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Synthesis of Lactams via Copper-Catalyzed Intramolecular Vinylation of Amides

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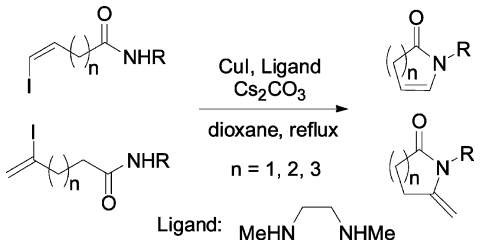
ABSTRACT



Copper-catalyzed intramolecular vinylation of iodoenamides were investigated for the first time. With CuI as the catalyst and *N,N′*-dimethylethylenediamine as the ligand, a number of iodoenamides underwent cyclization in dioxane leading to the formations of five- to seven-membered lactams in moderate to excellent yields.

Lactams are of considerable interest in a number of areas ranging from drug discovery to polymer industry. Preparations of lactams have long been an important topic in organic chemistry and continue to be actively pursued.[1] We report here that the copper-catalyzed intramolecular vinylation of amides provides an efficient and general entry to five- to seven-membered lactams.

The formation of aryl C−X bonds (X = O, S, N, etc.) via copper-catalyzed coupling between aryl halides and hetero-centered nucleophiles has drawn a great deal of attention in the past few years.[2,3] The high stability and low costs of copper catalysts enable these transformations to be a useful complement to the more extensively investigated palladium-catalyzed processes.[4] More recently, this methodology was successfully extended to the synthesis of enamides by coupling of amides with vinyl halides.[5] It could be envisioned that, if the vinylation could proceed intramolecularly, it might provide a facile route for the synthesis of lactams of various ring sizes. However, to our surprise, such a process had never previously been reported in the literature. Only a few examples of the palladium-catalyzed intramolecular vinylation of amides were reported, which led to the formation of cyclic amines rather than lactams.[6] Due to the importance of lactams in organic synthesis, we carried out the following

(1) For recent review articles, see: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (c) Shiraki, R.; Tadano, K.-I. *Rev. Heteroat. Chem.* **1999**, *20*, 283. (d) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681. (e) Ley, S. V.; Cox, L. R.; Meek, G. *Chem. Rev.* **1996**, *96*, 423.

(2) For reviews, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(3) For the latest examples, see: (a) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529. (b) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578. (c) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778. (d) Cristau, H.-J.; Cellier, P. P.; Spimdler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695. (e) Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Mehdinejad, H. *Synlett* **2004**, 1517. (f) Kim, K.-Y.; Shim, J.-T.; Lee, K.-S.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 117. (g) Nandakumar, M. V. *Tetrahedron Lett.* **2004**, *45*, 1989. (h) Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311. (i) Li, C. S.; Dixon, D. D. *Tetrahedron Lett.* **2004**, *45*, 4257. (j) Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915.

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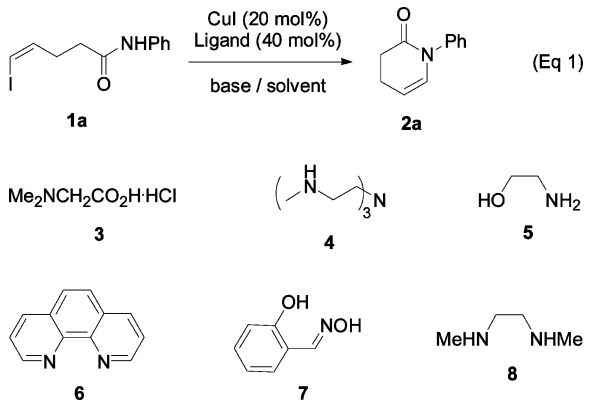
investigation to explore the scope and limitation of this possible methodology.



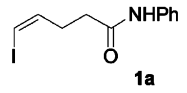
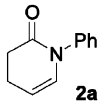
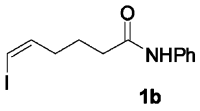
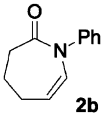
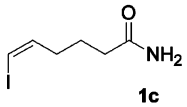
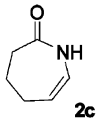
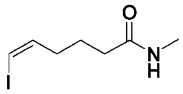
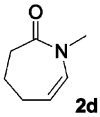
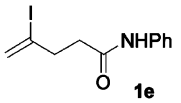
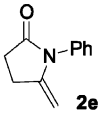
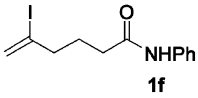
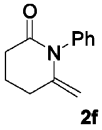
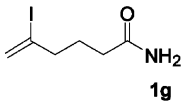
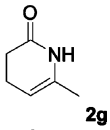
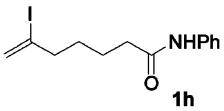
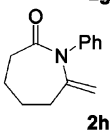
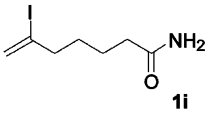
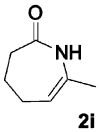
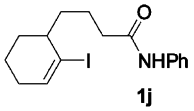
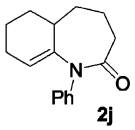
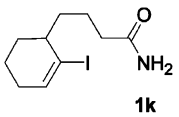
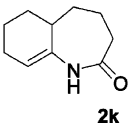
Thus, we prepared (*Z*)-5-iodo-*N*-phenylpent-4-enamide (**1a**) as the prototypical substrate to screen the experimental conditions (eq 1). The substrate concentration was set at 0.03 M for ease of comparison. The results are summarized in Table 1. As the use of an appropriate ligand would allow a mild procedure for the C−N bond formations,[5] we carried out an initial ligand screen with CuI (20 mol %) as the catalyst and Cs_2CO_3 (2 equiv) as the base in dioxane at refluxing temperature. To our delight, among the six frequently used ligands (**3**−**8**) examined, *N*,*N*′-dimethylethylenediamine (**8**) gave the best result (entries 1−7, Table 1). When the base was switched to K_2CO_3 or K_3PO_4, the product yield was lowered (entries 8 and 9, Table 1). Changing the solvent to THF or CH_3CN also gave very low yields of product probably because their boiling points were not high enough (entries 10 and 11, Table 1). This was evidenced by running

Table 1. Optimization of Experimental Conditions for **1a**

entry	ligand	base	solvent	temp. (°C)	yield (%)[a]
1	none	Cs_2CO_3	dioxane	100	0
2	**3**	Cs_2CO_3	dioxane	100	90
3	**4**	Cs_2CO_3	dioxane	100	67
4	**5**	Cs_2CO_3	dioxane	100	26
5	**6**	Cs_2CO_3	dioxane	100	86
6	**7**	Cs_2CO_3	dioxane	100	9
7	**8**	Cs_2CO_3	dioxane	100	98
8	**8**	K_2CO_3	dioxane	100	80
9	**8**	K_3PO_4	dioxane	100	82
10	**8**	Cs_2CO_3	THF	68[b]	5
11	**8**	Cs_2CO_3	CH_3CN	82[b]	9
12	**8**	Cs_2CO_3	dioxane	80	trace

[a] Isolated yield based on **1a**. [b] Refluxing temperature.

Table 2. Synthesis of Lactams **2a**−**k**

entry	substrate	CuI (mol%)[a]	product	yield (%)[b]
1	 **1a**	10	 **2a**	91
2	 **1b**	10	 **2b**	86
3	 **1c**	20	 **2c**	44[c]
4	 **1d**	20	 **2d**	14
5	 **1e**	10	 **2e**	95
6	 **1f**	10	 **2f**	86
7	 **1g**	20	 **2g**	86
8	 **1h**	20	 **2h**	73
9	 **1i**	20	 **2i**	46
10	 **1j**	20	 **2j**	83
11	 **1k**	20	 **2k**	45

[a] Reaction conditions: substrate (0.03 M), CuI:**8** = 1:2, Cs_2CO_3 (2 equiv), dioxane, reflux, 20 h. [b] Isolated yield based on **1**. [c] Compound **9** was also obtained in 25% yield.

the reaction in dioxane at 80 °C, which gave only a trace amount of **2a** (entry 12, Table 1). Reducing the amount of CuI to 10 mol % afforded **2a** in a slightly lower yield (91%). The above trend was also observed when we used (*Z*)-6-iodohex-5-enamide (**1c**) as the model substrate. Thus, we concluded that the optimized combination for this reaction was to use dioxane as the solvent, Cs_2CO_3 as the base, and *N*,*N*′-dimethylethylenediamine **8** as the ligand.

We then synthesized a number of iodoenamides to explore the scope of intramolecular vinylation under the optimized conditions. The amount of CuI used was either 10 or 20 mol %, depending on the ease of cyclization. The results are summarized in Table 2.

As illustrated in Table 2, we first tested the substrates **1a**−**d** with terminal (*Z*)-vinylic iodine substitution, which were readily prepared from the corresponding alkynes by reaction with BuLi/I_2[7] followed by reduction with $TsNHNH_2$/NaOAc.[8] The corresponding six- and seven-membered lactams with an internal double bond could be achieved (entries 1−4, Table 2). The *N*-phenyl-substituted substrate **1b** gave the seven-membered lactam **2b** in excellent yield. With *N*-unsubstituted substrate **1c**, the expected product, caprolactam **2c**, was obtained in moderate yield along with the 14-membered lactam **9** in 25% yield, whose structure was unambiguously established by its X-ray diffraction analysis (Figure 1). Compound **9** apparently resulted from the bimolecular

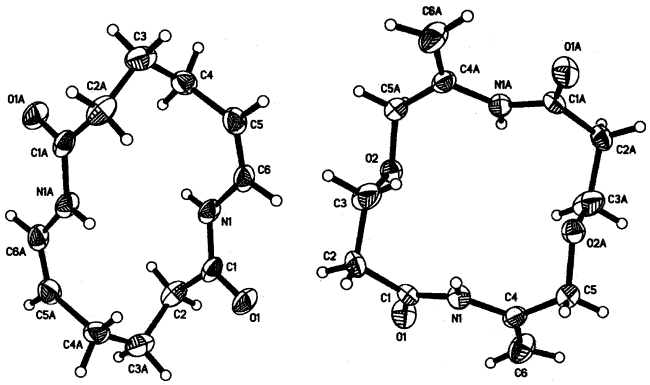
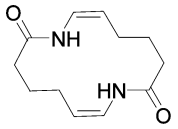


Figure 1. ORTEP drawings of compounds **9** and **13**.

reaction of **1c**. For *N*-methyl-substituted substrate **1d**, the cyclized product **2d** was isolated in only 14% yield, while most of the starting material remained unchanged. This trend (Ph > H > Me) might probably be attributed to the different basicities of the nucleophiles (NH) in the starting amides.

We next screened the substrates **1e**−**k** having an iodine substituent on the internal side of the C═C double bond; these could be easily prepared from the corresponding alkynes by reaction with TMSCl/NaI.[9] Compound **1e** gave the corresponding γ-lactam **2e** in almost quantitative yield (entry 5, Table 1). Moreover, the reactions of substrates **1f** and **1h** led to the formation of δ-lactam **2f** and caprolactam **2h** with an exocyclic double bond in high yield (entries 6 and 8, Table 2). In comparison, their N-unsubstituted analogues **1g** and **1i** gave lactams **2g** and **2i** in 86 and 46% yields, respectively, probably because the expected products with an exocyclic double bond were less stable than **2f** or **2h** and underwent isomerization under the experimental conditions (entries 7 and 9, Table 2).

As an extension, we synthesized iodoenamides **1j** and **1k** and subjected them to the same experimental conditions as above. Bicyclic compounds **2j** and **2k** were achieved in 83 and 45% yields, respectively (entries 10 and 11, Table 2). This result illustrated the potential application of the above methodology in natural product synthesis because the bicyclic benzazepine skeleton is widely embedded in a number of alkaloids such as Stenine.[10]



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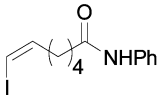

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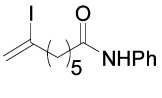

11

Our attempt to further extend the methodology to the synthesis of eight-membered lactams via the reaction of substrate **10** or **11** was unsuccessful under the optimized experimental conditions.

The above results clearly demonstrated that the Cu(I)-catalyzed intramolecular vinylation of iodoenamides is a viable method for the synthesis of lactams. The intramolecular vinylation also showed a different reactivity pattern from that of the intermolecular vinylation. As reported by Buchwald et al., the coupling of acetamide with ordinary vinyl iodides with Cs_2CO_3 as the base and diamine **8** as the ligand proceeded in high efficiency at 50 °C or even at room temperature.[5d] In contrast, the cyclization of iodoenamides **1a**−**k** required reaction temperatures higher than 80 °C. While the intermolecular amidation of vinyl bromides worked well in dioxane with *N*,*N*-dimethylglycine HCl salt **3** as the additive,[5h] bromoenamides are unlikely to be a good choice

(5) (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443. (b) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (c) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650. (d) Jiang, L.; Job, G. E.; Klapars, A.; Buchald, S. L. *Org. Lett.* **2003**, *5*, 3667. (e) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (f) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (g) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577. (h) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809.

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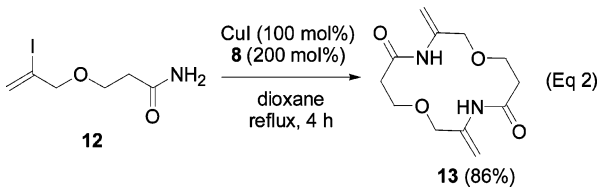
(11) Relatively low concentration is necessary for cyclization in some cases. For example, the reaction of **1c** at 0.5 M concentration afforded the expected product **2c** in only 14% yield along with the formation of the dimer **9** in 55% yield.

of substrate for intramolecular vinylation. For example, 5-bromo-*N*-phenylhex-5-enamide, the bromo analogue of **1f**, gave only 14% yield of the cyclized product **2f** under the optimized conditions. An obvious reason for these differences is that the intramolecular reactions operate at low concentrations in order to avoid the competing intermolecular reactions,[11] while intermolecular couplings are run at high concentrations (such as 1 M).[5] More importantly, the steric requirement could play a key role in the intramolecular vinylation of amides. This is further exemplified by the reaction of iodoenamide **12** shown in eq 2. Treatment of **12** with CuI and diamine **8** in dioxane (0.03 M) at refluxing temperature for 4 h afforded the 14-membered lactam **13** exclusively in 86% yield rather than the expected caprolactam.[12] The X-ray structure of **13** is presented in Figure 1. The formation of **13** and **9** are particularly interesting, which indicates that this method might be applied to the efficient synthesis of certain macrocyclic lactams.

In conclusion, we have developed a mild and efficient protocol for the copper-catalyzed intramolecular coupling of



(Eq 2)

iodoenamides, allowing the convenient preparations of five-, six-, and seven-membered *N*-vinylic lactams. In addition, macrocyclic lactams (such as **13**) can also be achieved via this method, which should be of important application in organic synthesis.

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Supporting Information Available: Synthesis and characterizations of compounds **1a**−**k**, **2a**−**k**, **12**, and **13** and X-ray crystal data of **9** and **13** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) When a catalytic amount of CuI (10 mol %) was employed, only a trace amount of **13** could be detected along with unidentified decomposition products, probably because **13** was not very stable under the reaction conditions for a prolonged time. An alternative explanation might be that Cu(I) acted as a chelating template for the formation of **13**.