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A New Synthesis of Imidazolidin-2-ones via Pd-Catalyzed Carboamination of *N*-Allylureas

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Abstract

A new strategy for the preparation of substituted imidazolidin-2-ones in two steps from readily available *N*-allylamines is described. Addition of the amine starting materials to isocyanates affords *N*-allylureas, which are converted to imidazolidin-2-one products with generation of two bonds and up to two stereocenters when treated with aryl bromides and catalytic amounts of $\text{Pd}_2(\text{dba})_3/\text{Xantphos}$ in the presence of NaOtBu .

Cyclic urea moieties are found in a broad array of biologically active molecules¹ and have been employed as monomeric units for biomaterials that exhibit greater stability than many peptides.² For example, imidazolidin-2-ones³ and other cyclic ureas⁴ are utilized as structural elements in a number of molecules with potent anti-HIV activity such as **1**.³

Cyclic ureas are most commonly constructed via treatment of 1,2-diamine precursors with phosgene equivalents such as carbonyl diimidazole.^{5,6} Although a number of 1,2-diamines can be accessed with available methods, many require multistep sequences for their preparation.⁷ Thus, alternative strategies for the construction of imidazolidin-2-ones would provide more facile access to derivatives that are not readily available. In addition, methods that allow for preparation of a variety of products from a common starting material would allow straightforward generation of analogs that could be used to optimize biological activity or pharmaceutical properties.

We have recently reported a new method for the construction of pyrrolidines via Pd-catalyzed carboamination reactions of γ -aminoalkenes with aryl bromides.^{8,9,10} We reasoned that a related strategy could potentially be employed in a straightforward, two-step synthesis of cyclic

ureas. As shown in eq 1, treatment of readily available allylic amines with isocyanates followed by Pd-catalyzed carboamination would provide a general approach to a diverse array of 5-membered cyclic ureas bearing different substituents on N1, N3, and C4. Moreover, this approach would have a significant advantage over existing methods for the synthesis of substituted imidazolidin-2-ones as a C–C bond is formed at the same time the heterocyclic ring is closed.¹¹ In this letter we describe our preliminary studies on the construction of 4-substituted imidazolidin-2-ones using this strategy.

(1).

In our initial experiments we examined the carboamination of 1-allyl-3-ethyl-1-phenylurea (**2**), which was prepared in 92% yield via addition of *N*-allylaniline to ethyl isocyanate. Treatment of **2** with 4-bromotoluene and NaOtBu in the presence of 1 mol % Pd₂(dba)₃ and 2 mol % Xantphos¹² afforded the desired imidazolidin-2-one **3** in 59% isolated yield. The major side products observed in this reaction derive from the base-mediated decomposition of **2** to afford *N*-allylaniline.¹³ Other ligands examined for this transformation including dppe,¹² dppf,¹² and P(*o*-tol)₃ provided lower yields of **3** due to the formation of a side product resulting from oxidative cyclization without incorporation of the *p*-tolyl group.¹⁴

(2).

With suitable reaction conditions in hand, we examined the Pd-catalyzed carboamination of several different acyclic ureas. As shown in Table 1, the nature of the *N*-substituents affected the yield of the cyclization reactions. For example, the carboamination of 1-allyl-3-ethyl-1-methylurea (**7**)¹⁵ with 2-bromonaphthalene proceeded in comparable yield (68%, entry 12) to the analogous transformation of **2** (73% yield, entry 1). However, treatment of 1-allyl-1-methyl-3-phenylurea (**4**) with 2-bromonaphthalene under identical conditions provided a 97% isolated yield of **9** (entry 2).

Substrates bearing *N*1-methyl and *N*3-benzyl groups (**6**, entry 8), and *N*1-benzyl and *N*3-(*p*-methoxyphenyl) groups (**5**, entries 6–7) were also transformed to the desired products in moderate to good yield.¹⁶ The efficient reactivity of the latter substrate (**5**) is particularly noteworthy, as the *N*-benzyl and *N*-(4-methoxyphenyl) substituents can potentially be cleaved from the product under orthogonal conditions to allow further functionalization.¹⁷ Unfortunately, the method was not effective for transformation of a urea substrate in which *N*3 was unprotected.¹⁸ In addition, attempts to cyclize a substrate bearing a *N*3-(α -methylbenzyl) group failed to provide the cyclic urea product.

The urea carboamination reactions were found to be effective with a broad array of aryl bromides, including substrates bearing functional groups such as nitriles (entry 8), *tert*-butyl esters (entry 6), trifluoromethyl substituents (entry 4), non-enolizable ketones (entry 5), and *ortho*-substituents (entries 7 and 10). Although reactions involving electron-poor and electron-neutral aryl halides generally provided good to excellent yields of the substituted imidazolidin-2-one products, modest yields were obtained with the electron-rich 4-bromoanisole (entry 11).

To probe both the scope and the mechanism of these transformations further, three substrates bearing internal alkenes and one substrate bearing a 1,1-disubstituted alkene were prepared and subjected to the carboamination reaction conditions. The 1,1-disubstituted compound **20** was converted to **21** in 77% yield under our standard reaction conditions (eq 3).

(3).

As shown in eq 4, treatment of butenyl-substituted urea **22** with **23** in the presence of NaOtBu and the $\text{Pd}_2(\text{dba})_3/\text{Xantphos}$ catalyst generated **24** in 50% yield. Interestingly, although **22** was employed as a 4:1 mixture of *E*:*Z* isomers, product **24** was obtained as a single diastereomer. The unreacted *Z*-isomer was observed by ^1H NMR analysis of the crude reaction mixture, which suggests the *E*:*Z* mixture is effectively resolved to a single product diastereomer due to the differences in kinetic reactivity between the two isomers. Crystallographic analysis of **24** indicated that the reaction had proceeded with *syn*-addition of the arene and the urea nitrogen across the carbon-carbon double bond. This *syn*-addition selectivity is analogous to that previously observed in Pd-catalyzed carboamination reactions of γ -unsaturated amines.⁸

(4).

The Pd-catalyzed carboamination of cyclopentene derivative **25** with 4-bromotoluene proceeded under our standard conditions to afford *syn*-addition product **26** in excellent yield (84%) with $>20:1$ diastereoselectivity (eq 4).¹⁹ However, attempts to effect the cyclization of the cyclohexene-containing substrate **27** using the Pd/Xantphos catalyst provided only trace amounts of the desired product. After some experimentation, a catalyst composed of $\text{Pd}_2(\text{dba})_3$ and PEt_3 was found to provide the cyclized product **28** in 46% yield with $>20:1$ dr (eq 5). Interestingly, the product **28** was determined to be arylated at C-5 rather than the expected C-4 position; the addition again occurred with *syn*-stereochemistry.^{20,21}

(5).

(6).

The stereochemical and regiochemical outcome of the transformations of **22**, **25**, and **27** suggest the mechanism of the *N*-allylurea carboaminations is analogous to that previously described for related transformations of γ -aminoalkenes.^{8,20} As shown in Scheme 1, oxidative addition of the aryl bromide to Pd(0) would generate **29**, which could be transformed to **30** (*n* = 1) upon reaction with the urea substrate **25** and NaOtBu. *Syn*-insertion of the alkene into the Pd–N bond would generate **31** (*n* = 1), which would provide **26** upon C–C bond-forming reductive elimination.

The unexpected isomer **28** is likely formed from β -hydride elimination of **31** (*n* = 2) to afford **32**. Reinsertion of the alkene into the Pd–H bond of **32** with reversed regiochemistry followed by reductive elimination from **33** would afford **28**. The conversion of **31** to **32** is presumably thermodynamically favorable, as this transformation would alleviate a steric interaction between the metal and the N-Ph substituent.²⁰ Although this side reaction is not observed in the Pd/Xantphos-catalyzed reaction of **25**, the use of PEt₃ for the coupling of **27** likely slows the rate of C–C bond-forming reductive elimination of **31** (*n* = 2),²² thus allowing access to the alternative mechanistic path.²⁰ The rate of C–C bond-forming reductive elimination from **33** appears to be greater than the rate of alkene displacement from **32**, as oxidative cyclization products are not observed in significant amounts under these conditions.

In conclusion, we have developed a new method that allows the two-step construction of a wide array of imidazolidin-2-ones from readily available starting materials. The key Pd-catalyzed carboamination reaction proceeds in good to excellent yield with excellent levels of diastereoselectivity. These transformations represent the first examples of urea carboamination reactions that proceed with selectivity for products of *syn*-addition, and are complementary to existing Wacker-type *anti*-carboaminations¹¹ in terms of both the types of C–C bonds that are formed and the stereochemistry of the products. Further studies directed toward expanding the scope and synthetic utility of these transformations are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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11. Tamaru has described Pd(II)-catalyzed Wacker-type carbonylation reactions of *N*-allylureas and *O*-allylcarbamates that effect ring closure with concomitant C–C bond formation to afford imidazolidin-2-ones and oxazolidin-2-ones bearing carbonyl functionality at C-4 see: (a) Tamaru Y, Hojo M, Higashimura H, Yoshida Z-i. *J Am Chem Soc* 1988;110:3994–4002. (b) Harayama H, Abe A, Sakado T, Kimura M, Fugami K, Tanaka S, Tamaru Y. *J Org Chem* 1997;62:2113–2122. [PubMed: 11671516]
12. Xantphos = 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene; dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1'-bis(diphenylphosphino)ferrocene.
13. The formation of *N*-allylaniline was observed in reactions of 2 that were monitored by ¹H NMR spectroscopy. The *N*-allylaniline underwent further transformation to provide mixtures of unidentified products. The formation of *N*-allylaniline was also observed when 2 was heated with NaOtBu in the absence of Pd.
14. This product was assigned as 3-ethyl-4-methyl-1-phenyl-1,3-dihydroimidazol-2-one based on ¹H NMR analysis.
15. The formation of side products resulting from base-mediated isomerization of the *N*-allyl group to a *N*-1-propenyl group were observed in reactions of 7. This isomerization also occurred when 7 was heated with NaOtBu in the absence of Pd.
16. Substrates 4–7, 20, 22, 25, and 27 were obtained in 79–97% yield from treatment of the corresponding allylamine with the appropriate isocyanate as described above.
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18. Attempts to transform substrates bearing unprotected N3 moieties led to the formation of products resulting from tandem *N*-arylation and carboamination in low yield (ca. 30%). For a related reaction of aliphatic amines see: Yang Q, Ney JE, Wolfe JP. *Org Lett* 2005;7:2575–2578. [PubMed: 15957894]
19. The connectivity and stereochemistry of 26 and 28 were determined through ¹H NMR COSY and nOe experiments. See the Supporting Information for complete details of stereochemical assignments.
20. Related isomers have been observed in Pd/P(t-Bu)₂Me-catalyzed carboaminations of *N*-(*p*-methoxyphenyl)-2-(cyclopent-2-enylethyl)amine. See: Ney JE, Wolfe JP. *J Am Chem Soc* 2005;127:8644–8651. [PubMed: 15954769]
21. A small amount of *N*-(cyclohex-2-enyl)aniline was observed as a side product in this reaction.
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Scheme 1.
Mechanism

Table 1

Imidazolidin-2-one Synthesis^a

entry	substrate	ArBr	product	yield ^b
1				73%
2				97%
3				83%
4				92%
5				85%
6				75%
7				71%
8				80%
9				58%

entry	substrate	ArBr	product	yield ^b
10			17	63%
11			18	35%
12			19	68%

^a Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 1.2 equiv NaOtBu, 1 mol % Pd₂(dba)₃, 2 mol % Xantphos, Toluene (0.17–0.25 M), 110 °C. Reactions were complete in 30min–8h; reaction times have not been minimized.

^b Isolated yield (average of two or more experiments).