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Synthesis of Purines and Other Fused Imidazoles from Acyclic Amidines and Guanidines

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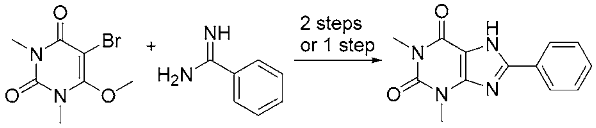
ABSTRACT



Purines, xanthines, and other fused imidazoles can be prepared from amidines or guanidines, with retrosynthetic disconnection at the ring fusion. Ring closure proceeds using Cu(I), with no special ligands required. The method allows for easy modification of the heterocyclic nucleus and is tolerant of functionality pendant to the ring system.

The purine nucleus is found in a wide variety of biologically active molecules including nucleotides, enzyme cofactors, intracellular second messengers, and pharmaceutical agents.[1] Methods for preparing analogues of these important molecules generally rely on substitution of the intact purine ring system. However, modification of the core is not a straightforward process, and the preparation of alternate heterocyclic systems often requires harsh reaction conditions that do not tolerate much functionality about the ring system. One retrosynthetic disconnection that would allow a high degree of variability within the core is formation of the imidazole ring (B ring) after assembly of any desired A ring (Figure 1). During the course of a program to prepare novel inhibitors of dipeptidyl peptidase IV,[2] we discovered an approach of this nature. The reaction is widely applicable to fused imidazole ring systems and occurs under milder conditions than traditional methods for preparing these molecules.

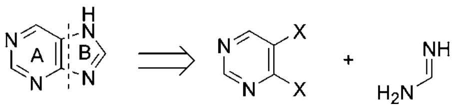
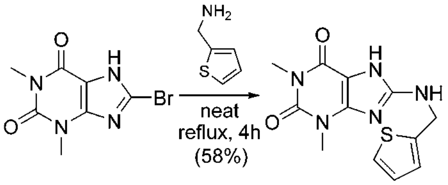


Figure 1. Disconnection of the purine nucleus at the ring fusion.

The xanthine system is a well-known scaffold for biologically active molecules, *e.g.*, caffeine. We wished to prepare xanthine mimetics with an amine substituent at the 8-position, but available methods required the use of a large excess of amine and extended heating times for introduction of this substituent[3] (Scheme 1). Guanidines such as Boc-aminopiperidine **1** are readily available in high yield via substitution of *N*-pyrazinylguanidine hydrochloride.[4] If these could be

Scheme 1. Traditional Substitution of Purine 8-Position



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(1) (a) Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J. D. *Molecular Biology of the Cell*, 3rd ed.; Garland: New York, 1994; p 736. (b) Gao, Z.; Duhl, D.; Harrison, S. D. *Ann. Rep. Med. Chem.* **2003**, *38*, 193.

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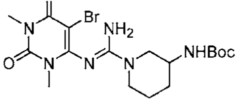
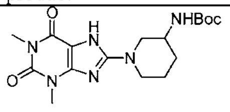
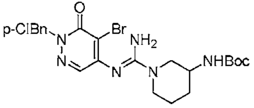
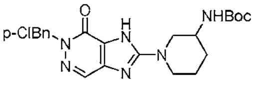
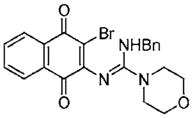
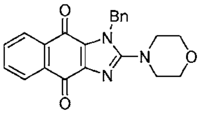
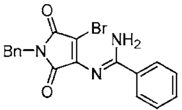
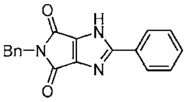
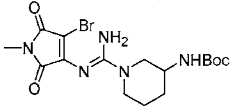
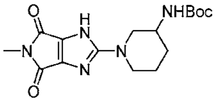
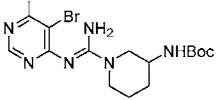
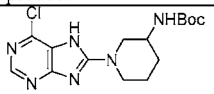
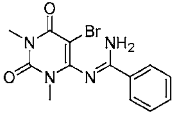
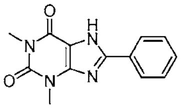
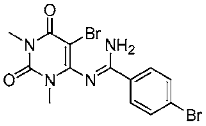
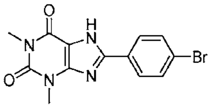
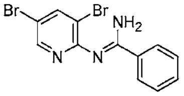
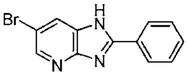
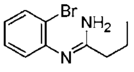
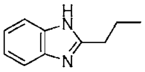
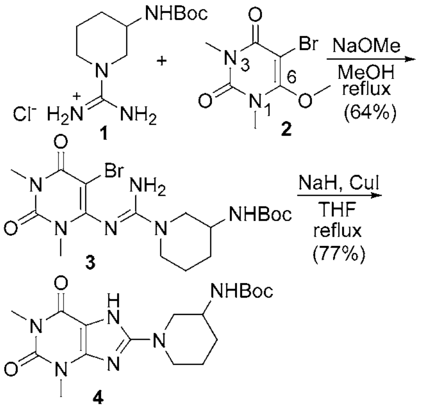
Table 1. Fused Imidazole Systems Prepared from Acyclic Guanidines and Amidines[a]

entry	acyclic precursor[a]	product[b]	yield[c]
1			77
2			81
3			84
4[d]			94
5			55
6[e]			73
7[f]			82
8			53
9			73
10			37

[a] Experimental procedures for the preparation of these amidines and fused imidazoles can be found in the Supporting Information. [b] Reactions were run in THF or dioxane solution at *ca.* 0.1 M substrate with 5 equiv of NaH and 5 mol % of CuI. For most substrates, 30 min at 65 °C was sufficient to effect complete ring closure. More electron-rich substrates (entries 9, 10) required higher temperatures. [c] Isolated yields. Ring closures were quantitative for all systems except entry 10 by HPLC or TLC. Some baseline material was present by TLC for entry 10. [d] One-pot sequence from benzamidine and dibromo-*N*-methylmaleimide gave 63%. [e] The acyclic pyrimidinoguanidine contained some inseparable 5-chloro compound. This can be isolated following ring closure of the bromide. [f] One-pot sequence gave the xanthine in 20% (unoptimized) yield.

fused to a uracil derivative such as bromide **2** under mild conditions, it would allow for easy modification of virtually any portion of the purine nucleus. Addition of the guanidine at the pyrimidine 6-position proceeded smoothly (Scheme 2), but initial attempts to close the ring under acidic, basic, or Pd-mediated conditions failed to give the desired product. However, when guanidinobromide **3** was allowed to stir with sodium hydride and a catalytic amount of copper(I) iodide at 65 °C, ring closure proceeded smoothly to give xanthine **4**.

Scheme 2. Mild Conditions for Purine 8-Substitution



The same chemistry can be used to close other fused imidazole ring systems, allowing for the easy assembly of substituted purine analogues (Table 1). Electron-deficient systems such as pyridazinone, quinone, and maleimide all proceeded under similar conditions, *i.e.*, addition−elimination of guanidine **1** followed by ring closure. Aromatic bromides are suitable for ring closure, but chlorides do not react.

The reaction also succeeds with amidines. Addition-elimination of benzamidines to uracils followed by ring closure gave the expected products (Table 1, entries 7, 8). More electron-rich systems such as *N*-pyridylamidine or *N*-phenylamidine (Table 1, entries 9, 10) were not readily accessible via addition−elimination chemistry, so these were prepared from arylamines and benzonitrile or butyronitrile (see the Supporting Information for details). These systems required higher temperatures for ring closure, but the reaction nonetheless gave the desired product. This strategy represents an alternative to the traditional preparation of benzimidazoles from phenylenediamines and carboxylic acids. If the addition reaction is run in an aprotic solvent, the second reaction can be performed in the same vessel (Table 1, entries 4, 7). The one-pot reaction did not succeed when the addition was performed using ethanol and potassium ethoxide or DMF and aq K_2CO_3. Although addition did occur, CuI addition

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(2) Wiedeman, P. E.; Trevillyan, J. M. *Curr. Opin. Inv. Drugs* **2003**, *4*, 412.

(3) Blythin, D. J.; Kaminski, J. J.; Domalski, M. S.; Spilter, J.; Solomon, D. M.; Conn, D. J.; Wong, S.-C.; Verbiar, L. L.; Bober, L. A.; Chiu, P. J. S.; Watnick, A. S.; Siegel, M. I.; Hilbert, J. M.; McPhail, A. T. *J. Med. Chem.* **1986**, *29*, 1099.

(4) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497.

did not catalyze ring closure in these media. We tried to extend this methodology to amides in the hope of producing either oxazoles or indolones, but amides failed to give any ring-closure products under the same conditions we used to prepare fused imidazoles.

Sodium hydride was our base of choice, but alkoxides and Cs_2CO_3 also promoted efficient ring closure in aprotic solvents. Reaction rates with other bases were significantly slower, but some ring closure was apparent with most of the bases we explored (Table 2). In particular, KOAc (Table 2, entry 6) gave the expected product, opening the possibility of performing the ring closure under very mild conditions with substrates intolerant of strong bases. Dioxane, THF, DMF, and DMSO all were suitable solvents.

Table 2. Percent Ring Closure for Table 1, Entry 7 with Various Bases[a]

entry	base	% product	entry	base	% product
1	NaH	>99	8	K_2CO_3	37
2	*t*-BuOK	>99	9	Na_2CO_3	35
3	NaOEt	>99	10	Et_3N	24
4	NaOMe	>99	11	*i*-Pr_2EtN	18
5	Cs_2CO_3	>99	12	$NaHCO_3$	12
6	KOAc	52	13	imidazole	<1
7	K_3PO_4	39	14	none	<1

[a] Reactions were run in dioxane at 100 °C at 0.12 M for 30 min with 5 mol % of CuI and 5 equiv of base. Each reaction was then checked by reversed-phase HPLC, and the ratio of product to starting material was determined by comparison with a standard curve.

The ring-closure mechanism likely follows the Cu-assisted aromatic nucleophilic substitution pathways outlined by Lindley.[5] Copper(I) is essential for the ring closure, but copper(I) iodide alone did not give the reaction. In recent years, Buchwald and co-workers have explored the copper-catalyzed coupling of different nitrogen functionalities with aryl halides.[6] The amidines and guanidines described here react under similar conditions, though no special copper ligands are required.

In conclusion, we have identified a general method for the preparation of fused imidazole systems. It allows for assembly of the ring system at the ring fusion, and the cores can be prepared in one step from an amidine or a guanidine and an A-ring precursor. The reaction works best on electron-deficient ring systems, but it can be performed on more electron-rich systems at elevated temperatures. Compared to previous methods, it offers the advantages of easily obtained reagents, lower temperatures, and relatively mild conditions for the preparation of fused imidazoles. It also increases the diversity of available starting materials, since many *o*-bromoanilines are commercially available or can be prepared in one step from the precursor anilines and aniline derivatives. In most cases, the ring closure proceeds cleanly, and pure products are obtained upon routine aqueous workup. This is an important advantage, since many purines are poorly soluble in common organic solvents and can be difficult to purify. The method has proven useful for the preparation of potent DPPIV inhibitors, and it will make the preparation of new purines and other fused imidazole systems simpler than is possible using previous methods.[7]

Acknowledgment. We dedicate this work to Professor Clayton Heathcock in recognition of his many contributions to the field of organic chemistry and in honor of his academic retirement. We also thank the R4MC and R47R scientists for their support of this work.

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

OL0504751

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[5] Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

[6] (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578.

[7] A series of DPPIV inhibitors prepared using this methodology will be reported soon.