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Application of the palladium-catalyzed N-arylation of hydrazones to deactivated heteroaryl halides in the synthesis of pyrazoles

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Abstract—A versatile synthesis of heteroaryl pyrazoles from deactivated heteroaryl halides was demonstrated with different 1,3-bifunctional substrates under acidic conditions. Practical conditions for the transhydrazonation/cyclization step were developed.
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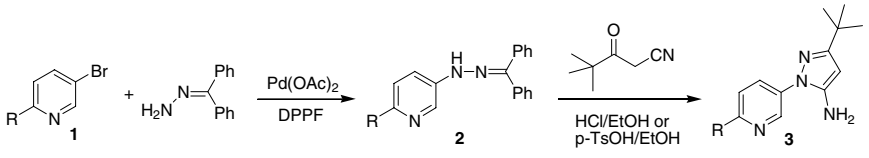
Aryl pyrazoles are key substructures in a large variety of compounds of important biological activities and pharmacological properties.[1] Recently we have reported a versatile synthesis of arylpyrazoles via palladium-catalyzed arylation of hydrazones to arylbromides followed by tandem transhydrazonation/cyclization with a variety of 1,3-diketones, ketoesters and equivalent functionalities[2] (Scheme 1). Recent developments of Pd catalyzed amination reactions of deactivated aryl bromides, aryl chlorides and triflates,[3] triggered our interest in examining the applicability of hydrazone coupling[4] to deactivated *N*-heteroaryl compounds. We sought methods to transform these species to pyrazoles via transhydrazonation/cyclization, in the presence of substituents labile to strong acidic conditions.

Initial attempts for the amination of the deactivated 5-bromo-2-methoxy-pyridine (**1b**) to benzophenone hydrazone was examined using the DPPF/$Pd(OAc)_2$ catalytic system. Under these conditions, the desired product **2b** was obtained in 20% yield. Furthermore, the subsequent transhydrazonation/cyclization of hydrazone **2b** under the previously reported conditions (TsOH or HCl (conc.)/refluxing EtOH) furnished pyrazole **3** in poor yields (<15%). A variety of conditions were examined in order to improve the amination step (Table 1). BINAP/$Pd(OAc)_2$ provided low conversion of **2b** to **3b**. However, a moderate yield was obtained with $Pd(OAc)_2$ using (*o*-biphenyl)P(*t*-Bu)$_2$ as ligand. The yield was substantially improved when Pd_2 (dba)$_3$ was used with either 1-(*N*,*N*)-dimethylamino-1′-(PCy_2)-biphenyl or (*o*-biphenyl)P(*t*-Bu)$_2$ as ligand. These results show similarity to the palladium-catalyzed couplings of amines and benzophenonehydrazone to unactivated arylhalides.[3] Benzophenone–hydrazone (1.4 equiv) was found to be necessary to reduce the formation of the



Scheme 1.

Keywords: Synthesis of heteroaryl pyrazoles; Inactivated heteroaryl halides.
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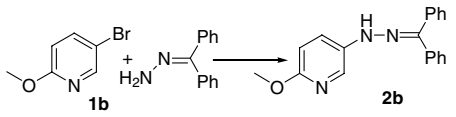
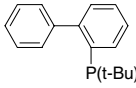
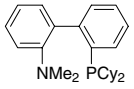
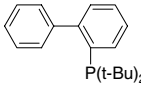
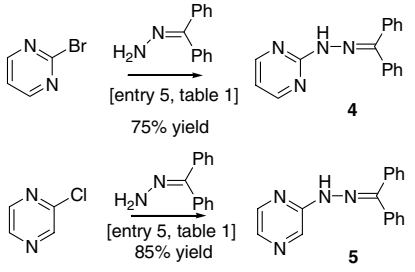
Table 1



Entry	Conditions	Yield (%)
1	$Pd(OAc)_2$, DPPF, *t*BuONa, toluene, 90 °C, 16 h	<10
2	$Pd(OAc)_2$, BINAP, *t*BuONa, toluene, 90 °C, 16 h	<10
3	$Pd(OAc)_2$, *t*BuONa, toluene, 90 °C, 16 h 	50
4	$Pd_2(dba)_3$, *t*BuONa, toluene, 90 °C, 16 h 	95
5	$Pd_2(dba)_3$, *t*BuONa, toluene, 90 °C, 16 h 	95



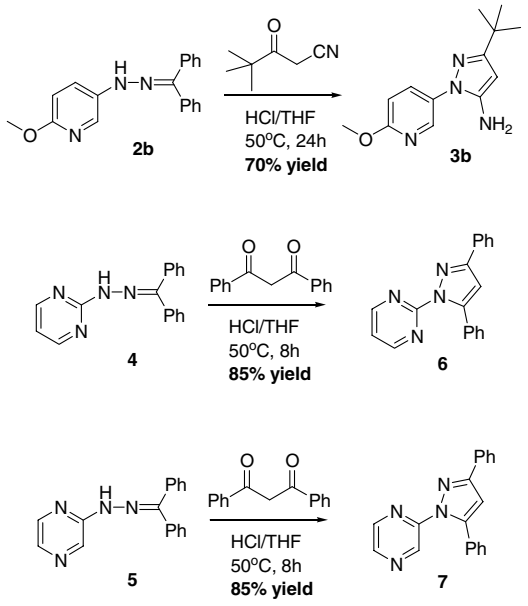
Scheme 2.

corresponding bis-arylated side product to below 1% (Schemes 2 and 3).

The amination conditions of entry 5 were applied to the coupling of benzophenonehydrazone with 2-bromopyrimidine and 2-chloropyrazine. In both examples the desired heteroarylhydrazone was obtained in good isolated yield.[5,6]

Attempts to convert hydrazone **2b** to pyrazole **3b** using the previously reported conditions of TsOH or HCl in EtOH under reflux for 8–12 h, led to the formation of **3b** in only 20% yield. Different solvents and temperatures were examined to ultimately provide **3b** in 70% yield under the conditions of (6 N) HCl in THF with heating at 50 °C for 16 h. These conditions were then applied successfully to the transformation of hydrazones **4** and **5** to pyrazoles **6** and **7** in 85% yield.[5]

In summary, we have demonstrated the applicability of the Pd catalyzed N-arylation of benzophenone hydrazone to deactivated heteroaryl halides and successfully applied the transhydrazonation/cyclization sequence under practical conditions to provide heteroaryl pyrazoles in good yields.



Scheme 3.

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5. All new compounds were characterized by full spectroscopic data. Yields refer to chromatographed materials with purity of >95%.
6. *Typical procedures*: Pd catalyzed coupling of benzophenone hydrazone was carried on with minor modification of the general procedure for catalytic amination of aryl bromides reported in Ref. 3. A mixture of the heteroarylhalide (4.24 mmol) with (*o*-biphenyl)P(*t*-Bu)$_2$ (38.0 mg, 0.027 mmol, 0.03 equiv), $Pd_2(dba)_3$ (40.0 mg, 0.0424 mmol, 0.01 equiv), *t*BuONa (0.57 g, 5.94 mmol, 1.4 equiv) and benzophenonehydrazone (1.20 g, 5.94 mmol, 1.4 equiv) in

toluene (6.6 mL) was heated under Ar atmosphere to 90 °C until heteroaryl halide had been consumed based on HPLC analysis (8–16 h). The mixture was cooled to rt, NH_4Cl saturated solution (2.0 mL) was added and the organic solution washed with aqueous HCl (1 M, 4 mL) and then with brine (4 mL), dried over Na_2SO_4, concentrated under reduced pressure, the crude product was then purified by column chromatography.

2b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.55 (m, 6H), 7.32 (m, 6H), 6.70 (d, $J = 8.84$ Hz, 1H), 3.92 (s, 3H); ^{13}C NMR: 158.8, 144.9, 138.2, 136.2, 132.6, 131.0, 129.7, 129.4, 129.1, 128.2, 128.1, 126.4, 125.3, 110.8, 53.5. MS m/z 304.57 $(M+1)^+$.

4: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (m, 3H), 7.7 (m, 2H), 7.51 (m, 3H), 7.32 (m, 5H), 6.72 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR: 161.7, 160.6, 152.2, 139.6, 134.6, 131.9, 131.8, 131.2, 130.8, 130.3, 129.6, 115.5. MS m/z 275.52 $(M+1)^+$.

5: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (d, $J = 1.4$ Hz, 1H), 8,15 (d, $J = 2.8$ Hz, 1H), 8.02 (d, $J = 2.8$ Hz, 1H), 7.95 (d, $J = 1.4$ Hz, 1H), 7.55 (m, 5H), 7.32 (m, 5H); ^{13}C NMR: 154.9, 150.9, 144.1, 140.1, 138.8, 134.9, 134.7, 132.5, 132.4, 131.8, 131.5, 131.0, 129.7. MS m/z 275.54 $(M+1)^+$.

Pyrazole formation: To the solution of benzophenonehydrazone (16.5 mmol) and trimethylacetylacetonitrile or dibenzoylmethane (24.7 mmol) in THF (17 mL), 6 N HCl (13.8 mL, 5 equiv) was added at 25 °C then the mixture heated to 40 °C for 8–16 h. Water (40 mL) was added then the THF removed under reduced pressure followed by addition of EtOAc (40 mL). A saturated solution of $NaHCO_3$ was then added to reach pH = 9. The aqueous phase was separated, then extracted with EtOAc (10 mL). The combined organics were dried (Na_2SO_4), concentrated and then purified by column chromatography to provide the product in 70–85% yield.

3b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.77 (d, $J = 8.6$ Hz, 1H), 6.82 (d, $J = 8.6$ Hz, 1H), 5.52 (s, 1H), 3.96 (s, 3H), 3.65 (bs, 2H), 1.28 (s, 9H); ^{13}C NMR: 162.9, 162.7, 145.1, 142.5, 135.7, 129.7, 111.4, 87.8, 53.8, 32.3, 30.3. MS m/z 247.30 $(M+1)^+$.

6: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, $J = 4.8$ Hz, 2H), 8,00 (d, $J = 7.8$ Hz, 2H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.35 (m, 6H), 7.15 (t, $J = 4.8$ Hz, 1H), 6.83 (s, 1H); ^{13}C NMR: 156.7, 156.0, 151.8, 144.5, 130.5, 129.7, 126.7, 126.4, 126.3, 124.5, 117.3, 106.0. MS m/z 299.61 $(M+1)^+$.

7: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (d, $J = 1.3$ Hz, 1H), 8,47 (d, $J = 2.5$ Hz, 1H), 8.27 (dd, $J_1 = 2.5$ Hz, $J_2 = 1.3$ Hz, 1H), 7.95 (d, $J = 8.3$ Hz, 2H), 7.45 (t, $J = 8.3$ Hz, 2H), 7.35 (m, 6H), 6.85 (s, 1H); ^{13}C NMR: 154.7, 150.1, 146.9, 143.4, 143.1, 141.4, 133.4, 131.7, 130.0, 129.8, 129.7, 129.5, 129.4, 127.1, 108.6. MS m/z 299.65 $(M+1)^+$.