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Pd-Catalyzed One-Pot Synthesis of Polysubstituted Acrylamidines from Isocyanides, Diazo Compounds, and Imines

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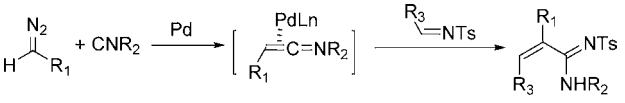
ABSTRACT



A novel and efficient Pd-catalyzed one-pot reaction of ethyl diazoacetate, isocyanides, and imines for the synthesis of acrylamidines was developed. The multicomponent reaction may have occurred through an unpredicted ring-opening process of the ketenimine−imine [2 + 2] intermediate to form the acrylamidine products.

Multicomponent reactions, which involve three or more starting materials to furnish the desired products in a one-pot cascade reaction pattern, have been extensively applied in organic synthesis because of their conciseness and high efficiency.[1] Ketenimines as potential intermediates have attracted much attention in this area, and the cascade reactions based on ketenimines are widely explored, typically by trapping the ketenimine intermediates *via* nucleophilic addition, radical addition and/or pericyclic reactions, and so forth.[2] In such reactions, the ketenimine intermediates are generally generated *in situ* through copper-catalyzed azide−alkyne cycloaddition reaction (CuAAC)[2e,3] or other traditional methods[2] such as Wittig reactions,[4] elimination reactions,[5] rearrangement reactions,[6] and

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(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) von Wanglin, A. J.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 4286. (d) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (e) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (f) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (g) Tejedor, D.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484. (h) Wessijohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796. (i) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (j) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969.

(2) For some important reviews about ketenimine chemistry, see: (a) Krow, G. R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 435. (b) Barker, M. W.; McHenry, W. E. *The Chemistry of Ketens, Allenes and Related Compounds*, Part 2; John Wiley & Son: New York, 1980; p 701. (c) Perst, H. *Methoden der Organischen Chemie* (Houben-Weyl); Stuttgart: New York, 1993; Vol. E15, Part 3, pp 2531−2710. (d) Yoo, E. J.; Chang, S. *Curr. Org. Chem.* **2009**, *13*, 1766. (e) Kim, S. H.; Park, S. H.; Choi, J. H.; Chang, S. *Chem.—Asian J.* **2011**, *6*, 2618. (f) Lu, P.; Wang, Y. *Synlett* **2010**, 165. (g) Lu, P.; Wang, Y. *Chem. Soc. Rev.* **2012**, *41*, 5687.

(3) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(4) (a) Cheg, Y.; Ma, Y.; Wang, X.; Mo, J. *J. Org. Chem.* **2009**, *74*, 850. (b) Yang, Y.; Shou, W.; Hong, D.; Wang, Y. *J. Org. Chem.* **2008**, *73*, 3574. (c) Froeyen, P. *Acta Chem. Scand., Ser. B* **1974**, *28*, 586.

(5) (a) Katagiri, T.; Handa, M.; Asano, H.; Asanuma, T.; Mori, T.; Jukurogi, T.; Uneyama, K. *J. Fluorine Chem.* **2009**, *130*, 714. (b) Fromont, C.; Masson, S. *Tetrahedron* **1999**, *55*, 5405. (c) Stevens, C. L.; French, J. C. *J. Am. Chem. Soc.* **1954**, *76*, 4398. (d) Bestmann, H. J.; Lienert, J.; Mott, L. *Liebigs Ann. Chem.* **1968**, *718*, 24.

(6) For selective examples of ketenimine formation via rearrangement reactions, see: (a) DeKover, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y. *J. Org. Chem.* **2011**, *76*, 5092. (b) Zhang, Y.; Dekorver, K. A.; Lohse, A. G.; Zhang, Y.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899. (c) Bendikov, M.; Duong, H. M.; Bolanos, E.; Wudl, F. *Org. Lett.* **2005**, *7*, 783. (d) Gornowicz, G. A.; West, R. *J. Am. Chem. Soc.* **1971**, *93*, 1714.

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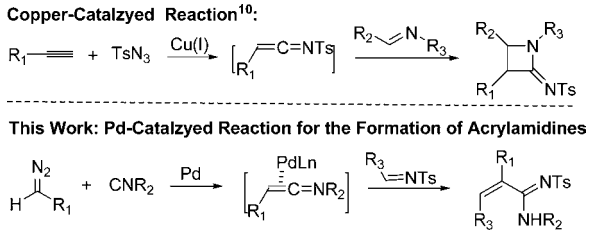
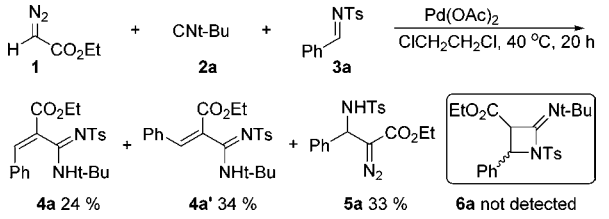
coupling reactions of isocyanides with carbenes or diazo compounds.[7] Recently, we reported an amidation reaction through hydrolysis of a ketenimine intermediate, which was formed *in situ* through the Pd-catalyzed reaction of isocyanides with *N*-tosylhydrazones.[8]

It is well documented that the reaction of ketenimines with imines proceeds through a [2 + 2] cycloaddition process to produce 2-iminoazetidines,[9] as in the case of the copper-catalyzed three-component reaction[10] of sulfonyl azides, 1-alkynes, and imines (Scheme 1). We envisioned that the same cyclic products may be obtained by using imines to trap the ketenimine intermediates generated *in situ* from the Pd-catalyzed reaction of isocyanides and diazo compounds. However, to our surprise, the $Pd(OAc)_2$-catalyzed one-pot reaction of ethyl diazo acetate **1**, *t*-BuNC **2a**, and *N*-benzylidene-4-methylbenzenesulfonamide **3a** afforded three products at 40 °C in 1,2-dichloroethane, but no [2 + 2] cycloaddtion product **6a** was detected (Scheme 2). One isolated product was determined to be **5a**, which was formed through the direct reaction of ethyl diazo acetate **1** with imine **3a**. The other two products were isomers, one of which was unambiguously determined to be (*E*)-ethyl 2-(*N*-*tert*-butyl-*N*′-tosylcarbamimidoyl)-3-phenylacrylate **4a** by X-ray crystallographic analysis.[11] The other one **4a**′, however, was unstable and transformed into **4a** slowly in different solvents such as ethyl acetate, chloroform, and methanol, which we speculated to be the *Z*-isomer of **4a** according to the analysis of the ^{1}H NMR and mass spectroscopic data.

Scheme 1. Pd-Catalyzed One-Pot Reaction for the Formation of Acrylamidines



Scheme 2. Pd-Catalyzed One-Pot Reaction of Ethyl Diazoacetate, *t*-BuNC, and *N*-Benzylidene-4-methylbenzenesulfonamide



The unexpected formation of the acrylamidine product was interesting since the amidine skeleton is the key structure for many potent bioactive compounds,[12] such as NR2B subtype-selective antagonists[13a] and selective muscarinic agonists.[13b] Synthetic methods for such structures are rare. The efficiency of the novel chemistry in our Pd-catalyzed one-pot reaction for the synthesis of those structures promoted us to optimize the reaction conditions. As shown in Table 1, under the catalysis of 4 mol % $Pd(OAc)_2$, the three-component reaction was explored in 1,2-dichloroethane at different reaction temperatures. The ratio of acrylamidine product **4a** increased at elevated temperatures, which was obtained in 70% yield at 80 °C and 75% yield at 100 °C, respectively, accompanied by a small amount of the unstable isomer **4a**′ and byproduct **5a** (Table 1, entries 2 and 3). Other solvents such as MeCN, DMF, toluene, THF, and 1,4-dioxane were also screened, and DCE showed the best results (Table 1, entries 4−8). Different Pd, Rh, and Cu catalysts were also tested, and all gave inferior results by comparison with that of $Pd(OAc)_2$ (Table 1, entries 9−14) .

Table 1. Condition Screening[a]

entry	catalyst	solvent	*t* (°C)	yield (%)[b] **4a/4a**′	yield (%)[b] **5a**
1	$Pd(OAc)_2$	DCE	40	24/34	33
2	**$Pd(OAc)_2$**	**DCE**	**80**	**70/9**	**13**
3	**$Pd(OAc)_2$**	**DCE**	**100**	**75/6**	**9**
4	$Pd(OAc)_2$	MeCN	80	54/11	26
5	$Pd(OAc)_2$	dioxane	80	46/8	43
6	$Pd(OAc)_2$	toluene	80	11/–	57
7	$Pd(OAc)_2$	THF	80	14/–	80
8	$Pd(OAc)_2$	DMF	80	25/–	26
9	$PdCl_2$	DCE	80	43/12	38
10	$Pd_2(dba)_3$	DCE	80	36/16	34
11	$Pd(PPh_3)_4$	DCE	80	31/15	43
12	$Rh_2(OAc)_4$[c]	DCE	80	57/17	16
13	$Rh(PPh_3)_3Cl$[c]	DCE	80	51/15	22
14	CuI[d]	DCE	80	31/15	47

[a] Reagents and reaction conditions: **1** (0.6 mmol, 1.2 equiv), **2a** (1.5 mmol, 3.0 equiv), **3a** (0.5 mmol, 1.0 equiv), catalyst (4 mol %), solvent (1.5 mL), 20 h. [b] Isolated yield. [c] Catalyst (2 mol %). [d] Catalyst (10 mol %).

(7) (a) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964. (b) Aumann, R. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1456. (c) Fernández, I.; Cossio, F. P.; Sierra, M. A. *Organometallics* **2007**, *26*, 3010. (d) Hudall, T. W.; Moorhead, E. J.; Gusev, D. G.; Bielawski, C. W. *J. Org. Chem.* **2010**, *75*, 2763. (e) Cheng, L.-Q.; Cheng, Y. *Tetrahedron* **2007**, *63*, 9359. (f) Cheng, Y.; Cheng, L.-Q. *J. Org. Chem.* **2007**, *72*, 2625. (g) Canac, Y.; Conejero, S.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *J. Am. Chem. Soc.* **2005**, *127*, 7312. (h) Merceron, N.; Miqueu, K.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **2002**, *124*, 6806. (i) Ciganek, E. *J. Org. Chem.* **1970**, *35*, 862.

(8) Zhou, F.; Ding, K.; Cai, Q. *Chem.—Eur. J.* **2011**, *17*, 12268.

(9) (a) van Camp, A.; Gossens, D.; Moya-Portuguez, M.; Marchand-Brynaert, J.; Ghosez, L. *Tetrahedron Lett.* **1980**, *21*, 3081. (c) Alajarín, M.; Vidal, A.; Tovar, F.; Arrieta, A.; Lecea, B.; Cossío, F. P. *Chem.—Eur. J.* **1999**, *5*, 1106.

(10) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157.

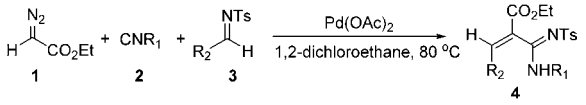
(11) See Supporting Information.

(12) (a) Boyd, G. V. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1991; Vol. 2, Chapter 8. (b) Dunn, P. J. Amidines and N-Substituted Amidines. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Tayler, R. J. K., Eds.; Elsevier: New York, 2005; Vol. 5, pp 655−699.

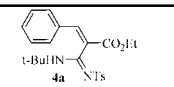
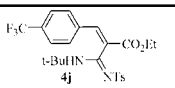
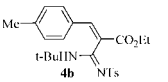
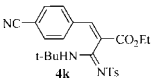
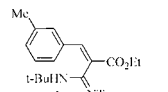
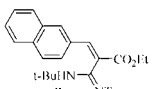
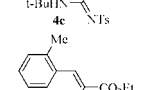
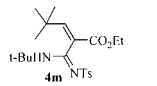
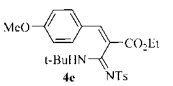
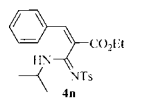
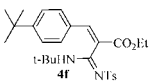
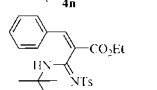
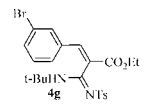
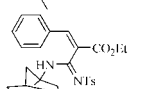
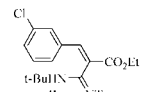
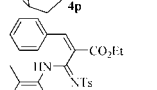
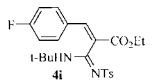
(13) (a) Thominiaux, C.; de Bruin, B.; Bramoullé, Y.; Hinnen, F.; Demphel, S.; Valette, H.; Bottlaender, M.; Besret, L.; Kassiou, M.; Dollé, F. *Appl. Radiat. Isot.* **2006**, *64*, 348. (b) Ojo, B.; Dunbar, P. G.; Durant, G. J.; Nagy, P. I.; Huzl, J. J., III; Periyasamy, S.; Ngur, D. O.; El-Assadi, A. A.; Hoss, W. P.; Messer, W. S., Jr. *Bioorg. Med. Chem.* **1996**, *4*, 1605.

With the optimized conditions in hand, we then explored the scope of substrates, and the results are shown in Table 2. First, a series of aryl imines derived from aryl aldehydes and $TsNH_2$ were tested. It was found that both electron-donating and -withdrawing substituent groups on the aryl ring of imines were well tolerated. In most cases, the corresponding *E*-acrylamidine products were obtained in moderate to good yields, accompanied by a small amount of byproduct **5** (Table 2, **4a**–**4l**). In some cases, the unstable isomers **4′** were detected. When the imine derived from $TsNH_2$ and the aliphatic pivalaldehyde was explored, the reaction became complicated and furnished the desired product **4m** in low yield. Further, other isocyanides were explored and afforded the corresponding products in moderate to good yields (e.g., **4n**–**4q**).

Table 2. Investigation of the Scope of 3-CR for the Synthesis of *E*-Acrylamidines[a]

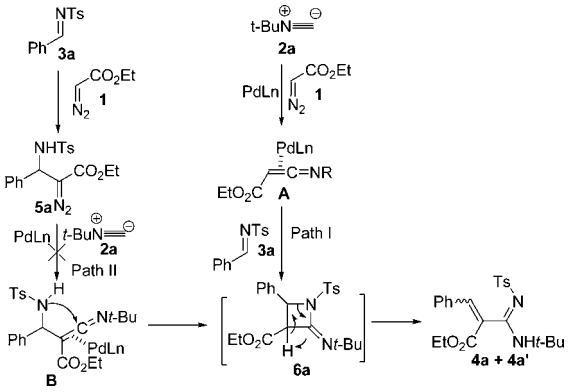


1 2 3 4

product	yield (%)[b]	product	yield (%)[b]
 **4a**	70	 **4j**	84
 **4b**	82	 **4k**	78
 **4c**	81	 **4l**	67
 **4d**	76	 **4m**	31
 **4e**	46	 **4n**	68
 **4f**	71	 **4o**	64
 **4g**	65	 **4p**	76
 **4h**	73	 **4q**	32
 **4i**	79		

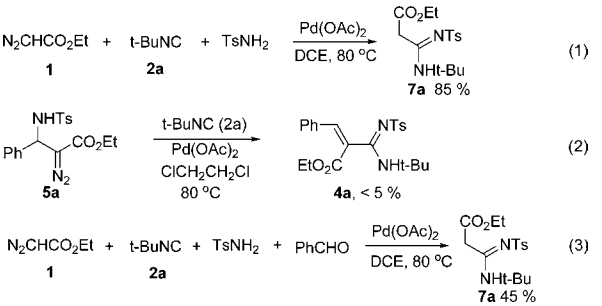
[a] Reagents and reaction conditions: **1** (0.6 mmol, 1.2 equiv), **2** (1.5 mmol, 3.0 equiv), **3** (0.5 mmol, 1.0 equiv), catalyst (4 mol %), solvent (1.5 mL), 16–24 h. [b] Isolated yields.

Scheme 3. Two Proposed Processes for the Formation of **4a** (Path II was excluded)

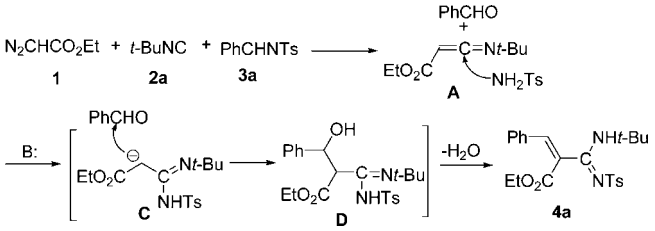


Based on the literature reports[2] and our experimental observations, we speculated that the acrylamidine product **4a** may be formed through an unpredicted ring-opening process of ketenimine–imine [2 + 2] product **6a**, which may be unstable under the reaction conditions. As shown in Scheme 3, two plausible mechanisms for the formation of **4a** were proposed: (1) Under the influence of the Pd catalyst, ethyl diazoacetate **1** first reacted with isocyanide **2a** to form ketenimine intermediate **A** (Path I). The formation of such a ketenimine intermediate was confirmed by trapping it with other nucleophiles such as $TsNH_2$ (Scheme 4, eq 1). Ketenimine intermediate **A** then underwent a [2 + 2] reaction with imine **3a** to produce the four-membered ring intermediate **6a**, which may be unstable under the reaction conditions and undergoes a rapid ring-opening reaction to deliver the acrylamidine products **4a** and its isomer **4a′**. (2) Another possible process (Path II) involves ethyl diazoacetate **1** directly reacting with imine **3a** to deliver compound **5a**, which was isolated as a stable byproduct in the three-component reaction. Compound **5a** may act as an intermediate to react with *t*-BuNC **2a** under the influence of the Pd catalyst to form the ketenimine intermediate **B**, which then undergoes an intramolecular ring-closure–opening process to deliver the desired product **4a**. However, a controlled experiment revealed that the reaction of **5a** with **2a** under the same conditions was

Scheme 4. Some Controlled Experiments for the Understanding of Reaction Mechanism



Scheme 5. A Possible Four-Component Reaction Process Was Excluded through a Controlled Experiment



very complicated and only afforded product **4a** in less than 5% yield (Scheme 4, eq 2), which means that such a pathway may not be responsible for the high yield of **4a** in the Pd-catalyzed three-component reaction.

Further, we still suspected that the reaction may also proceed through another process as shown in Scheme 5. First, the imine **3a** was hydrolyzed to produce $TsNH_2$ and benzaldehyde. The $TsNH_2$ would attack ketenimine intermediate **A** to generate intermediate **C**, which may subsequently attack benzaldehyde to produce intermediate **D**. This intermediate was then dehydrated to deliver the acrylamidine product. To exclude such a possibility, we performed a four-component reaction under the same reaction conditions (Scheme 4, eq 3). No acrylamidine product **4a** was detected, and the only isolated product was the amidine **7a**, which was formed through direct attack of ketenimine intermediate **A** by $TsNH_2$. The benzaldehyde did not participate in the reaction at all.

In summary, we have developed a novel and efficient Pd-catalyzed one-pot reaction of ethyl diazoacetate, isocyanides, and imines for the synthesis of acrylimidines, which may be formed through an unpredicted ring-opening process of the ketenimine−imine [2 + 2] product. Further study and application of this reaction are ongoing in our laboratory.

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Supporting Information Available. Full experimental procedures, characterization data for all the compounds, and crystal structure (CIF) of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.