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Regioselective and enantioselective synthesis of seven-membered ring cyclic arylguanidine and urea derivatives

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Abstract—Cycloaddition reaction of 2-vinylpyrrolidines with carbodiimides in the presence of palladium acetate and dpppentane affords seven-membered ring cyclic arylguanidines in good yields and conversions. When 1-butyl-4-methyl-2-vinylpyrrolidine **1c** was used as a mixture of *trans* and *cis* isomers in a 4:1 ratio, and reacted with bis(2-chlorophenyl)carbodiimide **2a**, high stereoselectivity was achieved and only the *trans* seven-membered cyclic guanidine was obtained. A methyl group in the 4-position of the pyrrolidine ring and the chloro substituent in the *ortho* position of the carbodiimide may be responsible for the enhanced product ratio in favor of the *trans* isomer.
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1. Introduction

Seven-membered ring heterocycles have recently attracted attention due to their biologically activities, such as seven-membered ring cyclic ureas DMP 323 and DMP 450, which are notable members of a promising class of highly potent HIV protease inhibitors.[1] Recent reports have also shown that cyclic cyanoguanidines[2] and sulfamide[3] analogues of DMP 323 display high inhibitory activity. In initially reported routes to DMP 323, DMP 450 and related compounds, the urea moiety was formed by reaction of highly toxic phosgene, or a phosgene derivative, with an O-protected diaminediol.[4] Recently, the utility of functionalized 1,4-diamines, produced via a temporary phosphorus tether (P-tethers)/ring-closing metathesis (RCM)/hydrolysis sequence, was demonstrated in the synthesis of a number of structurally diverse DMP 323 analogues, including the seven-membered ring heterocyclic ureas and sulfamides.[5] More recently, catalytic carbonylation of functionalized diamines afforded the core structure of DMP 323 and DMP 450.[6] However, there is still need for further development of metal-catalyzed synthesis methodology, since the direct metal-catalyzed synthesis of seven-membered ring heterocycles could provide an attractive alternative to the multiple step synthetic routes to prepare seven-membered ring ureas and related compounds. There are examples of the reaction of three- or four-membered ring heterocycles such as thiiranes,[7] aziridines,[8] oxiranes,[9] azetidines[10] and oxetanes[11] with heterocumulenes to form five- or six-membered ring heterocycles. Only a few successful metal-catalyzed reactions are known for the preparation of seven-membered cyclic compounds.[12,13]

We previously reported the first use of 2-vinylpyrrolidines and aryl isocyanates for cycloaddition reactions catalyzed by palladium complexes, thus affording 1, 3-diazepan-2-one derivatives in high regioselectivity and good yields.[14] Herein, we describe the first examples of the highly regioselective palladium-catalyzed cyclization reaction of 2-vinylpyrrolidines with carbodiimides for the formation of arylguanidines derivatives. This reaction provides a convenient entry to seven-membered ring cyclic arylguanidines, analogues of 1, 3-diazepan-2-one derivatives that are of interest in the pharmaceutical sector. Moreover, an asymmetric catalytic synthesis of seven-membered ring cyclic ureas and arylguanidines by adding a chiral ligand to the reaction mixture is also described herein.

2. Results and discussion

2.1. Cycloaddition reaction of 2-vinylpyrrolidines with various carbodiimides

The reaction of *N*-butyl-2-vinylpyrrolidines **1a** (0.2 mmol) with bis(*p*-chlorophenyl)-carbodiimide **2c** (0.4 mmol) was first investigated by using reaction conditions similar to those described for the reaction of 2-vinylpyrrolidines with aryl isocyanates. These reaction conditions are not suitable for the present reaction, that is reaction of **1a** with **2c** in the presence of 15 mol% $Pd(OAc)_2$ and 60 mol% PPh_3 in 3 mL

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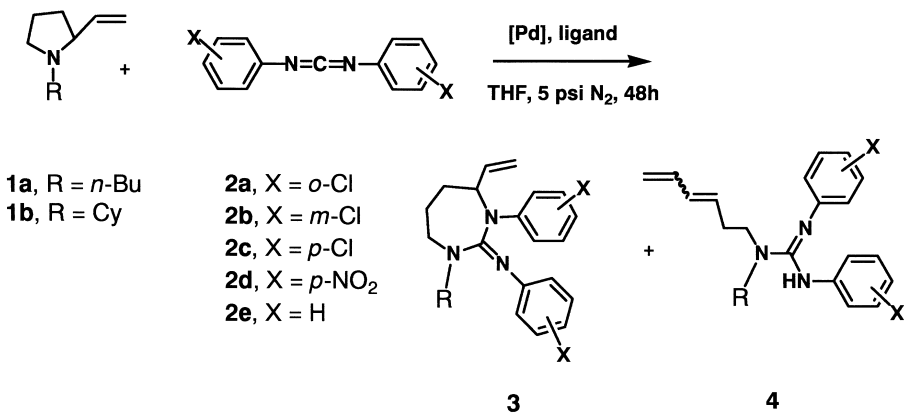


Scheme 1.

Table 1. Optimized cyclization reaction of 1-butyl-2-vinylpyrrolidine **1a** with bis(*p*-chlorophenyl)carbodiimide **2c** catalyzed by palladium[a]

Entry	Equiv. (**2c**/**1a**)	Palladium/ligand (mol%)	Conv. (%)[b]	Yields (%)[c] **3c**, **4c** (ratio)[d]
1	2	$Pd(OAc)_2/PPh_3$ (15:60)	<10	0
2	1.2	$Pd(OAc)_2$/dppf (15:30)	100	0, 35
3	2	$Pd(OAc)_2$/dppp (15:30)	75	14, 56 (20:80)
4	2	$Pd(OAc)_2$/dppb (15:30)	65	11, 42 (21:79)
5	2	$Pd(OAc)_2$/dpppentane (15:30)	97	**56**, **28** (67:33)
6	1.5	$Pd(OAc)_2$/dpppentane (15:30)	95	**70**, **11** (86:14)
7	1.1	$Pd(OAc)_2$/dpppentane (15:30)	51	39, 5 (88:12)
8	2	$Pd_2(dba)_3{\cdot}CHCl_3$/dpppentane (15:30)[e]	33	25, 3 (93/7)

[a] $Pd(OAc)_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphine ligand were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1a** and **2c** under 5 psi at 130 °C in a glass autoclave.
[b] The conversion was determined from GC by using biphenyl as an internal standard or was calculated based on the crude ^1H NMR of the mixture.
[c] Isolated yield based on the pyrrolidine **1a** used.
[d] Based on the isolated yield of **3c** and **4c**, and in most cases **4c** consisted a 1:1 ratio of *trans* and *cis* isomers.
[e] The reaction was conducted at 135 °C.

THF under argon, resulted in no conversion at room temperature (Scheme 1). When the reaction temperature was increased to 130 °C, only 10% conversion was achieved with none of the expected product formed at all (Table 1, entry 1). The bidentate phosphine ligand dppf, which has similar basicity to PPh_3, only gave the ring-opened product **4c** in 35% yield and 100% conversion at 130 °C in 48 h, accompanied by unidentified products (Table 1, entry 2). The alkyl phosphine ligands dppp and dppb showed similar selectivity, affording both the cyclic guanidine **3c** and ring-opened compound **4c**, which can be separated by GC and silica gel chromatography very well. The ring-opened product **4c** was usually formed as the major product (Table 1, entries 3 and 4). We found that the more basic bidentate phosphine dpppentane was the ligand of choice for achieving higher regioselectivity. Under the same reaction conditions as those described above, products **3c** and **4c** were obtained in a 67:33 ratio and in 84% yield and 97% conversion (Table 1, entry 5). This result is also consistent with these we reported previously indicating that phosphine ligands with higher basicity favor the formation of ring-cyclized products.[14]

It is noteworthy that the amount of carbodiimide used has a significant effect on the selectivity of the product formed. When the number of equivalents of **2c** to **1a** was reduced from 2 to 1.1 equiv., the ratio of **3c**/**4c** (88:12) increased, but the yield and conversion were lower (Table 1, entries 6 and 7). Use of 15 mol% of $Pd_2(dba)_3{\cdot}CHCl_3$ and 30 mol% of dpppentane gave **3c**/**4c** in a higher ratio (93/7), but in low yield and conversion (28 and 33%, respectively, Table 1, entry 8).

Based on the reaction conditions above, we concluded that the catalytic system consisting of palladium acetate and dpppentane is preferred for this reaction. Reaction of several 2-vinylpyrrolidines **1a**–**c** and carbodiimides **2a**–**f** was investigated, and the results are summarized in Tables 2 and 3.

Note that in all the reactions of 2-vinylpyrrolidines **1a**–**c** with carbodiimides **2a**–**c** (except **1a** with **2c**), greater regioselectivity was obtained and the desired cyclic arylguanidines **3** were formed exclusively. Only traces, if any, of **4** was observed in these reactions (Table 2). For example, when 1-butyl-2-vinylpyrrolidine **1a** was used as the substrate for reaction with 1.2 equiv. of bis(*o*-chlorophenyl)carbodiimide **2a** and bis(*m*-chlorophenyl)carbodiimide **2b**, in the presence of 10 mol% $Pd(OAc)_2$ and 20 mol% dpppentane at 130 °C for 24 and 36 h, **3a** and **3b** were isolated in 81 and 83% yields with 98 and 99% conversions, respectively, and only a trace of **4a** was observed in both cases (Table 2, entries 1 and 2).

Due to steric effects, 1-cyclohexyl-2-vinylpyrrolidine **1b** exhibited less reactivity compared to **1a**, and slightly higher, and longer, reaction temperature and times, respectively, are needed, affording products in moderate yields and conversions. Reaction of **1b** with 1.5 equiv. of **2a** and **2b** at 145 °C for 48 h gave **3d** and **3e** in 45 and 51% yields, and in 51 and 60% conversions, respectively, (Table 2, entries 4 and 5).

Table 2. Palladium catalyzed cyclization reactions of 2-vinylpyrrolidine **1** with carbodiimides **2** in THF[a]

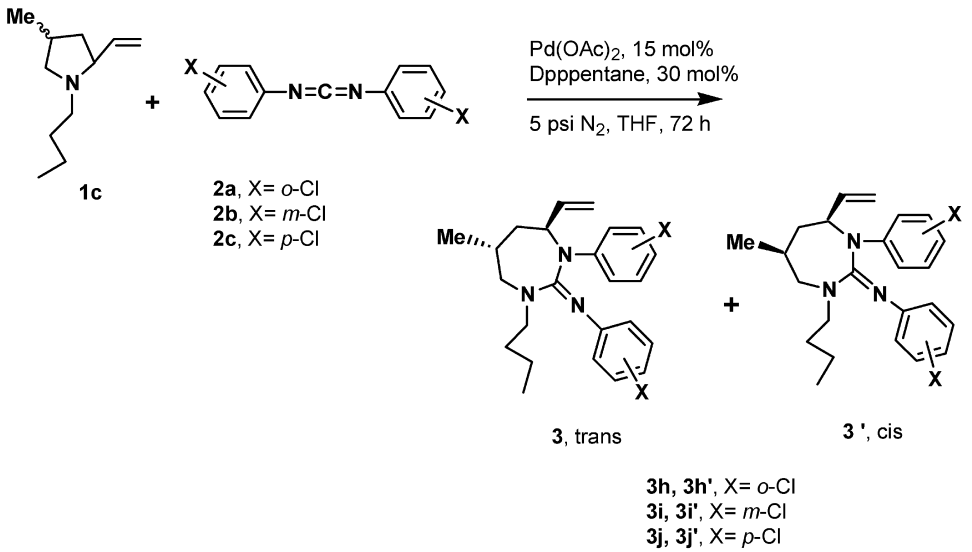
Entry	1	2 (equiv.)	$Pd(OAc)_2$/dpppentane (mol%)	Time (h)	Conv. (%)[b]	3, Yield (%)[c]	4, Yield, %[c] (*trans*/*cis*)[d]
1	**1a**	**2a** (1.2)	(10:20)	24	98	**3a**, 81	Trace
2	**1a**	**2b** (1.2)	(10:20)	36	99	**3b**, 83	0
3	**1a**	**2c** (1.5)	(15:30)	48	95	**3c**, 70	**4c**, 11 (50:50)
4	**1b**	**2a** (1.5)	(15:30)	48	51	**3d**, 45	0
5	**1b**	**2b** (1.5)	(15:30)	48	60	**3e**, 51	0
6	**1b**	**2c** (1.5)	(15:30)	48	35	**3f**, 23	Trace
7	**1a**	**2d** (1.5)	(15:30)	48	98	**3g**, trace	**4g**, 45 (70:30)
8	**1a**	**2e** (2)	(15:30)	48	<20	0	0

[a] $Pd(OAc)_2$ and dpppentane were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1** and **2** under 5 psi at the specified temperature in a glass autoclave.
[b] The conversion was determined by GC using biphenyl as the internal standard or was calculated based on the crude ^{1}H NMR of the mixture.
[c] Isolated yield based on the pyrrolidine **1** used.
[d] Based on ^{1}H NMR.

When **2c** was used as the reactant, however, the cycloaddition reaction gave **3f** in a lower isolated yield of 23% (Table 2, entry 6). The strength of the electron-withdrawing substituent on an aryl carbodiimide significantly affects the nature of the formed product. When bis(*p*-nitrophenyl)-carbodiimide **2d** was used in the reaction with **1a**, the substrate was nearly fully consumed in 48 h at a relatively lower temperature of 110 °C but gave only traces of **3g** with the ring-opened product **4g** isolated in 45% yield (Table 2, entry 7). Some unknown products were obtained as well. No reaction occurred between bisphenylcarbodiimide **2e** and **1a** at 150 °C for 2 days (Table 2, entry 8). These results may be understood based on the fact that an electron-withdrawing group at the *para*-position of aryl carbodiimides generally enhances the rate of the ring-opening reaction. Aryl carbodiimides with an electron-donating group, or with no substituent, make the electrophilic carbodiimide carbon atom less reactive towards the nucleophilic nitrogen of the (π-allyl)palladium intermediate generated by oxidative addition of pyrrolidine to the palladium-(0) species.

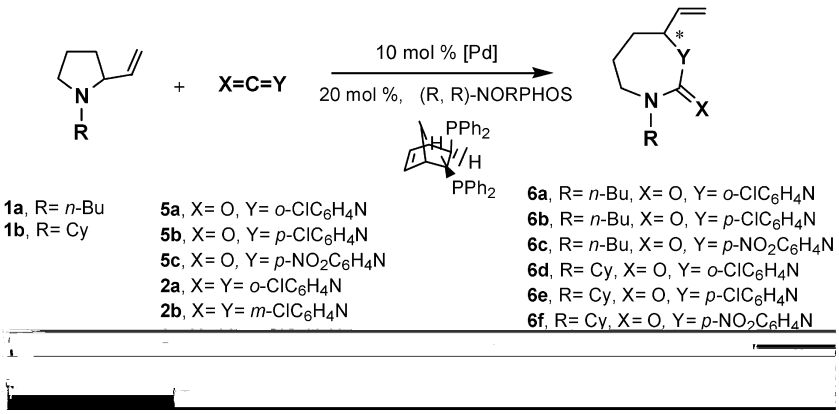
We also investigated the stereoselectivity of the reaction by using 1-butyl-4-methyl-2-vinylpyrrolidine **1c** as the substrate. The latter was a 4:1 mixture of *trans* and *cis* isomers (inseparable by GC and TLC). Reaction of **1c** with bis(chlorophenyl)carbodiimides **2a–c** were sluggish possibly because of the steric hindrance caused by the methyl group in **1c**. Nevertheless, the products were isolated in moderate to good yields (Table 3). Reaction of **1c** with **2c** at 140 °C led to both *trans* and *cis* isomers in 31 and 8%

Table 3. Cyclization reactions of 1-butyl-4-methyl-2-vinylpyrrolidine **1c** with carbodiimides **2** catalyzed by $Pd(OAc)_2$ and dpppentane in THF[a]



Entry	2 (1.5 equiv.)	Conv.[b] (%)	3 (yield, %)[c]	3′ (yield, %)[c]
1	**2a**	42	**3h**, 35	**3h′**, trace
2	**2b**	79	**3i**, 36	**3i′**, 35
3	**2c**	45	**3j**, 31	**3j′**, 8

[a] $Pd(OAc)_2$ and dpppentane were premixed for 30 min in 3.0 mL of dry, degassed THF followed by addition of **1c** and **2** under 5 psi N_2 at 140–145 °C in a glass autoclave.
[b] The conversion was determined by GC using biphenyl as the internal standard, or was calculated based on the crude ^{1}H NMR of the mixture.
[c] Isolated yield based on the pyrrolidine **1c** used.



Scheme 2.

yields (45% conversion), respectively, (Table 3, entry 3). When bis(*m*-chlorophenyl)carbodiimide **2b** was used as the reactant, the total yield of the products increased to 71%, but in low stereoselectivity, and almost the same ratio of *trans* and *cis* isomers was obtained. All the *trans* and *cis* isomers obtained can be easily separated by means of GC and silica gel columns (Table 3, entry 2). Under the same reaction conditions, bis(*o*-chlorophenyl)carbodiimide **2a** gave greater stereoselectivity, with the *trans* product **3h** obtained in 35% yield and in 42% conversion, and only traces of the ring-opened product was observed (Table 3, entry 1). The higher selectivity may be due to steric hindrance by the *ortho* substituents on the phenyl rings, and the methyl group of the pyrrolidine ring. All the reactions may proceed via the formation of a (π-allyl)palladium complex as described previously.[14]

2.2. Asymmetric cyclization reactions of 2-vinylpyrrolidines with aryl isocyanates and carbodiimides using chiral phosphine ligands

The enantioselective variant of the reaction was next investigated (Scheme 2), because this may be a more convenient way to synthesize the biologically relevant targets through one-pot asymmetric catalytic cyclization reactions. To our knowledge, this report is the first example of the asymmetric catalytic synthesis of seven-membered ring diazepan-2-ones and arylguanidines. Several chiral ligands were investigated for the cycloaddition reactions of 1-butyl-2-vinylpyrrolidines **1a** and **1b** with *p*-chlorophenyl isocyanate **5b**. The NORPHOS type ligand with $Pd_2(dba)_3 \cdot CHCl_3$ or $Pd(OAc)_2$ is efficient for the cycloaddition reaction.[16]

Figure 1. ORTEP view of **6d**.