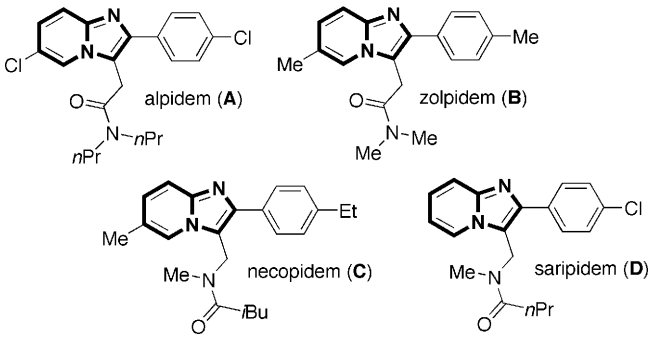
Multicomponent Reactions

DOI: 10.1002/anie.200907291

General and Efficient Copper-Catalyzed Three-Component Coupling Reaction towards Imidazoheterocycles: One-Pot Synthesis of Alpidem and Zolpidem**

*Natalia Chernyak and Vladimir Gevorgyan**

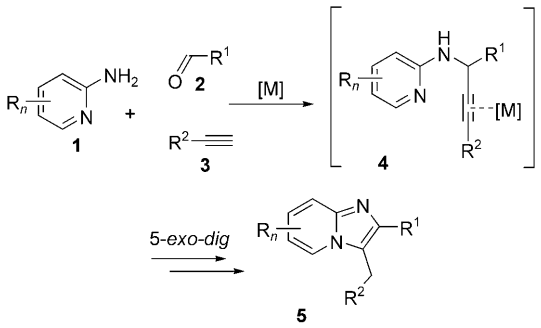
Imidazopyridine is an important pharmacophore, and is widely found in many biologically active compounds.[1] In particular, imidazo[1,2-*a*]pyridine is an essential fragment present in pharmacologically important molecules, which include several anxyolytic drugs,[2] such as alpidem (**A**),[2a,b] necopidem (**C**), saripidem (**D**), and the drug used to treat insomnia zolpidem (**B**)[2c,d] (Scheme 1). Although a variety of



Scheme 1. Imidazo[1,2-*a*]pyridine-based drugs.

synthetic methods for the synthesis of these important frameworks has been developed,[3] most of them are limited in scope and require multistep preparation of the starting materials.[4] Accordingly, development of straightforward and general methods for the synthesis of imidazo[1,2-*a*]pyridines from easily available precursors is highly warranted. Herein, a general and efficient synthesis of imidazopyridines **5** by the copper-catalyzed three-component coupling (TCC) reaction of 2-aminopyridines **1** with aryl aldehydes **2** and alkynes **3** is reported (Scheme 2).

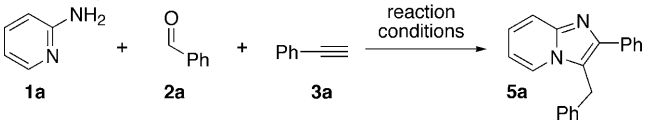
We reasoned that the imidazo[1,2-*a*]pyridyl core **5** could be assembled by a π-philic metal-catalyzed 5-*exo-dig* cyclization[5] of propargylamine **4** (Scheme 2). The latter, in turn, should be accessible through a three-component coupling



Scheme 2. Synthesis of imidazopyridines by a TCC approach.

reaction of 2-aminopyridine **1**, aldehyde **2,** and terminal alkyne **3**.[6] Notably, the 5-*exo-dig* cyclization of **4** to **5** should secure the formation of the imidazo[1,2-*a*]pyridylmethyl unit, a common fragment of the previously mentioned, biologically important molecules[2] (Scheme 1). To test this hypothesis, we examined the reaction in the presence of different metal catalysts. Accordingly, $NaAuCl_4$, known to be an efficient catalyst for the synthesis of indolizines through a TCC reaction,[7] was first tested. However, no desired product was formed under these reaction conditions (Table 1, entry 1). Further optimization revealed copper salts to be more efficient catalysts for this transformation. Thus, reactions in the presence of 5 mol% of $Cu(OTf)_2$ produced **5a** in 10%

Table 1: Optimization of the TCC reaction conditions.[a]



1a **2a** **3a** **5a**

Entry	Catalyst (mol%)	Solvent	*T* [°C]	Yield of **5a** [%][b]
1	$NaAuCl_4 \cdot 2H_2O$ (5)	toluene	120	0
2	$Cu(OTf)_2$ (5)	toluene	120	10
3	CuCl (10)	toluene	120	55
4	CuCl (50)	toluene	120	74
5	CuCl (5), $Cu(OTf)_2$ (5)	MeCN	100	15
6	CuCl (5), $Cu(OTf)_2$ (5)	DMA	120	78
7	**CuCl (5), $Cu(OTf)_2$ (5)**	**toluene**	**120**	**93**
8	CuCl (5), $Cu(OTf)_2$ (5)	toluene	120	76[c]

[a] Reaction conditions: 2-aminopyridine (0.1 mmol), benzaldehyde (0.105 mmol), acetylene (0.11 mmol), CuCl (0.005 mmol), $Cu(OTf)_2$ (0.005 mmol), solvent (1 M, 0.1 mL), 16 h. [b] Yields were determined by GC-MS analysis with pentadecane as an internal standard. [c] Reaction was performed in air. DMA = *N*,*N*-dimethylacetamide.

[*] N. Chernyak, Prof. V. Gevorgyan
Department of Chemistry, University of Illinois at Chicago
845 West Taylor Street, Room 4500, Chicago, IL 60607 (USA)
Fax: (+1) 312-355-0836
E-mail: vlad@uic.edu
Homepage: http://www.chem.uic.edu/vggroup

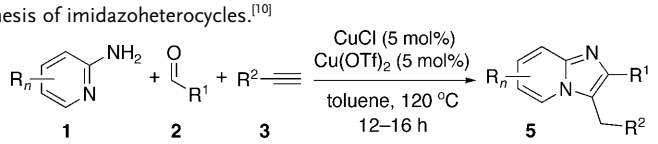
[**] The support of the NIH (1P50 GM-086145) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200907291.

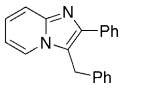
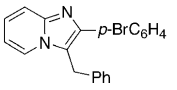
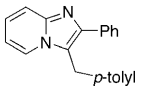
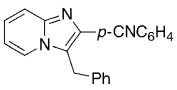
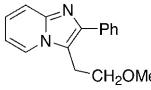
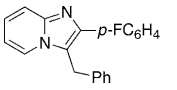
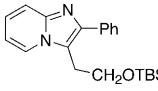
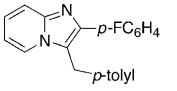
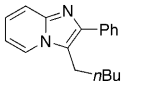
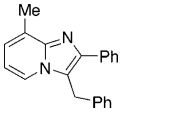
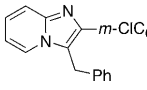
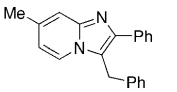
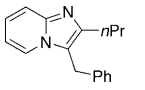
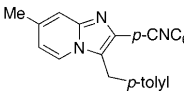
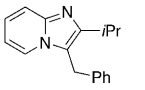
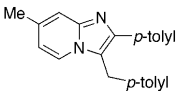
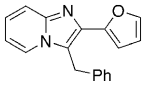
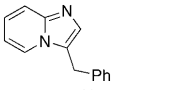
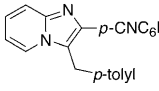
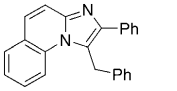
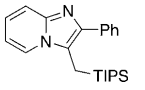
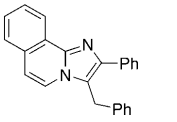
yield (Table 1, entry 2). Meanwhile, the use of 10 mol% of CuCl resulted in a dramatic improvement in the yield (55%; Table 1, entry 3). However, reactions in the presence of 50 mol% of CuCl produced **5a** in only 74% yield. (Table 1, entry 4). Employment of the CuCl/Cu(OTf)$_2$[8] binary catalytic system[9] in MeCN at 100°C provided the desired product **5a** in 15% yield (78%; Table 1, entry 5). Surprisingly, the use of DMA at 120°C substantially improved the reaction outcome (78%; Table 1, entry 6). Finally, replacement of DMA with the less polar toluene afforded imidazopyridine **5a** from 2-aminopyridine **1a** (1 equiv), aldehyde **2a** (1.05 equiv), and alkyne **3a** (1.5 equiv) in excellent yield (93%; Table 1, entry 7). The reaction performed in air provided **5a** in lower yield (76%; Table 1, entry 8).

Next, the generality of this novel TCC reaction was examined (Table 2). To our delight, we found this transformation to be very general for a wide range of aldehydes and alkynes, and provided easy access to densely substituted imidazopyridine derivatives **5**. Thus, employment of different alkyne substrates, bearing aryl (Table 2, entries 1, 2, 6–10, and 12–22), alkyl (Table 2, entries 3–5), or silyl (Table 2, entry 11) substituents, produced imidazopyridines in good to exellent yields. Aryl and alkyl aldehydes also displayed good reactivity in this reaction. A variety of functional groups substituted at the aromatic ring of the aldehyde substrate, such as chloro (Table 2, entry 6), bromo (Table 2, entry 12), cyano (Table 2, entries 10, 13, and 18) and fluoro (Table 2, entries 14 and 15) groups were tolerated. The reaction with propyl and isopropyl aldehydes was uneventful, and furnished C2-alkyl-substituted imidazopyridines **5g** and **5h**, respectively (Table 2, entries 7 and 8). Employment of furan-2-carbaldehyde led to bishetaroaryl compound **5i** in 78% yield (Table 2, entry 9). Formaldehyde, however, was less reactive and provided monosubstituted imidazopyridine **5t** in moderate yield (Table 2, entry 20). Furthermore, 2-aminoquinoline and 2-aminoisoquinoline reacted well in this transformation, thus affording imidazoquinoline **5u** and imidazoisoquinoline **5v**, respectively, in good yields (Table 2, entries 21 and 22).

Table 2: Synthesis of imidazoheterocycles.[10]

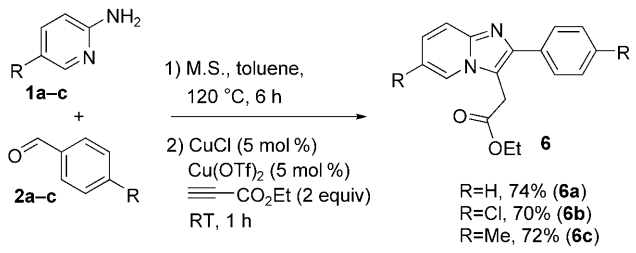


1 **2** **3** **5**

Entry		Product	Yield [%][a]	Entry		Product	Yield [%][a]
1	**5a**		92	12	**5l**		89
2	**5b**		90	13	**5m**		80
3	**5c**		79	14	**5n**		90
4	**5d**		70	15	**5o**		86
5	**5e**		44[b]	16	**5p**		50[c]
6	**5f**		81	17	**5q**		61
7	**5g**		56[b]	18	**5r**		87
8	**5h**		60	19	**5s**		83
9	**5i**		78	20	**5t**		50[c]
10	**5j**		82	21	**5u**		70
11	**5k**		73	22	**5v**		65

[a] Yield of isolated product. [b] Product decomposes upon prolonged heating. [c] Some 2-aminopyridine and benzaldehyde did not react. [d] Corresponding imine was isolated in 48% yield. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

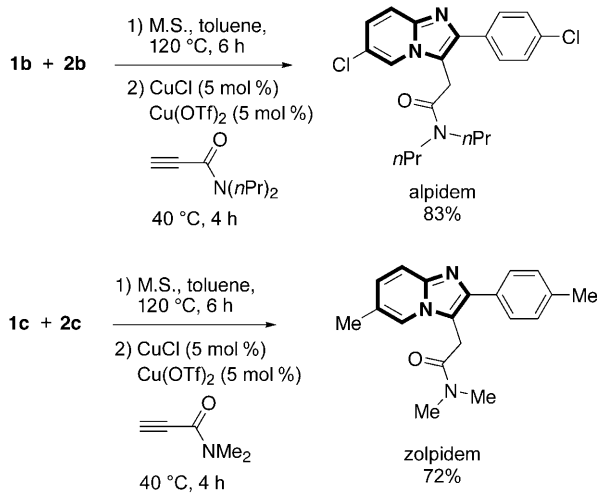
Next, we attempted the synthesis of alpidem (**A**) and zolpidem (**B**) through this novel three-component coupling reaction. It should be mentioned that these drugs are usually synthesized by multistep procedures.[11] We hypothesized that **A** and **B** could rapidly be accessed through a three-component coupling reaction of the appropriate aminopyridine, aldehyde, and corresponding propiolamide. We recognized that employment of propiolamide as a starting material would be challenging, as this Michael acceptor would not be tolerated in the first step of the sequence. Thus, we performed model studies of the TCC reaction with propiolates (Scheme 3). It was found that imidazopyridines **6a–c** could be synthesized in good yields in a one-pot fashion, where ethyl



Scheme 3. Model studies of the one-pot TCC reaction. M.S. = molecular sieves (4 Å).

propyolate and copper catalysts were added to the reaction mixture upon completion of the dehydrocondensation step.

By using the newly established protocol, the one-pot syntheses of zolpidem and alpidem were carried out by employing the corresponding propiolamides (Scheme 4). Gratifyingly, the sequential TCC reaction of 2-amino-5-



Scheme 4. One-pot synthesis of alpidem and zolpidem.

chloropyridine (**1b**) and *p*-chloroaldehyde (**2b**) with *N*,*N*-dipropylpropiolamide produced alpidem (**A**) in 83% yield. Likewise, the reaction of 2-amino-5-methylpyridine (**1c**), and *p*-tolualdehyde (**2c**) with *N*,*N*-dimethylpropiolamide afforded zolpidem (**B**) in 72% yield.

In conclusion, we have developed a general and highly efficient method for the synthesis of imidazopyridine derivatives by the copper-catalyzed three-component coupling reaction of aryl, heteroaryl, and alkyl aldehydes with 2-aminopyridines and terminal alkynes. The employment of 2-aminoquinoline and 2-aminoisoquinoline as coupling partners in this transformation led to imidazoquinoline and imidazoisoquinoline frameworks in good yields. The synthetic utility of this novel TCC reaction has been illustrated in a highly efficient one-pot synthesis of alpidem and zolpidem.

Experimental Section

Typical procedure for the synthesis of imidazopyridines **5a–v**: 2-Aminopyridine **1** (0.5 mmol), CuCl (2.5 mg, 0.025 mmol, 5 mol%), $Cu(OTf)_2$ (9.04 mg, 0.025 mmol, 5 mol%), and aldehyde **2** (only added at this point if solid) was added to a Weaton (1 mL) microreactor in a glovebox under an inert atmosphere. Subsequently, anhydrous toluene (500 μL, 1M), aldehyde **2** (0.525 mmol, 1.05 equiv), and alkyne **3** (0.75 mmol, 1.5 equiv) were added to the mixture. The microreactor was capped with a Teflon pressure cap and placed into a preheated (120°C) aluminum heating block. The reaction mixture was heated at 120°C until full consumption of 2-aminopyridine **1** (as evident by GC-MS analysis). Upon completion (12–16 h) of the reaction the mixture was filtered through a plug of neutral alumina (eluent: EtOAc). The filtrate was concentrated under reduced pressure to give the crude material, which was purified by column chromatography on silica gel (eluent: Et_3N/EtOAc/hexanes 4:17:84), and afforded imidazopyridine **5**.

Received: December 26, 2009
Published online: March 8, 2010

Keywords: cyclization · heterocycles · homogeneous catalysis · imidazopyridines · multicomponent reactions

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[7] B. Yan, Y. Liu, *Org. Lett.* **2007**, *9*, 4323.

[8] Apparently, CuCl is a better catalyst for the synthesis of propargylamine **4** by the three-component coupling reaction of the corresponding 2-aminopyridine, aldehyde, and acetylene, whereas $Cu(OTf)_2$ is more efficient for the subsequent 5-*exo-dig* cyclization of **4** to give the imidazo[1,2-a]pyridyl core **5**. See Ref. [9] and the discussion therein.

[9] For use of the Cu^{I}/Cu^{II} binary system in the synthesis of benzofuran derivatives, see: N. Sakai, N. Uchida, T. Konakahara, *Tetrahedron Lett.* **2008**, *49*, 3437.

[10] See the Supporting Information for details.

[11] a) Y. Sumalatha, T. R. Reddy, P. P. Reddy, B. Satyanarayana, *ARKIVOC* **2008**, *2*, 315; b) J. Allen, G. Parent, A. Tizot, *J. Labelled Compd. Radiopharm.* **1986**, *23*, 807; c) J. Allen, A. Tizot, *J. Labelled Compd. Radiopharm.* **1986**, *23*, 393; for patents, see the Supporting Information.

