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Concise, flexible syntheses of 4-(4-imidazolyl)pyrimidine cyclin-dependent kinase 2 (CDK2) inhibitors

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ABSTRACT

A flexible six-step synthesis of potential cyclin-dependent kinase 2 (CDK2) inhibitors is reported. The synthesis involves the condensation between 3-chloro-4,4-dimethoxy-2-butanone and amidines, which provides acetyl-imidazoles and late stage palladium-catalyzed N-arylation to give the target pyrimidine derivatives.

Protein kinases play important regulating roles in cellular processes such as transcription, cell cycle, metabolism, apoptosis and neuronal development.[1] Mutations which deregulate the function of these kinases result in many diseases, such as cancer, and neurodegenerative and cardiovascular disorders. Among the 11 members of the CDK family identified, cyclin-dependent kinase 2 (CDK2) is known to play important roles in the cell cycle.[2,3] Recently, these protein kinases have attracted increased attention and small molecule CDK inhibitors have been identified as potential therapeutic agents. In this context, a number of CDK inhibitors such as flavopiridol (**1**) and (*R*)-roscovitine (CYC202) (**2**) have proved their efficacy for the treatment of cancer (Fig. 1). More recently, flavopiridol (**1**) was investigated for the treatment of oesophageal, lung and liver cancers and was demonstrated to have a strong effect against lymphatic leukaemia.[4]

Due to growing interest in CDKs as potential targets for cancer chemotherapy, several pharmaceutical companies have developed new classes of CDK2 inhibitors. Following earlier studies,[5] AstraZeneca scientists found that replacement of the imidazo[1,2-*a*]pyridine in **3** or imidazo[1,2-*b*]pyridazine in **4** with an imidazole-pyrimidine sulfone **5** gave rise to inhibitors with superior physicochemical properties and cellular potency (Fig. 2).[6] This group reported the synthesis of imidazole-pyrimidine sulfone **5** and its analogues using derivatives of 5-methyl-isoxazoles **8** as the synthetic equivalent of acetyl-imidazoles **9** and the key transformations are outlined in Scheme 1.[7]

Herein, we report an alternative synthesis of the regioisomeric 4-acetylimidazoles **13a–c** by the condensation of 3-chloro-4,4-dimethoxy-2-butanone (**10**) and amidines **11** (Scheme 2). Subsequent N-alkylation and conversion into imidazole-pyrimidine sulfones **21a–c**, afforded novel CDK2 inhibitors, which contained an unusual hexamethylenediamine side chain. This functionality is present in BS-181, which is the most selective CDK7 inhibitor, reported to date.[8]

Condensation of 3-chloro-4,4-dimethoxy-2-butanone (**10**)[9] with the amidines **11a–c**[10,11] gave the imidazoles **12a–c**. These reactions were optimally carried out using an excess of amidines **11** with sodium acetate and chloro-ketone **10** in anhydrous 1,4-dioxane at reflux for 16 h (**12a**, **12b**) or 36 h (**12c**) (Scheme 3).

Subsequent *N-iso*-propylation of **12** proved to be more complicated than expected.[12] Whilst the use of basic conditions in polar

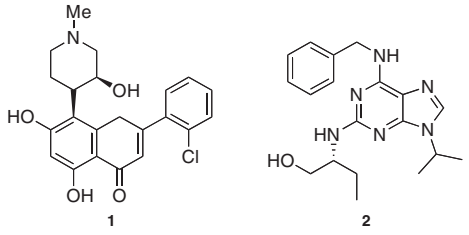

Figure 1. CDK2 inhibitors flavopiridol (**1**) and (*R*)-roscovitine (**2**).

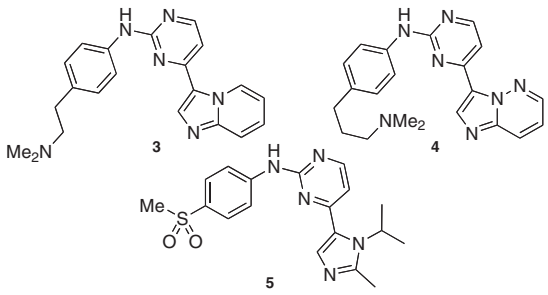

Figure 2. CDK2 inhibitors developed by AstraZeneca.

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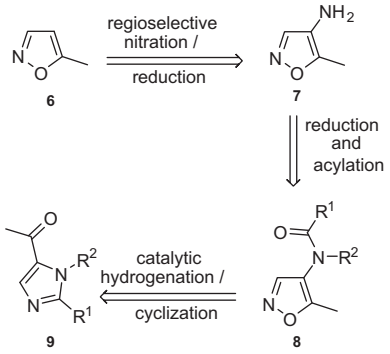
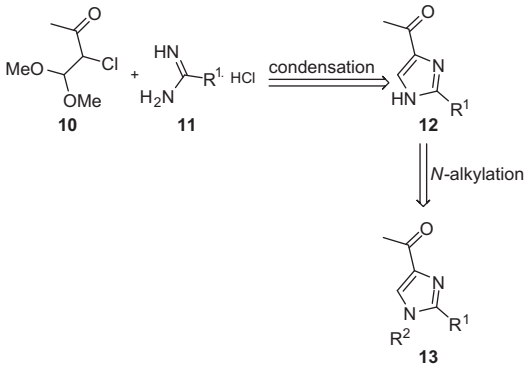
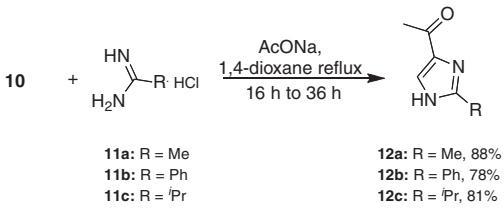


Scheme 1. Six-step synthesis of *N*-alkylated acetyl-imidazoles **9** from 5-methyl-isoxazole **6**.

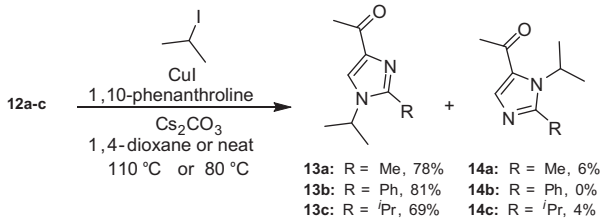


Scheme 2. Two step synthesis of *N*-alkylated acetyl-imidazoles from building blocks **10** and **11**.

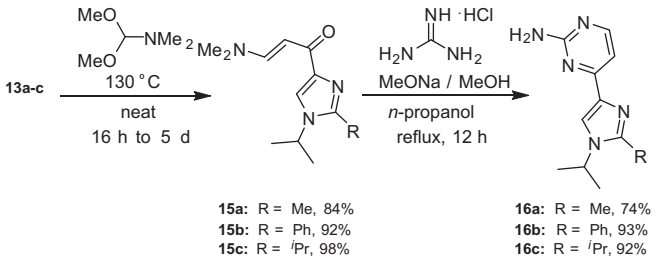


Scheme 3. Condensation reaction between the chloride **10** and amidines **11**.

solvents failed to give any alkylation products, we found that reaction of imidazoles **12** with *iso*-propyl iodide in the presence of copper(I) iodide, 1,10-phenanthroline and caesium carbonate in 1,4-dioxane or without solvent gave the expected *N*-*iso*-propyl-4-acetylimidazoles **13** in good yields and with excellent levels of regioselectivity. The minor regioisomers (**14a**, **14c**), detected and quantified by ^{1}H NMR spectroscopy, were easily removed by flash chromatography (Scheme 4). The structures of the imidazoles **13** were assigned unambiguously by NOE or NOESY experiments.



Scheme 4. Copper-catalyzed N-alkylation of imidazoles **12**.



Scheme 5. Synthesis of the 4-substitued 2-aminopyrimidines **16**.

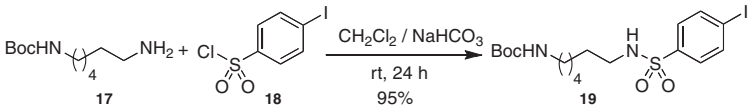
After developing an efficient synthesis of the 4-acetylimidazoles **13**, we next examined the introduction of the 2-aminopyrimidine moiety. Acetyl-imidazoles **13** were converted into enones **15** by reaction with neat DMF-dimethyl acetal. Subsequent reaction with excess guanidine hydrochloride and sodium methoxide in *n*-propanol at reflux gave the desired 4-substitued 2-amino-pyrimidines **16** in excellent yields over the two-step sequence (Scheme 5).

The sulfonamide unit **19** (Scheme 6) was readily prepared in 95% yield by condensation of 4-iodobenzenesulfonyl chloride (**18**) with mono-Boc-protected 1,6-diaminohexane **17**[13] using a biphasic system of dichloromethane and saturated aqueous sodium hydrogen carbonate at room temperature for 24 h.[14]

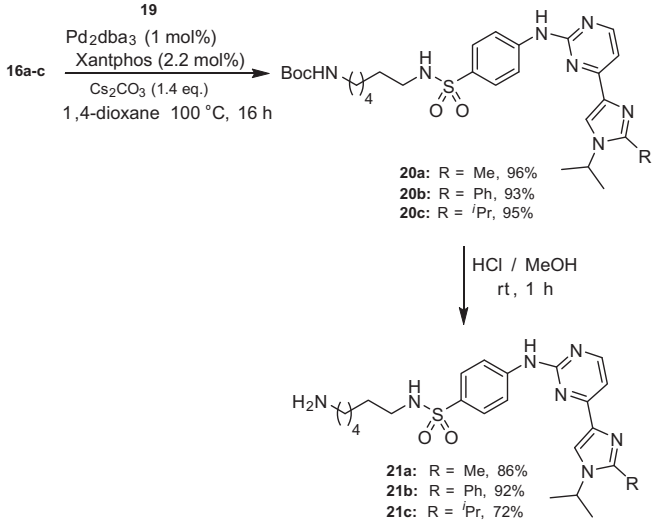
Attempted copper-catalyzed Ullmann arylation of 2-aminopyrimidines **16a–c** with 4-iodobenzenesulfonamide **19** using copper(I) iodide (25–100 mol %) and *N*,*N*′-dimethylethylenediamine (25–100 mol %), potassium or caesium carbonate in 1,4-dioxane at 100 °C[15] was unsuccessful and gave no coupled product. In contrast, palladium-catalyzed coupling with Pd_2dba_3 (1 mol %), Xantphos (2.2 mol %) and caesium carbonate in 1,4-dioxane at 100 °C gave the desired products **20** in excellent yields (Scheme 7),[16], which were Boc-deprotected using methanolic hydrogen chloride to provide amines **21a–c**.

With amines **21a–c** in hand, we evaluated their ability to inhibit several kinases and also their cellular activity. Initially we hoped to see good CDK7 inhibition, because we observed excellent CDK7 selectivity and potency with the hexamethylene diamine side chain in BS-181, containing the pyrazolo[1,5-*a*]pyrimidine core.[8] Changing this functionality on the pyrazolopyrimidine scaffold for more drug-like moieties resulted in diminished potency and selectivity. Therefore we decided to incorporate the BS-181 side chain in this new series of inhibitors, to seek to introduce CDK7-selectivity. Computational studies suggested that this side chain could form the same interaction with CDK7 as in BS-181 and analogues of BS-181. In addition, substituent changes at the imidazole C-2 position were expected to improve CDK7 selectivity. Unfortunately, these predictions were not confirmed by the experimental data. Table 1 shows the effects of imidazole C-2 substitution on activity. The imidazole **21a** with the small methyl group (entry 1) showed moderate CDK7 potency and low nM CDK2 inhibition. Changing to the *iso*-propyl group (**21c**, entry 3), resulted in decreased activity for CDK2 by 10-folds with hardly any inhibition of CDK7. Further increasing the steric bulk to a phenyl in imidazole **21b** completely suppressed inhibition (entry 2). The data shows good selectivity for CDK2 over CDK7 in the first two cases, with moderate IC_{50} values.

This observed influence of the size of the 2-position substituent is in good agreement with compounds prepared in the AstraZeneca laboratories,[6] suggesting a similar binding mode. Imidazole-pyrimidines **21a** and **21c** showed moderate growth inhibition of MCF-7 cells but this effect was at reduced levels for analogue **21b**. In general, the cellular data did not follow the kinase data, suggesting that imidazolyl-pyrimidines **21a–c** may also inhibit other targets.



Scheme 6. Formation of 4-iodobenzene-sulfonamide **19**.



Scheme 7. Palladium-catalyzed N-arylation and completion of the synthesis.

Table 1
CDK2, CDK7 and cellular inhibition by amines **21**

Entry	Amine	IC_{50}[a] CDK2 (nM)	IC_{50} CDK7 (nM)	GI_{50}[a] (μM)	TGI[a] (μM)	LC_{50}[a] (μM)
1	**21a**	26	1139	33	36	45
2	**21b**	4800	3425	37	75	>100
3	**21c**	225	3402	28	34	41

[a] IC_{50}: concentration that inhibits 50% of enzyme activity; GI_{50}: concentration that inhibits 50% of cell growth; TGI: concentration when cell growth stops; LC_{50}: concentration with 50% cell death.

In summary, the synthesis of the target imidazolyl-pyrimidines **21** have been achieved in six steps with overall yields ranging from 35% (R = Me, ^{i}Pr) to 46% for (R = Ph). Our synthetic approach uses a condensation reaction leading to 4-acetyl-imidazoles and palladium-catalyzed N-arylation of substituted 2-aminopyrimidines. Further applications of this methodology are under investigation and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.074.

References and notes

1. Noble, M. E. M.; Endicott, J. A.; Johnson, L. N. *Science* **2004**, *303*, 1800.
2. Pines, J. *Adv. Cancer Res.* **1995**, *66*, 181.
3. Morgan, D. O. *Annu. Rev. Cell Dev. Biol.* **1997**, *13*, 261.
4. Byrd, J. C.; Lin, T. S.; Dalton, J. T.; Wu, D.; Phelps, M. A.; Fischer, B.; Moran, M.; Blum, K. A.; Rovin, B.; Brooker-McEldowney, M.; Broering, S.; Schaaf, L. J.; Johnson, A. J.; Lucas, D. M.; Heerema, N. A.; Lozanski, G.; Young, D. C.; Suarez, J.-R.; Colevas, A. D.; Grever, M. R. *Blood* **2007**, *15*, 399.
5. (a) Anderson, M.; Beattie, J. F.; Breault, G. A.; Breed, J.; Byth, K. F.; Culshaw, J. D.; Ellston, R. P. A.; Green, S.; Minshull, C. A.; Norman, R. A.; Pauptit, R. A.; Stanway, J.; Thomas, A. P.; Jewsbury, P. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3021; (b) Byth, K. F.; Culshaw, J. D.; Green, S.; Oakes, S. E.; Thomas, A. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2245.
6. Jones, D. C.; Andrews, D. M.; Barker, A. J.; Blades, K.; Byth, K. F.; Finlay, M. R. V.; Geh, C.; Green, C. P.; Johannsen, M.; Walker, M.; Weir, H. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6486.
7. Reiter, L. A. *J. Org. Chem.* **1987**, *52*, 2714.
8. Ali, S.; Heathcote, D.; Kroll, S. H. B.; Scheiper, B.; Jogalekar, A. S.; Patel, H.; Brackow, J.; Siwicka, A.; Periyasamy, M.; Tolhurst, T. S.; Kanneganti, S. K.; Snyder, J. P.; Liotta, D.; Aboagye, E. O.; Barrett, A. G. M.; Coombes, R. C. *Cancer Res.* **2009**, *69*, 6208.
9. Reiter, L. A. *J. Org. Chem.* **1984**, *49*, 3494.
10. For the synthesis of amidines via trihaloethyl imidates, see: Caron, S.; Wei, L.; Douville, J.; Ghosh, A. *J. Org. Chem.* **2010**, *75*, 945; by reduction of amidoximes with potassium formate, see: Nadrah, K.; Dolenc, M. S. *Synlett* **2007**, 1257; by addition of amines to amides, see: Charette, A. B.; Grenon, M. *Tetrahedron Lett.* **2000**, *41*, 1677.
11. Schaefer, F. C.; Krapcho, A. P. *J. Org. Chem.* **1961**, *27*, 1255.
12. (a) Seto, M.; Miyamoto, N.; Aikawa, K.; Aramaki, Y.; Kanzaki, N.; Iizawa, Y.; Baba, M.; Shiraishi, M. *Bioorg. Med. Chem.* **2005**, *13*, 363; (b) Kaur, N.; Monga, V.; Josan, S. J.; Lu, X.; Gershengorn, M. C.; Jain, R. *Bioorg. Med. Chem.* **2006**, *14*, 5981; (c) Barrow, J. C.; Nantermet, P. G.; Stauffer, S. R.; Ngo, P. L.; Steinbeiser, M. A.; Mao, S. S.; Carroll, S. S.; Bailey, C.; Colussi, D.; Bosserman, M.; Burlein, C.; Cook, J. J.; Sitko, G.; Tiller, P. R.; Miller-Stein, C. M.; Rose, M.; McMasters, D. R.; Vacca, J. P.; Selnick, H. G. *J. Med. Chem.* **2004**, *46*, 5294.
13. Gardner, R. A.; Ghobrial, G.; Naser, S. A.; Phanstiel, O., IV *J. Med. Chem.* **2004**, *47*, 4933.
14. Christy, S. J.; Lim, B. B.; Vilner, B. J.; Geyer, B. C.; Bowen, W. D. *J. Med. Chem.* **1998**, *41*, 2445.
15. Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, *36*, 6084.
16. Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.