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Efficient Construction of Five-Membered Aromatic and Nonaromatic Heterocycles from 1,6-Enynes by a Palladium-Catalyzed Domino Coupling/Cycloisomerization Process

Tuan-jie Meng,[†] Yimin Hu,*[,†] and Shaowu Wang*[,†,‡]

[†]*Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, Institute of Organic Chemistry, School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, China and* [‡]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, China*

yiminhu@mail.ahnu.edu.cn; swwang@mail.ahnu.edu.cn

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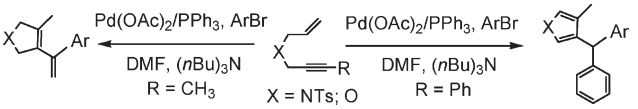

General and efficient methods for the construction of five-membered aromatic and nonaromatic heterocycles by palladium-catalyzed coupling/cycloisomerization of 1,6-enynes and aryl halides have been developed. Results indicate that substituents at the terminus of the alkynes have a significant effect on the selective formation of the products.

Introduction

Five-membered heterocycles are important synthetic targets as a result of their occurrence in numerous natural products, their important roles in diverse living processes, and their utility as versatile intermediates.[1] As a consequence, the development of synthetic routes for the construction of these heterocycles has been a major research objective for decades. Although several general approaches are presently available, the search for new methodologies proceeding more efficiently and involving readily available starting materials still remains an important area of research.

Recently, there has been much attention focused on the transformations of enynes catalyzed by transition metals for the syntheses of potentially important heterocyclic compounds.[2] Palladium is the most versatile catalyst among the transition metals used in enyne cyclization reactions. Palladium-catalyzed cyclization reactions of enynes and coupling with other synthetic units have been reported, such as CO (Pauson−Khand reaction),[3] aryl boronic acids,[4] bimetallic reagents,[5] hydrides,[6] and acetic acid.[7] These can be separated into those that form a π-allyl palladium intermediate previous to the enyne cyclization[4] and those that "trap" the alkenylpalladium product of the enyne cyclization.[3,5−7] Furthermore, alkenylrhodium compounds are important intermediates in coupling/cyclization reactions of acetylenic compounds with organometallic reagents because of the mild reaction conditions.[8] Despite the extensive

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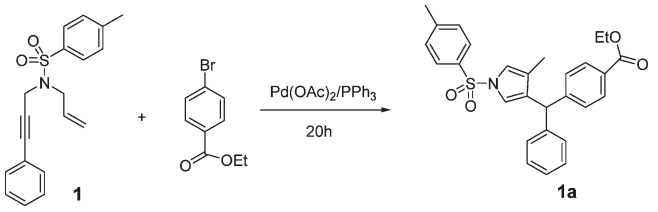
TABLE 1. Palladium-Catalyzed Reaction for Construction of the Heterocycles[a]



entry	[Pd] (mol %)	base (equiv)	solvent	time (h)	temp (°C)[b]	yield (%)[c]
1	$[Pd(OAc)_2]/PPh_3$ (1:2)	$(n\text{-}Bu)_3N$ (2)	DMF	15	100	0
2	$[Pd(OAc)_2]/PPh_3$ (3:6)	$(n\text{-}Bu)_3N$ (2)	DMF	20	120	15
3	$[Pd(OAc)_2]/PPh_3$ (3:6)	$(n\text{-}Bu)_3N$ (2)	DMF	20	130	45
4	$[Pd(OAc)_2]/PPh_3$ (3:6)	$(n\text{-}Bu)_3N$ (2)	DMF	18	140	75
5	$[Pd(OAc)_2]/PPh_3$ (3:6)	$(n\text{-}Bu)_3N$ (2)	DMF	20	150	75
6	$[Pd(OAc)_2]/PPh_3$ (3:6)	K_2CO_3 (2)	DMF	20	140	7
7	$[Pd(OAc)_2]/PPh_3$ (3:6)	$(n\text{-}Bu)_3N$ (2)	CH_3CN	22	100	0
8	$[Pd(OAc)_2]/PPh_3$ (3:6)	$(n\text{-}Bu)_3N$ (2)	toluene	20	130	20
9	$[Pd(OAc)_2]/PPh_3$ (2:4)	$(n\text{-}Bu)_3N$ (2)	DMF	20	140	63
10	$[Pd(dba)_2]$ (2)	$(n\text{-}Bu)_3N$ (2)	DMF	25	140	12
11	$[Pd(PPh_3)_4]$ (2)	$(n\text{-}Bu)_3N$ (2)	DMF	20	140	17

[a]All reactions were carried out under argon using **1** (1.0 equiv), ethyl 4-bromobenzoate (1.2 equiv), $Pd(OAc)_2$ (3 mol %), PPh_3, base, and solvent (5 mL) at indicated temperature. [b]Oil bath temperature. [c]Isolated yield.

precedent on five-membered heterocycle syntheses,[2] palladium-catalyzed cyclization and coupling of enynes with aryl halides has been less explored. In continuing our studies on 1,6-diene compounds,[9] we found that the cyclization reactions between 1,6-enynes and aryl bromides proceeded by a different pathway to give unexpected cyclic products. Herein we wish to report the palladium-catalyzed cyclization between enynes and aryl bromides to form five-membered heterocycles.

Results and Discussion

The reaction conditions using *N*-allyl-4-methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide (**1**) and ethyl 4-bromobenzoate as representative substrates in the presence of a catalytic palladium system was surveyed (Table 1). No desired product was observed when the reaction was performed at 100 °C, and most of the staring material remained unchanged (Table 1, entry 1). The product **1a** could be obtained in 75% yield when the reaction temperature was raised to 140 °C (Table 1, entry 4) in the presence of 3 mol % of $Pd(OAc)_2$, 6 mol % of PPh_3, and 2 equiv of base $(n\text{Bu})_3N$. However, no significant increase in the yield of product **1a** was observed as the reaction temperature was raised from 140 to 150 °C (Table 1, entries 4 and 5). Therefore, the reaction temperature was fixed at 140 °C for subsequent experiments. The base additive plays an important role in the overall efficiency of the reaction; we discovered that the isolated yields of **1a** dropped from 75% to 7% when the base was changed from tributylamine to potassium carbonate. (Table 1, entries 5 and 6). Different organic solvents, such as CH_3CN, toluene, and DMF, were tested in the synthesis of **1a** under the standard conditions (140 °C, 3 mol % $Pd(OAc)_2$, 6 mol % PPh_3, 2 equiv of $(n\text{Bu})_3N$). As shown in Table 1 (entries 5, 7, and 8), we can see that the best results were obtained in DMF. Further lowering of the catalyst loadings from 3 to 2 mol % resulted in a decrease of product yields from 75% to 63% (Table 1, entries 5 and 9). Other palladium catalysts such as $Pd(dba)_2$ and $Pd(PPh_3)_4$ exhibited catalytic activity lower than that of $Pd(OAc)_2$ with regard to the isolated yields of the product (Table 1, entries 10 and 11). The optimized reaction conditions use $Pd(OAc)_2$ (3 mol %) as the catalyst, PPh_3 (6 mol %) as the ligand, tributylamine as a base, DMF as the solvent, 20 h for the reaction time, and 140 °C for the reaction temperature. These conditions were used in the following studies unless otherwise noted.

With the optimized conditions in hand, we then examined the scope and limitations of this methodology. The reactions of substrates *N*-allyl-4-methyl-*N*-(3-phenylprop-2-ynyl)benzenesulfonamide (**1**) and (3-(allyloxy)prop-1-ynyl)benzene (**2**) with a number of aryl halides were performed, and the results are compiled in Table 2. It was found that the reaction of the aryl halides having electron-withdrawing groups, such as methoxycarbonyl, formyl, chloro, sulfonyl, cyano, and acetyl, with **1** or **2** gave the five-membered aromatic heterocycles in moderate to good yields. In general, higher yields of the five-membered aromatic heterocycles were obtained when the benzene ring of the aryl halide was more electronic-deficient. As a consequence, the reaction of **1** with 1-bromo-4-chlorobenzene gave the product in 43% yield (entry 5), while the reaction of **1** with 4-bromophenyl methyl sulfone or 4-bromobenzonitrile gave the corresponding products in 76% and 80% yield, respectively (entries 7 and 8). However, the corresponding five-membered aromatic heterocycles were not isolated when aryl halides such as 4-bromotoluene and 1-bromo-4-methoxybenzene, which incorporated electron-donating substituents on the benzene ring, reacted with either **1** or **2**. Instead unidentified products were detected, indicating that the electronic properties of the aryl halides have a strong effect on the reaction.

To further broaden the scope of this reaction, we tested reactions of *N*-allyl-4-methyl-*N*-(but-2-ynyl)benzenesulfonamide (**3**) with aryl halides under the aforementioned conditions. The reactions also proceeded smoothly; however, the desired 1,3,4-substituted pyrroles were not isolated. Instead, a series of 1,3,4-substituted 3-pyrrolines were obtained in good yields

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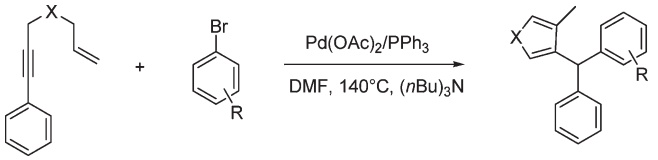
TABLE 2. Synthesis of Five-Membered Aromatic Heterocycles[a]



1: X = NTs; 2: X = O

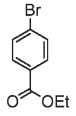
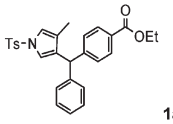
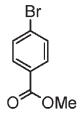
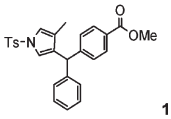
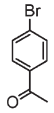
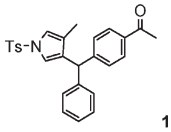
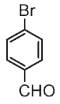
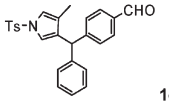
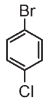
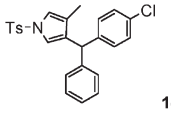
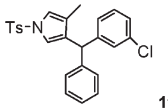
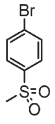
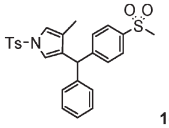
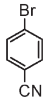
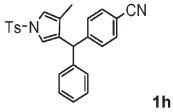
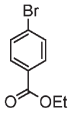
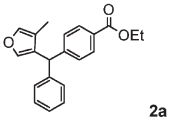
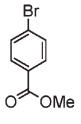
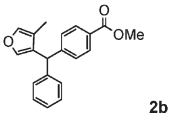
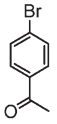
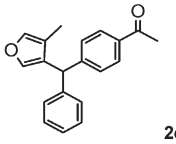
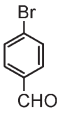
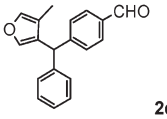
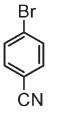
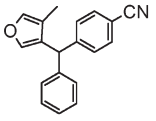
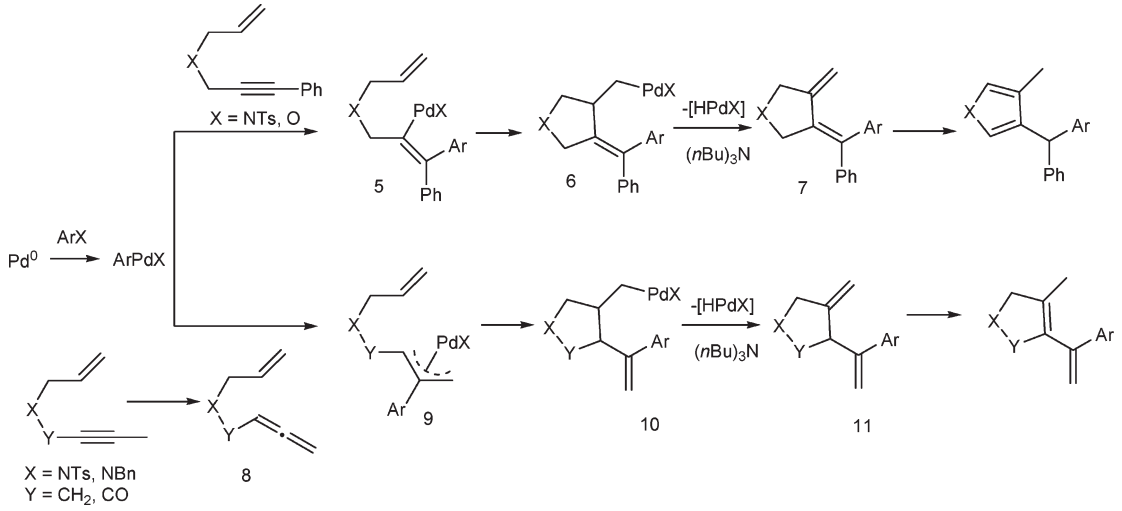
entry	enyne	ArBr	product	yield(%)[b]
1	1		 **1a**	75
2	1		 **1b**	72
3	1		 **1c**	75
4	1		 **1d**	78
5	1		 **1e**	43
6	1		 **1f**	37
7	1		 **1g**	76
8	1		 **1h**	80
9	2		 **2a**	69
10	2		 **2b**	70

TABLE 2. Continued

entry	enyne	ArBr	product	yield(%)[b]
11	2		 **2c**	73
12	2		 **2d**	75
13	2		 **2e**	75

[a]Reaction conditions: 3 mol % $Pd(OAc)_2$, 6 mol % PPh_3, 2 equiv of *n*-Bu_3N, 1.2 equiv of ArX, DMF, 140 °C, in an atmosphere of argon. [b]Isolated yields.

SCHEME 1. Proposed Mechanistic Pathways for the Formation of Different Heterocyclic Compounds



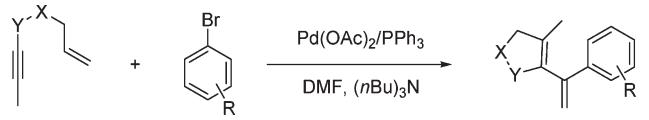
(Table 3, entries 1−7). Similarly, reactions of *N*-allyl-*N*-benzylbut-2-ynamide (**4**) led to the 1,3,4-substituted 3-pyrroline-2-ones in good yields at lower temperatures and shorter reaction times (Table 3, entries 9−15). Again, reactions of **4** with aryl halides having electron-withdrawing groups led to the desired product in higher yields, whereas reactions of **4** with aryl halides having electron-donating groups did not afford the products. Reaction of **4** with bromobenzene gave a much lower yield of the product than aryl halides having electron-withdrawing groups (entries 8 and 16). When aryl halides with both C−Br and C−Cl bonds on the benzene ring were reacted, the C−Br bond coupled selectively with the 1,6-enynes (entries 5, 13, and 14).

All the resulting heterocyclic compounds were confirmed by ^1H NMR, ^{13}C NMR, and HR-MS analyses. The representative compounds of **1h** was additionally characterized by X-ray crystallography analysis.[10]

Mechanism. On the basis of the above observations, plausible mechanisms for the selective formation of five-membered aromatic heterocycles and nonaromatic heterocycles are proposed in Scheme 1. Different substituents at the terminus of the alkynes give rise to the formation of different products. (1) When the terminus was a phenyl group, insertion of arylpalladium(II) halide into an alkyne moiety produced the intermediate **5**, which then reacted with the carbon−carbon double bond through a carbopalladation reaction to afford **6**. After β-elimination, **6** produced HPdBr and **7**, which then led to five-membered aromatic heterocycles through isomerization of exocyclic double bonds. A reductive elimination assisted by tributylamine regenerated Pd(0). (2) When the terminus alkyne bore a methyl

(10) (a) Sheldrick, G. M. *SHELXL97, Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, **1997**. (b) Sheldrick, G. M. *SHELXS97, Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, **1997**. (c) Sheldrick, G. M. *Acta Crystallogr. A* **1990**, *46*, 467.

TABLE 3. Synthesis of Five-Membered Nonaromatic Heterocycles[a]



3: X = NTs, Y = CH_2
4: X = NBn, Y = CO

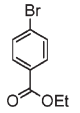
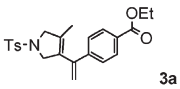
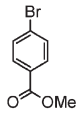
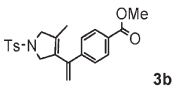
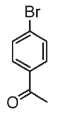
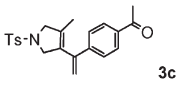
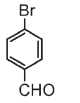
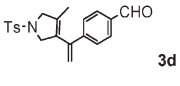
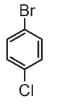
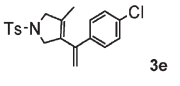
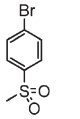
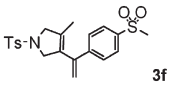
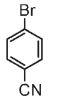
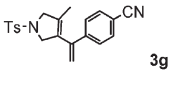
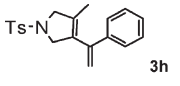
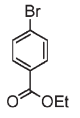
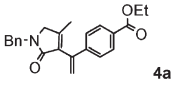
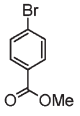
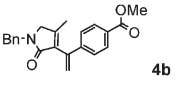
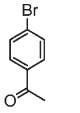
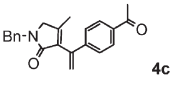
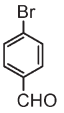
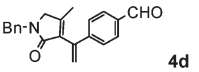
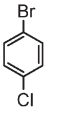
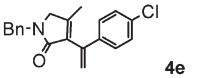
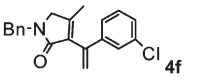
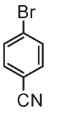
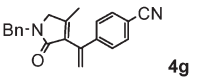
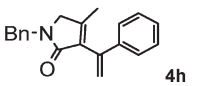
entry	enyne	ArX	product	yield(%)[b]
1	3		 **3a**	69
2	3		 **3b**	71
3	3		 **3c**	74
4	3		 **3d**	75
5	3		 **3e**	60
6	3		 **3f**	77
7	3		 **3g**	75
8	3		 **3h**	23
9[c]	4		 **4a**	84
10[c]	4		 **4b**	87
11[c]	4		 **4c**	81

TABLE 3. Continued

entry	enyne	ArX	product	yield(%)[b]
12[c]	4		 **4d**	85
13[c]	4		 **4e**	73
14[c]	4		 **4f**	70
15[c]	4		 **4g**	82
16[c]	4		 **4h**	34

[a]Reaction conditions: 3 mol % $Pd(OAc)_2$, 6 mol % PPh_3, 2 equiv of n-Bu_3N, 1.2 equiv of ArX, DMF, 140 °C in an atmosphere of argon. [b]Isolated yields. [c]120 °C, 4 h.

group, the carbon−carbon triple bond isomerizated to give intermediate **8**,[11] which inserted to the Ar−Pd bond and led to π-allyl palladium intermediate **9**. Then another carbon−carbon double bond inserted to the C−Pd bond of **9** to afford intermediate **10**, which gave intermediate **11** via classical β-H elimination. Five-membered nonaromatic heterocycles were obtained through isomerization of carbon−carbon double bond of **11**. To provide evidence for the mechanism via intermediate **8**, the reaction of *N*-allyl-4-methyl-*N*-(but-2,3-dien)benzenesulfonamide with ethyl 4-bromobenzoate under the same conditions was examined, and **1a** was obtained in 15% yield. The yield is lower, most probably because of the polymerization of *N*-allyl-4-methyl-*N*-(but-2,3-dien)-benzenesulfonamide at high temperature.[12] Other possible reaction pathways cannot be ruled out.

Conclusion

We present an efficient method for the synthesis of five-membered heterocycles by treatment of readily available 1, 6-enynes with aryl halides bearing electron-withdrawing substituents via a domino coupling/cycloisomerization process in the presence of a catalytic amount of palladium catalyst. The electron-withdrawing groups could be methoxycarbonyl, formyl, chloro, sulfonyl, cyano, and acetyl. This process provides a new and general methodology for the synthesis of aromatic and nonaromatic heterocycle derivatives from 1,6-enynes by changing substituents at the terminus of the alkynes. The results obtained demonstrated that multiple carbon−carbon bond-forming processes can operate with a single catalytic system using palladium. Further studies into the scope, mechanism, and synthetic application of this reaction are being carried out in our laboratory.

Experimental Section

Typical Procedure for the Palladium-Catalyzed Cyclization Reaction of 1,6-Dienynes with Aryl Halides. Enyne **1** (1.0 equiv), 4-bromobenzonitrile (1.2 equiv), $Pd(OAc)_2$ (3 mol %), and PPh_3 (6 mol %) were added to a degassed solution of (nBu)$_3$N (2 equiv) in DMF (5 mL), and the mixture was stirred at room temperature for 0.5 h and then heated at 140 °C for 20 h. The reaction mixture was then cooled, quenched with water, and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with hydrochloric acid (5%, 20 mL), sodium carbonate (5%, 20 mL), and saturated sodium chloride solution, dried over $MgSO_4$, and concentrated. The residue wes purified by flash column chromatography on a silica gel eluting with petroleum ether and ethyl acetate to give **1h** (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.4 Hz, 2 H), 7.56 (d, J = 7.8 Hz, 2 H), 7.31−7.24 (m, 5H), 7.18 (d, J = 8.1 Hz, 2 H), 7.02 (d, J = 7.8 Hz, 2 H), 6.91 (s, 1 H), 6.43 (s, 1 H), 5.19 (s, 1 H), 2.43 (s, 3 H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 144.8, 141.2, 136.1, 132.3, 131.2, 129.9, 129.6, 128.7, 127.1, 126.8, 124.1, 120.3, 119.2, 118.9, 110.5, 48.6, 21.7, 10.5; FT-IR (KBr): ν_{max} 2224, 1597, 1371, 1170, 1072, 812, 667 cm^{-1}. HRMS (EI) m/z: calcd for $C_{26}H_{22}N_2O_2S$: 426.1402, found 426.1397.

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(12) (a) Mochizuki, K.; Tomita, I. *Macromolecules* **2006**, *39*, 6336. (b) Kino, T.; Taguchi, M.; Tazawa, A.; Tomita, I. *Macromolecules* **2006**, *39*, 7474.

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Supporting Information Available: Experimental details, X-ray CIF data of **1h**, and other spectral data for the cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.