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REGULAR ARTICLE

Transition metal-promoted synthesis of 2-aryl/heteroaryl-thioquinazoline: C-S Bond formation by "Chan-Lam Cross-Coupling" Reaction

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Abstract. An efficient method for the synthesis of *S*-aryl/heteroaryl-quinazoline has been developed through the cross-coupling of 1,4-dihydroquinazoline with a variety of aryl and heteroaryl boronic acids assisted by $[Cu(OAc)_2]$ as the catalyst for the formation of carbon-sulfur bonds. This newly developed method demonstrates that the conditions of the traditional copper-catalyzed Chan-Lam reaction can be improved. Optimized reaction involves base, solvent and catalyst.

Keywords. Chan-Lam coupling; quinazoline; boronic acids; copper acetate.

1. Introduction

The quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological activities.[1] Quinazoline is the core ring of numerous drug compounds, the scaffold of which always includes a thiol substituent at position-2 of the quinazoline ring.

Transition-metal-catalyzed carbon-heteroatom cross-coupling reactions represent great contribution to the recent growth of organic synthesis.[2] Although aryl sulfides have broad application in the pharmaceutical industry and material science[3] and as intermediates in organic synthesis,[4] the formation of carbon-sulfur bonds has received less attention. Difficulties in C-S bond formation can be attributed to the sulfur species rapidly and irreversibly deactivating the catalyst.[5] So the efficient formation of the C-S bond is one of the most important aspect of organic chemistry.

2. Experimental

2.1 *Materials and Methods*

All the reagents and chemicals were procured from commercial sources (SD Fine Chemicals, India; Aldrich) and used without any further purification. Melting points are uncorrected and were determined in open capillary tubes in melting point apparatus. TLC was performed on silica gel-G and spotting was done using iodine/$KMnO_4$ staining or UV light. IR spectra were recorded with Perkin-Elmer 1000 instrument in KBr phase. ^{1}H NMR was recorded on VARIAN 300MHz instrument and Mass spectra were recorded on Agilent-LC-MS instrument. The following experimental procedures are representative of the general procedures used to synthesize all compounds.

2.2 *Synthesis of the compounds*

Compounds **a** to **r** were prepared by following a general synthetic procedure in which the solution of 1,4-dihydroquinazoline-2-thiol (100 mg, 0.609 mmol) in dichloromethane (4 mL) was added the $Cu(OAc)_2$ (166 mg, 0.913 mmol), Et_3N (0.43 mL, 3.045 mmol) and stirred for 10–15 min at RT, followed by addition of substituted boronic acid (1.219 mmol). The reaction mixture was stirred at RT for 12 h. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2×15 mL). The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4, filtered the solvent, and concentrated under reduced pressure to give the crude compound. The crude compound was purified by flash column chromatography (100–200 mesh silica gel), eluted at 10–20% ethyl acetate/pet ether to afford the *S*-substituted quinazoline derivative. The characterization data for the compounds are given below.

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2.2.1 *2-(p-tolylthio) quinazoline (Table 4, Entry a)*: Pale yellow solid. [Yield: 130 mg, 85%] R_f: 0.7, 8% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{15}H_{12}N_2S$ for (M+H): Calculated: 252.3; Found, 253.3 (82.3%). IR/cm^{-1}: 1796.91, 1615.00, 1548.45, 1483.60, 1439.43, 1369.55, 1216.85, 1159.01, 1094.48, 968.86, 863.36, 777.29, 757.23, 688.92 and 660.43. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.15 (1H, s), 7.83–7.77 (3H, m), 7.53–7.50 (3H, m), 7.35 (1H, t, $J = 7.6$ Hz), 7.25 (1H, d, $J = 2.0$ Hz), 2.40 (3H, s). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.63, 150.96, 138.90, 135.45, 134.47, 132.07, 129.92, 129.63, 128.93, 127.31, 126.53, 122.61, 105.0, 22.07 ppm. MR: 50–53°C.

2.2.2 *2-Allylsulfanyl-quinazoline (Table 4, Entry b)*: Yellow thick mass. [Yield: 95 mg, 77%] R_f: 0.6, 8% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{11}H_{10}N_2S$ for (M+H): Calculated: 202.06; Found, 202.99 (99.64%). IR/cm^{-1}: 1709.17, 1615.84, 1559.81, 1549.91, 1485.23, 1370.78, 1219.10, 1164.34, 1134.86, 1100.05, 918.46, 755.83 and 691.90. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.14 (1H, s), 7.84–7.80 (3H, m), 7.53–7.49 (1H, m), 6.10–6.03 (1H, m), 5.38 (1H, dd, $J =$ 17.2, 1.0 Hz), 5.15 (1H, d, $J = 9.6$ Hz), 3.96 (2H, d, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 400 MHz): 167.72, 160.16, 150.82, 134.41, 133.57, 127.37, 126.93, 126.25, 122.38, 117.77, 67.04 ppm.

2.2.3 *2-(4-Isopropyl-phenylsulfanyl)-quinazoline (Table 4, Entry c)*: Pale Yellow thick mass [Yield: 147 mg, 87%] R_f: 0.7, 10% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{17}H_{16}N_2S$ for (M+H): Calculated: 280.10; Found, 281.31 (83%). IR/cm^{-1}: 1733.29, 1616.78, 1579.22, 1547.95, 1370.14, 1218.33, 1160.81, 1095.79, 866.12, 754.49, 695.67 and 466.67. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.16 (1H, s), 7.83–7.77 (3H, m), 7.51 (2H, t, $J = 7.4$ Hz), 7.39–7.36 (2H, m), 7.30 (1H, d, $J = 8.0$ Hz), 2.98–2.94 (1H, m), 1.56 (6H, d, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.82, 151.17, 145.35, 134.67, 134.51, 132.34, 129.91, 129.17, 128.91, 127.50, 126.73, 122.83, 34.67, 29.88, 28.91 ppm.

2.2.4 *2-(pyridin-4-ylsulfanyl)-quinazoline (Table 4, Entry d)*: Off white solid [Yield: 125 mg, 86%] R_f: 0.2, 20% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{13}H_9N_3S$ for (M+H): Calculated: 239.05; Found, 239.89 (94.51%); IR/cm^{-1}: 1734.59, 1610.63, 1555.78, 1465.06, 1367.47, 1215.38, 1154.65, 1123.18, 1091.58, 873.12, 789.83, 765.85, 705.15 and 689.89. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.16 (1H, s), 8.8 (2H, s), 8.04 (1H, d, $J = 8.0$ Hz), 7.83 (2H, t, $J = 7.6$ Hz), 7.75 (1H, d, $J = 8.4$ Hz), 7.54 (1H, t, $J =$ 7.80 Hz), 7.45 (1H, s). ^{13}C NMR ($CDCl_3$, 400 MHz): 167.03, 160.71, 150.87, 134.69, 127.34, 127.28, 126.88, 122.82 ppm. MR: 128–131°C.

2.2.5 *2-(3-Methoxy-phenylsulfanyl)-quinazoline (Table 4, Entry e)*: Pale yellow solid [Yield: 146 mg, 90%] R_f: 0.7, 10% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{15}H_{12}N_2OS$ for (M+H): Calculated: 268.07; Found, 269.10 (98.49%); IR/cm^{-1}: 1612.24, 1577.80, 1556.60, 1477.28, 1374.57, 1271.7, 1246.72, 1165.47, 1097.34, 1070.97, 1022.92, 790.26, 756.38 and 690.53. ^{1}H NMR (DMSO-d_6, 300 MHz): 9.36 (1H, s), 8.04 (1H, d, $J = 8.10$ Hz), 7.92 (1H, t, $J =$ 7.05 Hz), 7.69–7.60 (3H, m), 7.54–7.48 (1H, m), 7.17 (1H, d, $J = 8.40$ Hz), 7.05 (1H, t, $J = 7.50$ Hz), 3.7 (3H, s). ^{13}C NMR ($CDCl_3$, 400 MHz): 168.09, 160.35, 159.98, 150.94, 136.78, 134.25, 131.22, 127.23, 127.20, 126.28, 122.47, 120.99, 118.23, 111.57, 55.92 ppm. MR: 115–118°C.

2.2.6 *2-(3-Nitro-phenylsulfanyl)-quinazoline (Table 4, Entry f)*: Yellow solid [Yield: 152 mg, 88%] R_f: 0.6, 12% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{14}H_9N_3O_2S$ for (M+H): Calculated: 283.04; Found, 284.0 (96.58%); IR/cm^{-1}: 1615.72, 1595.94, 1551.74, 1506.14, 1339.60, 1219.04, 1160.58, 1094.35, 1084.34, 845.68, 753.10, 741.87, 730.40 and 685.89. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.20 (1H, s), 8.28 (2H, d, $J = 3.60$ Hz), 7.92–7.86 (4H, m), 7.80 (1H, d, $J = 8.80$ Hz), 7.61–7.57 (1H, m). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.8, 151.17, 145.35, 134.67, 134.51, 132.34, 129.91, 129.18, 128.91, 127.5, 126.73, 122.83, 110.2. MR: 170–173°C.

2.2.7 *5-(quinazolin-2-ylthio)thiophen-2-carbaldehyde (Table 4, Entry g)*: Pale yellow solid [Yield: 152 mg, 92%] R_f: 0.5, 15% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{13}H_8N_2OS_2$ for (M+H): Calculated: 272.01; Found, 272.75 (92.29%); IR/cm^{-1}: 2924.51, 2853.80, 2676.12, 1742.58, 1655.34, 1615.65, 1464.92, 1413.14, 1369.13, 1221.49, 1163.32, 1096.19, 1017.36, 799.83, 753.55 and 660.41. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.92 (1H, s), 9.22 (1H, s), 7.91–7.87 (3H, m), 7.76 (1H, d, $J = 3.0$ Hz), 7.62–7.58 (1H, m), 7.43 (1H, t, $J = 2.85$ Hz). MR: 92–96°C.

2.2.8 *2-(benzo[b]thiophen-2-ylthio)quinazoline (Table 4, Entry h)*: Yellow solid [Yield: 147 mg, 82%] R_f: 0.4, 17% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{16}H_{10}N_2S_2$ for (M+H): Calculated: 294.03; Found, 294.81 (85.65%); IR/cm^{-1}: 1738.12, 1615.94, 1572.95, 1555.68, 1456.52, 1367.47, 1168.10, 1109.49, 964.14, 838.87, 746.13, 723.83 and 556.93. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.19 (1H, s), 7.85–7.81 (6H, m), 7.66 (1H, s), 7.57–7.53 (1H, m), 7.40–7.37 (1H, m). ^{13}C NMR ($CDCl_3$, 400 MHz): 167.36, 160.84, 150.96, 143.61, 139.31, 134.74, 132.46, 129.91, 127.36, 125.14, 124.34, 124.01, 122.78, 122.11 ppm. MR: 139–143°C.

2.2.9 *2-((2,3-dichlorophenyl)thio)quinazoline (Table 4, Entry i)*: Off white solid [Yield: 162 mg, 87%] R_f: 0.7, 10% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{14}H_8Cl_2N_2S$ for (M+H, M+3H): Calculated: 305.98; Found, 307.0, 308.9 (92.36%); IR/cm^{-1}: 1733.89, 1623.19, 1456.97, 1384.47, 1370.21, 1263.66, 1093.34, 752.77, 611.82 and 497.49. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.17 (1H, s), 7.87–7.78 (4H, m), 7.57–7.53 (3H, m). ^{13}C NMR ($CDCl_3$, 400 MHz): 162.24,

160.98, 151.07, 136.55, 134.97, 134.25, 133.69, 133.06, 130.95, 130.23, 127.57, 127.47, 127.14, 122.97 ppm. MR: 119–122°C.

2.2.10 *2-(Quinolin-3-ylsulfanyl)-quinazoline (Table* 4*, Entry j)*: Off white solid [Yield: 146 mg, 83%] R_f: 0.2, 10% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{17}H_{11}N_3S$ for (M+H): Calculated: 289.07; Found, 290.15 (98.58%); IR/cm^{-1}: 1616.17, 1579.18, 1548.27, 1486.28, 1440.35, 1370.07, 1218.78, 1162.53, 1097.67, 879.43, 865.32, 830.59, 790.89, 754.48, and 689.64. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.11 (1H, s), 8.98 (1H, dd, J = 4.4, 1.6 Hz), 8.21–8.00 (3H, m), 7.98 (1H, dd, J = 8.8, 6.4 Hz), 7.85–7.74 (3H, m), 7.56–7.52 (1H, m), 7.48–7.44 (1H, m). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.9, 151.39, 151.12, 148.34, 136.26, 135.89, 134.86, 133.93, 130.19, 129.0, 128.76, 127.55, 127.47, 127.0, 122.94, 121.76 ppm. MR: 130–133°C.

2.2.11 *2-Phenethylsulfanyl-quinazoline (Table* 4*, Entry k)*: Yellow thickmass [Yield: 146 mg, 90%] R_f: 0.7, 8% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{16}H_{14}N_2S$ for (M+H): Calculated: 266.09; Found, 267.08 (98.96%). IR/cm^{-1}: 1734.64, 1616.51, 1550.10, 1484.23, 1370.08, 1275.41, 1261.54, 1164.36, 1100.69, 1035.59, 791.14, 750.90 and 698.46. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.16 (1H, s), 7.89–7.82 (3H, m), 7.54–7.49 (1H, m), 7.35–7.30 (4H, m), 7.25–7.21 (1H, m), 3.51 (2H, t, J = 9.6 Hz), 3.13 (2H, t, J = 7.6 Hz). ^{1}H NMR (DMSO-d_6, 400 MHz): 167.12, 161.04, 150.01, 140.32, 135.07, 128.59, 128.36, 128.12, 126.59, 126.27, 126.22, 122.10, 48.57, 34.85 ppm.

2.2.12 *2-((3-bromophenyl)thio) quinazoline (Table* 4*, Entry l)*: Yellow thick mass [Yield: 158 mg, 82%] R_f: 0.8, 5% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{14}H_9BrN_2S$ for (M+H, M+3H): Calculated: 315.97; Found, 316.75, 318.76 (97.34%). IR/cm^{-1}: 1741.93, 1614.70, 1557.78, 1446.96, 1370.79, 1219.32, 1161.27, 1095.68, 1018.49, 969.06, 865.47 and 750.85. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.15 (1H, s), 7.85–7.74 (4H, m), 7.55–7.51 (2H, m), 7.42–7.38 (1H, m), 7.34–7.29 (1H, m). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.72, 151.0, 137.42, 134.55, 133.58, 131.53, 130.78, 130.59, 127.95, 127.33, 126.70, 122.63, 109.99 ppm.

2.2.13 *2-(4-Trifluoromethoxy-phenylsulfanyl)-quinazoline (Table* 4*, Entry m)*: Yellow oil [Yield: 149 mg, 76%] R_f: 0.5, 15% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{15}H_9F_3N_2OS$ for (M+H): Calculated: 322.04; Found, 323.0 (90.42%). IR/cm^{-1}: 1621.7, 1579.88, 1559.74, 1371.17, 1258.38, 1222.55, 1162.16, 1096.13, 789.31 and 756.04. ^{1}H NMR ($CDCl_3$, 300 MHz): 9.18 (1H, s), 7.86–7.82 (2H, m), 7.76 (1H, d, J = 8.4 Hz), 7.64 (2H, t, J = 12.4 Hz), 7.57–7.52 (1H, m), 7.47 (1H, t, J = 8.1 Hz), 7.30 (1H, s). ^{13}C NMR ($CDCl_3$, 300 MHz): 167.11, 160.74, 158.4, 150.87, 139.26, 134.72, 132.64, 130.0, 129.1, 127.34, 125.6, 122.2, 121.7, 115.0, 111.2 ppm.

2.2.14 *2-(Furan-2-ylsulfanyl)-quinazoline (Table* 4*, Entry n)*: Yellow thick mass [Yield: 100 mg, 72%] R_f: 0.5, 15% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{12}H_8N_2OS$ for (M+H): Calculated: 228.04; Found, 229.0 (90.13%). IR/cm^{-1}: 1618.12, 1579.39, 1549.90, 1372.06, 1275.19, 1260.71, 1162.74, 1098.89, 1010.64, 868.12, 750.70 and 486.79. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.16 (1H, s), 8.22 (1H, s), 7.92–7.83 (2H, m), 7.81–7.73 (2H, m), 7.55–7.50 (2H, m). ^{13}C NMR ($CDCl_3$, 300 MHz): 167.39, 159.94, 150.29, 133.89, 131.72, 129.52, 127.74, 126.66, 125.95, 125.25, 124.72, 121.94 ppm.

2.2.15 *2-((3-(trifluoromethyl)phenyl)thio)quinazoline (Table* 4*, Entry o)*: Yellow thick mass [Yield: 149 mg, 80%] R_f: 0.6, 12% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{15}H_9F_3N_2S$ for (M+H): Calculated: 306.04; Found, 307.2 (92.60%). IR/(cm^{-1}): 1579.88, 1559.74, 1371.17, 1258.38, 1222.55, 1162.16, 1096.13, 789.31, 756.04 and 702.8. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.17 (1H, s), 8.01 (1H, s), 7.76 (1H, d, J = 8.8 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.59-7.53 (2H, m), 7.35 (1H, t, J = 8.0 Hz), 7.76 (1H, d, J = 7.6 Hz), 7.00 (1H, d, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.7, 155.2, 150.6, 134.7, 132.6, 132.7, 131.8, 129.4, 129.3, 128.4, 127.6, 126.5, 125.7, 122.7, 119.2 ppm.

2.2.16 *2-(naphthalen-2-ylthio) quinazoline (Table* 4*, Entry p)*: Colorless oil [Yield: 158 mg, 90%] R_f: 0.6, 10% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{18}H_{12}N_2S$ for (M+H): Calculated: 288.07; Found, 289.0 (93.94%). IR/cm^{-1}: 1618.12, 1579.39, 1549.90, 1460.04, 1372.06, 1275.19, 1260.71, 1162.74, 1098.89, 1010.64, 868.12, 750.70, 598.45 and 486.79. ^{1}H NMR ($CDCl_3$, 300 MHz): 9.17 (1H, s), 7.84–7.82 (3H, m), 7.77 (1H, s), 7.58 (1H, d, J = 1.2 Hz), 7.55–7.52 (2H, m), 7.33–7.26 (2H, m), 6.67 (1H, s). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.63, 151.0, 146.13, 143.65, 134.6, 128.4, 127.6, 127.3, 127.2, 126.6, 122.6, 115.10, 111.4, 110.0 ppm.

2.2.17 *2-(biphenyl-2-ylthio) quinazoline (Table* 4*, Entry q)*: Yellow thick mass [163 mg, Y: 85%] R_f: 0.7, 12% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{20}H_{14}N_2S$ for (M+H): Calculated: 314.09; Found, 315.0 (85.68%). IR/cm^{-1}: 1734.34, 1616.75, 1457.04, 1435.81, 1385.01, 1370.63, 1160.21, 1095.67, 755.44, 697.46 and 481.81. ^{1}H NMR ($CDCl_3$, 400 MHz): 9.17 (1H, s), 7.95 (1H, s), 7.84–7.78 (2H, m), 7.70–7.63 (3H, m), 7.57–7.51 (2H, m), 7.46–7.41 (2H, m), 7.38–7.29 (1H, m), 7.22–7.11 (1H, m), 6.77 (1H, s). ^{13}C NMR ($CDCl_3$, 400 MHz): 166.84, 161.26, 157.44, 151.27, 144.58, 134.9, 128.6, 127.65, 127.5, 127.3, 125.7, 123.2, 123.0, 121.6, 117, 111.83 ppm.

2.2.18 *Morpholine(4-(quinazolin-2-ylthio)phenyl)methanone (Table* 4*, Entry r)*: Pale yellow oil [Yield: 192 mg, 90%] R_f : 0.6, 12% EtOAc/Pet ether; Analysis: LC-MS: m/z $C_{19}H_{17}N_3O_2S$ for (M+H): Calculated: 351.10; Found,

351.77 (92.77%). IR/cm^{-1}: 1765.18, 1633.82, 1557.88, 1549.48, 1434.67, 1371.09, 1278.81, 1257.72, 1162.29, 1113.73, 1024.09, 761.32, 740.61, 692.14 and 492.15. ^{1}H NMR ($CDCl_3$, 300 MHz): 9.15 (1H, s), 7.85–7.80 (2H, m), 7.77–7.67 (3H, m), 7.56–7.52 (3H, m), 3.50–3.90 (8H, m). ^{13}C NMR ($CDCl_3$, 300 MHz): 160.62, 150.97, 148.81, 148.08, 134.49, 129.42, 127.29, 126.53, 122.57, 121.83, 115.60, 108.87, 101.53, 66.68, 59.67 ppm.

3. Results and Discussion

The replacement of a multistep chemical synthesis with a transition metal catalyzed redox reaction is a powerful strategy to improve the efficiency and sustainability of synthesis.[6,7] The potential of a transition metal catalyzed transformation is maximized when combined with straight-forward reaction conditions and the formation of widely utilized synthetic building blocks.

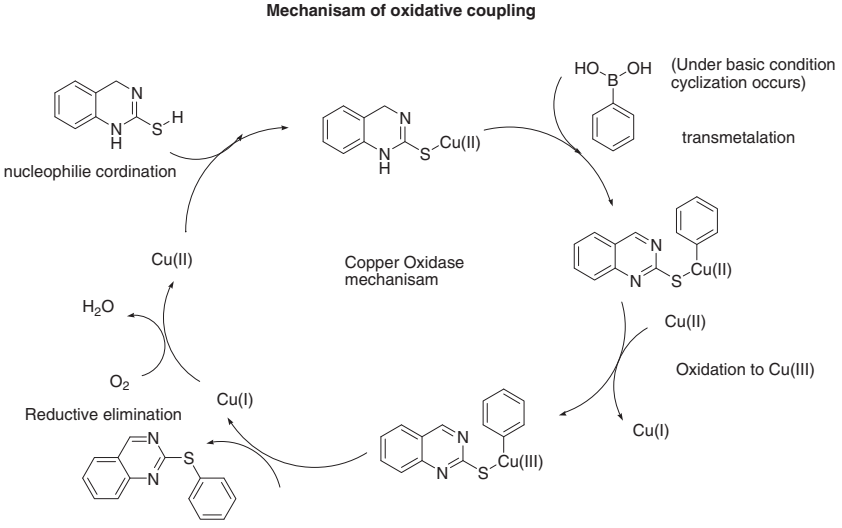
Recent work in the Chan,[8] Cundy,[9] and Evans[10] laboratories have revealed the efficiency of copper(II) acetate in mediation of the cross-coupling of aryl boronic acids and phenols or amines to give biaryl ethers and aryl alkyl amines. We sought to develop a similar procedure for the formation of aryl alkyl sulfides and report here in the success of this approach. In general, this reaction (Scheme 1) proceeds as follows: Aryl boronic acids (2–2.2 equiv.) are allowed to react with a limiting quantity of quinazoline thiol (1.0 equiv.) with the mediation of copper(II) acetate and triethylamine in CH_2Cl_2 to give alkyl sulfides in 75–90% yield. The reaction proceeds facilely with a variety of aryl boronic acids. We set out to explore the scope of the method with respect to the substitution of the aryl ring (Table 4). In general, the reaction is unaffected by electronic factors but moderately affected by steric hindrance of the reaction center. We also examined the scope of the method with respect to the nature of the thiol nucleophile. These studies revealed that most thiols would enter into cross-coupling with phenyl boronic acid under the standard conditions (Table 3). Thus, this method can afford the diphenyl sulfide, the product of coupling of a primary thiol.

The functional group tolerance is good. The reaction proceeds with both electron-rich and electron-deficient aryl boronic acids, and works in the presence of additional functional groups including halides, esters, ethers, nitriles and aldehydes (Table 4, entries a–r).

Table 1. Optimization of the amine (base) for the cross coupling.

Entry	Base (Equiv)	[a]Yield [%]	
		$Cu(OAc)_2$	$CuSO_4$
1	Pyridine (1)	40	25
2	Pyridine (5)	65	45
3	Et_3N (2)	75	50
[b]**4**	**Et_3N (5)**	**88**	**60**
5	DMAP (1)	30	22
6	DMAP (5)	45	30
7	Cs_2CO_3 (5)	35	15
8	Na_2CO_3 (5)	10	0
9	K_2CO_3 (5)	20	5
10	CsF (5)	45	0
11	TBAF (5)	52	22
12	KF (5)	30	10

[a]Isolated yields.
[b]Reaction condition: triethyl amine (5 eq.), Cu $(OAc)_2$ (Y: 88%).



Scheme 1. Synthesis of *S*-aryl/heteroaryl-quinazoline derivatives through the cross-coupling of 1,4-dihydroquinazoline with various boronic acids.

The most straightforward method for the synthesis of aryl/heteroaryl-thioquinazoline involves either cross-coupling of dihydro quinazoline with substituted boronic acid (Scheme 1) or a nucleophilic attack of aryl thiols by preformed thio-quinazoline.

To study the scope of the reaction in a further set of experiments, we examined the scope and generality of the approach for the cyclization followed by aromatization of 1,4-dihydro quinazoline with a series of alkyl and aryl boronic acids under optimum reaction conditions. Our results showed that both alkyl and aryl thiols can be efficiently converted to the corresponding cross-coupled products (Table 4).

Recently, we reported[11] that copper catalyzed the formation of *S*-aryl quinazoline in a tandem one-pot, three component reaction of 2-amino benzylamine, carbon disulfide and aryl halide. These results prompted us to investigate further C-S bond formation reactions of 2-thio-1,4-dihydroquinazoline with various aryl/heteroaryl boronic acids. The desired *S*-substituted quinazolines are obtained in excellent yields with short reaction times and a low catalytic amount of copper.

2-Aminobenzylamine can be transformed into dithiocarbamate by the reaction with carbon disulfide, then followed by cyclization to yield 1,4-dihydro quinazoline as a white solid.[10] Dithiocarbamate is an important synthetic reagent to synthesize various biologically active heterocyclic compounds (Table 1).[12–14]

Optimization of reaction conditions for Cu-catalyzed coupling of 2-thio-1,4-dihydroquinazolines and *p*-tolyl boronic acid is done. Our initial attempt to explore an effective catalytic system for the reaction in the presence of $CuSO_4$ and pyridine under N_2 atmosphere at room temperature gave yield of 26%. We found that the removal of base, i.e., pyridine from the reaction mixture is difficult and tedious, which resulted in a lower yield of the product. Upon further screening for the conditions, fortunately, when we switched to copper acetate as catalyst, triethylamine as base and $CHCl_3$ as solvent, the yield increased to 60%. To our surprise, the yield could be significantly increased when changing the solvent to dichloromethane as the solvent. No significant improvement of the yield of the desired product **1a** was observed when other copper salts, such as $CuCl_2$ and CuI were used as the catalysts (Table 2, entries 3, 4 and 7, 8). To improve the yield, different solvents were examined and CH_2Cl_2 gave the best yield compared with other solvents (Table 3, entries 1–14). Interestingly, when the reaction time was shortened to 8 h, the yield increased to 88% (Table 4).

The experiment was performed with commercially available substituted boronic acids and *S*-1,4-dihydro

Table 2. Evaluation of copper salts.

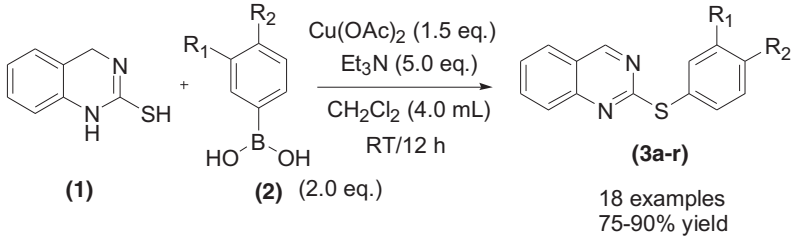
Entry	Copper salt (Equiv)	Base (Equiv)	Yield [%]
1	$Cu(OAc)_2$ (1.5)	Pyridine (5.0)	50
2	$Cu(OAc)_2$ (1.5)	Et_3N (5.0)	90
3	$CuCl_2$ (1.5)	Et_3N (5.0)	45
4	$CuCl_2$ (1.5)	Pyridine (5.0)	30
5	$CuSO_4$ (1.5)	Pyridine (5.0)	50
6	$CuSO_4$ (1.5)	Et_3N (5.0)	70
7	CuI (1.5)	Pyridine (5.0)	45
8	CuI (1.5)	Et_3N (5.0)	60
9	Cu(II) (1.5)	Et_3N (5.0)	45
10	$Cu(OAc)_2$ (1.5)	Pyridine/Et_3N (5.0)	65

Table 3. Optimization reaction conditions in the copper-catalyzed coupling of thiol with substituted boronic acid.

Entry	Base	Solvent	Catalyst	[a]Yield [%]
1	Pyridine	CCl_4	$CuSO_4.5H_2O$	No reaction
2	Et_3N	CCl_4	$CuSO_4.5H_2O$	No reaction
3	Pyridine	CCl_4	$Cu(OAc)_2$	No reaction
4	Et_3N	CCl_4	$Cu(OAc)_2$	No reaction
5	Pyridine	$CHCl_3$	$CuSO_4.5H_2O$	42
6	Et_3N	$CHCl_3$	$CuSO_4.5H_2O$	55
7	Pyridine	$CHCl_3$	$Cu(OAc)_2$	50
8	Et_3N	$CHCl_3$	$Cu(OAc)_2$	60
9	Pyridine	CH_2Cl_2	$CuSO_4.5H_2O$	55
10	Et_3N	CH_2Cl_2	$CuSO_4.5H_2O$	40
11	Pyridine	CH_2Cl_2	$Cu(OAc)_2$	62
[b]12	**Et_3N**	**CH_2Cl_2**	**$Cu(OAc)_2$**	**90**
13	Et_3N	THF	$Cu(OAc)_2$	55
14	Et_3N	DMF	$Cu(OAc)_2$	65

[a]Isolated yields.
[b]Reaction condition: triethyl amine (5 eq.), Cu $(OAc)_2$ (1.5 eq.) DCM. (Y: 90%).

Table 4. Substituent effects in the cross coupling of thiol with substituted boronic acid.



R_1 and R_2 = H, Cl, Br, CH_3, CF_3, OCF_3, heterocyclic, biphenyl and morpholine

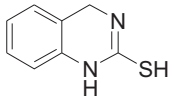
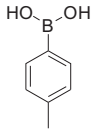
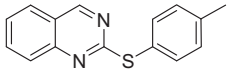
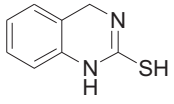
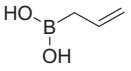
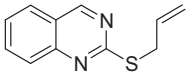
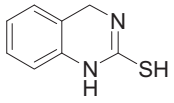
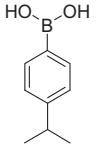
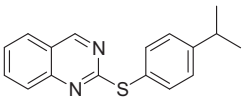
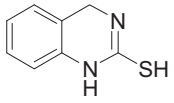
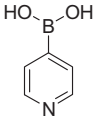
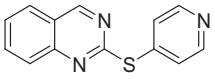
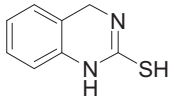
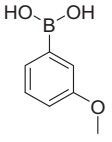
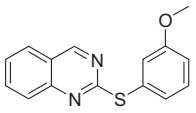
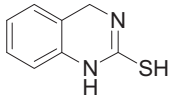
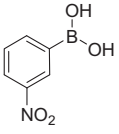
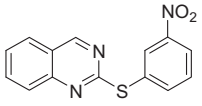
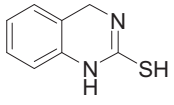
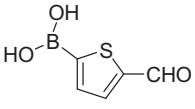
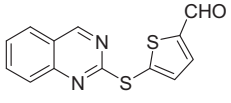
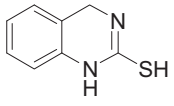
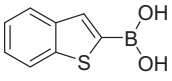
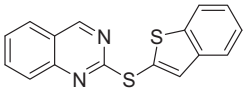
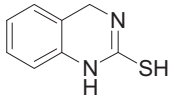
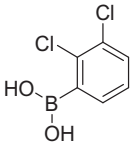
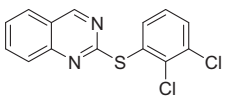
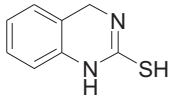
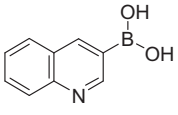
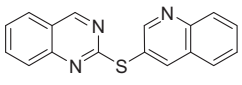
Entry	1,4-dihydroquinazoline-2-thiol (1)	Boronic acid (2)	Product[b] (3)	Yield[a] (%)
a				85
b				77
c				87
d				86
e				90
f				88
g				92
h				82
i				87
j				83

Table 4. (continued)

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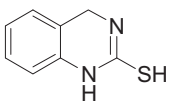
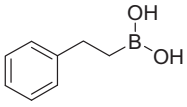
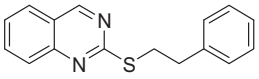
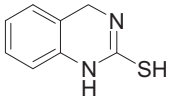
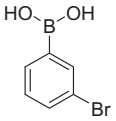
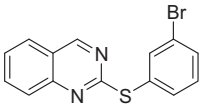
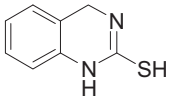
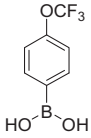
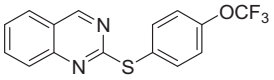
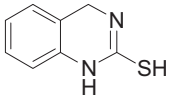
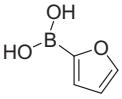
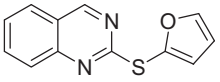
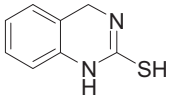
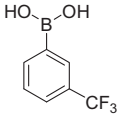
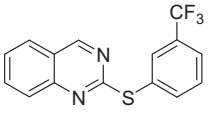
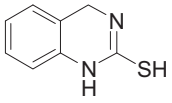
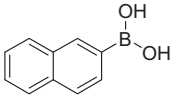
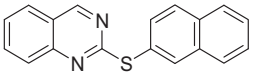
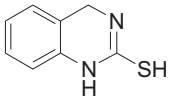
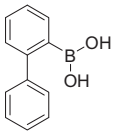
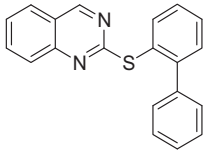
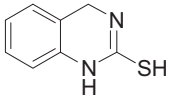
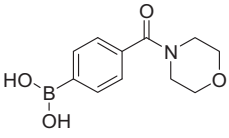
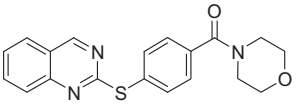
k				90
l				82
m				76
n				72
o				80
p				90
q				85
r				90

[a]Isolated yields.
[b]All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry.

quinazolines by using $Cu(OAc)_2$, Et_3N as a base in dichloromethane at r.t. for 12 h. In this reaction, aromatization on 1,4-dihydroquinazolines is followed by *S*-alkylation. This is a novel route for this synthesis. The desired *S*-alkyl quinazolines was isolated in good yields. In this, several boronic acids such as aromatic, substituted aromatic, heterocyclic compounds were screened to optimize the method. It was observed that using $Cu(OAc)_2$, Et_3N in dichloromethane gave the best results under normal conditions. Reactions occurred with good yields, broad scope, and high tolerance of functional groups.

We have reported an efficient synthesis of a C-S bond formation *via* aromatization in normal argon atmospheric conditions. We have reported a general synthetic protocol for the formation of aryl-sulfur bonds, using copper(II) catalysts. The optimized protocol tolerates a variety of electron-donating and electron-withdrawing groups on the aryl boronic acids. The scope and generality of this method were later harnessed to synthesize a range of other analogues, listed in Table 4.

4. Conclusions

In conclusion, a new method for the cross-coupling of heteroaromatic thioethers with boronic acids has been described. The readily available starting materials and mild and neutral reaction conditions suggest that this procedure could find wide applicability in synthesis and drug design.

Supplementary Information (SI)

NMR, IR and mass spectra of the synthesized compounds are reported in Supplementary Information, available at www.ias.ac.in/chemsci.

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