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A convenient and rapid approach for the synthesis of 1-benzyl-3-heterocyclic pyrazoles

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ABSTRACT

A variety of 1-benzyl-3-heterocyclic pyrazoles were rapidly assembled by a two-step N-benzylation/Suzuki coupling sequence. A one-pot variation of this sequence is demonstrated.

1. Introduction

Regiocontrolled access to small, polar heterocycles has become an increasingly important part of a medicinal chemist's repertoire to examine structure–activity relationships (SARs) and adjust physicochemical properties of lead molecules. As part of a medicinal chemistry program, we were interested in rapidly evaluating an *N*-benzyl-3-heterocyclic pyrazole lead compound. Recently, methods to access (het)aryl-substituted imidazoles and pyrazoles via the corresponding boronic acids or esters have been published.[1,2] Herein, we disclose a method to rapidly prepare 1-benzyl-3-heterocyclic pyrazole analogs (**1**) derived from commercially available 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (**2**) (see Fig. 1).

2. Results and discussion

In order to explore the SAR of a lead 3-(4-pyrimidinyl)pyrazole **1**, we wished to survey a range of N-substituents as well as a range of heterocycles at the 3-position. Initial exploration of the benzyl moiety of **1** while maintaining 4-pyrimidine constant at the 3-position was facilitated by the commercial availability of 1-(pyrimidin-4-yl)ethanone (**3**). Thus, **3** was treated with DMF·DMA in refluxing DMF to provide intermediate **4**.[3] Subsequent ring closure with hydrazine hydrate in EtOH at room temperature afforded compound **5** in 75 % yield. Benzylation of **5** was first accomplished using 4-chlorobenzyl bromide and Cs_2CO_3 in DMF. After aqueous work-up and flash chromatography, the reaction yielded two distinct regioisomers (**1a** and **6a**) in roughly 10:1 ratio (Scheme 1). NOESY analysis of the major isolate confirmed benzylation at the N-1 position. A strong correlation between the proton at the 5-position of the pyrazole ring and the two protons on the phenyl ring ortho to the carbon linker was observed upon irradiation of the methylene protons of the benzyl group.[4] Similar regioselectivity

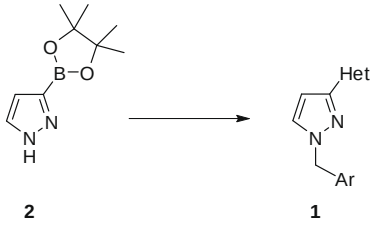
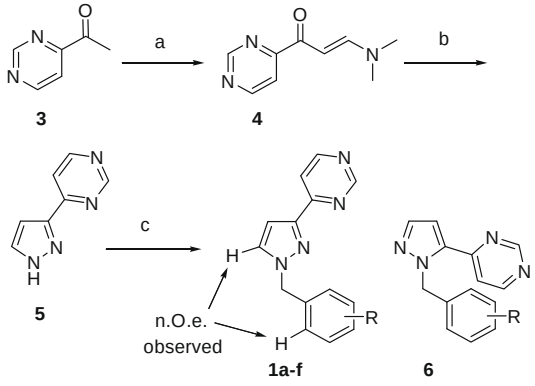


Figure 1. *N*-Benzyl-3-heterocylic pyrazoles.



Scheme 1. Reagents and conditions: (a) DMF·DMA, DMF, 150 °C 18 h, 87%; (b) hydrazine hydrate, EtOH, rt 18 h, 75%; (c) R-benzyl bromide Cs_2CO_3, MeCN, 80 °C 2 h.

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Table 1
3-(4-Pyrimidinyl)-*N*-benzylpyrazoles obtained by benzylation of **5**.

Compd	R	% Yield
1a	4-Cl	48
1b	H	47
1c	3-Cl	41
1d	2-Cl	70
1e	3-CF_3	43
1f	3-CH_3	62

was also observed for the benzylation of other analogs. In addition, the chemical shift of the benzylic protons of **1** typically appeared 0.6 ppm upfield when compared to benzylic protons of **6**, and thus served as diagnostic protons for identification of the desired regioisomer.[5]

Simplification of the benzylation procedure by replacement of DMF with acetonitrile allowed for filtration, concentration and purification by chromatography. Using this methodology we were able to rapidly synthesize a variety of substituted benzyl analogs in moderate to good yields (Table 1, compounds **1a–f**).

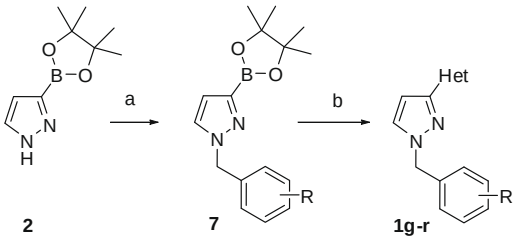
A facile, parallel-enabled approach to altering the pyrazole 3-substituent that did not rely on the three-step method depicted in Scheme 1 was sought. However, few methods to make 3-heterocyclic pyrazoles are amenable to parallel synthesis.[6] Thus, benzylation of **2** followed by Suzuki cross-coupling would allow for rapid generation of 3-heterocyclic pyrazole analogs. Early attempts to effect N-benzylation of **2** provided less than 10 % of desired product **7** (R = H) after aqueous work-up and chromatography. Although these results were discouraging, we believed the reaction was progressing, and that the boronate-ester group of the pyrazole was undergoing protodeboronation[7] or hydrolysis during aqueous work-up and/or silica gel purification. To better understand the fate of boronate **7**, the crude reaction mixture was filtered, concentrated and subjected to LC–MS, GC–MS, and NMR analysis. Reverse phase LC–MS showed only the boronic acid hydrolysis product of **7**. However, GC–MS and NMR analysis confirmed complete conversion of **2** into **7**, ca. 8 % of the undesired regioisomer and a trace of protodeboronated product. To avoid this decomposition, the crude reaction products **7** were used directly in the Suzuki cross-coupling.

To our satisfaction, Suzuki reaction of crude **7** with 5-fluoro-2-chloropyrimidine gave the desired product **1g** in 22 % yield over two steps. Although this yield was less than optimal, higher yields were achieved with more activated heterocycles. Most importantly, we now had a method to readily access heterocycles at the 3-position of the pyrazole core. This process was further optimized by preparing intermediate **7** on scale and using the crude boronate ester for a series of Suzuki reactions. With this in place, a number of 3-heterocyclic pyrazole analogs were synthesized in parallel (Table 2, compounds **1g–r**).

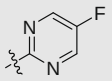
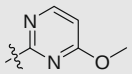
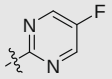
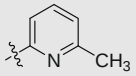
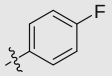
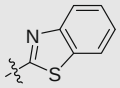
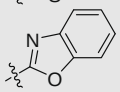
We believed that this pyrazole benzylation/Suzuki coupling approach to compounds **1** could be simplified even further if both steps were carried out in a one-pot reaction sequence. Indeed, it was found that compounds **1** could be prepared directly from **2** in one pot through initial benzylation of **1** in the presence of excess Cs_2CO_3 followed by addition of 5 mol % $Pd(PPh_3)_4$ and aryl halide (Table 3).

In conclusion, we have described a rapid and convenient method to prepare 1-benzyl-3-heterocyclic pyrazole analogs (**1**) derived from commercially available 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (**2**). This two-step sequence is amenable to a one-pot synthesis, allowing for variation of substituents at two positions of the pyrazole and rapid examination of the series SAR.

Table 2
3-Heteroaryl-*N*-benzylpyrazoles obtained by Suzuki coupling of crude **7**

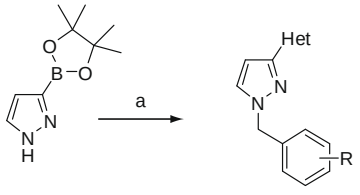


2 **7** **1g-r**

Compd	Het	R	X	% Yield
1g		H	Cl	22
1h	2-Pyrimidinyl	3-CF_3	Br	28
1i		3-CF_3	Cl	44
1j		3-CF_3	Cl	43
1k		3-CF_3	Cl	51
1l	2-Pyridazinyl	3-CF_3	Cl	41
1m	phenyl	3-CF_3	Br	48
1n		3-CF_3	Br	50
1o		3-CF_3	Cl	51
1p		3-CF_3	Br	20
1q	2-Thiazolyl	3-CF_3	Br	22
1r	2-Furyl	3-CF_3	Br	35

Conditions: (a) R-benzyl bromide, Cs_2CO_3, MeCN, 80 °C 2 h; (b) Het-X, $Pd(PPh_3)_4$ Na_2CO_3, *i*PrOH/toluene/H_2O, 80 °C 18 h.

Table 3
3-Heteroaryl-*N*-benzylpyrazoles obtained by one-pot alkylation/Suzuki coupling of boronate ester **2**



2 **1**

Compd	Het	R	% Yield
1a	4-Pyrimidinyl	4-Cl	47
1c	4-Pyrimidinyl	3-Cl	43
1d	4-Pyrimidinyl	2-Cl	49
1s	2-Pyridinyl	4-Cl	36
1t	2-Pyridinyl	2-Cl	27

Conditions: (a) (i) R-benzyl bromide, Cs_2CO_3 (3 equiv), MeCN, 80 °C 2 h; (ii) heterocyclic-Cl, $Pd(PPh_3)_4$, H_2O, 80 °C 18 h.

3. Experimental

3.1. Typical experimental procedure for preparation and Suzuki coupling of 7

To a solution of 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (1.0 g, 5.1 mmol) in acetonitrile (35 mL) were added 3-(trifluoromethyl)benzyl bromide (1.23 g, 5.2 mmol) and cesium carbonate (2.5 g, 7.7 mmol). The reaction mixture was heated at 80 °C for 2 h. The reaction mixture was cooled, filtered, and concentrated to provide **7** as a yellow solid. To a solution of crude **7** (125 mg, 0.36 mmol) in toluene/*i*PrOH/water (7 mL) were added 2-chlorobenzothiazole (61 mg, 0.36 mmol), $Pd(PPh_3)_4$ (21 mg, 0.018 mmol), and sodium carbonate (95 mg, 0.9 mmol). The reaction mixture was heated at 80 °C for 18 h. After cooling to room temperature, the mixture was concentrated and purified using flash chromatography, eluting from 10:90 EtOAc/heptane to 50:50 EtOAc/heptane affording **1o** (65 mg, 51 %) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.45 (s, 2H), 7.05 (d, J = 2.4 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 7.42–7.50 (m, 4H), 7.54 (s, 1H), 7.58, (d, J = 4.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.4, 1H); ^{13}C NMR ($CDCl_3$ 100.51 MHz) δ 56.13, 106.13, 121.89, 123.20, 124.66, 125.51, 126.44, 129.75, 131.23, 131.59, 134.60, 137.04, 147.30, 153.90, 161.97 ppm; *m/z* (CI) 360 ($[M+H]^+$, 100%); Anal. Calcd for $C_{18}H_{12}F_3N_3S$: C, 60.16; H, 3.37; N, 11.69. Found: C, 59.94; H, 3.04; N, 11.56.

3.2. Typical experimental procedure for the one-pot benzylation/Suzuki coupling of 2

To a suspension of 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole (50 mg, 0.26 mmol) and Cs_2CO_3 (273 mg, 0.77 mmol) in acetonitrile (2 mL) was added 4-chlorobenzyl bromide (53 mg, 0.26 mmol). The reaction mixture was heated at 80 °C for 2 h. $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), 2-chloropyridine (25 μL, 0.27 mmol), and 50 μL water were added. The reaction mixture was stirred at 80 °C for 18 h. After cooling to room temperature, the mixture was filtered through Celite and concentrated. Purification by flash chromatography eluting with a 0–50% EtOAc in heptane gradient gave **1s** (25 mg, 36%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.34 (s, 2H) 6.89 (d, J = 2.35 Hz, 1H) 7.15–7.21 (m, 3H) 7.27–7.33 (m, 2H) 7.39 (d, J = 2.35 Hz, 1H) 7.69 (m, 1H) 7.86–7.96 (m, 1H) 8.58–8.65 (m, 1H); *m/z* (CI) 270 ($[M+H]^+$, 100%).

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5. The benzylic protons for **1a** = δ 5.37 ppm and **6a** = δ 6.01 ppm; **1b** = 5.40 ppm and **6b** = δ 6.05 ppm; **1e** = δ 5.46 ppm; **1g** = δ 5.45 ppm; **1l** = δ 5.47 ppm.
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