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Chemoselective Arylamidine Cyclizations: Mild Formation of 2-Arylimidazole-4-carboxylic Acids

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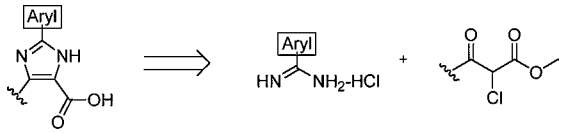
ABSTRACT



A versatile, one-pot synthesis of 2-arylimidazole-4-carboxylic acids from arylamidines and methyl-2-chloroacetoacetate is described. The transformation is chemoselective, and reaction conditions are mild. Moreover, the flexibility of the strategy offers rapid access to two important classes of biaryl compounds, both 2-arylimidazoles and 2-arylpyrimidines, depending simply upon solvent and base selection.

The importance of heterocycle construction in modern organic chemistry and drug design cannot be overemphasized. In particular, 2-aryimidazoles represent an important class of structures as a result of their reported antifungal,[1] NPY5 receptor antagonism,[2] and macromolecular ligand[3] properties. 2-Substituted imidazoles have been prepared by palladium-catalyzed couplings[4] or cyclocondensation chemistry.[5a−c]

Recently, we became interested in the preparation of 2-arylimidazoles having a carboxylic acid functional group in the 4-position. Since arylamidines are known to undergo cyclocondensations with α-halo ketones,[6] the use of arylamidines and halogenated acetoacetates seemed like a reasonable place to begin. Moreover, the proposed transformation would install the requisite carboxylic acid directly. Halogenated acetoacetates have been shown to undergo five-membered ring forming reactions with a variety of similar bidentate nucleophiles such as aminopyridines,[7] aminopyrazines,[8] aminopyridazines,[9] aromatic thiols,[10] arylcarboxamides,[11] and arylthiocarboxamides.[12]

Surprisingly, there are relatively few reports related to the preparation of 2-arylimidazoles from acetoacetates and arylamidines (Scheme 1). For example, Campbell and coworkers prepared a pyrrolopyrimidine from a substituted 2-chloroacetoacetate that could not cyclize to the imidazole.[13] DeAncos reported that the reaction between benza-

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(5) (a) From 2-bromoacetoacetaldehyde: Lipinski, C. A.; Blizniak, T. E.; Craig, R. H. *J. Org. Chem.* **1984**, *49*, 566. (b) From hydroximines: Gopalsamy, A.; Shi, M. X. *Org. Lett.* **2003**, *5*, 3907. (c) From vicinal tricarbonyls: Brackeen, M. F.; Stafford, J. A.; Feldman, P. L.; Karanewsky, D. S. *Tetrahedron Lett.* **1994**, *35*, 1635.

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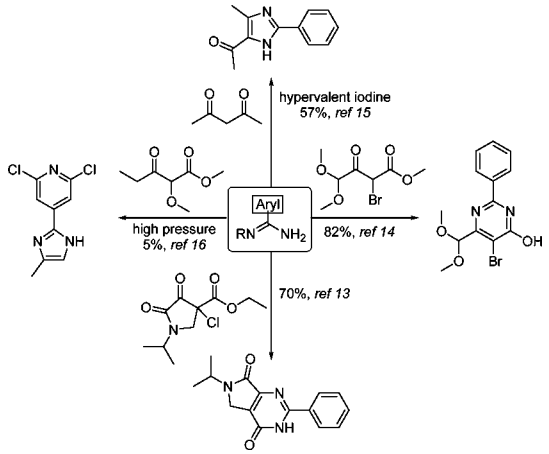
Scheme 1. Related Arylamidine Cylizations



midine and a 2-bromoacetoacetate in chloroform led to *pyrimidine* formation in 82% yield.[14] Alternatively, a 2-arylimidazole was prepared in 57% yield from benzamidine and a diketone but hydroxy(tosyloxy)iodobenzene, a hypervalent iodine sourse, was required.[15] Finally, Jezewski reacted a 2-methoxyacetoacetate and reported the formation of a 2-arylimidazole as a decomposition product isolated in 5% yield under nonideal reaction conditions (10.0 kbar, 65 h).[16]

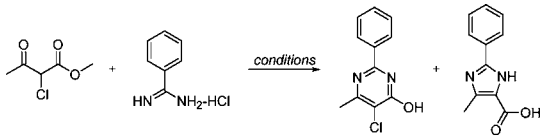
Intrigued by the untapped potential of this reaction, we set out to establish reaction conditions that would provide the desired 2-arylimidazole-4-carboxylic acids more efficiently. Herein, we report that arylimidazole analogues can be selectively formed under aqueous basic conditions. Optimized reaction conditions are depicted in Table 1.

In general, reactivity was observed under most conditions with the exception of no base (entry 1), large excess of base (entry 10), or some solvents such as DMA (entry 3). Optimization of arylimidazole formation began with the screening of numerous bases in water (partial data shown).

The best chemoselectivity was observed in the presence of hydroxide bases (entries 6−9). Tertiary amine bases in water provided weaker selectivity (entry 11) as did elevated temperatures (entry 18) or excess acetoacetate (entry 20). Selectivity for arylpyrimidine formation was observed under most nonaqueous conditions with the exception of DBU in acetonitrile (entry 17). Triethylamine in acetone (entry 12), THF (entry 14), or acetonitrile (entry 15) provided the best selectivity, with acetonitrile having a slightly cleaner reaction profile. Excess base in this solvent system provided little advantage (entry 16).

Mechanistically, it is presumed that the amidine has three paths of reactivity (Scheme 2). Condensation with the ketone (rate = k_1) must occur regardless of which biaryl system is ultimately formed. Under aqueous basic conditions, formation of the carboxylate slows the rate of condensation with the amidine (k_3). Therefore, displacement of the chloride (rate = k_2) becomes preferred. This route results in imidazole formation. Alternatively, in the absence of ester hydrolysis, amidine condensation with the methyl ester (rate = k_3) is preferred to chloride displacement (rate = k_2) and this path proceeds towards the formation of the pyrimidine.

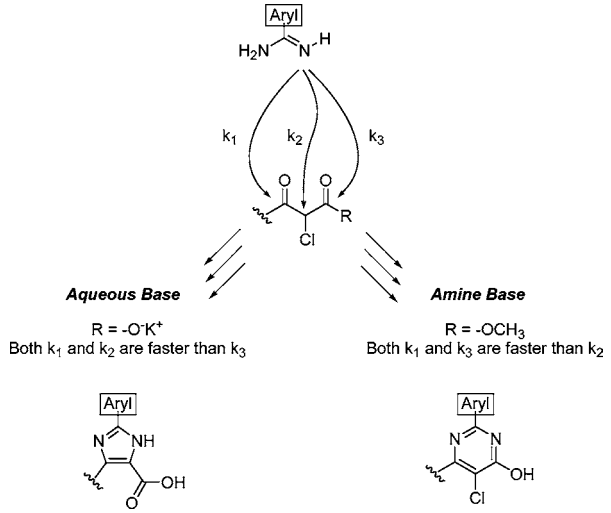
Table 1. Optimization of Reaction Conditions[a]



no.	base (mol %)	solvent	ratio 3:4
1	none	MeCN	nr
2	NaOH (120)	MeCN	1:1
3	NaOH (120)	DMA	trace
4	NaOH (120)	MeOH	1:2
5	NaOH (120)	EtOH/H_2O (2:1 v/v)	1:1
6	NaOH (120)	H_2O	1:3
7	Na_2CO_3 (120)	H_2O	1:1
8	K_2HPO_4 (120)	H_2O	1:1
9	KOH (120)	H_2O	1:4
10	KOH (500)	H_2O	trace
11	Et_3N (120)	H_2O	1:1
12	Et_3N (120)	acetone	5:1
13	Et_3N (120)	DMA	trace
14	Et_3N (120)	THF	3:1
15	Et_3N (120)	MeCN	5:1
16	Et_3N (500)	MeCN	5:1
17	DBU (120)	MeCN	trace
18[b]	NaOH (120)	H_2O	1:2
19[b]	Et_3N (120)	MeCN	4:1
20[c]	NaOH (120)	H_2O	1:1
21[c]	Et_3N (120)	MeCN	4:1

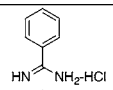
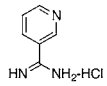
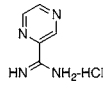
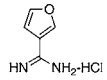
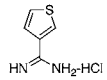
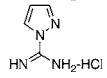
[a] All reactions were run under nitrogen and at 600 mM, **1** (100 mol %), and **2** (100 mol %) unless noted otherwise. Ratios were measured by HPLC with UV detection at 220 nm and indicate apparent crude reaction profiles. [b] 80 °C. [c] **1** (200 mol %).

Scheme 2. Rationale for Selectivity



(13) Campbell, J. B.; Firor, J. W. *J. Org. Chem.* **1995**, *60*, 7687.
(14) DeAncos, B.; Delgado, F.; Martin, M. R. *An. Quim.* **1995**, *91*, 413.
(15) Zhang, P. F.; Chen, Z. C. *Synthesis-Stuttgart* **2001**, *14*, 2075.
(16) Jezewski, A.; Jurczak, J.; Lidert, Z.; Tice, C. M. *J. Heterocycl. Chem.* **2001**, *38*, 645.

Table 2. Representative Amidine Substrates[a]

#	Aryl-amidine	Cond-itions	Aryl-imid.	Aryl-pyrim.	Ratio[a] Imid:Pyrim
1		A	71%	-	4:1
		B	-	83%	1:5
2		A	64%	-	3:1
		B	-	81%	1:3
3		A	51%	-	5:1
		B	-	43%	1:2
4		A	84%	-	5:1
		B	-	90%	1:8
5		A	68%	-	5:1
		B	-	88%	1:2
6		A	45%	-	3:1
		B	-	59%	1:2

[a] Percentages indicate isolated yields. Ratios were measured by HPLC with UV detection at 220 nm and indicate apparent crude reaction profiles. Conditions A and B are described in the general procedure section of Supporting Information.

The current route offers a number of advantages over previous strategies. First, the reaction conditions are one-pot, fast, and mild; there is no need for harsh oxidants such as hypervalent iodine, high temperature, or high pressure. Second, the resulting 2-arylimidazoles contain a useful carboxylic acid functional group in the 4-position that is easily derivatizable. Finally, the biaryl product profile of the reaction can be tuned by a simple adjustment in reaction conditions. This unique attribute can be fully exploited in biaryl library format where clever access to diversity and ease of reagent selection are critical.

Application of these two sets of optimal conditions (Table 1, entries 9 and 15) to the synthesis of a small series of simple heterocyclic biaryls is depicted in Table 2. All reactions led cleanly to the formation of arylimidazoles and arylpyrimidines with the predicted biaryl product preferred. The same reactions performed under microwave irradiation (see General Procedure, Condition C) resulted in similar chemoselectivity and mass balance but reduced reaction times (data not shown).

These simple protocols for selectivity provide rapid access to a wide variety of novel biaryls starting from inexpensive and readily available starting materials reacting under simple chemical conditions.

Supporting Information Available: Spectroscopic and analytical data are available for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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