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Chemo- and regioselective halogenation of 4-(pyrazol-4-yl)-pyrimidines

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ABSTRACT

A convenient and selective halogenation of 4-(pyrazol-4-yl)-pyrimidines is described herein. This method allows quick access to a diverse set of pyrazolyl-pyrimidine derivatives.

Derivatives of pyrazolyl-pyrimidine have been reported as promising pharmaceutical agents for the treatment of cancer,[1] neurodegenerative diseases,[2] diabetes,[3] and inflammation.[4] Among these, an increasing number of 4-(pyrazol-4-yl)-pyrimidines have been applied as a platform to generate inhibitors of various kinases including Aurora kinases, c-Jun N-terminal kinases, p38 MAPK, and Raf kinases.[1,5] The general structures of such inhibitors can be summarized as shown in Figure 1. On many occasions, the pyrimidine C(2) position is decorated with amines (R1NH) which presumably interact with the backbone of protein targets via a hydrogen bond. In such scaffolds, the pyrazoles are further functionalized with different aromatic/heteroaromatic/heterocyclic rings (R4 or R6) to gain potency and/or selectivity. Published procedures to construct such ring systems involve generation of the central pyrazole core from 1-aryl-2-pyrimidinylethanone **1** (Eq. 1),[6] or the Sandmeyer reaction of 3-aminopyrazoles followed either by displacement of the resulting halogen with heterocycles (Eq. 2)[5e] or by Suzuki coupling (Eq. 3).[1,5g] Amine substituents are introduced to the C(2) position of the pyrimidines by displacement of a methylsulfonyl group.

At the outset of our program to generate structure–activity relationships around 4-(pyrazol-4-yl)-pyrimidines against kinase targets, few literature examples were present for the chemo- and regioselective halogenation of 4-(pyrazol-4-yl)-pyrimidines. Most of the reactions utilized a preassembled 3-aminopyrazole functionality (e.g., **3** or **5**) for the Sandmeyer conversion.[5e,g] Recognizing the utility of such substrates for the rapid assembly of analogs via palladium-catalyzed reactions, we investigated facile and selective halogenation reactions of 4-(pyrazol-4-yl)-pyrimidines. Herein, we report the scope of such reactions and the application of the resulting halogenated derivatives for further functionalization.

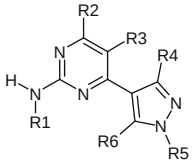
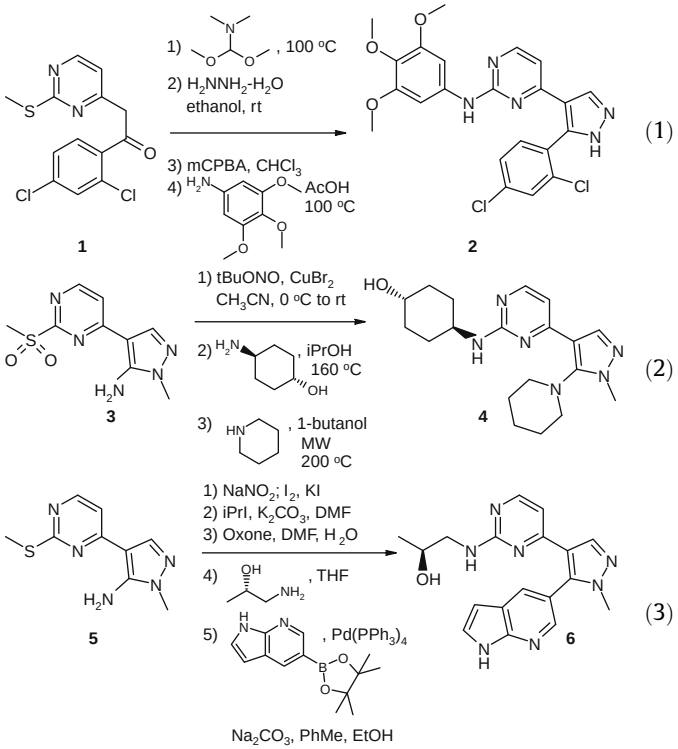


Figure 1.



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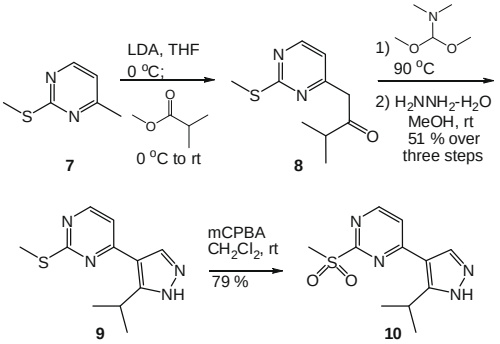
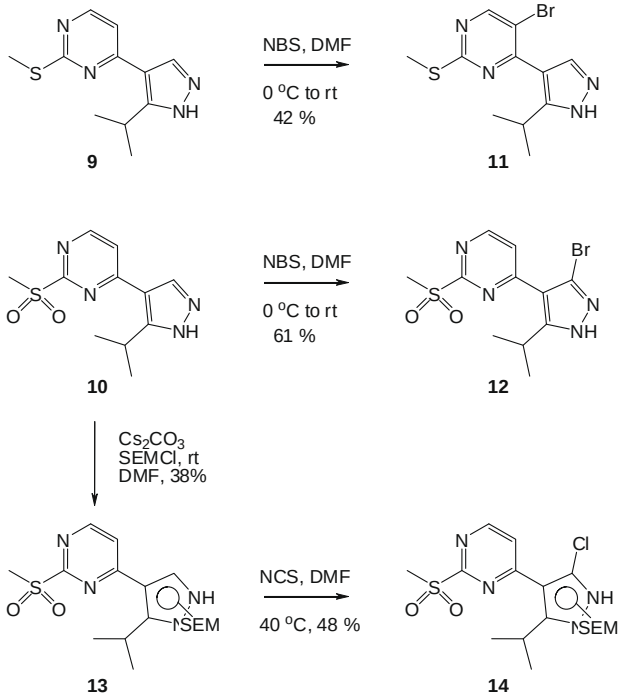


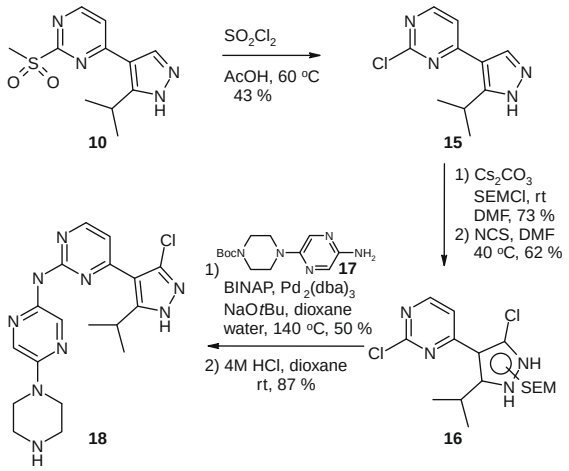
Scheme 1.

Our investigation of selective halogenation reactions focused on the use of 4-(5-isopropyl-pyrazol-4-yl)-pyrimidines **9** and **10** as starting materials. Preparation of 2-thiomethyl-pyrimidine **9** commenced with acylation of 4-methyl-2-thiomethyl-pyrimidine **7** to afford the ketone **8**. Treatment of **8** with the dimethyl acetal of dimethylformamide, followed by condensation with hydrazine provided **9** (Scheme 1).[6] Subsequent oxidation of **9** with *meta*-chloroperbenzoic acid provided 2-methylsulfonyl-pyrimidine **10** in 79% yield.

Treatment of **9** with *N*-bromosuccinimide in dimethylformamide provided 5-bromo-pyrimidine **11** in 42% yield (Scheme 2).[7] The regioselectivity of the bromination was guided by electrophilic substitution to the 5-position of the pyrimidine as determined by NMR.[8] Interestingly, 2-methylsulfonyl-pyrimidine **10** underwent bromination using identical conditions to afford exclusively 3-bromo-pyrazole **12** in 61% yield, suggesting that conversion to the methylsulfonyl group sufficiently reduced the electron density of the pyrimidine ring to render the 3-position of the pyrazole the most reactive site for electrophilic bromination.[9] Chlorination of **10** using *N*-chlorosuccinimide gave a complex mixture of products.[10] However, following protection of the 1*H*-pyrazole with a



Scheme 2.



Scheme 3.

2-(trimethylsilyl)-ethoxymethyl group, chlorination of the resulting pyrazole **13** with *N*-chlorosuccinimide proceeded cleanly in dimethylformamide at 40 °C to afford **14** in 48% yield. Both protection and chlorination of the pyrazole resulted as a mixture of protected pyrazole isomers.[11]

While searching for optimal conditions for the chlorination of **10**, we observed that treatment of **10** with sulfuryl chloride in acetic acid at 60 °C gave 2-chloro-pyrimidine **15** as the major product in 43% yield (Scheme 3).[12] To our knowledge, this is the first example of conversion of a 2-methylsulfonyl-pyrimidine into a 2-chloro-pyrimidine with sulfuryl chloride. Compound **15** was further elaborated via protection with a 2-(trimethylsilyl)-ethoxymethyl group and chlorination with *N*-chlorosuccinimide to afford bischloro 4-(pyrazol-4-yl)-pyrimidine **16** in 31% yield over two steps. With **16** in hand, an opportunity for diversifying the pyrimidine C(2) position via Buchwald–Hartwig cross-couplings with non-nucleophilic amines was recognized.[13] Utilizing slightly modified reaction conditions which included the addition of a small amount of water, a coupling reaction between **16** and **17** proceeded smoothly to give the desired product in 50% yield.[14] Removal of both the 2-(trimethylsilyl)-ethoxymethyl group and the *tert*-butyloxycarbonyl group provided **18** in 87% yield.[14]

In summary, we have demonstrated several selective halogenation reactions of 4-(pyrazol-4-yl)-pyrimidine derivatives. This convenient preparation of versatile synthetic intermediates enabled rapid assembly of a series of novel kinase inhibitors. Further studies on such analogs will be reported in due course.

Acknowledgments

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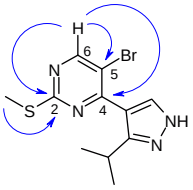
7. Sulfoxide by-products with and without one bromine atom were observed in the low resolution mass spectrum after the work-up.
8. *Compound* **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.24 (s, 1H), 3.59–3.75 (m, 1H), 2.49 (s, 3H), 1.29 (d, J = 7.03 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.56, 159.69, 158.75, 153.07, 138.91, 114.31, 113.15, 25.69, 22.18, 14.43; MS m/z $(M+H)^+$: 315.3



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The structure was determined by 2D NMR analysis including COSY, HSQC, HMBC and ROESY. HMBC correlations from H(6) to C(2), C(4) and C(5) were detected supporting the proposed structure.

9. *Compound* **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 5.52 Hz, 1H), 8.09 (d, J = 5.52 Hz, 1H), 3.73–3.90 (m, 1H), 3.31 (s, 3H), 1.31 (d, J = 7.03 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.76, 160.96, 158.06, 153.82, 127.62, 120.73, 113.34, 39.21, 26.19, 21.36; MS m/z $(M+H)^+$: 347.3.
10. The low resolution mass spectrum of the crude product showed a mixture of the desired product (minor) and compounds (major) with higher molecular weight which could not be identified.
11. The ratio of regioisomers was not preserved during the chlorination. To see more about the SEM group transposition: Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 3042–3048.
12. *Compound* **15**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (d, J = 5.4 Hz, 1H), 8.04 (s, 1H), 7.48 (d, J = 5.4 Hz, 1H), 3.82 (m, 1H), 1.24 (d, J = 7.1 Hz, 6H); $(M+H)^+$: 223.3.
13. Many attempts to replace methylsulfonyl group of **10** with non-nucleophilic amines (e.g., pyridin-2-ylamine) failed.
14. Slightly modified Buchwald–Hartwig reaction conditions were applied for the coupling reaction: To a solution of **16** (100 mg, 0.26 mmol) in 1,4-dioxane (4 mL) in a sealed tube were added **17** (76 mg, 1.05 equiv), BINAP (17.1 mg, 0.10 equiv), NaO*t*Bu (37.2 mg, 1.5 equiv), $Pd_2(dba)_3$ (11.8 mg, 0.05 equiv) and water (0.10 mL). N_2 was bubbled through the resulting mixture for 10 min to degas. The reaction mixture was sealed and heated at 140 °C for 90 min. After cooling to room temperature, the mixture was filtered through a pad of Celite and concentrated in vacuo. The brown residue was recrystallized from acetonitrile to give a yellow powder coupling product (89 mg) in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, J = 1.4 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 7.86 (d, J = 1.4 Hz, 1H), 7.58 (br s, 1H), 7.05 (d, J = 5.2 Hz, 1H), 5.49 (s, 2H), 3.69 (t, J = 8.2 Hz, 2H), 3.60–3.48 (m, 9H), 1.50 (s, 9H), 1.28 (d, J = 6.9 Hz, 6H), 0.95 (t, J = 8.2 Hz, 2H), 0.00 (s, 9H); HR-MS m/z $(M+H)^+$: meas. 630.3097 calcd 630.3103. The coupling product (80 mg) was dissolved in 1,4-dioxane (2.0 mL) and treated with a solution of HCl in 1,4-dioxane (4.0 M, 0.095 mL, 3.0 equiv). The resulting mixture was sonicated for 8 h at room temperature and treated with diethyl ether. The precipitate was collected and washed with diethyl ether and ethyl acetate to give tan powder **18** (48 mg) in 87% yield as a HCl salt. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 6.8 Hz, 1H), 8.37 (d, J = 1.4 Hz, 1H), 8.22 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 6.8 Hz, 1H), 4.16 (q, J = 7.0 Hz, 1H), 3.93 (t, J = 5.3 Hz, 2H), 3.42 (t, J = 5.3 Hz, 2H), 1.39 (d, J = 7.0 Hz, 6H); HR-MS m/z $(M+H)^+$: meas. 400.1765 calcd 400.1765.