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# Two convenient regioselective syntheses of 1-*N*-alkyl-3-aryl-4-[pyrimidin-4-yl]-pyrazoles

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ABSTRACT

Two regioselective synthetic routes for 1-*N*-alkyl-3-aryl-4-[pyrimidin-4-yl]-pyrazoles of generic formula **1** were developed. These highly efficient and scalable routes circumvent the generally observed poor regioselectivity for the pyrazole alkylation.

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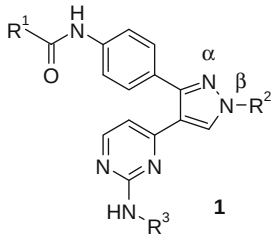
The aurora kinases are a family of serine/threonine kinases, which play crucial roles in the cell cycle. Deregulation of Aurora kinase activity can result in mitotic abnormality and genetic instability, leading to defects in spindle assembly, chromosome alignment and cytokinesis. Both the expression and the kinase activity of Aurora kinase are found to be up-regulated in many human cancers. Taken together, these data suggest the potential utility of Aurora kinase inhibitors as novel agents to treat cancer. Our quest for a Aurora kinase inhibitor as a potential agent to treat cancer led us to the investigation of a pyrazole template as an interesting scaffold.

One scaffold we investigated in pursuit of novel Aurora kinase inhibitors was the 1-*N*-alkyl-3-aryl-4-[pyrimidin-4-yl]-pyrazoles, such as **1**. This scaffold allows for the arrangement of three diversity elements around the central pyrazole core. However, at the start of our investigation, to the best of our knowledge, there was no published report of a concise, scalable and regioselective synthesis of such compounds. This Letter summarizes our exploration into the regioselective synthesis of these trisubstituted pyrazoles.




**1**

Our initial synthesis of 1-*N*-alkyl-3-aryl-4-[pyrimidin-4-yl]-pyrazoles following published procedures[1,2] is summarized in Scheme 1.

Commercially available ethyl *para*-amino-benzoate **2** was acylated, and then reacted with the lithium anion of 4-methyl-2-thiomethyl-pyrimidine to afford ketone **3**. Treatment of **3** with the dimethyl acetal of dimethylformamide (DMF–DMA), followed by reaction with hydrazine, yielded pyrazole **4**. Oxidation of the sulfide afforded the sulfone **5**. Alkylation of the 1*H*-pyrazole core resulted in a 1:1 mixture of the desired β-isomer **6b** and the α-regioisomer **6a**.

The mixture of regioisomers was then reacted with aniline, in the presence of sodium hexamethyldisilazide at low temperature, to afford a 1:1 mixture of regioisomers **7a** and **7b**. Separation of the regioisomers (**6a**/**6b** or **7a**/**7b**) was possible, but the ease of separation was compound dependent and required development of the appropriate chromatographic method. Furthermore, the lack of regioisomeric control in the alkylation automatically reduces the overall yield, hampering any scale-up campaign required for effective SAR investigation.

Facing these challenges, we explored alternative synthetic approaches to the desired β-isomer. Few regioselective synthetic procedures favoring the β-substituted 1-*N*-alkyl-3,4-diaryl-pyrazole have been reported in the literature.[1b] Most of them are based on the formylation of an arylbenzylketone, followed by reaction with monosubstituted hydrazine ($R^2NHNH_2$) and spontaneous cyclization to form the β-$R^2$-substituted pyrazole ring.[1b,2] This approach was successful for $R^2$ = acyl and aryl, but failed for $R^2$ = alkyl, limiting the scope of our SAR.

Building on the chemistry displayed in Scheme 1, we initially attempted to identify conditions that would favor the β-alkylation of a 3-aryl-4-[pyrimidin-4-yl]-1-*N*-*H*-pyrazole such as **5**. The direct alkylation of 1-*N*-*H*-pyrazoles with alkyl halides in the presence of inorganic base was generally non-selective, as previously reported for the case of 3,4-diaryl pyrazoles and confirmed in our hands (data not shown).[3] Use of different alkylating agents (halides or triflates) and bases (sodium hydride, cesium carbonate, or potassium *t*-butoxide) afforded 1:1 mixtures of isomers.[4]

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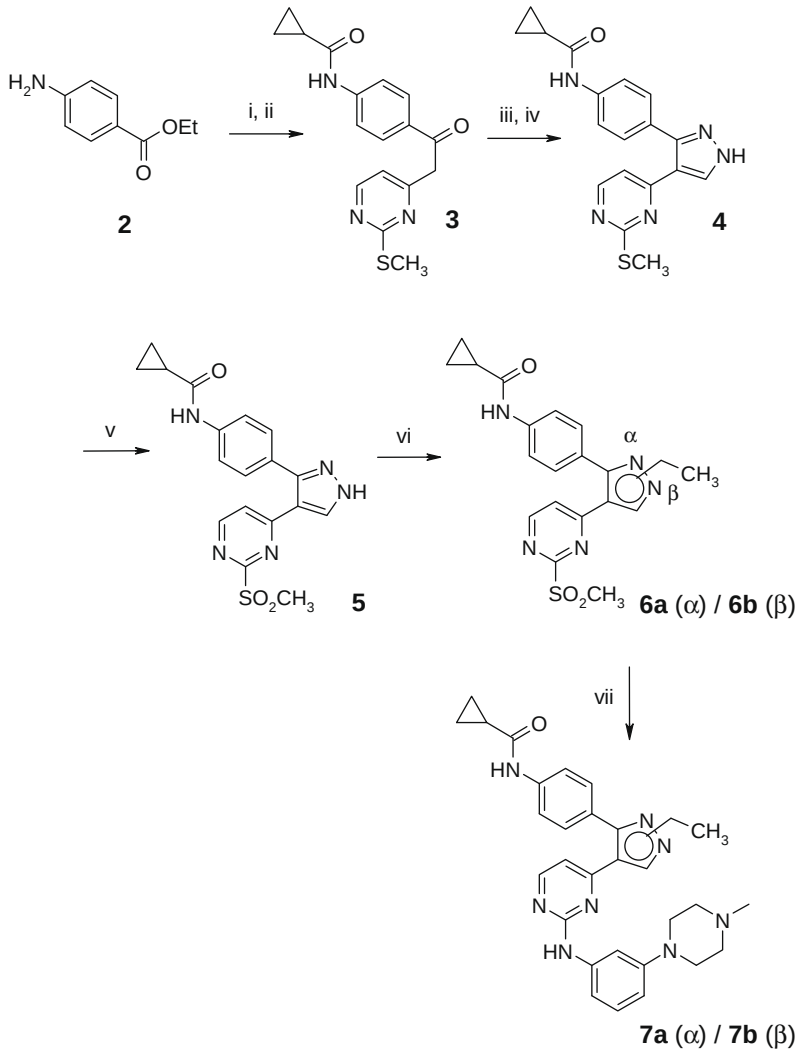
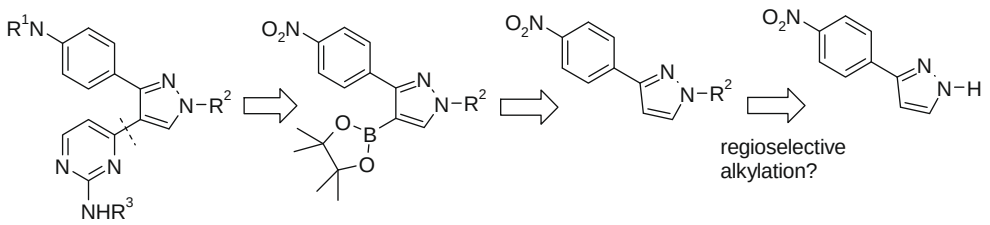


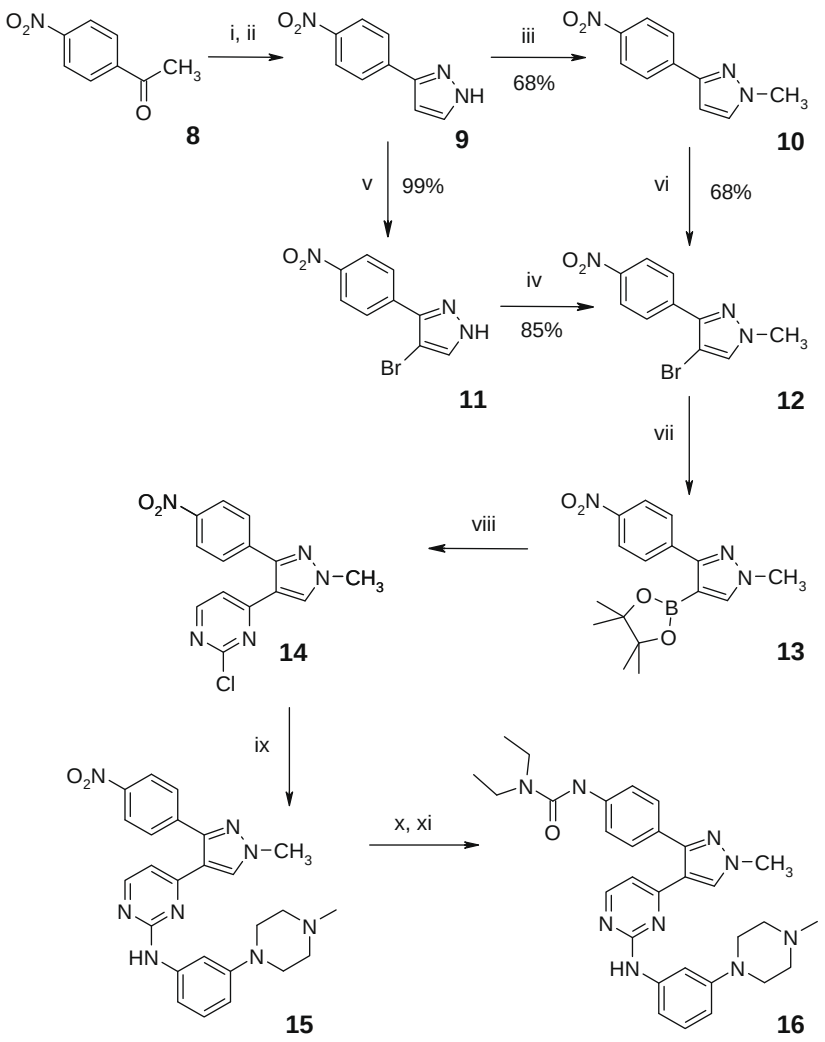

**Scheme 1.** Reaction conditions: (i) cyclopropylcarbonyl chloride, $NEt_3$, $CH_2Cl_2$, 93%; (ii) 4-methyl-2-thiomethyl-pyrimidine, LiHMDS, −78 °C to 10 °C, THF, 98%; (iii) DMF-DMA; (iv) $N_2H_4{\cdot}H_2O$, EtOH, 70% (two steps); (v) *m*CPBA, $CH_2Cl_2$, 22%; (vi) KO*t*-Bu, MeI, DMF, 0 °C, 58% (1:1); (vii) 3-(4-methyl-piperazin-1-yl)aniline, NaHMDS, −78 to 20 °C, (67% for **7a**, 64% for **7b**).

Since the alkylation of 3,4-disubstituted pyrazoles proceeds without selectivity, we decided to explore the regioselectivity for the alkylation of a related substrate, 3-aryl-4-*H*-pyrazoles. We hoped that the distinct electronic environment of the ring system would allow for more selective alkylations. Such 3-aryl-4-*H*-pyrazoles would also be highly attractive from a synthetic standpoint, since they can be easily prepared from commercially available acetophenones. Furthermore, substitution at C4 could be easily introduced by regiospecific halogenation of the pyrazole ring, followed by borylation and Suzuki coupling. The retrosynthetic scheme for the synthesis of **1** using 3-aryl-4-*H*-pyrazoles as intermediates is shown in Scheme 2.

The synthetic route that is shown in Scheme 3 was thus implemented. Commercially available acetophenone **8** was sequentially treated with DMF–DMA and hydrazine, affording pyrazole **9** in 96% yield. Alkylation of **9** using MeI in the presence of $Cs_2CO_3$, followed by recrystallization from ethanol, afforded the pure desired β-isomer **10** in 68% yield. We were pleasantly surprised that this reaction not only afforded mostly the desired β-isomer but also was easily performed in multigram scale.[5] Bromination of **10** using bromine afforded the desired pure 4-bromo regioisomer **12** in 68% yield. Alternatively, **9** could be reacted with NBS to afford 4-bromo pyrazole **11**. Alkylation of **11** was also highly regioselective and scalable (up to at least 20 g), affording **12** in 85% yield. Pyrazole




**Scheme 2.**

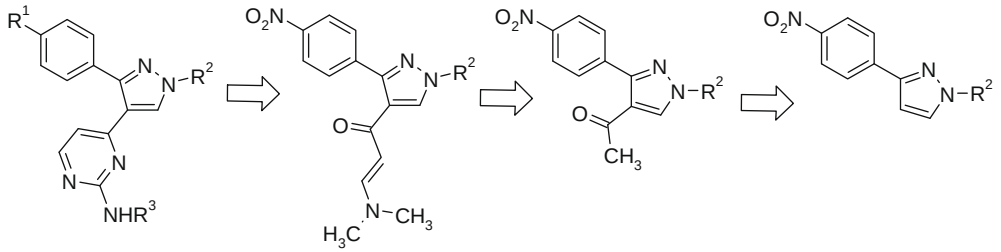



**Scheme 3.** Reaction conditions: (i) DMF–DMA, DMF, 80 °C; (ii) $N_2H_4{\cdot}H_2O$, EtOH, 70 °C, 96% (two steps); (iii) MeI, $Cs_2CO_3$, DMF, 68%; (iv) MeI, NaH, DMF, 0 °C, 85%; (v) NBS, DMF, 68%; (vi) $Br_2$, $CHCl_3$, 68%; (vii) pinacol boronate ester, $PdCl_2(PPh_3)_2$, KOAc, dioxane, 100 °C, 61%; (viii) 2,4-dichloropyrimidine, $PdCl_2(PPh_3)_2$, $Na_2CO_3$, EtOH, water, 75%; (ix) 3-(4-methyl-piperazin-1-yl)aniline, HCl, *i*-PrOH, 120 °C, 99%; (x) Sn, 6 N HCl, EtOH, 92%; (xi) phosgene, diethylamine, THF, 58%.

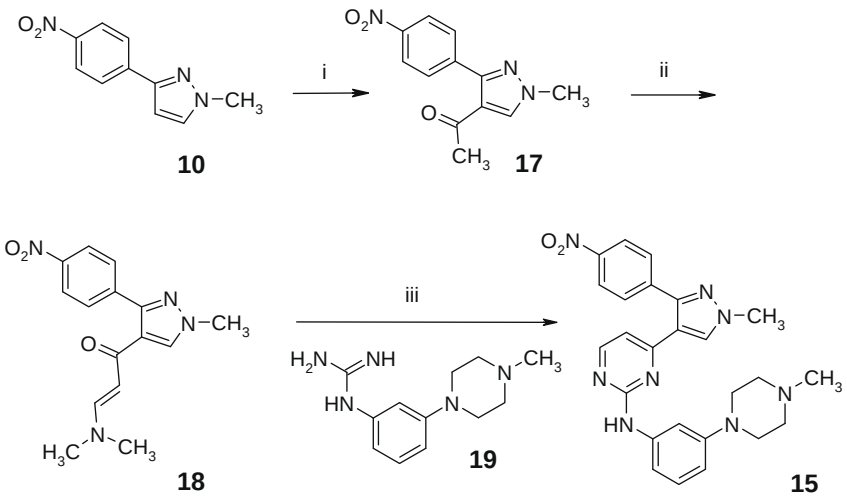
**12** was converted to the pinacol boronate ester **13**, and then was coupled to 2,4-dichloropyrimidine under the standard Suzuki conditions to form **14**, a versatile intermediate containing two orthogonal diversity points. As shown in Scheme 3, nucleophilic displacement of the chloride with aniline under thermal conditions afforded compound **15**. Reduction of the nitro group, followed by treatment with phosgene and an amine, afforded compound **16**. The route that is shown in Scheme 3 affords the desired 3-aryl-4-[pyrimidin-4-yl]-1-alkyl-pyrazoles with excellent regioselectivity. It also allows for the late orthogonal introduction of two diversity elements through the use of intermediate **14**. This route was then used to explore the SAR of **1**.

The high regioselectivity seen in the alkylation of **9** allows for an alternative route to **1**, as outlined in Scheme 4. The pyrimidine ring could be formed by condensation of a guanidine and an enaminone.[6,7] The enaminone would be derived from a 4-acetyl-3-aryl-1-*N*-alkyl pyrazole, which could be formed from the regioselective acetylation of the previously described 3-aryl-1-*N*-alkyl pyrazole.

The validation of this second route is represented in Scheme 5. Compound **10** was treated with acetic anhydride in the presence of sulfuric acid to afford **17**,[8] which was converted to the enaminone **18** in 91% yield.[9,10] Condensation of **18** with the guanidine **19**[11] in anhydrous conditions gave pyrimidine **15**. Reduction of the nitro



**Scheme 4.**




**Scheme 5.** Reaction conditions: (i) $Ac_2O$, concd $H_2SO_4$ (cat), 64%; (ii) DMF di-*t*-butylacetal, DMF, 91%; (iii) $K_2CO_3$, DMF, 62%.

group, followed by urea formation, afforded the desired target **16**. This second route is highly convergent, consisting of eight linear steps from **8** (plus the required synthesis of the guanidine **19**) with very good overall yield.

In summary, two novel, highly efficient, and scalable routes to trisubstituted 1-alkyl-3-aryl-4-[pyrimidin-4-yl]-pyrazoles were developed. Both the routes are based on the highly regioselective β-alkylation of 1-*H*-3-aryl-4-*H*-pyrazoles, eliminating the need for potentially cumbersome isomer separation. In addition, the synthetic routes described allow for convenient introduction of diversity at the R1 and R3 positions. Detailed biological data for this class of compounds will be published elsewhere.

Two novel, regioselective, and scalable routes to trisubstituted 1-alkyl-3-aryl-4-[pyrimidin-4-yl]-pyrazoles have been developed. These routes allow for the easy isolation of the desired β-substituted pyrazole and for the efficient SAR exploration around the central core.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.113.

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4. Interestingly, reaction of the 1-*H*-*N*-pyrazole with isocyanates or acyl chlorides afforded the beta isomer preferentially, in a 10:1 ratio or greater.
5. HPLC analysis of the crude reaction mixture showed a β-to-α ratio of 11:1.
6. (a) Bredereck, H.; Effenberger, F.; Bosch, H. B. *Dtsch. Chem. Ges.* **1964**, *97*, 3397; (b) Gudmundsson, K.; Johns, B. *Org. Lett.* **2003**, *5*, 1369.
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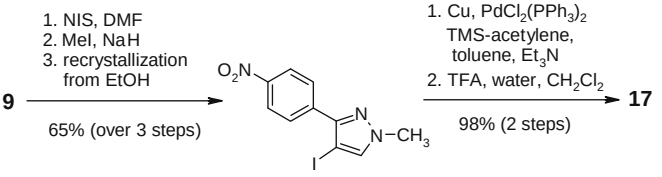
8. Compound **17** was also prepared from **9** in similar overall yield using a longer synthetic sequence based on the 4-iodo pyrazole intermediate shown below:

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10. The enaminone was also prepared by reaction of the arylmethylketone with DMF–DMA as the solvent, but the yield was lower.
11. Guanidine **19** was prepared by treating 3-(4-methyl-piperazin-1-yl)-aniline with 1,3-bis(*tert*-butoxy-carbonyl)guanidine, followed by deprotection with 12 N HCl.