Synthesis of Novel 3-Substituted Pyrrolo[2,3-*b*]quinoxalines via an Intramolecular Heck Reaction on an Aminoquinoxaline Scaffold

Jie Jack Li

Department of Medicinal Chemistry, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, Ann Arbor, Michigan 48105

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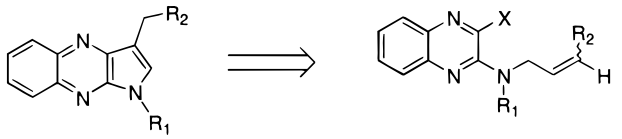
The importance of quinoxalines as pharmaceutical agents is manifested by the marketing of Brimonidine [5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxalinamine] as an antiglucoma agent.[1a] Many drug candidates bearing quinoxaline core structures are in clinical trials in antiviral,[1b] anticancer, antibacterial,[1c] and CNS (central nervous system) therapeutic areas. In an ongoing medicinal chemistry program, we needed to synthesize conformationally constrained 3-substituted pyrrolo[2,3-*b*]quinoxalines. Extensive literature search revealed that few efficient syntheses exist for palladium-catalyzed reactions on *the pyrazine motif* of the quinoxaline ring,[2] although palladium-catalyzed reactions on the benzene part are rather straightforward and usually proceed in good yields.[3] As far as pyrrolo[2,3-*b*]quinoxalines are concerned, Ames et al. prepared 3-substituted pyrrolo[2,3-*b*]quinoxalines from 2-alkynyl-3-chloroquinoxalines by annulation with methylamine.[4] Retrosynthetic analysis indicated that the desired 3-substituted pyrrolo-[2,3-*b*]quinoxalines can also be synthesized from appropriately substituted 3-haloquinoxalin-2-ylamines (Scheme 1). The obvious choice for this cyclization was an intramolecular Heck reaction, which has been extensively studied, and numerous examples can be found on pyrrole annulation onto a benzene ring to synthesize an indole.[5] Quinoxalines with their unique 1,4-diazine moiety are not the ideal substrates for the Heck reaction because they are not only more labile than the simple benzene counterpart (see ref 11) but also strong chelating agents and behave as either monodentate or bidentate ligands under different conditions.[6a] Aminoquinoxalines are especially strong chelating agents,[6b] and catalytic efficiency is difficult to achieve for such substrates. Therefore, the success of this methodology was hinged upon proper selection of reaction conditions. Herein, we report a facile synthesis of a variety of 3-substituted pyrrolo[2,3-*b*]-quinoxalines via an intramolecular Heck reaction of allyl-3-haloquinoxalin-2-ylamines under Jeffery's "ligand-free" conditions.[5o,7] Our method not only allows access to many novel 3-substituted pyrrolo[2,3-*b*]quinoxalines but also complements Ames' method.

Scheme 1



A rapid entry into the desired substrates is shown in Scheme 2. Treatment of 2,3-dihaloquinoxalines **1** with 2 equiv of allylamines **2** in refluxing 1,4-dioxane furnished the corresponding allyl(3-haloquinoxalin-2-yl)amines **3** in 90−98% yields. Allylbenzylamine (entries 1 and 2) was prepared by treating 4 equiv of allylamine with benzyl chloride in refluxing THF.[8] *cis*-4-Benzyloxybuten-2-ylamine (entry 6) was synthesized via the Mitsunobu reaction of *cis*-4-benzyloxy-2-buten-1-ol with phthalimide followed by hydrazinolysis.[9] Cinnamylamine (entry 7), in turn, was prepared via the Gabriel reaction from cinnamyl bromide.[10]

Although under classic Heck conditions, the desired 3-substituted pyrrolo[2,3-*b*]quinoxalines **4** was produced from **3**, the reaction was slow (>72 h) and low yielding (<20%). The low rate and yield may be attributed to the poisoning of the palladium catalyst via complexation to the aminoquinoxalines.[6a] This is in line with our previous

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(11) When tetrabutylammonium chloride was used for reactions of bromoquinoxalines, S_NAr reaction was predominant, giving rise exclusively to the corresponding chloroquinoxalines.

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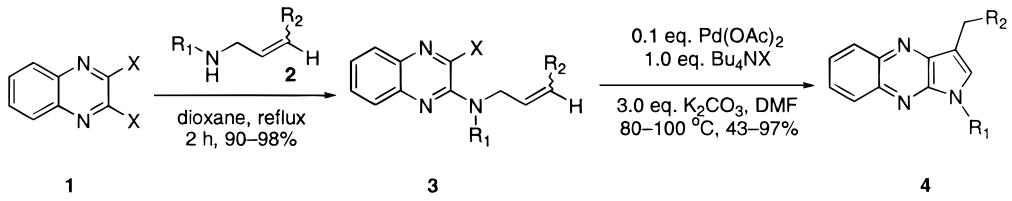
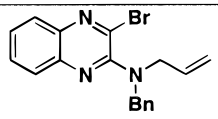
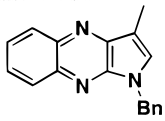
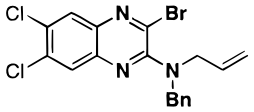
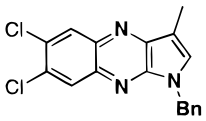
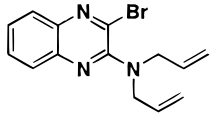
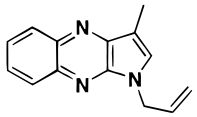
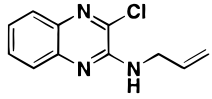
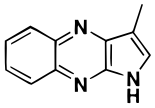
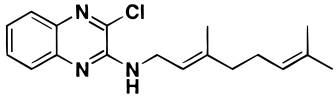
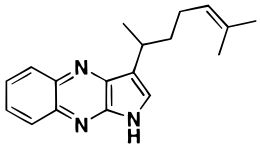
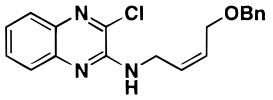
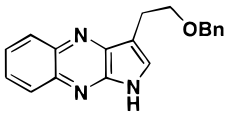
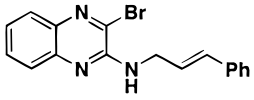
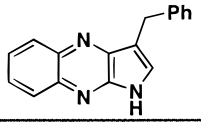
Scheme 2



X = Br, Cl, R_1 = H, allyl, benzyl, R_2 = H, alkyl, phenyl, benzyloxymethyl

Table 1. Pyrrole Annulation onto an Aminoquinoxaline Scaffold: Synthesis of 3-Substituted Pyrrolo[2,3-*b*]quinoxalines via an Intramolecular Heck Reaction

Entry	Substrate	Product	Yield (%) mp (°C)
1			**83** 145–6
2			**26–32** 160–2
3			**97** 96–8
4			**67** 267–8
5			**57** 119–21
6			**43** 171–3
7			**65** 205–6

observations that the Stille reactions of 3-bromoquinoxalin-2-ylamines completely failed when the coupling partners also possessed strong coordination sites (e.g., 2-tri-*n*-butylstannylpyrazine and 2-tri-*n*-butylstannylpyrimidine).[2c] On the contrary, under Jeffery's "ligand-free" conditions,[7] the reaction was more facile and gave higher yields. The enhanced reactivity and yield are presumably due to the coordination and thereby solvation of the palladium intermediates by chloride ions present in the reaction mixture. Once the "locked" palladium catalyst is released from the substrates, the catalytic cycle continues smoothly. Thus, heating allyl-3-haloquinoxalin-2-ylamines **2** in DMF at 80−100 °C in the presence of catalytic palladium acetate, 1 equiv of tetrabutylammonium chloride or bromide,[11] and 3 equiv of potassium carbonate afforded 3-substituted pyrrolo[2,3-*b*]quinoxalines **4** in moderate to excellent yields. Apparently, the external double bond from the initial cyclization process undergoes a facile rearrangement to deliver the thermodynamically more stable pyrrole ring, as well precedented in the literature. As expected, the reaction rate for chloroquinoxalines is slower than that of bromoquinoxalines. The reactions for bromoquinoxalines were completed within 30 min at 80 °C, whereas the reactions for chloroquinoxalines took 120 min at 100 °C.

Table 1 summarizes the results for the application of the methodology to a series of substrates. Excellent yields were obtained for substrates with pendant tertiary amines, whereas 3-substituted pyrrolo[2,3-*b*]quinoxalines were isolated for substrates with pendant secondary amines in only moderate yields, presumably due to the presence of the NH moiety. The limitations of this method may reside in the fact that the reaction is not efficient for substrates having electron-withdrawing groups on the benzene ring of the quinoxaline structure. For instance, only 26−32% yields were obtained for the substrate with chlorine substituents on the benzene part of the quinoxaline ring (entry 2).

In conclusion, 3-substituted pyrrolo[2,3-*b*]quinoxalines have been synthesized from allyl(3-halo-quinoxalin-2-yl)-amines under Jeffery's "ligand-free" conditions. Our method not only allows access to many novel 3-substituted pyrrolo[2,3-*b*]quinoxalines but also complements Ames' method.

Experimental Section

General Methods. Melting points are uncorrected. The ^{1}H NMR spectra were recorded at 400 MHz, and the ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm (δ) and referenced to the residual proton signal for $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.49 ppm). The J coupling constants are reported in hertz (Hz). Elemental analyses were performed by Quantitative Technologies Inc. and are within 0.4% of theory. Reagents were purchased from commercial suppliers and used without further purification. Merck silica gel 60 was used for flash chromatography (230−400 mesh).

Representative Procedure for Preparation of the Substrates (Allylbenzyl-(3-bromoquinoxalin-2-yl)amine, Entry 1). To a solution of 2,3-dibromoquinoxaline (576 mg, 2.0 mmol) in 1,4-dioxane (25 mL) was added benzyl allylamine (734 mg, 5.0 mmol). The resulting solution was refluxed in for 24 h and cooled to room temperature. The reaction mixture was filtered through a pad of silica gel, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography eluting with EtOAc/Hex (1:16) to afford the desired product as a greenish oil (700 mg, 99% yield): R_f = 0.40, EtOAc/Hex (1:16); IR (neat, cm^{-1}) 3063, 2858, 1535, 1410, 758; ^{1}H NMR ($CDCl_3$) δ 7.91 (dd, J = 1.5, 8.2 Hz, 1H), 7.85 (dd, J = 1.3, 7.0, 8.5 Hz, 1H), 7.65 (ddd, J = 1.5, 8.2 Hz, 1H), 7.53 (dd, J = 1.4, 7.1 Hz, 1H), 7.45 (m, 2H), 7.29 (m, 3H), 6.06 (m, 1H), 5.26 (m, 2H), 4.77 (s, 2H), 4.13 (d, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 153.0, 139.8, 139.0, 134.6, 134.0, 130.2, 129.0, 128.4, 128.3, 127.8, 127.2, 127.1, 118.7, 53.4, 53.3; HRMS calcd for $C_{18}H_{16}BrN_3$ (M+H)$^+$ 354.0528, found 354.0607.

Representative Procedure for the Intramolecular Heck Reaction (1-Benzyl-3-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline, Entry 1). To a solution of allylbenzyl-(3-bromoquinoxalin-2-yl)amine (500 mg, 1.42 mmol) in DMF (15 mL) was added $Pd(OAc)_2$ (32 mg, 0.14 mmol), K_2CO_3 (580 mg, 4.25 mmol), and Bu_4NBr (456 mg, 1.42 mmol). The resulting mixture was stirred at 80 °C for 30 min and cooled to room temperature. The mixture was diluted with CH_2Cl_2 (100 mL), washed with water (3 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography to furnish 1-benzyl-3-methylpyrrolo[2,3-*b*]quinoxaline as a yellow solid (321 mg, 83% yield): mp 145−146 °C; R_f = 0.26, EtOAc/Hex (1:1); IR (KBr, cm^{-1}) 3048, 2926, 1452, 1112, 756; ^{1}H NMR (DMSO) δ 8.25 (dd, J = 1.7, 7.1 Hz, 1H), 8.11 (dd, J = 1.5, 8.0 Hz, 1H), 7.65 (m, 2H), 7.45 (s, 1H, pyrrolyl H), 7.29 (m, 5H), 5.48 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (DMSO) δ 142.8, 142.2, 140.3, 139.3, 137.1, 135.1, 129.2, 128.8, 128.2, 127.9, 127.8, 127.6, 126.2, 110.0, 47.7, 8.8; MS (APCI), m/z 274.0 (M$^+$+1); Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.53; N, 15.37. Found: C, 78.90; H, 5.29; N, 15.37.

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Supporting Information Available: Characterization data for substrates and products in entries 2−7 and ^{1}H NMR spectra for all substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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