670–3678; (b) Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Dalla Valle, F.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362–4379.
12. Yuan, Q.; Ma, D. *J. Org. Chem.* **2008**, *73*, 5159–5162.
13. Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry. A Guide for Synthetic Chemists*; Baldwin, J. E., Williams, R. M., Eds.; Pergamon: Amsterdam, 2000.
14. Li, J. J.; Yue, W. S. *Tetrahedron Lett.* **1999**, *40*, 4507–4510.
15. Dinsmore, A.; Garner, C. D.; Joule, J. A. *Tetrahedron* **1998**, *54*, 3291–3302.
16. Li, J. J. *J. Org. Chem.* **1999**, *64*, 8425–8427.
17. Arcadi, A.; Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Tetrahedron Lett.* **2004**, *45*, 2431–2434.
18. Keivanloo, A.; Bakherad, M.; Rahimi, A.; Taheri, S. A. N. *Tetrahedron Lett.* **2010**, *51*, 2409–2412.
19. Keivanloo, A.; Bakherad, M.; Rahimi, A. *Synthesis* **2010**, *10*, 1599–1602.
20. (a) Palimkar, S. S.; Kumar, P. H.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2006**, *62*, 5109–5115; (b) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89–92; (c) Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693–697; (d) Zhang, H.-C.; Hong, Y.; White, K. B.; Maryanoff, B. E. *Tetrahedron Lett.* **2001**, *42*, 4751–4754; (e) Sun, L. P.; Wang, J. X. *Synth. Commun.* **2007**, *37*, 2187–2193; (f) Palimkar, S. S.; More, V. S.; Kumar, P. H.; Srinivasan, K. V. *Tetrahedron* **2007**, *63*, 12786–12790; (g) Oskooie, H. A.; Heravi, M. M.; Behbahani, F. K. *Molecules* **2007**, *12*, 1438–1446; (h) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307–3310; (i) Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 221–224.
21. (a) Raju, S.; Kumar, P. R.; Mukkanti, K.; Annamalai, P.; Pal, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6185–6189; (b) Reddy, E. A.; Barange, D. K.; Islam, A.; Mukkanti, K.; Pal, M. *Tetrahedron* **2008**, *64*, 7143–7150; (c) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221–8225; (d) Batchu, V. R.; Subramanian, V.; Parasuraman, K.; Swamy, N. K.; Kumar, S.; Pal, M. *Tetrahedron* **2005**, *61*, 9869–9877; (e) Novak, Z.; Szabo, A.; Repasi, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327–3329.
22. (a) McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2000**, *43*, 4993–4997; (b) McGuigan, C.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1215–1217; (c) McGuigan, C.; Yarnold, C. J.; Jones, G.; Velazquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 4479–4484; (d) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854–1862; (e) Janeba, Z.; Balzarini, J.; Andrei, G.; Snoeck, R.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **2005**, *48*, 4690–4696.
23. Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531–4534.