ORGANIC LETTERS

2008
Vol. 10, No. 13
2737−2740

Successive Copper(I)-Catalyzed Cross-Couplings in One Pot: A Novel and Efficient Starting Point for Synthesis of Carbapenems

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Received April 14, 2008

ABSTRACT

An efficient approach for synthesizing a series of 2-sulfide carbapenems has been developed using two successive Cu(I)-catalyzed cross-couplings in a single pot. The method involves highly selective intramolecular coupling of lactam and dihaloalkene using 2,2′-bipyridine as a ligand, followed by intermolecular C−S formation in the presence of another ligand (1,10-phenanthroline, PPh_3) and mercaptan.

As the latest members of the β-lactam family, carbapenem antibiotics occupy a central role in fighting bacterial infection due to their broad-spectrum activity and excellent resistance to β-lactamase.[1] Carbapenems are characterized by a five-membered enamine ring fused to the β-lactam ring. However, thienamycin **1**, the first carbapenem isolated from *Streptomyces cattleya*,[2] could not be marketed due to its chemical and biological instabilities. Thus, extensive efforts over the past decades have sought to synthesize more promising compounds based on this leading structure.

Currently, a number of carbapenems are in clinical use, such as imipenem, panipenem, ertapenem, biapenem, Meropenem, and doripenem. Unlike penicillins and cephalosporins, whose precursors are produced by industrial fermentation, carbapenems can be made only through total synthesis, since no effective enzymatic process for their production has been described.[3] Developing an efficient methodology for constructing the carbapenem skeleton still remains challenging for organic synthesis because of its highly strained four−five fused ring system. A great deal of synthetic efforts have been devoted to the synthesis of the bicyclic nucleus, involving Rh-mediated carbenoid N−H insertion,[4] intramolecular Wittig-type reaction,[5] radical cyclization,[6] Dieckmann condensation,[7] and cyclizations catalyzed by Pd[8] or other

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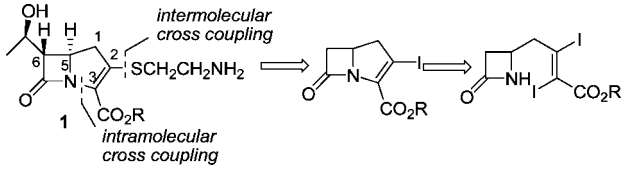
10.1021/ol800845r CCC: $40.75
Published on Web 05/30/2008

transition metals.[9] Only the Rh−carbene process has proven to be practical for synthesizing a series of carbapenems. This method involves four reaction sequences: diazetization of β-ketoester, Rh-catalyzed carbene insertion to the N−H bond, activation of the ketoester with phosphoryl chloride or triflic anhydride, and last, incorporation of a C-2 side chain. Despite its successful industrial application, this procedure suffers several drawbacks, such as the use of an expensive catalyst, harsh reaction conditions, and long reaction steps. Therefore, there is still great interest in an economical protocol that can rapidly lead to varieties of carbapenems to meet clinical demands and that can uncover new types of carbapenems with enhanced performance.

In view of the fact that carbapenems possess both vinyl sulfide and enamide groups, we speculated that a series of carbapenems could be synthesized through two successive cross-coupling reactions as shown in Scheme 1. Metal-

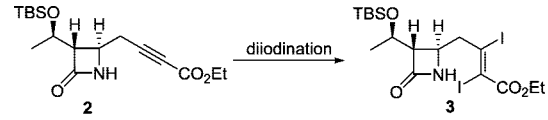
Scheme 1. Structure of Thienamycin and Synthetic Strategy



catalyzed carbon−heteroatom bond formation has attracted much attention in organic synthesis, such as copper-catalyzed cross-coupling reactions[10] for the synthesis of enol ethers,[11] vinylsulfide, and enamides. N-Vinylation reactions catalyzed by copper(I), particularly in combination with bidentate amine ligands, is a mild and efficient protocol for stereo-controlled coupling of vinyl halides with amides.[12] In addition, synthesis of vinyl sulfides via copper(I)-catalyzed stereospecific cross-coupling of vinyl iodides and thiols has recently been developed.[13] In this paper, we report an efficient synthesis of carbapenems based on this two successive coupling strategy. In our procedure, the C−S side chains are incorporated in an intermolecular manner, and the bicyclic nucleus is made by an intramolecular regioselective coupling[14] of β-lactam with an endo-orientated vinyl iodide.

Previously, we reported a convenient method for the preparation of 4-propargyl-2-azetidinone **2** from 4-acetoxy-2-azetidinone and propargyl bromides via a zinc-mediated Barbier-type reaction.[15] Subsequently, we investigated the stereoselective diiodination of the alkyne **2** to give the (*E*)-1,2-diiodoalkene **3**, using a modified method (Scheme 2),

Scheme 2. Synthesis of the (*E*)-1,2-Dihaloalkene Intermediate



NIS, ICl/NaI, then $NaHSO_3$, 79%; or I_2/NaI, 88%

in which the β-lactam nitrogen was first selectively iodinated by NIS, the triple bond was diiodinated by ICl/NaI, and finally the iodide substituted on the nitrogen was removed by $NaHSO_3$, giving an overall yield of 79%.[16] The triple bond could also be diiodinated directly and selectively by treating with iodine in the presence of a source of iodide ion.

Starting from (*E*)-α,β-diiodoacrylic acid ester **3**, we set out to study Cu(I)-catalyzed intramolecular C−N coupling. Initial ligand screening was performed using CuI with Cs_2CO_3 or K_3PO_4 as the base. To our delight, among the seven ligands examined, *N*,*N*′-dimethylethylenediamine (**L1**), *N*,*N*-dimethylglycine (**L2**), and 2,2′-bipyridine (bpy) (**L6**) gave good results. **L6**, in particular, produced the desired enamide at 87% yield (Table 1, entries 2, 3, and 7). When using 1,10-phenanthroline (**L3**) or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (**L4**) as ligand, deiodination occurred to give the precursor **2** in 40−50% yield (entries 4 and 5). We also tested other copper(I) systems like copper thiophene-2-carboxylate (CuTC) and $[Cu(phen)(PPh_3)_2]NO_3$, which have shown excellent reactivities for synthesis of enamides[12b] and vinylsulfide.[13] No product was formed using CuTC (entry 11), while $[Cu(phen)(PPh_3)_2]NO_3$ gave only unproductive results similar to those obtained with **L3** and **L4** (entry 10). Notably, under Mori's conditions[17] with $Pd(OAc)_2$/DPEphos, deiodination occurred and gave more than 50% alkyne side product, along with a trace of cyclization product (entry 12).

On the basis of the good performance of bpy, several other solvents and bases were screened. Toluene was the best solvent, while polar solvents such as DMF, NMP, THF, and ethanol gave much lower yields. Cs_2CO_3 or K_2CO_3 gave

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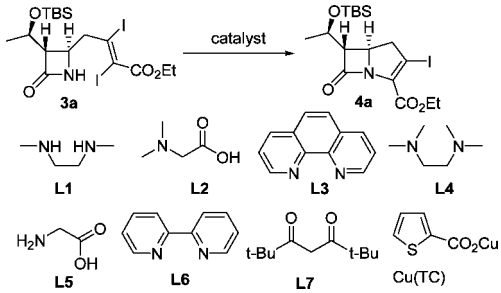
Table 1. Copper(I)-Catalyzed Intramolecular N-Vinylation Reaction



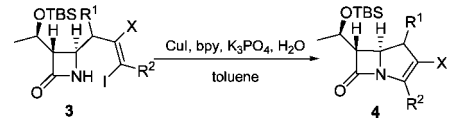
entry	catalyst[a]	T (°C)	base	t (h)	yield[b,c] (%)
1	None	40	K_3PO_4	40	24
2	CuI/**L1**	40	Cs_2CO_3	17	72
3	CuI/**L2**	rt	Cs_2CO_3	3	71
4	CuI/**L3**	40	K_3PO_4	25	5(50)
5	CuI/**L4**	40	K_3PO_4	25	6(44)
6	CuI/**L5**	40	Cs_2CO_3	48	32
7	CuI/**L6**	40	K_3PO_4	50	87
9	CuI/**L6**	40	K_3PO_4	21	94[d]
8	CuI/**L7**	40	K_3PO_4	20	18
10[e]	$[Cu(phen)(PPh_3)_2]NO_3$	40	K_3PO_4	15	8(42)
11[e]	Cu(TC)	70	Cs_2CO_3	30	0
12[f]	$Pd(OAc)_2$/DPEphos	100	K_2CO_3	1	<3(51)

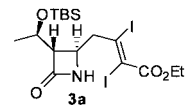
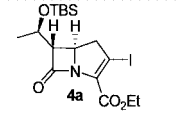
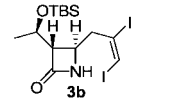
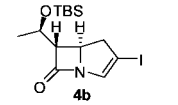
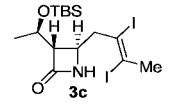
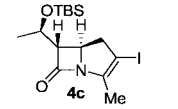
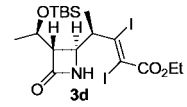
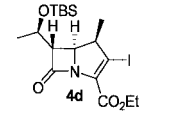
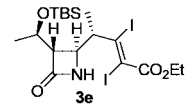
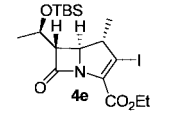
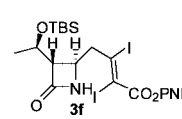
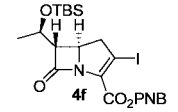
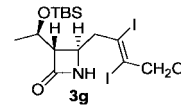
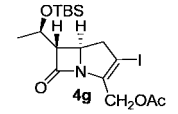
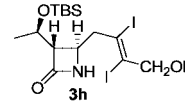
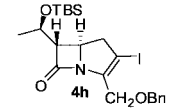
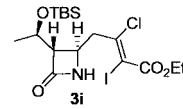
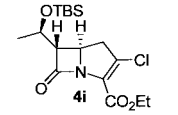
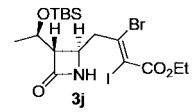
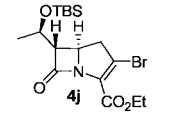
[a] Unless otherwise indicated, reactions were performed using 20 mol % of CuI, 40 mol % of ligand, and 2.0 equiv of base. [b] Isolated yield. [c] The alkyne compound **2** is given in parentheses. [d] 1 equiv of H_2O as additive. [e] 20 mol % of catalyst was used. [f] 10 mol % of $Pd(OAc)_2$ and 15 mol % of DPEphos were used.

yields ~2−5% lower than K_3PO_4. We found that by using K_3PO_4 in combination with 1 equiv of H_2O the coupling could be completed within 21 h to give the desired product in 94% yield (entry 9). The product 2-iodocarbapenem **4a** was stable in solid form for months at room temperature in the dark. Moreover, its structure was confirmed unambiguously by X-ray crystallography.[18]

Next, the range of possible substrates was investigated under the following conditions: CuI/2,2′-bipyridine as catalyst, K_3PO_4 as base with 1 equiv of H_2O as additive, and toluene as solvent (Table 2). For all substrates tested, intramolecular coupling took place in excellent yields. The important 1β- or 1α-methyl 2-iodocarbapenem intermediates for synthesis of 1-methyl carbapenem were formed smoothly in good yield without epimerization of the allylic carbon (entries 4 and 5). In particular, the substrate *p*-nitrobenzyl ester gave a reaction that produced **4f** (entry 6) in 94% yield, and this can be readily transformed into important carbapenems now on the market. Diiodoalkenes without an electron-withdrawing ester group were also found to be excellent substrates for cyclization (entries 2 and 3). The allylic compounds **3g** and **3h** gave desired products that offer the potential to functionalize the acetoxy methylene or benzyloxy methylene groups in the final carbapenems (entries 7 and 8). The α-iodo, β-chloro, or bromo-acrylic acid esters, which were prepared by dihalogenating the N-iodonation product of **2** using IX/NaX (X = Cl or Br) instead of I_2/NaI, could also undergo rapid cyclization to yield the corresponding 2-chlorocarbapenem or 2-bromicarbapenem (entries 9 and 10), while these substrates show low reactivity and only moderate selectivity in the intermolecular versions.[19] In all cases, no intermolecular coupling was ob-

Table 2. CuI/bpy-Catalyzed Intramolecular Cross-Coupling for Synthesis of 2-Iodocarbapenem[a]



entry	reactant	product	t (h)	yield[b]
1			21	94%
2			18	97%[c]
3			22	96%
4			24	92%
5			28	85%
6			24	94%
7			22	91%
8			24	95%
9			12	95%
10			13	92%

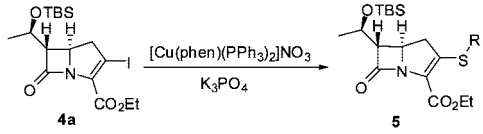
[a] The reaction was performed in the presence of 20 mol % of CuI and 40 mol % of bpy in 0.04 M toluene solution at 40 °C. [b] Isolated yield. [c] No H_2O was added.

(18) CCDC-671461 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

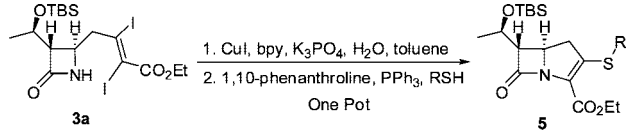
served, and no 4-exo cyclization products were detectable, even though this reaction mode has been applied in the synthesis of azetidine[20] and 2-methyleneoxetane.[21] Starting from 2-iodocarbapenem, we turned our attention to the copper(I)-promoted intermolecular C−S bond formation at the C-2 position. Initially, we applied the Venkataraman protocol[13] by using 20 mol % of soluble $[Cu(phen)(PPh_3)_2]NO_3$. This catalyst system was compatible with the sensitive structures, as indicated in Table 3. The

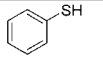
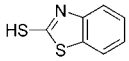
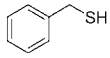
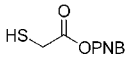
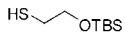
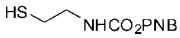
Table 3. Synthesis of Carbapenems Substituted with Sulfur at the C-2 Position

Method A:[a]



Method B:[b]



entry	RSH	product	A yield[c]	B yield[c]
1		**5a**	71%	68%
2		**5b**	95%	89%
3		**5c**	80%	76%
4		**5d**	82%	77%
5		**5e**	79%	75%
6		**5f**	63%[d]	62%[e]

[a] The reaction was performed with 20 mol % of catalyst in toluene at 60 °C. [b] 20 mol % of phenanthroline, 40 mol % of PPh_3, and 1.2 equiv of RSH were added after cyclization. [c] Isolated yield. [d] 100 mol % of catalyst was used. [e] 80 mol % of CuI, 1.0 equiv of phenanthroline, and 2.0 equiv of PPh_3 were added after the cyclization.

2-iodocabarpenems reacted with benzyl, aryl, alkyl, and heteroaryl thiol to give high yields of coupling products under milder conditions than ordinary alkene iodides, probably due at least in part to activation by a β-ester group (method A).[22] A stoichiometric amount of catalyst was required when coupling with protected 2-amino-ethanethiol, which leads to thienamcyin (entry 6). Considering that both successive couplings were catalyzed by copper(I) species, we reasoned that it might be possible to perform the requisite intramolecular N-vinylation and intermolecular S-vinylation in one pot without the need to isolate the monoiodocarbapenem intermediate or to add more CuI. Indeed, as shown in method B, one-pot synthesis of carbapenems could be performed by adding 1,10-phenanthroline (**L3**), PPh_3, and the corresponding thiol to the N-vinylation coupling mixture once the diiodoalkene was consumed completely. Comparison of the yields obtained by the one-pot and stepwise methods suggests that the catalytic activities of the CuI and phenanthroline were maintained even in the presence of bipyridine.

In conclusion, an efficient approach using two successive copper(I)-catalyzed couplings has been developed for the synthesis of carbapenems with a series of sulfide side chains at the C-2 position. The remarkable transformation in our sequence is the regioselective CuI/bpy-catalyzed intramolecular cross-coupling of the *trans*-diiodoalkene side chain with the β-lactam nitrogen to yield the key intermediate 2-iodocarbapenem, which further undergoes copper(I)/1,10-phenanthroline-mediated intermolecular coupling with different thiols to provide a series of carbapenems. In addition, the two successive couplings can be performed in one pot simply by adding a 1,10-phenanthroline ligand and thiol substrate to the completed N-vinylation coupling reaction; isolation of intermediates or addition of more copper(I) is unnecessary. The advantages of this novel synthetic methodology include the use of readily available starting materials and inexpensive catalyst, fewer synthetic steps, and mild reaction conditions. Notably, this protocol not only provides rapid access to the classical carbapenems but also allows for combinatorial diversification at the C-2 and C-3 positions. This creates the potential for exploring new types of carbapenem antibiotics with enhanced chemotherapeutic activities.

Acknowledgment. This work was financially supported by the Science & Technology Commission of Shanghai Municipality and the National Natural Science Foundation of China.

Supporting Information Available: General experimental metheods, X-ray crystallographic data for compound **4a**, and spectroscopic data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800845R

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