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Direct, Palladium-Catalyzed, Multicomponent Synthesis of β-Lactams from Imines, Acid Chloride, and Carbon Monoxide

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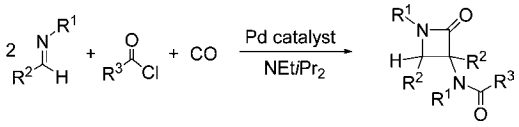
ABSTRACT



A new palladium-catalyzed synthesis of 3-amido-substituted β-lactams is reported. This process involves the one-pot coupling of four components, imines, carbon monoxide, and acid chloride, providing a flexible route to construct this class of heterocycle. The generation of β-lactams with two different imines can also be accomplished, providing a method to assemble these products with independent control over five separate substituents.

The development of efficient routes to synthesize β-lactams is an area of significant research interest.[1] This has been driven, in large part, by the importance of these molecules as constituents of antibiotics, ranging from penicillin-based substrates to a number of more recently developed compounds (e.g., penems, cephems, monobactams, carbapenems, and trinems).[2] β-Lactams have also been demonstrated to be important synthons in organic synthesis[3] and to be monomers in the generation of polyamides (e.g., poly(β-peptides)).[4] A number of classical[1] and more recently developed[5−13]

(1) For reviews on the synthesis of β-lactams: (a) Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (c) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (e) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631.

(2) (a) *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Royal Society of Chemistry: London, 1985. (b) Flynn, E. H. *Cephalosporins and Penicillins: Chemistry and Biology*; Academic Press, New York, 1972. (c) Singh, G. S. *Mini Rev. Med. Chem.* **2004**, *4*, 93. (d) Singh, G. S. *Mini Rev. Med. Chem.* **2004**, *4*, 69. (e) Hwu, J.; Ethiraj, K.; Hakimelahi, G. H. *Mini Rev. Med. Chem.* **2003**, *3*, 305. (f) Sader, H.; Gales, A. C. *Drugs* **2001**, *61*, 553.

(3) For reviews: (a) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (b) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226.

(4) For examples: (a) Cheng, J.; Deming, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 9457. (b) Eldred, S. E.; Pancost, M. R.; Otte, K. M.; Rozema, D.; Stahl, S. S.; Gellman, S. H. *Bioconjugate Chem.* **2005**, *16*, 694.

(5) (a) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414. (b) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518. (c) Mahadevan, V.; Geltzer, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2001**, *41*, 2781. (d) Lu, S.-M.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558.

(6) (a) Zhou, Z.; Alper, H. *J. Org. Chem.* **1996**, *61*, 1256. (b) Tanaka, H.; Abdul Hai, A. K. M.; Sadakane, M.; Okumoto, H.; Torii, S. *J. Org. Chem.* **1994**, *59*, 3040. (c) Kim, T.-J.; Shim, S.-C.; Kim, M.-C. *Bull. Korean Chem. Soc.* **2000**, *21*, 541. (d) Troisi, L.; De Vitis, L.; Granito, C.; Epifani, E. *Eur. J. Org. Chem.* **2004**, 1357. (e) Mori, M.; Chiba, K.; Okita, M.; Ban, Y. *Tetrahedron* **1985**, *41*, 375. (f) Mori, M.; Chiba, K.; Okita, M.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1979**, 698.

(7) (a) Annunziata, R.; Ciquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293. (b) Townes, J. A.; Evans, M. A.; Queffelec, J.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2537.

(8) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082.

(9) (a) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592. (b) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206.

(10) (a) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (b) Hegedus, L. S.; McGuire, J. *J. Am. Chem. Soc.* **1982**, *104*, 5538.

(11) (a) Doyle, M. P.; Kalinin, A. V. *Synlett* **1995**, 1075. (b) Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, *65*, 4375.

(12) Ley, S. V.; Cox, L. R.; Meek, G. *Chem. Rev.* **1996**, *96*, 423.

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methods are available to construct β-lactams. These include important metal-based methodologies, such as the metal-catalyzed carbonylative ring expansion of aziridines,[5] asymmetric Lewis acid-mediated processes,[9] and metal−carbene-based routes.[10,11]

In principle, an attractive approach to prepare molecules such as β-lactams would be to consider their structure, rather than arising from the cyclization of prepared substrates, as simply the product of multiple basic and readily available building blocks coupled together at once. In this regard, transition-metal catalysis can serve as a useful tool, where the diverse reactivity of metal complexes can be used to mediate the coupling of traditionally unreactive precursors. As others[14] and ourselves[15] have reported, this approach not only can provide a straightforward overall synthesis but also is amenable to structural diversification. We describe below the application of this approach to the construction of the amino acid-based β-lactam core **1**, the functional structure of many biologically relevant β-lactams (i.e., penicillin, nocardicins, and cephalosporins).[2] This was done by considering this structure to be comprised of four units, two imines, acid chloride, and carbon monoxide (Figure 1),

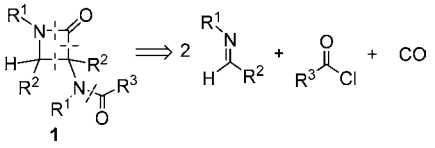
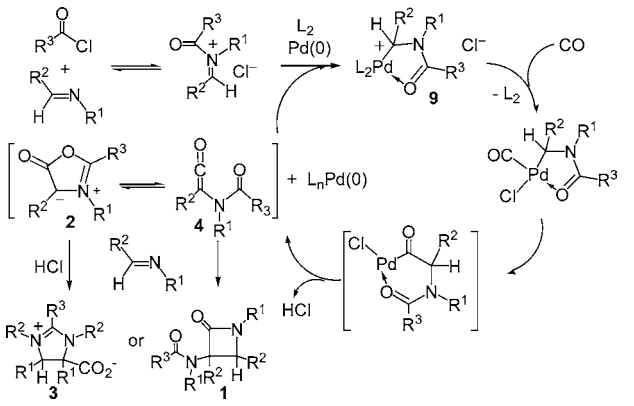


Figure 1. Multicomponent approach to β-lactams.

brought together in a palladium-catalyzed reaction. Considering the nature of the building blocks, this provides a modular method to construct a β-lactam, where five separate substituents can be independently varied in a single-pot reaction.

Our approach to a β-lactam synthesis is based on our previously reported palladium-catalyzed synthesis of imidazolines, illustrated in Scheme 1.[16] This reaction presumably occurs via the formation of a mesoionic 1,3-oxazolium-5-oxide (i.e., Münchnone) intermediate **2**, which undergoes a 1,3-dipolar cycloaddition with imine to generate **3**. Considering that Münchnones are known to be in equilibrium with their ketene isomer **4**,[17,18] we postulated that this catalytic coupling could be employed to provide access to 3-amido-substituted β-lactams by inducing the second equivalent of imine to undergo a formal [2 + 2] cycloaddition with the in situ generated ketene isomer **4**, rather than 1,3-dipolar addition.

Scheme 1. Postulated Mechanism for **1** and **3** Formation



Previous reports have demonstrated that *N*-alkyl-substituted imines react with Münchnones to generate β-lactams,[17] suggesting that the formation of **3** in this catalytic process is the result of the reaction conditions. To explore this phenomenon, the reactivity of the independently generated Münchnone **2a** has been examined (Figure 2).[19] The addition

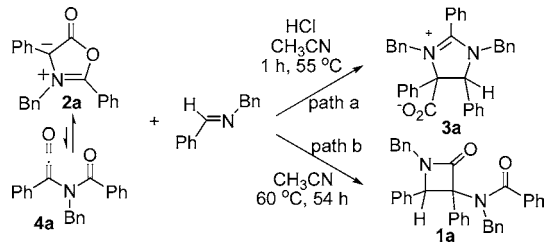


Figure 2. Acid influence on the reaction of münchnones with imines.

of Ph(H)C═NBn to Münchnone **2a** in the presence of HCl,[16] which is generated in the catalytic reaction, leads to the rapid formation of imidazoline **3a** in quantitative yield (path a). However, the reaction of **2a** with Ph(H)C═NBn in the absence of acid completely inhibits imidazoline formation and instead results in the formation of β-lactam **1a** in 79% yield. The role of acid in influencing this cyclization is not

(13) (a) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377. (b) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (c) Fujieda, H.; Kanai, M.; Kmbara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060 and references therein. (d) Ojima, I.; Park, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. *Tetrahedron Lett.* **1992**, *33*, 5737.

(14) Representative examples: (a) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786. (b) Cao, C.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 2880. (c) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 8081. (d) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (e) Wie, C. J.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472. (f) Ng, S. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 14194. (g) Braun, R. U.; Müller, T. J. *Synthesis* **2004**, *14*, 2391.

(15) (a) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (b) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474. (c) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107. (d) Siamaki, A.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050.

(16) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228.

(17) (a) Croce, P. D.; Ferraccioli, R.; La Rosa, C. *Tetrahedron* **1995**, *51*, 9385. (b) Huisgen, R.; Funke, E.; Schaefer, F. C.; Knorr, R. *Angew. Chem., Int. Ed.* **1967**, *6*, 367.

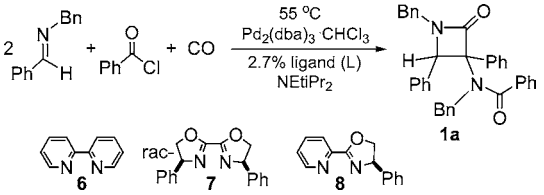
(18) (a) Potts, K. T. In *1,3 Dipolarcycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons Inc.: New York, 1983. (b) Gingrich, H. L.; Baum, J. S. In *Oxazoles*; Turchi, I. J., Ed.; John Wiley & Sons Inc.: New York, 1984. (c) Gribble, G. W. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Ed.; John Wiley & Sons Inc.: New York, 2002.

(19) For synthesis of **2**: Gribble, G. W.; Sponholtz, W. R.; Switzer, F. L.; D'Amato, F. J.; Byrn, M. P. *Chem. Commun.* **1997**, 993.

presently known, but it may be related to increasing the electrophilicity of the imine via protonation of nitrogen.[16,17a] This implies that eliminating the HCl generated during catalysis should allow this coupling to be directed toward β-lactams.

The ability of this chemistry to access β-lactams was first probed in the stoichiometric reaction of 0.5 equiv of $Pd_2(dba)_3 \cdot CHCl_3$ with 2 equiv of Ph(H)C=NBn, PhCOCl, 1 atm of CO, and base. Various inorganic (Cs_2CO_3 and NaOAc) and organic bases (NEt_3, proton sponge, and DBU) were examined; however, no identifiable products were produced. Changing the base to the more sterically hindered *N*,*N*-diisopropylethylamine (NEt^iPr_2) leads to the quantitative formation of $Et^iPr_2NH^+Cl^-$ and the generation of a trace amount of the desired 3-amido-substituted β-lactam **1a** (5%, Table 1, entry 1), along with the recovery of almost 1 equiv of free imine.

Table 1. Catalytic β-Lactam Synthesis: Method Development



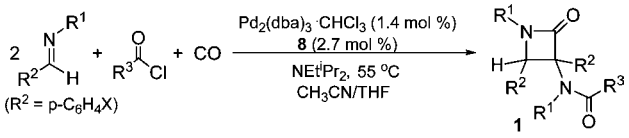
entry	L	[Pd][b]	% yield[c]
1[d]	–	100	5
2[d]	–	20	8.5
3[d]	–	5	30
4[a]	6	5	45
5[a]	7	5	55
6[a]	8	5	58
7[a]	8	2.8	64

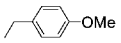
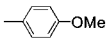
[a] Conditions: 1.2 mmol of imine, 0.54 mmol of acid chloride, 1 atm of CO, 0.54 mmol of NEt^iPr_2, and 2.7 mol % of L for 96 h at 55 °C in 1:1 CH_3CN/THF. [b] In mol %. [c] NMR yield. [d] In CD_3CN.

In contrast to the stoichiometric coupling, performing this reaction under catalytic conditions provides a synthetically useful method to access β-lactams. As shown in Table 1, this same reaction with a 5% catalyst loading results in the formation of β-lactam **1a** in 45% yield (entry 3). Interestingly, increasing the palladium loading actually inhibits the formation of **1a** (entries 1−3, vide infra). The efficiency of this catalysis can be further improved by the addition of a chelating ligand (entries 4−6).[20] The optimal results are obtained by using ligand **7** in a 1:1 THF/acetonitrile solvent mixture, which leads to the coupling of the imine, acid chloride, and carbon monoxide fragments into a single β-lactam product in 64% yield.[21,22]

(20) Bidentate ligands appear to inhibit the formation of 2-benzyl-3-phenyl-1-isoindolinone. The latter likely arises from the C−H bond activation of the aromatic R^3 in the *N*-acyliminium salt intermediate. The discussion of this process will be the subject of a future report.

Table 2. Palladium-Catalyzed β-Lactam Synthesis: Diversity[a]



compd	R^1	X	R^3	% yield[b]
1a	Bn	H	Ph	64 (58)
1b	Bn	CH_3	Ph	68 (61)
1c	Bn	SCH_3	Ph	60 (56)
1d	Bn	CF_3	Ph	38 (32)
1e	Bn	H		50 (45)
1f		H	Ph	67 (65)
1g		H	Ph	68 (66)
1h		H	Ph	76 (62)
1i		H	Ph	37 (27)
1j		H	Ph	60 (55)
1k	-ethyl	H	Ph	63 (56)

[a] Conditions: 1.2 mmol of imine, 0.54 mmol of acid chloride, 1 atm of CO, 0.54 mmol of NEt^iPr_2, 1.4 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, and 2.7 mol % of **8** for 96 h at 55 °C in 1:1 CH_3CN/THF. [b] NMR (isolated) yield.

As illustrated in Table 2, this multicomponent process is directly amenable to structural diversification. β-Lactam formation proceeds cleanly with a number of imines and acid chlorides, all generating product in good yields and as a trans-isomer. Importantly, functionalities such as aromatic ethers **1f**, thioethers **1c**, and heteroaromatics **1g** and **1h** do not appear to inhibit the reaction. In addition, both aryl and alkyl acid chlorides can be employed. However, the yields of β-lactams are lower with σ-electron-withdrawing substituents on the imines **1d** and **1i**. The latter is likely a consequence of the lower nucleophilicity of these imines, which inhibits their interaction with the acid chloride (vide infra). Considering that this reaction involves the simultaneous coupling of four reagents with the formation of four new bonds, these all represent efficient β-lactam syntheses, which typically involve up to a five-step synthesis via established procedures.[18]

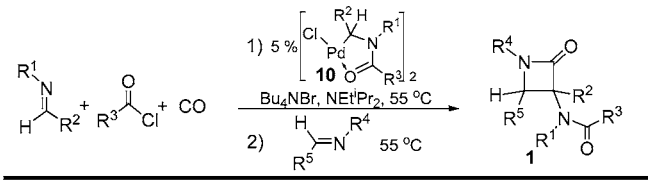
The mechanism of this coupling is believed to be that shown in Scheme 1, where an in situ generated *N*-acyliminium salt (formed from imine and acid chloride) undergoes oxidative addition to Pd(0) to form palladacycle **9**, followed by carbon monoxide insertion and β-hydride elimination to form Münchnone **2**.[23] In the presence of EtN^iPr_2, the HCl from the reaction mixture is removed, allowing imine cyclization to occur with the ketene isomer **4**, rather than Münchnone, resulting in the generation of β-lactam **1**. The

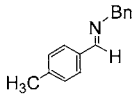
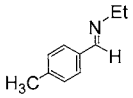
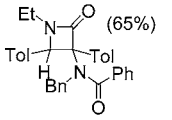
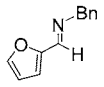
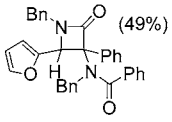
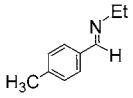
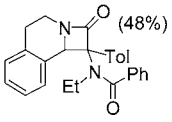
(21) COSY, HMQC, HMBC, and NOESY NMR experiments demonstrate that **1a** exists as a single isomer with transoid phenyl units.

(22) Control experiments show no β-lactam formation in the absence of a palladium catalyst.

(23) This mechanism is directly analogous to that demonstrated previously for Münchnone formation.[15b]

Table 3. Heterocoupled β-Lactam Synthesis[a]



compd	imine	acid chloride	imine	β-lactam (% yield)
1l		PhCOCl		 (65%)
1m		PhCOCl		 (49%)
1n		PhCOCl		 (48%)

[a] Conditions: 0.54 mmol of imine, 0.54 mmol of Bu_4NBr, 0.76 mmol of acid chloride, 0.84 mmol of NEt^iPr_2, 5 mol % of **10**, and CO (4 atm) for 24−30 h at 55 °C, followed by heating at 55 °C for 24 h with the second imine (0.54 mmol).

source of lower β-lactam yields under high palladium loading conditions (Table 2, entries 1−3) is suggested by control experiments, which show that $Pd_2(dba)_3{\cdot}CHCl_3$ mediates the decomposition of **2**, albeit at a slower rate than its formation.[24]

As suggested by the mechanism of β-lactam formation, this coupling requires the incorporation of two identical imines. Employing two distinct imines in this reaction results in poor control and the formation of a statistical mixture of β-lactam products.[25] However, we have previously shown that Münchnones can be generated from imine, acid chloride, and CO in the absence of an imine trap with catalyst **10**.[15b] Thus, performing this catalytic coupling with 1 equiv of imine, acid chloride, and carbon monoxide allows for the generation of **2**. Subsequent addition of imine and heating at 55 °C for 24 h generates β-lactam products in good yields (Table 3). This latter approach provides a method to construct the β-lactam in a single pot with independent control of five separate substituents on the heterocyclic core.

In conclusion, 3-amido-substituted β-lactams can be readily prepared by the palladium-catalyzed coupling of imine, carbon monoxide, and acid chloride in the presence of an amine base. Considering the mild conditions (1 atm of CO, 55 °C) and simple building blocks employed, this represents a facile route to the β-lactam core and provides direct access to 3-amido-substituted lactams of potential biological relevance.[2] The utilization of this process to catalytically generate other products from imine and carbon monoxide and the complete elucidation of the reaction mechanism are currently the subject of research in our laboratories.

Acknowledgment. We thank NSERC, FQRNT, and the CFI for their financial support.

Supporting Information Available: Synthesis and spectral data for β-lactam products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) The generation of **2** in the presence of 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ in CD_3CN, followed by heating to 55 °C for 24 h, results in the decomposition of ca. 30% of **2** (determined by ^1H NMR vs an internal standard) to an unidentifiable mixture of products. A similar reaction without $Pd_2(dba)_3{\cdot}CHCl_3$ present shows no appreciable loss of **2** after heating to 55 °C for 24 h.

(25) The palladium-catalyzed reaction of PhC(H)=NBn, PhC(H)=$NCH_2(p-C_6H_4OCH_3)$, CO, and PhCOCl provided a mixture of lactam products.