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Synthesis of tetrasubstituted pyrroles by palladium-catalyzed cyclization of propargylic carbonates with β-enamino esters

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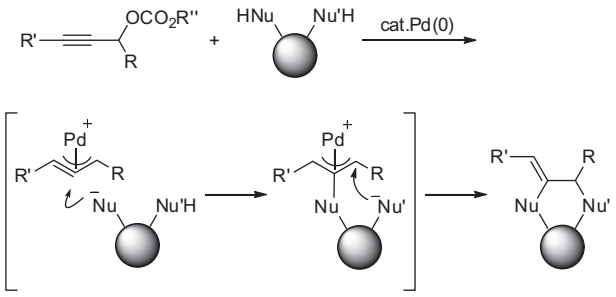
ABSTRACT

The reaction of propargylic carbonates with β-enamino esters in the presence of palladium catalyst is described. Various tetrasubstituted pyrroles were regioselectively synthesized via a successive nucleophilic cyclization.

Pyrroles are one of the most important class of heteroaromatic compounds which are components of a structural fragment of many biologically active natural products,[1] pharmaceutical agents,[2] and electronic and magnetic materials.[3] From this reason, constructive effort has been devoted toward developing a novel methodology for the synthesis of pyrroles.[4,5] However, in spite of the existence of a variety of these approaches, synthesis of highly substituted pyrroles remains challenging because it has difficult problems for the regioselectivity and the versatility.

Palladium-catalyzed reactions of propargylic carbonates with bis-nucleophiles have received considerable attention and have been extensively studied.[6,7] In this reaction, a substrate having two nucleophilic moieties within the molecule successively reacted with the π-propargylpalladium complex, resulting from propargylic carbonates with palladium, to afford the cyclized product (Scheme 1). A variety of substituted hetero- and carbocyclic molecules can be synthesized in one step by the choice of adequately designed nucleophilic molecules. During the course of our planning for further investigation of this cyclization process, we took notice of the nucleophilic activity of β-enamino esters. We report herein the palladium-catalyzed reaction of propargylic carbonates with β-enamino esters, in which various tetrasubstituted pyrroles have been constructed efficiently via a successive nucleophilic cyclization.

The initial reactions were attempted using benzyl 1-phenyl-2-propynyl carbonate (**1a**)[8] and tosyl-substituted β-enamino ester **2a** (Table 1). When **1a** and **2a** were treated with 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol % DPPB in THF at 50 °C, tetra- and trisubstituted pyrroles **3aa** and **4aa** were obtained in a 7:1 ratio and 81% yield (Table 1, entry 1). Although the reason is not clear, it is interesting to note that the trisubstituted pyrrole **4aa** was produced predominantly in the presence of bulkier phosphine ligands DPPF, BINAP, and DPEphos (entries 2–4). On the other hand, when DPPP was employed in the reaction, the tetrasubstituted pyrrole **3aa** was produced as the sole product in 86% yield (entry 5). The yield of **3aa** was increased to 96% in the reaction using DPPE (entry 6). The reaction of mesyl-substituted β-enamino ester **2b** with **1a** in the presence of DPPE also proceeded to afford the tetrasubstituted pyrrole **3ab** in 67% yield (entry 7). The yield of the corresponding product **3ac** was decreased to 33% yield when *p*-nitrobenzenesulfonyl-substituted substrate **2c** was used (entry 8), but the β-enamino



Scheme 1. Palladium-catalyzed cyclization of propargylic carbonates with bis-nucleophiles.

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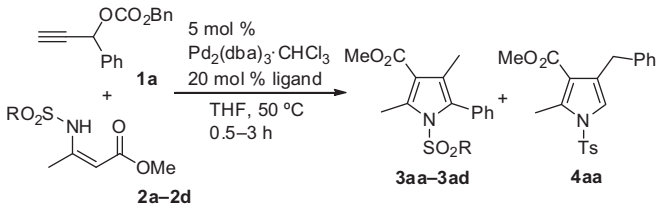
Table 1
The reactions of **1a** with **2a–2d**

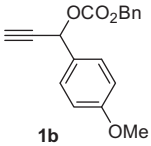
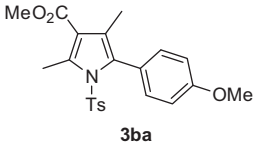
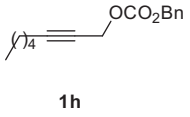
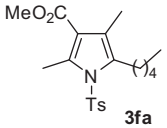
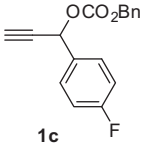
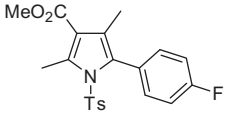
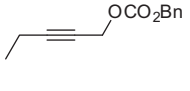
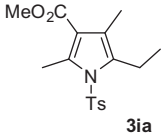
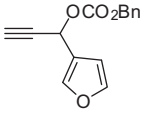
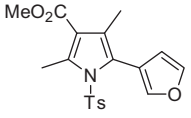
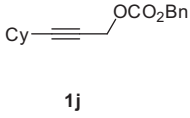
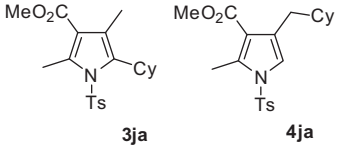
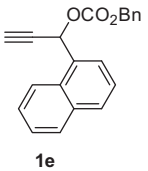
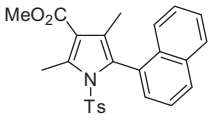
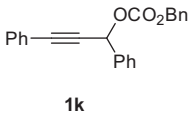
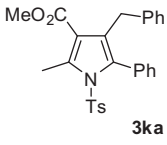
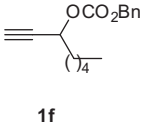
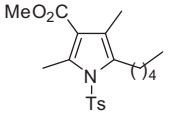
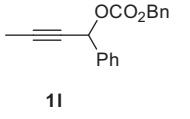
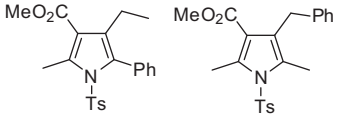
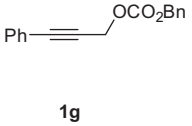
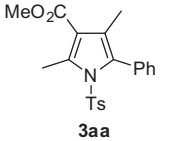
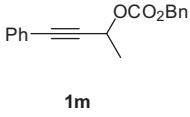
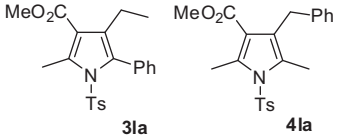


Entry	Ligand	R	Products	Yield (%)
1	DPPB	*p*-Tolyl (**2a**)	**3aa**:**4aa** = 7:1	81
2	DPPF	*p*-Tolyl (**2a**)	**3aa**:**4aa** = 1:1.5	92
3	BINAP	*p*-Tolyl (**2a**)	**3aa**:**4aa** = 1:2.2	96
4	DPEphos	*p*-Tolyl (**2a**)	**3aa**:**4aa** = 1:2.3	94
5	DPPP	*p*-Tolyl (**2a**)	**3aa**	86
6	DPPE	*p*-Tolyl (**2a**)	**3aa**	96
7	DPPE	Me (**2b**)	**3ab**	67
8	DPPE	*p*-Nitrophenyl (**2c**)	**3ac**	33
9	DPPE	2,4,6-Trimethyl-phenyl (**2d**)	**3ad**	99

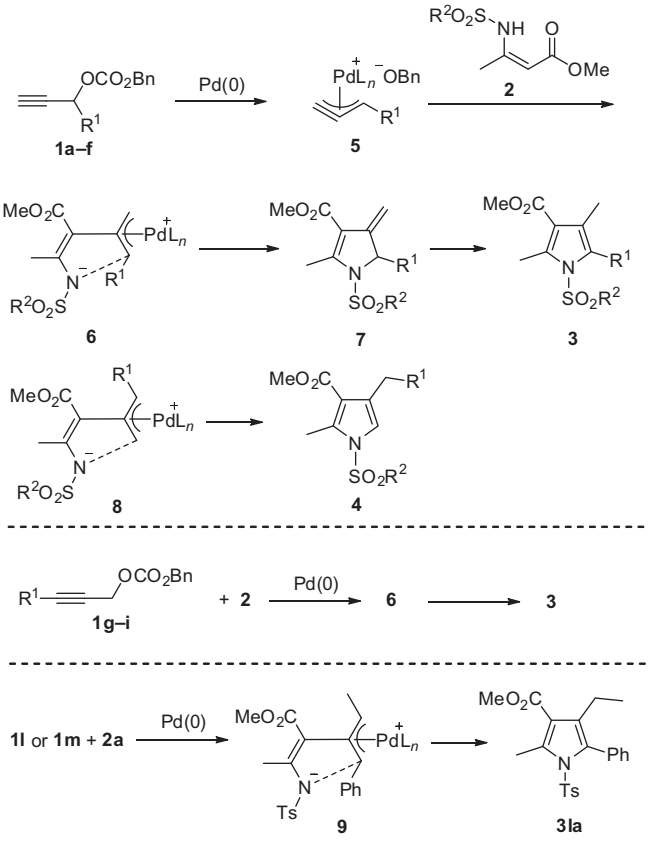
ester **2d** having a 2,4,6-trimethylbenzenesulfonyl group successfully reacted to produce the pyrrole **3ad** in 99% yield (entry 9).[9]

Having identified a useful set of reaction conditions to give tetrasubstituted pyrrole **3**, we next conducted the reactions of various propargylic carbonates **1b–m** with **2a** (Table 2). When the reactions of the substrates **1b** and **1c** containing a *p*-methoxyphenyl and a *p*-fluorophenyl group at the propargylic position were carried out, tetrasubstituted pyrroles **3ba** and **3ca** were obtained in 91% and 90% yield, respectively (entries 1 and 2). The substrates **1d** and **1e** having a 3-furyl and a 1-naphthyl group also reacted to produce the products **3da** and **3ea** in good yields (entries 3 and 4). Although the yield was low, the corresponding product **3fa** was obtained in the reaction of the pentyl-substituted substrate **1f** (entry 5). When the propargylic carbonate **1g** containing a phenyl group on the alkynyl moiety was subjected to the reaction, the tetrasubstituted pyrrole **3aa**, which was the same product from the reaction of **1a**, was obtained in 92% yield (entry 6). Similarly, the corresponding products **3fa** and **3ia** were obtained in high yields from the reactions using pentyl- and ethyl-substituted substrates **1h** and **1i** (entries 7 and 8). Interestingly, the reaction of the substrate **1j**, which has a cyclohexyl group on the alkynyl moiety, predominantly afforded the trisubstituted pyrrole **4ja** in 79% yield together with the tetrasubstituted product **3ja** in 15% yield (entry 9). The diphenyl-substituted substrate **1k** uneventfully reacted with **2a** to deliver the corresponding product **3ka** in 82% yield (entry 10). When benzyl 1-phenylbut-2-yn-1-yl carbonate (**1l**) was subjected to the reaction, the 5-phenyl-substituted pyrrole **3la** was selectively produced in 82% yield along with its regioisomer **4la** in 13% yield (entry 11). The same products **3la** and **4la** were obtained with a similar ratio from

Table 2
Reactions using various propargylic carbonates **1b–m** with **2a**[a]

Entry	Substrate **1**	Product	Yield (%)	Entry	Substrate **1**	Product	Yield (%)
1	 **1b**	 **3ba**	91	7	 **1h**	 **3fa**	91
2	 **1c**	 **3ca**	90	8	 **1i**	 **3ia**	94
3	 **1d**	 **3da**	76	9	 **1j**	 **3ja** **4ja**	**3ja** 15 **4ja** 79
4	 **1e**	 **3ea**	93	10	 **1k**	 **3ka**	82
5	 **1f**	 **3fa**	31	11	 **1l**	 **3la** **4la**	**3la** 82 **4la** 13
6	 **1g**	 **3aa**	92	12	 **1m**	 **3la** **4la**	**3la** 79 **4la** 13

[a] The reactions were carried out in the presence of **1** and **2a**, 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 20 mol % DPPE in THF at 50 °C for 3 h.



Scheme 2. Proposed reaction mechanism.

the reaction of benzyl 4-phenylbut-3-yn-2-yl carbonate (**1m**) (entry 12).

A plausible mechanism for the production of the pyrroles is shown in Scheme 2. By reacting with the palladium catalyst, the propargylic carbonates **1a–f** are transformed to the π-propargylpalladium complex **5**, which causes nucleophilic attack of the α-carbon of the β-enamino ester **2** leading to the π-allylpalladium intermediate **6**. Then the intramolecular nucleophilic attack of the sulfonamide anion to the π-allylpalladium proceeds regioselectively at the substituted carbon,[10] followed by isomerization of the resulting **7** to produce the tetrasubstituted pyrrole **3**. Trisubstituted pyrrole **4** would be formed via the intermediate **8**, in which nucleophilic attack occurs at the non-substituted carbon of the π-allylpalladium. As a reason for the low conversion from the pentyl-substituted substrate **1f** (entry 5 in Table 2), it is expected that β-elimination of palladium from the corresponding π-propargylpalladium intermediate **5** would occur prior to the nucleophilic attack.[11] The results about the conversion of the propargylic carbonates **1g–i** to the tetrasubstituted products **3** indicate that these reactions proceed via the formation of a common π-allylpalladium intermediate **6**. As a reason for the opposite regioselectivity in the reaction of the cyclohexyl-substituted substrate **1j** (entry 9 in Table 2), it is expected the nucleophilic attack occurs selectively at the non-substituted carbon of the π-allylpalladium **8** because of the bulkiness of the cyclohexyl group. In the case of the substrates **1l** and **1m** having a methyl and a phenyl group, the regioselective cyclization would proceed at the phenyl-substituted carbon of the π-allylpalladium species **9**, presumably because of the electronic effect of the phenyl group, to afford product **3la** as the major product.

In conclusion, the effort described above has led to the development of a palladium-catalyzed reaction of propargylic carbonates with β-enamino esters. This process regioselectively produces tetrasubstituted pyrroles having a variety of substituents via a successive nucleophilic cyclization. Since many biologically active compounds which have a pyrrole component have been reported, our methodology would provide a new protocol for the synthesis of these compounds with high efficiency.

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Supplementary data

Supplementary data (experimental procedures and characterization of the products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.019.

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8. We also attempted the reaction using methyl 1-phenyl-2-propynyl carbonate, in which the yield of **3aa** was slightly decreased in comparison with that of the benzyl carbonate **1a**.
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