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LETTERS

Cross-coupling of 1-aryl-5-bromopyrazoles: regioselective synthesis of 3,5-disubstituted 1-arylpyrazoles

Xiao-jun Wang,* Jonathan Tan and Karl Grozinger

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT 06877, USA

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Abstract

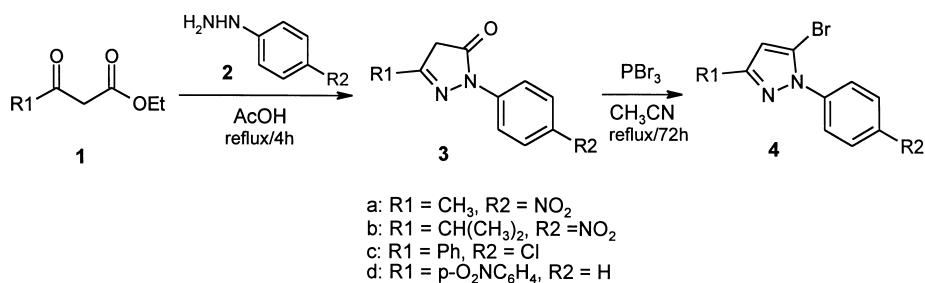
The cross-coupling of 1-aryl-5-bromopyrazoles **4** with alkynes, vinyltins and arylboronic acids promoted by $\text{Pd}(\text{PPh}_3)_4$ afforded unsymmetrical 3,5-disubstituted 1-arylpyrazoles **5–8** in excellent yields. 1-Aryl-5-bromopyrazoles **4** were prepared from their corresponding 1-arylpyrazolones **3** with PBr_3 in refluxing acetonitrile. © 2000 Elsevier Science Ltd. All rights reserved.

Condensation of 1,3-diketones and their equivalent 1,3-dienophilic synthons such as propargylic ketones with arylhydrazines has been widely used for synthesis of *N*-arylpyrazoles, often producing two regioisomers in the case of 3,5-disubstituted pyrazoles.¹ Another powerful tool is aromatic substitution of *N*-nonsubstituted pyrazoles with activated halogenated aromatics. This method, however, faces the same regiochemistry issue because pyrazole is an ambident nucleophile.² Although there are reports on regio-controlled synthesis of pyrazoles, they have had limited application.³ Because we required a variety of 3,5-disubstituted 1-arylpyrazole, we needed a general regio-controlled approach to this class of compounds. In this communication, we are pleased to report that cross-coupling of readily available 1-aryl-5-bromopyrazoles^{4,5} with terminal alkynes,⁶ organostannanes⁷ and arylboronic acids⁸ gives unsymmetrical 3,5-disubstituted 1-arylpyrazoles in excellent yields.

1-Aryl-5-bromopyrazoles were prepared as shown in Scheme 1. Pyrazolones **3** were made in good to excellent yields from condensation of ketoesters **1** with arylhydrazines **2** in refluxing acetic acid using a known method.⁹ Pyrazolones **3** were then converted to 5-bromopyrazoles **4** with PBr_3 in refluxing acetonitrile in 70–85% yields.¹⁰ Usually, less than 15% of the starting pyrazolones **3** was recovered from these reactions, and highly soluble 5-bromopyrazoles **4** were easily taken up into less polar solvents such as a mixture of hexane and ethyl acetate.

The cross coupling of 5-bromopyrazoles **4a–d** with terminal acetylenes was conducted in Et_3N as solvent at 70°C, and was promoted by $\text{Pd}(\text{PPh}_3)_4/\text{CuBr}\cdot\text{SMe}_2$. Greater than 90% yield of

* Corresponding author.



Scheme 1.

products **5–8a** were isolated as shown in Table 1. Similarly, the Stille reaction of **4a–d** with vinylstannane in THF at reflux for 4–6 h led to 5-vinylpyrazoles **5–8b** in excellent yields. Similar result (**5–8c**, Table 1) was also obtained from the Suzuki coupling between 5-bromopyrazole **4a–d** and arylboronic acids. Actually, the crude coupling products of **4** with acetylenes and arylboronic acids were clean enough for further elaboration with no need of purification. In an effort to prepare a large quantity of **6b**, the coupling of **4b** with propargyl alcohol was achieved with only 0.01 mol% PdCl₂ (with two equiv. of PPh₃) using triethylamine as a base in refluxing THF, and **6b** was obtained in quantitative yield. The same low loading of PdCl₂/2PPh₃ was also effective for the coupling of **4b** with phenylboronic acid. These results clearly indicate that the cross coupling reaction can serve as a general approach for synthesis of unsymmetrical 3,5-disubstituted 1-arylpyrazoles from their corresponding 5-bromopyrazoles.

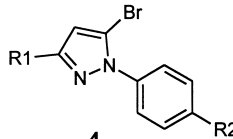
The following are representative procedures:

1-(4-Chlorophenyl)-3-phenyl-5-bromopyrazole (4c): to a solution of pyrazolone **2c** (2.00 g, 7.38 mmol) in acetonitrile (5 mL) was added PBr₃ (4.0 mL, 37 mmol) and the mixture was heated to reflux for 72 h. After being cooled to 0°C, the mixture was slowly quenched with ice/water and extracted with a 5:1 mixture of hexane and ethyl acetate. The extract was dried over MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 15:1) to give **4c** as a white solid (2.10 g, 84%). Mp: 88–89°C. ¹H NMR (400 MHz, CDCl₃) 7.86 (d, J = 7.0 Hz, 2H), 7.63, 7.52 (ABq, J = 9.0 Hz, 4H) 7.47 (dd, J = 7.0, 7.5 Hz, 2H), 7.38 (m, 1H), 6.84 (s, 1H). ¹³C NMR (400 MHz, CDCl₃) 153.7, 137.9, 134.7, 132.5, 129.6, 129.2, 129.0, 127.3, 126.1, 114.0, 108.5. MS m/e 333 (MH⁺). Anal. calcd for C₁₅H₁₀ClBrN₂: C, 54.00; H, 3.02; N, 8.40; Cl, 10.63. Found: C, 53.89; H, 2.93; N, 8.38; Cl, 10.77.

The cross-coupling of 4c with alkyne: to a solution of 5-bromopyrazole **4c** (300 mg, 0.90 mmol) in triethylamine (5 mL) was added Pd(PPh₃)₄ (21 mg, 0.018 mmol) and CuBr·SMe₂ (8 mg, 0.036 mmol), followed by 2-methyl-3-butyn-2-ol (0.10 mL, 0.99 mmol). The mixture was heated to 70°C for 1 h and cooled to room temperature. The solid was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 4:1) to give pyrazole **7a** (286 mg, 94%). Mp: 112–113°C. ¹H NMR (400 MHz, CDCl₃) 7.89 (d, J = 7.0 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H) 7.48–7.38 (m, 5H), 6.92 (s, 1H), 1.61 (s, 6H). ¹³C NMR (400 MHz, CDCl₃) 152.5, 138.7, 133.5, 132.6, 129.3, 129.2, 128.8, 126.2, 125.8, 124.8, 110.5, 110.4, 102.1, 72.0, 66.0. MS m/e 337 (MH⁺). Anal. calcd for C₂₀H₁₇ClN₂O: C, 71.32; H, 5.09; N, 8.32; Cl, 10.53. Found: C, 71.25; H, 5.03; N, 8.23; Cl, 10.80.

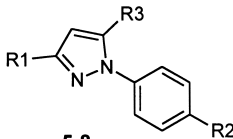
The cross-coupling of 4a with vinyl tributyltin: to a solution of 5-bromopyrazole **4a** (138 mg, 0.49 mmol) in THF (5 mL) was added Pd(PPh₃)₄ (21 mg, 0.018 mmol) followed by vinyl tributyltin (0.16 mL, 0.54 mmol). The mixture was heated to reflux for 6 h under N₂, it was then quenched

Table 1
Cross couplings of 5-bromopyrazoles **4** with terminal acetylenes, boronic acids and vinyl tins

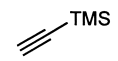
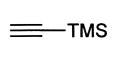
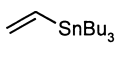
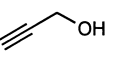
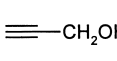
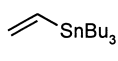
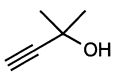
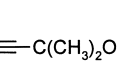
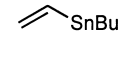
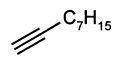
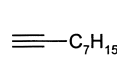
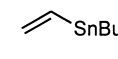


4

reagents
conditions



5-8

substrates	reagents	conditions ^a	R1	R2	R3	yields(%) ^{b,c}
4a ¹¹		A	CH ₃	NO ₂		95(5a)
4a		B	CH ₃	NO ₂		92(5b)
4a	PhB(OH) ₂	C	CH ₃	NO ₂	Ph	94(5c) ¹²
4b		A	CH(CH ₃) ₂	NO ₂		91(6a)
4b		B	CH(CH ₃) ₂	NO ₂		90(6b)
4b	PhB(OH) ₂	C	CH(CH ₃) ₂	NO ₂	Ph	93(6c)
4c ¹³		A	Ph	Cl		96(7a)
4c		B	Ph	C		95(7b)
4c	p-MeOC ₆ H ₄ B(OH) ₂	C	Ph	C	p-MeOC ₆ H ₄	95(7c) ^{3c}
4d		A	p-NCC ₆ H ₄	H		94(8a)
4d		B	p-NCC ₆ H ₄	H		90(8b)
4d	p-MeOC ₆ H ₄ B(OH) ₂	C	p-NCC ₆ H ₄	H	p-MeOC ₆ H ₄	97(8c)

a) condition A: 2% Pd(PPh₃)₄, 4% CuBr·SMe₂·Et₃N/70°C/1h. B: 2% Pd(PPh₃)₄, THF/reflux/4-6h.

C: 2% Pd(PPh₃)₄, 2M Na₂CO₃/THF/reflux/4h.

b) Isolated yield by column chromatography on silica gel.

c) All products had satisfied ¹H and ¹³C NMR, MS, high resolution MS or elemental analysis.

with saturated KF and extracted with EtOAc. The extract was dried over MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 10:1) to give pyrazole **5b** (103 mg, 92%). ¹H NMR (400 MHz, CDCl₃) 8.37, 7.70 (ABq, J = 9.0 Hz, 4H), 6.59 (dd, J = 17.6, 11.0 Hz, 1H), 6.46 (s, 1H), 5.82 (dd, J = 17.6, 1.0 Hz, 1H), 5.47 (dd, J = 11.0, 1.0 Hz, 1H), 2.38 (s, 3H). ¹³C NMR (400 MHz, CDCl₃) 151.4, 146.3, 144.9, 142.7, 125.1, 124.8, 124.6, 119.2, 106.8, 13.9. MS m/e 230 (MH⁺). Anal. calcd for C₁₇H₁₃ClN₂: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.76; H, 4.90; N, 18.15.

The cross-coupling of **4c** with arylboronic acids: to a solution of 5-bromopyrazole **4c** (200 mg, 0.60 mmol) in THF (5 mL) was added Pd(PPh₃)₄ (14 mg, 0.012 mmol) and 4-methoxyphenylboronic acid (110 mg, 0.7 mmol), followed by 2 M Na₂CO₃ (1.0 mL, 2.0 mmol). The mixture was heated to reflux for 4 h, and then quenched with water and extracted with EtOAc. The extract was dried over MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel (hexane:acetate, 15:1) to give pyrazole **7c** (210 mg, 97%). Mp: 104–105°C (lit.^{3c} 104–106°C).

Acknowledgements

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