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Copper-Mediated Synthesis of *N*-Acyl Vinylogous Carbamic Acids and Derivatives: Synthesis of the Antibiotic CJ-15,801

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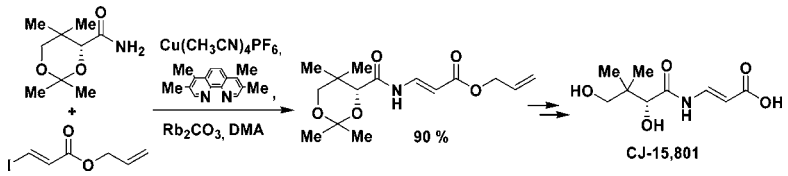
ABSTRACT



Copper(I)-mediated C–N bond formation has been employed to prepare both *N*-acyl vinylogous carbamic acids and ureas. The novel *N*-acyl vinylogous carbamic acid antibiotic, CJ-15,801, was synthesized using this methodology.

The *N*-acyl vinylogous urea is a uncommon moiety present in a number of bioactive natural products, including palytoxin,[1] enamidonin (**1**),[2] and the recently isolated cyclic lipopeptides K97-0239A and B (**2a,b**)[3] (Figure 1). Recently, the novel *N*-acyl vinylogous carbamic (*β*-amido acrylic) acid containing molecule, CJ-15,801 (**3**), was reported as an inhibitor of multiple-drug-resistant (MDR) *Staphylococcus aureus* strains.[4] On the basis of our previous work on the Cu(I)-catalyzed formation of enamides,[5] we planned to extend this C−N bond-formation methodology[6] to coupling of amides with *β*-iodo-acrylates and acrylamides to prepare both *N*-acyl vinylogous carbamic acids and ureas. In this Letter, we report our initial studies on this amidation process and application to the synthesis of the antibiotic CJ-15,801 and analogues.

Previous approaches to *N*-acyl vinylogous carbamic acids and ureas include acylation of vinylogous carbamates (*β*-aminoacrylates) followed by deprotection of the correspond-

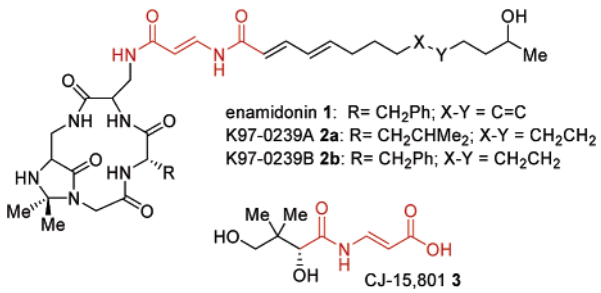


Figure 1. Representative natural products containing *N*-acyl vinylogous carbamic acids and ureas.

(1) (a) Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491. (b) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781. For reviews on palytoxin, see: (c) Moore, R. E. *Prog. Chem. Org. Nat. Prod.* **1985**, *48*, 81. (d) Kishi, Y. *Tetrahedron* **2002**, *58*, 6239.

(2) Koshino, S.; Koshino, H.; Matsuura, N.; Kobinata, K.; Onose, R.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 185.

(3) Ichigi, N.; Hiroshi, T.; Daisuke, M.; Noriko, T.; Susumu, K.; Satoshi, O. *Proc. Jpn. Acad., Ser. B* **2002**, *78B*, 45.

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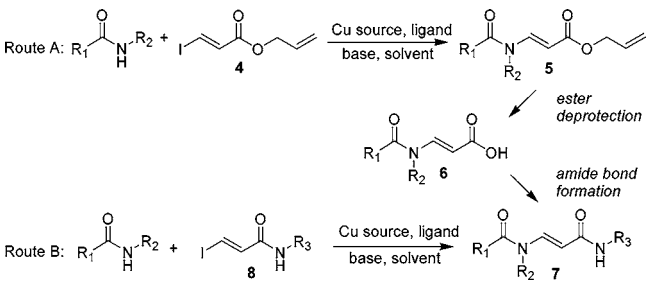
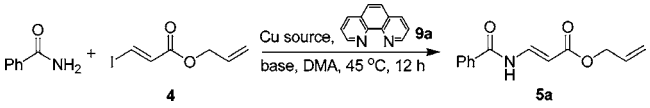
Scheme 1. Synthetic Routes to *N*-Acyl Vinylogous Carbamic Acids and Ureas



ing esters,[7] Pd (II)-catalyzed coupling of lactams and alkenes,[8] and elimination of thioacetals and phenylselenides to prepare the *N*-acyl vinylogous urea side chain of palytoxin.[9] In the latter methodology, *Z*-isomers were generally observed as the major, thermodynamic products. An overview of our current approach is depicted in Scheme 1. We have developed two routes to *N*-acyl vinylogous ureas using Cu(I)-catalyzed amidation. In route A, amidation of (*E*)-allyl-*β*-iodoacrylate **4**[10] affords *N*-acyl vinylogous carbamate **5**. Pd(0)-catalyzed deallylation[11] of **5** should afford *N*-acyl vinylogous carbamic (*β*-amidoacrylic) acid **6**, a substructure found in CJ-15,801. Amide coupling of **6** and amines provides *N*-acyl vinylogous ureas **7**. In route B, direct amidation of 3-iodo-*N*-alkyl-2-propenamides **8** affords **7**, which may also form the corresponding *Z*-isomers under thermodynamic control.[9]

Initial investigation of the cross-coupling of (*E*)-allyl-*β*-iodo acrylate **4** and benzamide (Table 1) with copper(I) thiophene-2-carboxylate (CuTC)[12] as the catalyst and Cs_2CO_3 as base afforded the desired product **5a** in trace amounts. However, addition of 1,10-phenanthroline **9a**[13] as ligand improved the yield of **5a** to 33% (entry 1).[14] CuI and $Cu(CH_3CN)_4PF_6$[15] were also examined as Cu(I) sources, in which case it was found that $Cu(CH_3CN)_4PF_6$ afforded a

Table 1. Evaluation of Copper Sources and Bases[a]



entry	Cu source	base (equiv)	amide (equiv)	yield (%)[b]	**4** (%)[c]
1	CuTC	Cs_2CO_3(2.0)	1.5	33	0
2	CuI	Cs_2CO_3(2.0)	1.5	36	0
3	$Cu(CH_3CN)_4PF_6$	Cs_2CO_3(2.0)	1.5	38	0
4	$Cu(CH_3CN)_4PF_6$	Rb_2CO_3(2.0)	1.5	33	15
5	$Cu(CH_3CN)_4PF_6$	K_2CO_3(2.0)	1.5	13	83
6	$Cu(CH_3CN)_4PF_6$	Rb_2CO_3(3.0)	3.0	45	10

[a] Reaction conditions: 10 mol % Cu source, 20 mol % ligand **9a**, 1.0 equiv of vinyl iodide **4**. [b] HPLC yields using benzophenone as internal standard. [c] Recovered **4** based on same HPLC analysis.

slightly improved yield (entry 3). In contrast to copper sources, different bases showed significant effects on reaction yields (entries 3−5). The weaker base K_2CO_3 afforded very low conversion (entry 5). Although the highest yield (38%) was obtained using Cs_2CO_3, severe decomposition of product **5a** and competitive dimerization of **4**[12b] were observed in control experiments. Rb_2CO_3 afforded optimal results employing an excess of amide (entry 6) and was used for further amidation experiments. A variety of ligands, including 3,4,7,8-tetramethyl-1,10-phenanthroline **9b**,[13c,16] 1,4-diaza-1,3-butadienes (DAB) **9c**, bis(arylimino)acenaphthenes (Ar-BIAN) **9d**,[17] and 2,2′-bipyridine **9e**, were next evaluated to further improve the yield of **5a** (Figure 2). In this case,

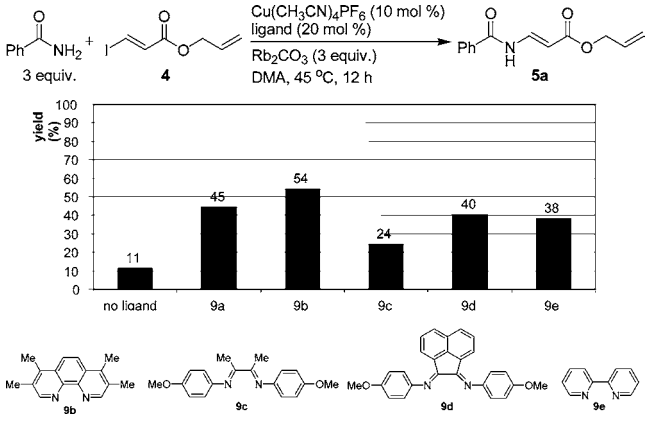


Figure 2. Evaluation of 1,10-phenanthroline and diimine ligands. Yields are based on HPLC analysis using benzophenone as internal standard.

phenanthroline ligand **9b** showed noticeable improvement over the parent **9a** and was employed for subsequent experiments.[18]

(6) For representative publications on Cu(I)-catalyzed amide arylation, see: (a) Klapars, A.; Antilla, J. C.; Huang, X., Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Klapars, A.; Huang, X., Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

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(8) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S. I. *Tetrahedron Lett.* **1992**, *33*, 6643.

(9) Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205.

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(11) For a review, see: Guibé, F. *Tetrahedron* **1998**, *54*, 2967.

(12) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.

(13) For use of 1,10-phenanthroline in Cu(I)-catalyzed C−N bond formation, see: (a) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657. (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. (c) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett.* **2002**, *43*, 7143.

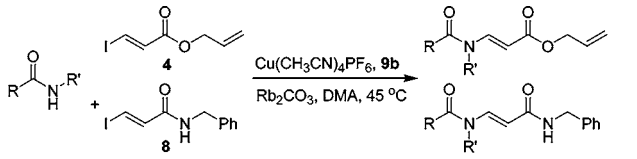
(14) Diamine ligands including *N*,*N*′-dimethylethylenediamine (refs 5c, 6) proved to be less effective than 1,10-phenanthroline for the transformation **4** → **5a**.

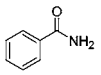
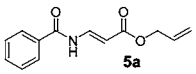
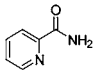
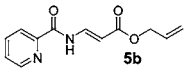
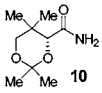
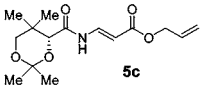
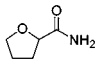
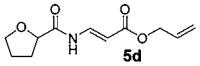
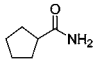
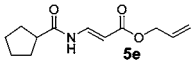
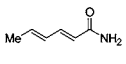
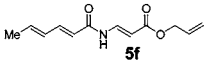
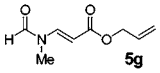
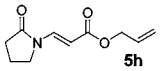
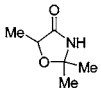
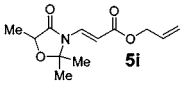
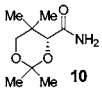
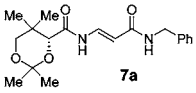
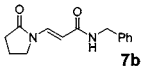
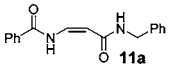
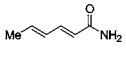
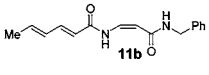
(15) (a) Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90. (b) For use of $Cu(CH_3CN)_4PF_6$ in C−O bond formation reactions, see: Kalinin, A.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986.

(16) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

(17) For use of Ar-BIAN ligands in copper-catalyzed aziridination and cyclopropanation, see: Llewellyn, D. B.; Adamson, D.; Arndtsen, B. A. *Org. Lett.* **2000**, *2*, 4165.

Table 2. Scope and Limitations[a]



entry	amide	time (h)	product	yield (%)[b]
1		12	 **5a**	55 71[c]
2		12	 **5b**	43
3	 **10**	19	 **5c**	90
4		15	 **5d**	61
5		15	 **5e**	6
6		12	 **5f**	58[c,d]
7		12	 **5g**	77
8		12	 **5h**	92[e]
9		12	 **5i**	72
10	 **10**	12	 **7a**	70[f]
11		12	 **7b**	72[f]
12		12	 **11a**	25[f]
13		12	 **11b**	18[f]

[a] Reaction conditions: 10 mol % $Cu(CH_3CN)_4PF_6$, 20 mol % ligand **9b**, 1.0 equiv of vinyl iodide **4** or **8**, 3.0 equiv of amide, and 3.0 equiv of Rb_2CO_3. [b] All yields are based on pure materials isolated by silica gel or neutral aluminum oxide chromatography. [c] DME as solvent. [d] 20 mol % $Cu(CH_3CN)_4PF_6$ was employed. [e] Reaction performed at room temperature. [f] Reaction performed at 60 °C.

Substrate scope was next investigated employing $Cu(CH_3CN)_4PF_6$, **9b** as ligand, Rb_2CO_3 as base, and DMA as solvent (Table 2). Amidation of vinyl iodide **4** with (*R*)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide (**10**)[19] afforded *N*-acyl vinylogous carbamate **5c** (entry 3), a precursor to CJ-15,801, in excellent yield. However, other primary amides afforded only moderate yields of the desired coupling products. We speculate that chelation of the α-oxygen[20] of amide **10** may stabilize the putative copper intermediate (Figure 3a). Further experiments supported this general hypothesis. As shown in entries 4 and 5, tetrahydro-2-furamide and cyclopentane-carboxamide demonstrated a significant difference in reaction yields. However, in contrast to Cu(II)-mediated *N*-arylation of amides,[21] no apparent α-nitrogen chelation effect was observed employing picolinamide (cf. entries 1 and 2). Lactams such as 2-pyrrolidinone afforded excellent yields at room temperature (entry 8). In contrast, *N*-alkylated secondary amides such as *N*-methylacetamide and *N*-methylbenzamide were found to be substantially less reactive except for *N*-methylformamide, which underwent efficient coupling (entry 7).

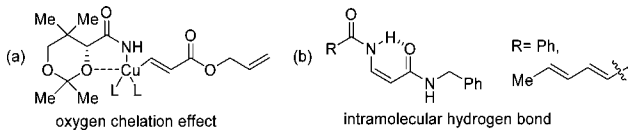


Figure 3.

After a brief survey of solvents to optimize C−N bond formation employing sorbamide, a model for the side chain of enamidonin and K97-0239A and B, we found that 1,2-dimethoxyethane (DME)[22] was a superior solvent to DMA. The yield significantly increased from less than 10% in DMA to 58% in DME (Table 2, entry 6). Entries 10−13 illustrate a one-step route to *N*-acyl vinylogous ureas by direct coupling of 3-iodo-*N*-benzyl-2-propenamide **8** and amides. Interestingly, coupling of conjugated amides and vinyl iodide **8** produced the thermodynamic *Z*-isomers **11a** and **11b** (entries 12 and 13). This preference may be related to the higher acidity of the NH in conjugated amides,[23] which favors the formation of an intramolecular hydrogen bond and stabilizes the *Z*-isomer (Figure 3b).[7a,9]

The synthesis of CJ-15,801 was next completed from amidation product **5c**. Because of the acid-labile nature of *N*-acyl vinylogous carbamic acids, mild and neutral deprotection methods were required. Deprotection of acetonide **5c** with $BiCl_3$ (aq CH_3CN, rt)[24] afforded allyl ester **12** (75%).

(18) For publications comparing electron-donating abilities of phenanthroline ligands, see: (a) Munakata, M.; Kitagawa, S.; Kosome, S.; Asahara, A. *Inorg. Chem.* **1986**, *25*, 2622. (b) Gasque, L.; Medina, G.; Ruiz-Ramírez, L.; Moreno-Esparza, R. *Inorg. Chim. Acta* **1999**, *288*, 106.

(19) Aquino, F.; Pauling, H.; Walther, W.; Plattner, D. A.; Bonrath, W. *Synthesis* **2000**, *5*, 731.

(20) For neighboring oxygen activation effects in Cu(I)-catalyzed coupling reactions, see: (a) Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703. (b) Gung, B. W.; Kumi, G. *J. Org. Chem.* **2003**, *68*, 5956.

(21) Lam. P. Y. S.; Deudon, S.; Hauptman, E.; Clark, C. G. *Tetrahedron Lett.* **2001**, *42*, 2427.

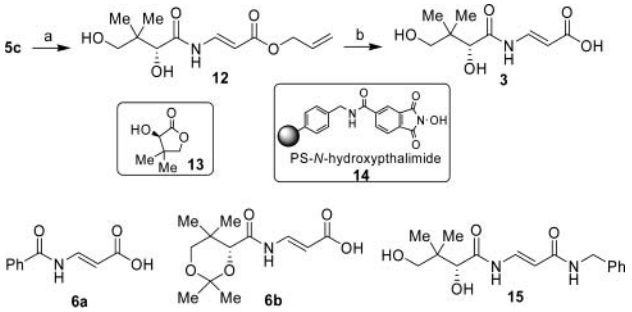
(22) (a) For DME as a bidentate ligand, see: Sjögren, M. P. T.; Frisell, H.; Åkermark, B. *Organometallics* **1997**, *16*, 942. (b) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133.

(23) pK_a (DMSO) of benzamide: 23.3; acetamide: 25.5. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(24) Swamy, N. R.; Venkateswarlu, Y. *Tetrahedron Lett.* **2002**, *43*, 7549.

More strongly acidic conditions (e.g., *p*-TsOH) afforded *R*-(−)-pantolactone **13** as the major product. Finally, CJ-15,801 **3** was obtained in 80% yield by deprotection of allyl ester **12** using $Pd(PPh_3)_4$ in conjunction with polymer-supported *N*-hydroxy-phthalimide **14** as an allyl cation scavenger.[25] Other allyl acceptors (e.g., morpholine, HOBt, PS-HOBt, and *N*-hydroxyphthalimide) were not effective due to the presence of byproducts that were difficult to separate from the labile target **3**. Synthetic CJ-15,801 was confirmed to be identical to a natural sample by ^1H and ^{13}C NMR, MS., $[\alpha]_D$, and reverse-phase HPLC analysis. *ent*-**3** and analogues **6a,b** and **15** were similarly prepared for exploration of their biological activities (Scheme 2).

Scheme 2. Synthetic Route to CJ-15,801 and Analogues[a]

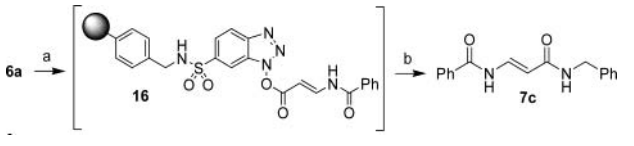


[a] Reaction conditions: (a) $BiCl_3$, aq CH_3CN, rt, 5 h, 75% (b) $Pd(PPh_3)_4$, **14**, THF, 35 °C, 12 h, 80%.

To access the (*E*)-*N*-acyl vinylogous urea isomers required for enamidonin and K97-0239A and B (Figure 1), we have performed amide formation using *N*-acyl carbamic acids (Scheme 3). In line with our previously described route to CJ-15,801 (Scheme 2), we planned to utilize polymer-supported reagent methodologies[26] to facilitate isolation of labile and potentially polar products. Coupling of *N*-acyl vinylogous carbamic acid **6a** with PS-HOBT[27] using ACTU[28]

(25) See Supporting Information for preparation of **14**. Further applications of this polymeric reagent are in progress and will be reported in a subsequent full paper. For a recent report of a polymeric scavenger for allyl cations, see: Humphrey, C. E.; Easson, M. A. M.; Tierney, J. P.; Turner, N. J. *Org. Lett*. **2003**, *5*, 849.

Scheme 3. Alternative Route to *N*-Acyl Vinylogous Ureas[a]



[a] Reaction conditions: (a) PS-HOBt, ACTU, 2,6-lutidine, DMF, rt, 4 h; (b) $BnNH_2$, THF, rt, 2 h, 81%

as coupling reagent led to active ester resin **16**. Treatment of the resin (2 equiv) with benzylamine (1 equiv) led to (*E*)-*N*-acyl vinylogous urea **7c** in high yield (81%) and purity (93%).[29]

In conclusion, copper(I)-mediated coupling of amides with β-iodo-acrylates and acrylamides has been employed to prepare *N*-acyl vinylogous carbamates and ureas. The *N*-acyl vinylogous carbamic acid antibiotic CJ-15,801 and analogues have been prepared using this methodology. Further investigation on the reaction scope and applications toward complex targets such as the *N*-acyl vinylogous urea lipopeptides will be reported in future publications.

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Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Recent reviews on polymer-supported reagents and scavengers: (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. *Perkin Trans. 1* **2000**, *23*, 3815. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650.

(27) (a) Pop, I. E.; Deprez, B. P.; Tartar, A. L. *J. Org. Chem*. **1997**, *62*, 2594. (b) PS-HOBT resin is available from Argonaut Technologies (www.argotech.com).

(28) ACTU = chloro-1,1,3,3-tetramethyluronium hexachloro-antimonate. See: http://www.argotech.com/PDF/resins/actu.pdf.

(29) Purity was determined by HPLC-ELSD (Waters Xterra RPC_{18} column (4.6 mm × 30 mm), 5−95% CH_3CN/H_2O over 2 min).