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A Direct, One Step Synthesis of Imidazoles from Imines and Acid Chlorides: A Palladium Catalyzed Multicomponent Coupling Approach

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Imidazoles have found utility in a diverse range of areas,[1] with examples including drug cores (e.g., angiotensin II inhibitors,[2a] anti-inflammatory,[2b] and anticancer[2c] agents), conjugated and functional polymers,[3a] natural products,[3b,c] and coordination complexes.[3d] Imidazoles are also important as ligands in metalloenzymes[4] and, more recently, have been found to serve as precursors to environmentally friendly ionic solvents[5] and carbene ligands.[6] In light of their wide use, many synthetic approaches have been developed to generate these heterocycles. This includes traditional cyclocondensation methods[1] (e.g., with presynthesized 1,2-diketones,[7a] α-sulfonylisocyanides,[7b] or α-ketoamides[7c]) and a number of efficient recent cyclization routes.[8] In addition, imidazoles can be prepared via stepwise substitution reactions on simple imidazoles, including catalytic C−H activation,[9] cross coupling,[10] or aromatic substitution reactions.[1,11]

While all effective, these methods often require multiple steps to prepare diversely substituted imidazoles. An intriguing alternative approach to imidazoles could involve considering their structure as made up of multiple, simple, and easily diversified reagents, put together all at once by metal catalysis. This can provide an attractive method to both easily generate products and, at the same time, independently vary substituents, in a single step, as illustrated in the Pauson−Khand,[12] alkyne trimerization,[13] amidocarbonylation,[14] and a range of more recent catalytic multicomponent syntheses.[15] We report herein the design of such a direct metal-catalyzed synthesis of imidazoles, providing overall a highly modular, one-step route to these heterocycles.

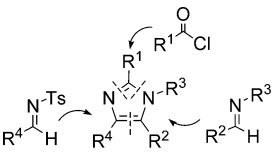
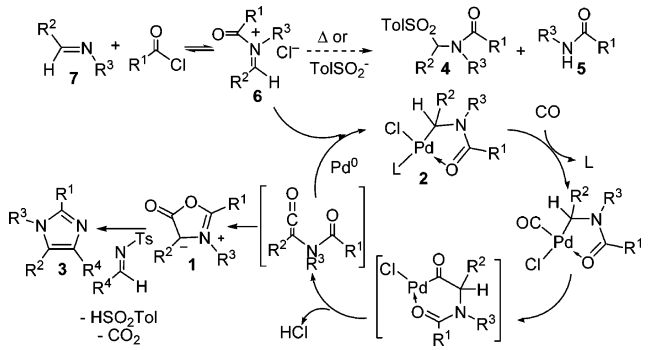


Figure 1. A multicomponent approach to imidazole synthesis.

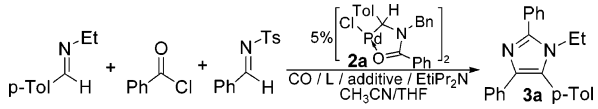
Our approach to this synthesis involves considering the imidazole core as the product of two imines and an acid chloride (Figure 1), each of which is readily available in many forms. This is based upon our recently observed palladium-catalyzed coupling of imine, acid chloride, and carbon monoxide to generate 1,3-oxazolium-5-olates (Münchnones, **1**).[16] As such, we considered the possibility that performing this catalytic reaction in the presence of *N*-tosyl-substituted imines, which can undergo in situ 1,3-dipolar cycloaddition with Münchnones,[8e] could provide a route to construct imidazoles. While mechanistically plausible (Scheme 1), this reaction would require the selective coupling of two similar imine substrates in a single reaction; a feature that has proven challenging for multicomponent reactions.[13] Nevertheless, our initial attempt toward this direct synthesis was encouraging. The reaction of (*p*-tolyl)HC═NEt, (Ph)HC═NTs, PhCOCl, and CO in the presence of the previously developed catalyst **2a**[16] led to the consumption of starting materials over the course of 24 h and did form imidazole **3a**, though in low yield (28%, Table 1).

Scheme 1. Postulated Mechanism for Imidazole Synthesis



Closer examination of the reaction products shows the low imidazole yield is due to two competing processes, leading to the formation an α-sulfonylamide **4** (25%) and amide **5** (46%) (Scheme 1). These presumably arise from the in situ generated iminium salt **6**, via either attack of the sulfonyl anion released by cycloaddition or decomposition, respectively.[17] On the basis of this postulate, the efficiency of this reaction can be improved by inhibiting these steps. First, since iminium salt decomposition to **5** is a thermal process competing with catalysis, its role can be limited by lowering the temperature and accelerating the reaction with CO pressure (entry 3). The addition of phosphine ligands can further accelerate catalysis, with the bulky P(*o*Tol)$_3$ allowing imidazole formation in 60% yield. The inhibition of sulfonylamide **4** proved more challenging since sulfonyl anion formation is part of the catalytic mechanism and its attack on **6** is rapid.[17] However, experiments with an independently synthesized **4** demonstrate that the addition of LiCl can lead to the equilibrium regeneration of **6**. Similarly, while several salts inhibit the reaction,[17] LiCl completely suppresses

Table 1. A One-Step Catalytic Synthesis of Imidazole **3a**



no.	temp (°C)	[CO][a]	Pd cat	L[b]	additive[c]	%[d]
1	65	1	**2a**		Bu_4NBr	28
2	45	1	**2a**		Bu_4NBr	28
3	45	4	**2a**		Bu_4NBr	43
4	45	20	**2a**		Bu_4NBr	48
5	45	4	**2a**	PPh_3		0
6	45	4	**2a**	P^{t}Bu$_3$		58
7	45	4	**2a**	P(*o*Tol)$_3$		60
8	45	4	**2a**	P(*o*Tol)$_3$	Bu_4NCl	25
9	45	4	**2a**	P(*o*Tol)$_3$	LiOTf	20
10	45	4	**2a**	P(*o*Tol)$_3$	LiBr	54
11	45	4	**2a**	P(*o*Tol)$_3$	LiCl	76
12	45	4	Pd_2dba_3·$CHCl_3$	P(*o*Tol)$_3$	LiCl	68
13	45	4	$Pd(PPh_3)_4$	P(*o*Tol)$_3$	LiCl	0
14	45	4	**2a**	P(*o*Tol)$_3$	LiCl	79[e]

[a] Measured in atm. [b] With 15 mol %. [c] With 3 equiv. [d] NMR yield. [e] With Ph(H)C═N($SO_2C_6H_4Cl$).

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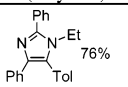
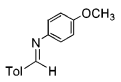
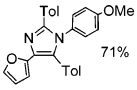
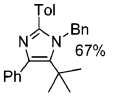
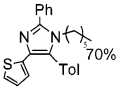
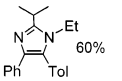
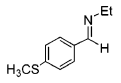
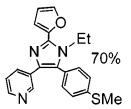
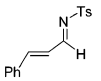
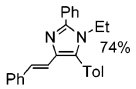
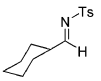
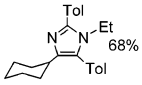
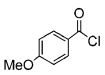
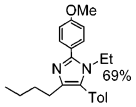
Table 2. A Modular Catalytic Synthesis of Imidazoles[a]

cpd	imine	acid chloride	tosyl imine	**3** (% yield)
a		PhCOCl		 76%
b		p-TolCOCl		 71%
c		p-TolCOCl		 67%
d		PhCOCl		 70%
e				 60%
f				 70%
g		PhCOCl		 74%
h		p-TolCOCl		 68%
i				 69%

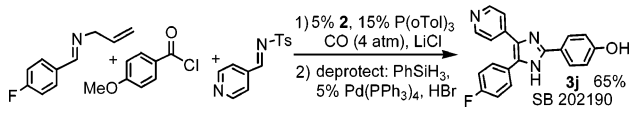
[a] Conditions: 0.68 mmol imine, 0.82 mmol tosyl imine, 0.95 mmol acid chloride, 5 mol % of **2**, 15 mol % of P(*o*Tol)$_3$, 3 equiv of NEt*i*Pr$_2$/LiCl, 4 atm CO, 45 °C, 18 h.

4 and provides, overall, a very selective method to catalytically couple these three reagents directly into an imidazole (entry 11). Notably, commercially available Pd_2dba_3 is also an effective catalyst for this reaction.

As shown in Table 2, since the building blocks employed are all commercially available or readily prepared, this reaction can be directly applied to the one-step synthesis of diversely substituted imidazoles. *N*-alkyl and *N*-aryl imines can be used in this coupling, as can imines of aromatic and even nonenolizable alkyl (**3c**) aldehydes. Similarly, aryl, heteroaryl, and alkyl acid chlorides can all be employed. Even greater diversity can be achieved with the *N*-tosylimines, including aryl, alkyl, heterocyclic, and α,β-unsaturated substituents. While enolizable imines cannot be employed with *N*-alkyl-substituted imines, they can be added via the *N*-tosylimine (**3h,i**). This reaction also displays good functional group compatibility and even proceeds in the presence of coordinating functionalities (**3d,f**), all generating substituted imidazoles in good yield.

Interestingly, while this reaction involves the simultaneous coupling of different imines, no products incorporating two of the same imine are observed. This selectivity is believed to result from the catalytic mechanism (Scheme 1).[16] In particular, the *N*-tosylimine is not sufficiently nucleophilic to interact with the acid chloride, thus it is only imine **7** that is incorporated into iminium salt **6** and ultimately forms Münchnone **1**. However, once **1** is generated, it reacts exclusively with the more electron-poor imine via cycloaddition. Consistent with this mechanism, the more electron-deficient *p*-chlorosulfonylimine leads to higher imidazole yield (Table 1, no. 14).[18] Important from a synthetic perspective, this provides complete regiochemical control of all the substituents about the ring, where each unit can be independently varied by choice of imine(s) and acid chloride reagents.

We have begun to probe the utility of this reaction to provide access to imidazole targets. **3j** has been demonstrated to be a potent p38 MAP kinase inhibitor and lead in the design of new anti-inflammatory agents.[2b] While the previously reported route to **3j** is a multistep process via 1,2-diketones, this catalytic coupling can allow the one-pot, regioselective assembly of **3j** directly from available imine and acid chloride substrates, after deprotection.



In conclusion, the palladium-catalyzed coupling of imines and acid chloride can be used to provide a new, one-step method to synthesize imidazoles. Considering the efficiency of this reaction, and availability of the building blocks, this provides a very straightforward method to assemble these products. Experiments directed toward its application to other targets are underway.

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Supporting Information Available: Synthesis and characterization of **3a**−**j**; experiments in ref 17. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Warming **6** to 65 °C with NEt*i*Pr$_2$ leads to **5** (63%, 12 h). **6** reacts with LiSO$_2$Tol form **4** in 5 min at rt. The addition of LiCl (3 equiv) to **4** regenerates **6** in 1/2 h (79%). Other salts in Table 1 do not react with **4**.
(18) Münchnone **1** also decomposes under the catalytic conditions (ref 16).

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