Pergamon

Tetrahedron Letters 40 (1999) 4507–4510

TETRAHEDRON LETTERS

Synthesis of 3-Aryl and 3-Heterocyclic Quinoxalin-2-ylamines *via* Pd-Catalyzed Cross-Coupling Reactions

Jie Jack Li*, and Wen Song Yue

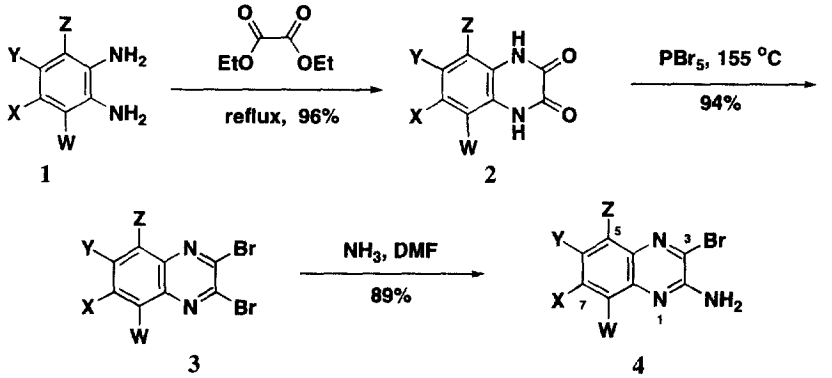
Medicinal Chemistry Department, Parke–Davis Pharmaceutical Research Division, Warner–Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 USA

Received 12 March 1999; revised 15 April 1999; accepted 16 April 1999

Abstract: Facile and high yielding Suzuki and Stille cross-coupling reactions of 3-bromo-quinoxalin-2-ylamines were developed to synthesize a variety of novel and diversely functinalized 3-aryl and 3-heterocyclic quinoxalin-2-ylamines. The preparation of the substrates and the remarkable impact that substituents have on the regiochemical outcome are discussed.

Keywords: quinoxalines, the Stille reaction, the Suzuki reaction, regiochemistry.

Conventional syntheses[1] of 3-aryl and 3-heterocyclic quinoxalin-2-ylamines generally involve phenylenediamines and appropriately substituted aryl α-ketoester analogs as the starting materials. This approach is not only lengthy and tedious, but also is seriously restricted by the commercial availability of aryl and heterocyclic α-ketoesters. Although Suzuki and Stille cross-coupling reactions on the benzene ring of quinoxalines have been reported in the synthesis of novel herbicides,[2] there are few reported palladium-catalyzed cross-coupling reactions on the pyrazine ring of quinoxalines. This is partially due to the π-electron deficient nature of the pyrazine ring. One report[3] discussed a Stille cross-coupling reaction between 2-butyl-3-chloroquinoxaline and benzyl stannane in 45% yield. Another publication[4] described a Stille cross-coupling of 2-chloroquinoxaline with simple 4-tri-*n*-butylstannyl-1,3-dithiole-2-thione in 10 to 24% yield. Herein, we report the application of facile, high yielding Suzuki and Stille cross-coupling reactions to synthesize a variety of novel and diversely functionalized 3-aryl and 3-heterocyclic quinoxalin-2-ylamines using a common intermediate, 3-bromo-quinoxalin-2-ylamine (**4**). This method provides quick access to many 3-aryl and 3-heterocyclic quinoxalin-2-ylamines from **4** in one step.

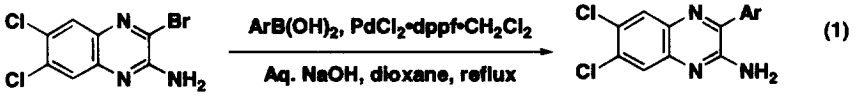


Scheme 1. (a) X = Y = Cl, W = Z =H; (b) W = NO_2, X = Y = Z = H; (c) Y = NO_2, W = X = Z = H; (d) Y = CF_3, W = X = Z = H; (e) X = Y = F, W = Z = H.

3-Bromo-quinoxalin-2-ylamines (**4**) were easily prepared in 3 steps. Appropriately substituted phenylenediamine **1** was heated under reflux with an excess of diethyl oxalate to furnish 1,4-dihydroquinoxaline-2,3-dione (**2**).[5] Dibromide **3** then was obtained by heating **2** with molten phosphorus pentabromide at 155 °C.[6] The S_NAr on **3** with an equivalent of ammonia proceeded smoothly by either

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00822-9

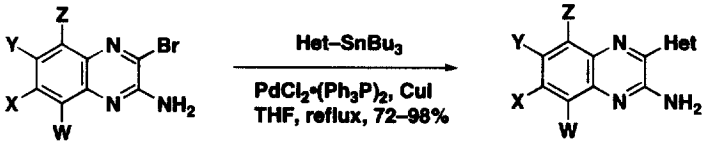
passing ammonia gas through a solution of **3** in DMF or by treating a THF solution of **3** with aqueous ammonium hydroxide solution to give the desired 3-bromo-quinoxalin-2-ylamine (**4**).[7] No significant amount of the diamine was detected within 30 min. when the first S_NAr was completed. Substitution of **3b** and **3c** occurred predominantly (>95:5 ratio) at C(2) and C(3) to give **4b** and **4c**, respectively. The former was confirmed by single crystal X-ray analysis of the Stille product **6g** (Table 1). S_NAr reaction of **3d** produced a ~2:1 mixture of regioisomers of **4d** (see **6i**), in which the major isomer was inferred to be the product from substitution at C(3) by analogy to literature precedents.[7]



(1)

4a **5**

In the presence of a strong base (NaOH, no reaction was observed when weaker bases were used), the Suzuki reactions with **4a** proceeded smoothly with some arylboronic acids (Equation 1) to give **5**, where aryl is 2-naphthalenyl (92% yield, mp = 260–1 °C), phenyl (61%, 214–5 °C), 3-pyridyl (52%,[8] 265–6 °C), or 3-nitrophenyl (75%, 244–5 °C). However, the requirement for strongly basic conditions to ensure the transmetallation to occur *via* an "ate" complex was disadvantageous because none of the heterocyclic boronic acids investigated survived the conditions, neither did substrates containing amide and ester functional groups. When **4a** was treated with 2,5-dichlorophenylboronic acid, additional coupling products due to displacement of the chloride by another molecule of 2,5-dichlorophenylboronic acid were observed. Moreover, in the presence of aliphatic amines, the debromination reaction occurred along with the Suzuki coupling reaction.

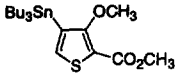
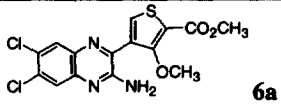
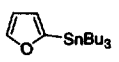
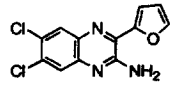
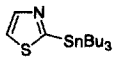
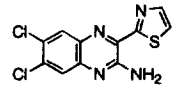
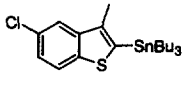
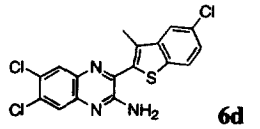
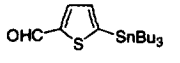
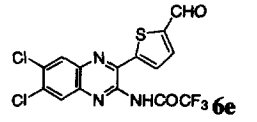
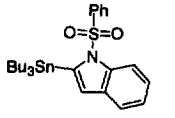
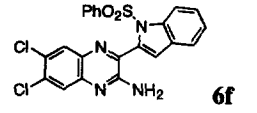
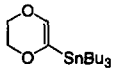
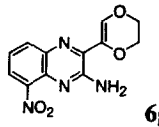
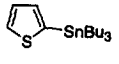
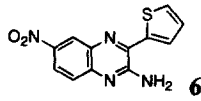
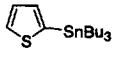
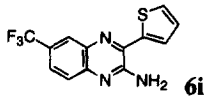
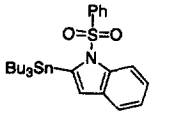
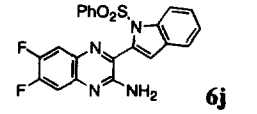
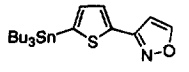
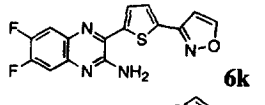
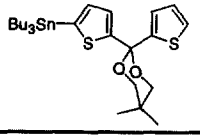
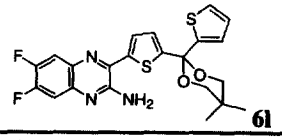


(2)

4 **6**

In contrast to the Suzuki reaction, the Stille reaction of **4** with various aryl and heterocyclic stannanes proved to be more general (Equation 2). The stannanes were prepared *via* (a) palladium(0)-catalyzed reaction between an aryl halide or a heterocyclic halide and hexaalkylditin [e.g. the stanannes in entries 1, 5 and 11 from methyl 4-bromo-3-methoxythiophene-2-carboxylate, 2-bromothiophene-5-carboxaldehyde, and 2-bromothiophene-5-(3-isoxazole), respectively];[9] (b) halogen/metal exchange of an arylhalide followed by quenching with a stannyl electrophile [e.g. the stannane in entry 4 from 2-bromo-5-chloro-3-methylbenzo(*b*)thiophene];[10] or (c) direct metalation of a substrate followed by quenching with a stannyl electrophile (e.g. the stannane in entry 12).[11] The Stille reaction facilitated successful preparation of a plethora of diversely functionalized 3-aryl and 3-heterocyclic quinoxalin-2-ylamines from **4** in one step in high yields. Representative examples are shown in Table 1. When substrate **4** was treated with various heterocyclic stannanes in the presence of 5% $PdCl_2•(Ph_3P)_2$ and 10% CuI[12] in refluxing THF, the Stille reactions were completed cleanly in 10 min. to 2.0 h to furnish the desired 3-heterocyclic quinoxalin-2-ylamines (**6**).[13] The reactions for stannanes without thiophenes (entries 2, 6, 7, and 10) were completed in ~10–30 min, whereas the thiophene-containing stannanes required ~2 h, presumably due to the poisoning effect of thiophenes to the palladium catalyst.[14] The reaction tolerates

Table 1. The Stille Cross-Coupling of **4** with Heterocyclic Stannanes*

Entry	Substrate (4)	Het–$SnBu_3$	Hetereocyclic Quinoxaline (6)	Yield (%) mp (°C)
1	X = Y = Cl W = Z = H **4a**		 **6a**	**74** 245–6
2	X = Y = Cl W = Z = H **4a**		 **6b**	**77** 235–7
3	X = Y = Cl W = Z = H **4a**		 **6c**	**81** 244–6
4	X = Y = Cl W = Z = H **4a**		 **6d**	**92** 291–2
5	X = Y = Cl W = Z = H **4a**'[15]		 **6e**	**92** 151–3
6	X = Y = Cl W = Z = H **4a**		 **6f**	**92** 119–22
7	W = NO_2 X = Y = Z = H **4b**		 **6g**	**72** 208–10
8	Y = NO_2 W = X = Z = H **4c**		 **6h**	**72** 271–2
9	Y = CF_3 W = X = Z = H **4d**		 **6i**	**98** 222–4
10	X = Y = F W = Z = H **4e**		 **6j**	**83** 241–3
11	X = Y = F W = Z = H **4e**		 **6k**	**84** >215 (dec.)
12	X = Y = F W = Z = H **4e**		 **6l**	**85** 183–5

*Satisfactory IR, ^1H and ^{13}C NMR spectra, and HRMS or Microanalyses were obtained for all new intermediates and products.

many functional groups as manifested by survival of the ester in **6a**, the sulfonamide in **6f** and **6j**, the isoxazole in **6k**, and the ketal moiety in **6l**. Although the Stille adduct from **4a** and 2-tri-*n*-butylstannylthiophene-5-carboxaldehyde (entry 5) was obtained in only 34% yield probably due to its reaction with the primary amine group, the problem was easily solved by protecting the primary amine as its corresponding trifluoroacetamide (**4a'**).[15] The limitations of this method reside in the failure of a few heterocyclic stannanes. For instance, even though 2-pyridyl-tri-*n*-butylstannane reacted with **4a** to give 3-(2-pyridyl)-quinoxalin-2-ylamine in 75% yield, no reaction was detected when **4a** was treated with 2-tri-*n*-butylstannylpyrazine under the same reaction conditions. The Stille reactions with 2-tri-*n*-butylstannyl-1-methylimidazole and 2-tri-*n*-butylstannylbenzothiazole also failed, although the Stille reaction of 2-tri-*n*-butylstannylthiazole proceeded smoothly (entry 3).

In conclusion, a mild and efficient synthesis of 3-aryl and 3-heterocyclic quinoxalin-2-ylamines (**6**) has been developed using the Suzuki or the Stille reactions from a common intermediate **4**. A full account of the scope and limitations of this method will be published in due course.

Acknowledgment We thank Mr. Scott N. VanderWel for preparing large quantities of **3a** and **4a**. We are indebted to Dr. J. Ronald Rubin for performing X-ray crystallography, Drs. Bharat K. Trivedi and Bruce D. Roth for helpful discussions.

References

1. Elslager, E. F.; Hess, C. A.; Werbel, L. M. *J. Med. Chem.* **1968**, *11(3)*, 630–1.
2. Selby, T. P.; Denes, R.; Kilama, J. J.; Smith, B. K. *ACS Symp. Ser.* **1995**, *584* (*Synthesis and Chemistry of Agrochemicals IV*), 171–85.
3. Kim, K. S.; Qian, L.; Dikinson, K. E. J.; Delaney, C. L.; Carol L.; Bird, J. E.; Waldron, T. L.; Moreland, S. *Bioorg. & Med. Chem. Lett.* **1993**, *3(12)*, 2667–70.
4. Dinsmore, A.; Garner, C. D.; Joule, J. A. *Tetrahedron* **1998**, *54(33)*, 9559–68.
5. Sarges, R.; Howard, H. R.; Browne, R. G.; Lebel, L. A.; Seymour, P. A.; Koe, B. K. *J. Med. Chem.* **1990**, *33(8)*, 2240–54.
6. Usherwood, E. H.; Whiteley, M. A. *J. Chem. Soc.* **1923**, 1069–83.
7. (a) Tanaka, K.; Takahashi, H.; Takimoto, K.; Sugita, M.; Mitsuhashi, K.; *J. Heterocyclic Chem.* **1992**, *29*, 771–7. (b) Iwata, S.; Sakajyo, M.; Tanaka, K.; *J. Heterocyclic Chem.* **1994**, *31*, 1433–8.
8. 21% of an ethyl derivative was also isolated because diethyl-3-pyridylborane was used.
9. (a) Kosugi, M.; Shimizu, K.; Ohtani, A.; Migita, T. *Chem. Lett.* **1981**, *6*, 829–30. (b) Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1983**, *56(12)*, 3855–6.
10. Pham, C. V.; Macomber, R. S.; Mark, H. B., Jr.; Zimmer, H. *J. Org. Chem.* **1984**, *49(26)*, 5250–3.
11. (a) Yang, Y.; Hörnfeldt, A-B.; Gronowitz, S. *Synthesis*, **1989**, *2*, 130. (b) Grisp, G. T. *Synth. Commun.* **1989**, *19(1&2)*, 307–15.
12. Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55(19)*, 5359–64.
13. Representative experimental procedure: A 50 mL round-bottom flask was charged with 3-bromo-quinoxalin-2-ylamine (**4a**, 1.03 g, 3.52 mmol), 1-benzenesulfonyl-2-tri-*n*-butylstannyl-1*H*-indole (2.30 g, 4.21 mmol), bis(triphenylphosphine)palladium(II) dichloride (259 mg, 0.35 mmol), CuI (77 mg, 0.70 mmol), and THF (40 mL). The yellow suspension was heated under reflux for 30 min, then cooled to room temperature. Charcoal was added and the reaction mixture was heated to boiling then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was chromatographed using silica gel eluting with 1:1 Hex/EtOAc to give the desired product **6f** as a yellow solid (1.51 g, yield 92%): mp 119–122 °C; R_f = 0.26, EtOAc/Hex (1:1); IR (KBr, cm^{-1}) 3485, 3388, 1619, 1592, 1447, 1412, 1373, 1344, 1177, 1090, 752, 728, 684, 590, 570; ^{1}H NMR (DMSO) 7.17 (s, 2H), 7.31 (dt, *J* = 0.9, 6.77 Hz, 1H), 7.43 (dt, *J* = 1.1, 7.32 Hz, 1H), 7.84 (s, 1H), 7.63 (m, 4H), 7.86 (d, *J* = 1.6 Hz , 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (DMSO) δ 153.6, 141.8, 141.1, 136.7, 136.4, 134.7, 134.6, 134.3, 132.8, 130.0, 129.6, 129.4, 126.9, 125.9, 125.7, 125.6, 124.2, 122.0, 114.7; MS (ACPI), *m/z* 469.0 (M^++1), 471.0 (M^++3); Anal. Calcd for $C_{22}H_{14}N_4Cl_2O_2S_1$: C, 56.30; H, 3.01; N, 11.94. Found: C, 56.22; H, 3.04; N, 11.82.
14. Smith, G. V.; Notheisz, F.; Zsigmond, A. G.; Bartok, M. *Stud. Surf. Sci. Catal.* **1993**, *75* (*New Frontiers in Catalysis, Pt. C*), 2463–6.
15. (a) **4a'** is the trifluoroacetamide derivative of **4a**, (b) freshly prepared stannane was used.