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One-Pot Construction of Pyrazoles and Isoxazoles with Palladium-Catalyzed Four-Component Coupling

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ABSTRACT

Four-component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide, and an aryl iodide furnishes pyrazole or isoxazole derivatives in the presence of a palladium catalyst. The reaction proceeds at room temperature and an ambient pressure of carbon monoxide in an aqueous solvent system.

Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials.[1] Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry. We have been studying to introduce a substituent into heteroaromatic compounds with a transition metal catalyst and have shown that several arylation reactions take place at the C−H bond of thiazoles and thiophenes.[2] In addition to the modification of heteroaromatic compounds, efficient construction of the ring structure is also an important issue in organic synthesis. Thereby, one-pot construction of heterocycles with simple organic molecules as the components, if successful, would be a facile and practical method.[3] We herein describe four-component one-pot construction of five-membered heteroaromatics, such as pyrazoles and isoxazoles, via a palladium-catalyzed coupling of terminal alkynes, hydrazine (hydroxylamine), carbon monoxide, and aryl iodides.

Treatment of phenylethyne (**1a**), aqueous hydrazine, carbon monoxide, and iodobenzene (**2a**) in the presence of $PdCl_2(PPh_3)_2$ in THF at room temperature and an ambient pressure of CO afforded 3,5-diphenylpyrazole (**3aa**) in 59% yield after stirring for 36 h. Table 1 summarizes the results of the four-component coupling reaction. The use of 3 equiv of 0.5 M aqueous hydrazine solution resulted in giving pyrazole in the highest yield, while the reaction with aqueous hydrazine of higher concentration resulted in inferior yields. The yield of pyrazole was found to be the best when 3 mol amount of hydrazine toward **2a** was employed. Although the reaction with a more excess amount afforded pyrazole **3aa** in a comparable yield, the use of a smaller amount of hydrazine was found to be less effective. The reaction with DMF as a solvent was also found to give **3aa** in 47% yield.

The reaction would be sequential reactions of carbonylative Sonogashira coupling[4] and following ring formation of α,*β*-

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[1] (a) Zificsak, C. A.; Hlasta, D. J. *Tetrahedron* **2004**, *60*, 8991. (b) Haino, T.; Tanaka, M.; Ikeda, K.; Kubo, K.; Mori, A.; Fukazawa, Y. *Tetrahedron Lett.* **2004**, *45*, 2277.

[2] (a) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (b) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (c) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011.

[3] An example of recent multicomponent construction of ring structures with a transition metal catalyst: (a) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (b) Krazinski, A.; Radic, Z.; Manetsch, R.; Raushel, J.; Taylor, P.; Sharpless, K. B.; Kolb, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 6686.

[4] (a) Mohamed Ahmed, M. S.; Mori, A. *Org. Lett.* **2003**, *5*, 3057. (b) Mohamed Ahmed, M. S.; Sekiguchi, A.; Masui, K.; Mori, A. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 160.

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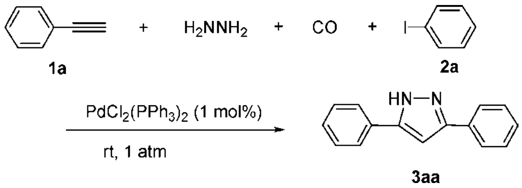
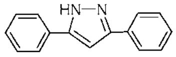
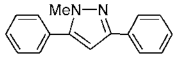
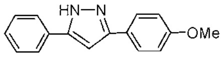
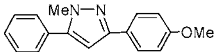
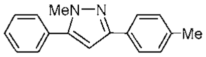
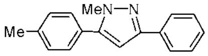
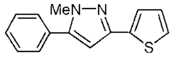
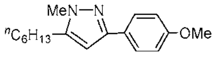
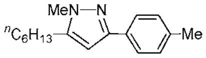
Table 1. Four-Component Coupling Reaction of **1a**, **2a**, CO, and Hydrazine[a]



aq NH_2NH_2			
concn, M	equiv	solvent	% yield
0.5	2	THF	53
0.5	3	THF	59
0.5	4	THF	58
1	3	THF	39
2	3	THF	35
0.5	3	DMF	47

[a] The reaction was carried out with **1a** (0.6 mmol) and **2a** (0.5 mmol) in THF or DMF (3 mL) under 1 atm of CO.

Table 2. Four-Component Coupling Reaction Leading to Pyrazole with R—≡—H and I—Aryl[a]

R in **1**	hydrazine	Aryl in **2**	product (%yield)
Ph	H_2NNH_2	Ph	 **3aa** (59)
Ph	$MeHNNH_2$	Ph	 **4aa** (91)
Ph	$PhHNNH_2$	Ph	(0)
Ph	H_2NNH_2	4-$MeOC_6H_4$	 **3ab** (80)
Ph	$MeHNNH_2$	4-$MeOC_6H_4$	 **4ab** (83)
Ph	$MeHNNH_2$	4-MeC_6H_4	 **4ac** (88)
4-MeC_6H_4	$MeHNNH_2$	Ph	 **4ca** (65)
Ph	$MeHNNH_2$	2-Thienyl	 **4ad** (85)
$^nC_6H_{13}$	$MeHNNH_2$	4-$MeOC_6H_4$	 **4eb** (93)[b]
$^nC_6H_{13}$	$MeHNNH_2$	4-MeC_6H_4	 **4ec** (93)[b]

[a] Unless otherwise noted, the reaction was carried out with a terminal alkyne (0.6 mmol), (methyl)hydrazine (1.5 mmol), and aryl iodide (0.5 mmol) in THF−H_2O (3 mL−3 mL) at room temperature for 24−36 h under an ambient pressure of carbon monoxide in the presence of $PdCl_2(PPh_3)_2$ (1 mol %). [b] The reaction was carried out with $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (2 mol %) as a catalyst.

alkynyl ketone with hydrazine.[5,6] The effect of concentration, the amount of hydrazine, and choice of the solvent, as shown in Table 1, exhibit the similar trend to our previous results on the Sonogashira coupling with aqueous ammonia.[4b] Accordingly, hydrazine would play dual roles, serving as the ring component as well as an activating agent for the palladium-catalyzed coupling reaction. Worthy of note is that formation of the ring structure took place in one pot, in which readily available reagents and substrates are employed. It should also be pointed out that the reaction is carried out at room temperature and an ambient pressure of carbon monoxide, suggesting procedural simplicity using common glassware with a rubber balloon.

Table 2 shows the results of the four-component reaction to form substituted pyrazoles with several terminal alkynes **1** and aryl iodides **2**. Methylhydrazine was also found to afford *N*-methyl pyrazoles **4** in excellent yields. On the other hand, the reaction with phenylhydrazine did not afford the corresponding pyrazole at all under similar conditions, probably due to the insufficient basicity of phenylhydrazine to undergo the palladium-catalyzed carbonylative coupling reaction smoothly.[7]

The formation of pyrazole proceeded in a regioselective manner similar to the results of Bishop,[5d] where the aryl substituent at the 5-position was derived from the terminal alkyne, while the one at the 3-position was from aryl iodide. Indeed, reactions with opposite substituents at the terminal alkyne and aryl iodide, respectively, afforded regioisomers **4ac** and **4ca**.[8] An alkylalkyne, 1-octyne (**1e**), also underwent the reaction, where use of CuI as a co-catalyst was found to be effective.

Although the mechanism of the total reaction is not clear yet, it can hardly be explained by the combination of tandem

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(5) (a) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3664. (b) Engelmann, A.; Kirmse, W. *Chem. Ber.* **1973**, *106*, 3092. (c) Grotjahn, D. B.; Van, S.; Combs, D.; Lev, D. A.; Schneider, C.; Rideout, M.; Meyer, C.; Hernandez, G.; Mejorado, L *J. Org. Chem.* **2002**, *67*, 9200. (d) Bishop, B. B.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. *Synthesis* **2004**, 43.

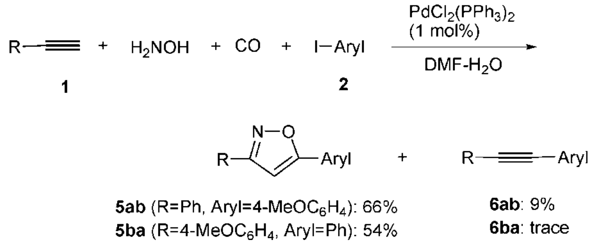
(6) For reviews concerning tandem reactions: (a) Wasike, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (b) Tieze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Negichi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.

(7) The reaction at room temperature for 24 h afforded 22% of noncarbonylative Sonogashira coupling product.

(8) Melting points of **4ac** (136−137 °C (lit. 135−137 °C)) and **4ca** (68−69 °C (lit. 70−72 °C)) indicated exclusive formation of each product. See also Supporting Information.

cross-coupling/ring-formation reactions. The reaction of α,*β*-alkynyl ketone with hydrazine has been shown to occur in a certain solvent, such as ethanol, within a few hours;[6] however, we confirmed that the reaction in THF−H_2O, which was the solvent system of the four-component coupling, resulted in no reaction in the presence and absence of the palladium catalyst. On the other hand, formation of α,*β*-alkynyl ketone was not observed by TLC analysis during the one-pot reaction. Thereby, the intermediate alkynyl ketone formed in the reaction mixture immediately reacted with hydrazine to pyrazole by a specific rate acceleration in the one-pot system. Further studies would be necessary for understanding of the reaction mechanism.

Scheme 1



It was found that isoxazoles **5** were formed when the reaction was carried out with hydroxylamine instead of hydrazine, as shown in Scheme 1. A terminal alkyne **1**, carbon monoxide, and aryl iodide **2** reacted with hydroxylamine. The reaction was also performed at room temperature and 1 atm of carbon monoxide. Treatment of phenylethyne (**1a**) with 4-methoxyiodobenzene (**2b**) in the presence of 3 equiv of $NH_2OH·HCl$ and 0.5 M aqueous ammonia under CO in DMF afforded isoxazole **5ab** in 66% yield accompanied by the formation of a small amount of noncarbonylative Sonogashira coupling product **6**.[4b,9] In the formation of isoxazole, DMF was found to be a favorable solvent, whereas THF resulted in no reaction. $NH_2OH·HCl/NH_3$ was a superior system for the generation of hydroxylamine in situ.[10] The reaction forming isoxazole was also regioselective to give the product bearing a substituent at the aryl group of the 3-position, being derived from the one of the terminal alkyne. The reaction of (4-methoxyphenyl)ethyne (**1b**) with iodobenzene (**1a**) yielded **5ba** in 54% yield.

It should be noted that one-pot construction of isoxazole via four-component coupling took place at room temperature, although several examples to form isoxazoles from α,*β*-alkynyl ketones and hydroxylamine were shown to proceed at elevated temperatures.[11,12]

In conclusion, pyrazoles and isoxazoles were synthesized via one-pot four-component coupling of terminal alkynes, hydrazine (hydroxylamine), carbon monoxide, and aryl iodide at room temperature and an ambient pressure of carbon monoxide in the presence of a palladium catalyst. Hydrazine and hydroxylamine play dual roles as a component of ring formation and an activating agent for the carbonylative coupling reaction. The method serves as a facile construction of the heteroaromatic ring, which would be widely applicable for the synthesis of biologically active molecules and advanced materials.

Acknowledgment. This work was partially supported by the Grant-in-Aid for Scientific Research (No. 16550092) by Japan Society for the Promotion of Science and by The Sumitomo Foundation.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Mori, A.; Mohamed Ahmed, M. S.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (c) Campbell, I. B. The Sonogashira Cu−Pd-catalyzed alkyne coupling reaction. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 217−235.

(10) The reaction with potassium carbonate resulted in giving the corresponding isoxazole (26% yield) accompanied by the noncarbonylative Sonogashira coupling product (20%).

(11) (a) Johnston, K. M.; Shotter, R. G. *J. Chem. Soc. C* **1968**, 1774. (b) Linderman, R. J.; Kirollos, K. S. *Tetrahedron Lett.* **1989**, *30*, 2049. (c) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2311.

(12) Although the reaction occasionally afforded a crude mixture of 5-hydroxyisoxazoline and **5**, the isoxazoline was converted to **5** during isolation and purification procedures.