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An Efficient Route to 4-Aryl-5-pyrimidinylimidazoles via Sequential Functionalization of 2,4-Dichloropyrimidine

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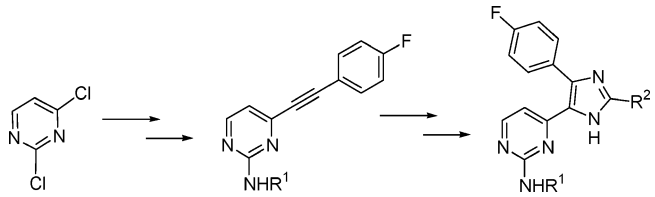
ABSTRACT



Starting from 2,4-dichloropyrimidine, a concise synthetic route to medicinally important 4-aryl-5-pyrimidinylimidazoles is described. Sequential substitution of the 4- and 2-chloro groups using a regioselective Sonogashira coupling, followed by nucleophilic substitution, led to pyrimidinylalkyne derivatives, which were then oxidized to their corresponding 1,2-diketones. These 1,2-diketones, on cyclocondensation with ammonium acetate and an aldehyde, furnished the desired pyrimidinyl imidazoles in good overall yields.

4,5-Diarylimidazoles, in which one of the aryl substituents is a heteroaryl group such as a pyridine or pyrimidine, form an important class of p38 MAPK (mitogen-activated protein kinase) inhibitors, vigorously pursued by a number of pharmaceutical companies as antiinflammatory drugs (Figure 1).[1−3]

Despite the heightened interest, preparation of these compounds has relied largely upon just two synthetic strategies.

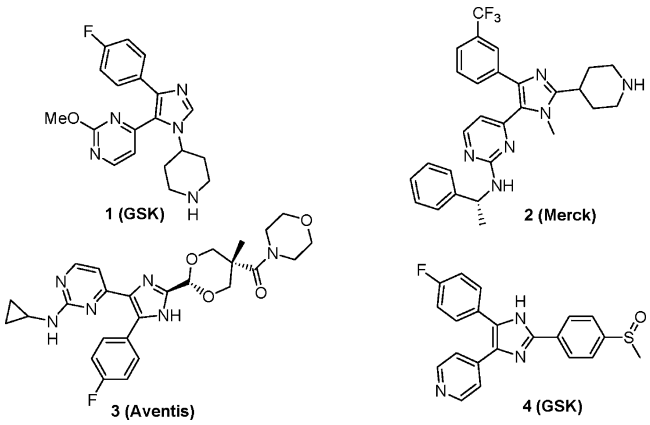


Figure 1. 4,5-Diarylimidazole class of p38 MAP kinase inhibitors.

Merck[4] and Aventis[5] scientists employed the cyclocondensation of substituted 1,2-dicarbonyl compounds with am-

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monia and an aldehyde. Although this reaction is quite efficient, preparation of the necessary pyrimidinyl-substituted dicarbonyl derivatives requires a lengthy sequence starting from 2-mercapto-4-methylpiperidine.

A notably elegant approach, developed by the SKB group,[6] involved the cycloaddition of substituted TosMIC with aldimines, originally pioneered by van Leusen.[7] More recently, Merck scientists[8] have reported a promising one-pot synthesis of imidazoles based on the cyclocondensation of an α-ketoamide with an amine, wherein the requisite α-ketoamide is generated in situ by a Stetter reaction involving an α-amidosulfone. In these cases also, access to the suitably elaborated pyrimidines required multistep sequences. To successfully exploit the particularly efficient condensation of 1,2-diketones bearing an electron-deficient pyrimidine moiety with an aldehyde and ammonia, a more succinct route to the requisite 1,2-diketone derivatives would clearly be advantageous. Herein, we wish to disclose our development of a novel approach to this important class of compounds. Relative to existing methods, our synthetic route is concise and appears suitable to provide ready access to a range of structurally related 1,2-diketone and imidazole analogues.

To more readily access the desired 1,2-diketone intermediates, we considered the oxidation of disubstituted acetylene compounds, which could be derived from the readily available 2,4-dichloropyrimidine through sequential substitution reactions (Figure 2).

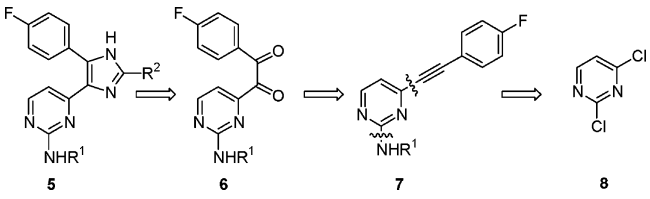
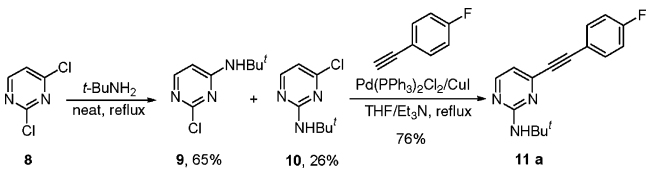


Figure 2. Retrosynthetic analysis.

Our initial explorations into selective substitution, outlined in Scheme 1, were not very encouraging. Reacting 2,4-

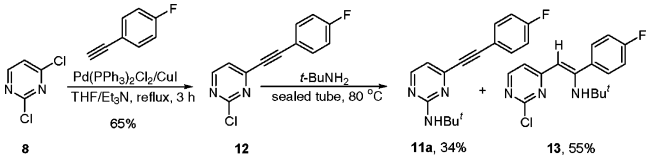
Scheme 1



dichloropyrimidine with *tert*-butylamine at 60 °C gave a mixture of 4- and 2-substitution products in 65% and 26% yield, respectively. This result clearly indicated that the chloro group at the 4-position is more reactive (albeit slightly) toward substitution with amine nucleophiles than the 2-position.[9−11] A variety of base and solvent combinations were investigated, but we could not find synthetically useful 2-position selectivity. On a smaller scale (5−10 g), the two regioisomers could be separated by column chromatography. The 4-chloro regioisomer **10** was then coupled with 4-fluorophenylacetylene, under standard Sonogashira coupling conditions,[12] to furnish the desired disubstituted acetylene **11a** in 76% yield. Although we obtained diarylacetylene **11a** in two steps, the poor regioselectivity in the nucleophilic substitution reaction rendered this approach impractical for large-scale synthesis.

By reversing the order of the substitution steps, we overcame the regioselectivity issues. A Sonogashira reaction between 2,4-dichloropyrimidine and 1-ethynyl-4-fluorobenzene smoothly afforded the desired regioisomer **12** as the major product in 65% isolated yield (Scheme 2). Unfortu-

Scheme 2



nately, treatment of **12** with *tert*-butylamine gave a mixture of the desired compound **11a**, along with the product of 1,2-addition across the alkyne, **13**. The structure of **13** was ascertained by NOE experiments.[13] To avoid this hydroamination reaction, a variety of conditions, such as Na_2CO_3/

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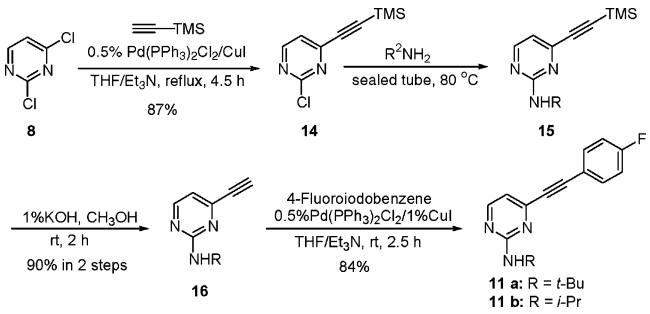
(12)) Sonogashera, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467−4470.

(13)) For the vinylic hydrogen, strong NOE was observed with 5-pyrimidinyl hydrogen and weaker effect with the 2-and 6-hydrogens of the 4-fluorophenyl. These aryl hydrogens, however, showed strong NOE with *t*-butyl hydrogens. See the Supporting Information for the NOE spectra.

EtOH, Et_3N/THF, NH_2Bu^t/THF, and Buchwald amination, were investigated with limited success.

We hypothesized that it might be possible to effect the nucleophilic substitution on the pyrimidine nucleus preferentially by changing the electronic and steric properties of the alkyne. Based on this line of reasoning, a new route was designed (Scheme 3). Sonogashira cross-coupling reaction

Scheme 3

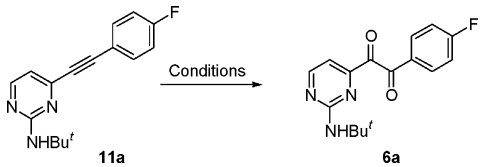


of (trimethylsilyl)acetylene with 2,4-dichloropyrimidine afforded the requisite alkyne **14** in 87% yield. Heating this intermediate in neat *tert*-butylamine at 80 °C gave exclusively the desired substitution product. Desilylation followed by another Sonogashira cross-coupling with 4-fluoroiodobenzene afforded compound **11a** in very good overall yield. This reaction sequence was performed successfully on 20−40 g scale without the need for column chromatography. It should be noted that accessing the intermediate **14** not only affords a more efficient route to **11** but also allows for a point of diversification for the design of new analogues.

With a reliable route to diaryl-substituted acetylenes **11** and **12** in hand, we set out to examine the key oxidation reaction. Initially, we focused our attention on the oxidation of **12**, for it would allow the introduction of the amine substituent after imidazole formation. Oxidation of diaryl-substituted acetylene to diketone is well precedented and a wide array of reagent systems have been reported.[14−16] However, we soon realized that oxidation of a diarylacetylene containing a pyrimidine group is far from trivial. Thus, in the case of **12** all our attempts using a battery of reagent systems resulted in no oxidation or over-oxidation.[17] Gratifyingly, in the case of **11a**, oxidation using $KMnO_4$ or $PdCl_2$/DMSO went smoothly on small scale (Table 1, entries 3 and 5). The stark reactivity difference between **11a** and **12** could be due to the reduced electron deficiency of the triple bond in compound **11a**.

The oxidation procedures using $KMnO_4$ and $PdCl_2$/DMSO were then investigated carefully. Although both procedures worked well on small scale, the $PdCl_2$/DMSO system suffered several drawbacks, requiring high Pd loading (∼10%), prolonged reaction time, and elevated temperatures

Table 1. Oxidation of **11a**



entry	conditions	results
1	$KMnO_4$,/CH_2Cl_2, H_2O, AcOH, Adogen 64, reflux, 3 h[18]	over-oxidation[a]
2	$KMnO_4$/CH_2Cl_2, AcOH, Adogen 64, reflux, 1.5 h[18]	30%
3	$KMnO_4$/acetone, H_2O, $MgSO_4$, $NaHCO_3$, rt, 45 min[19]	45%
4	I_2/DMSO, 150 °C, 16 h[20,21]	over-oxidation[a]
5	$PdCl_2$/DMSO, 130 °C, 4 h22	53%
6	NBS/DMSO, rt, 10 min[22]	bromination[b]
7	HBr/DMSO, 130 °C, 3 h	no reaction
8	$(CF_3COO)_2$IPh, DMSO, 130 °C, 3 h[24]	SM and over-oxidation[a]
9	$RuCl_3$/$NaIO_4$, H_2O/CH_3CN/CCl_4, reflux, 2 h[25,26]	no reaction
10	OsO_4, Me_3NO, *t*-BuOH, H_2O, reflux, 5 h[27,28]	bromination[b]

[a] 4-Fluorobenzoic acid was isolated. [b] Based on MS, the product was not isolated.

(130 °C) to achieve reasonably good conversion. Lower Pd loading caused incomplete reaction and raising the temperature caused side reactions. A Pd on C/$CuCl_2$/DMSO system produced similar results.[23] These methods also required column chromatography to purify the final product, making them less well-suited for largescale preparations. Although oxidation using $KMnO_4$ was more promising in terms of clean reaction and easy purification, over oxidation was a major disadvantage. After screening numerous conditions, it was found that the key to obtaining good yields was to use a very finely powdered form of $KMnO_4$[29] and to control the reaction time in a, acetone/H_2O solution buffered with $MgSO_4$ and $NaHCO_3$. Under these optimized conditions, the

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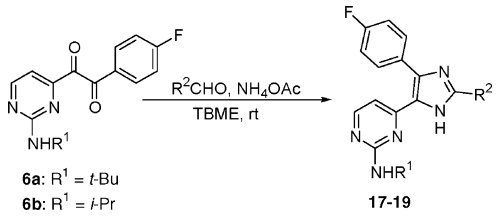
(28) Page, P. C. B.; Rosenthal, S. *Tetrahedron Lett.* **1986**, *27*, 1947−1950.
(29)) See ref 19. Permanganate reagent that worked best in our hands was a finely powdered form of $KMnO_4$ (Cairox M) purchased from Carus Chemical Co.

Table 2. Preparation of Imidazoles



6a: R^1 = *t*-Bu
6b: R^1 = *i*-Pr

17-19

no.	R^1	R^2	*T* (°C)/time (h)	yield (%)
17a	*t*-Bu	H	65/4	56
18a	*t*-Bu	4-ClC_6H_4	65/48	68
19a	*t*-Bu	$(CH_3O)_2CH$	rt/3	60
17b	*i*-Pr	H	65/3	52
18b	*i*-Pr	4-ClC_6H_4	65/48	62
19b	*i*-Pr	$(CH_3O)_2CH$	rt/3	58

desired diketone **6a** was obtained consistently in 65−70% yields on 5 g scale after simple aqueous workup and without column chromatography.

Using the method described above, isopropyl analogue **6b** was also prepared in good yield. Cyclocondensation of the diketones with ammonium acetate and an aldehyde (Table 2) efficiently provided various pyrimidinyl-substituted imidazoles.

In summary, we have developed a concise, six-step sequence to synthesize 4-aryl-5-pyrimidinylimidazoles—an important scaffold useful in antiinflammatory drug research. The methodology is well-suited to the preparation of a number of related analogues.

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Supporting Information Available: Representative experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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