JOC Article

Palladium-Catalyzed Selective Synthesis of 2-Allyltetrazoles

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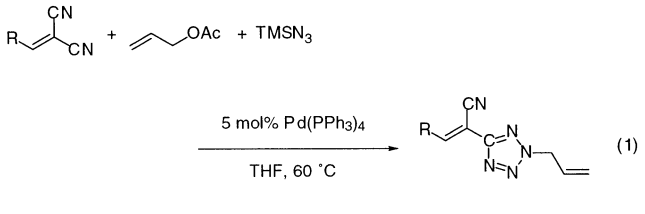
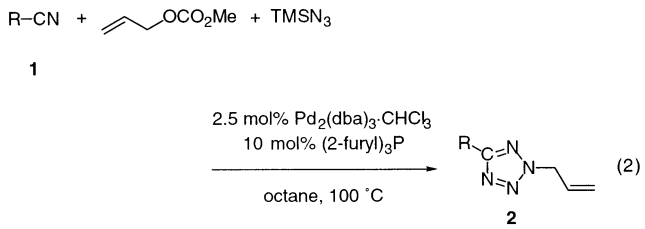
The palladium-catalyzed three-component coupling (TCC) reaction of cyano compounds, allyl methyl carbonate, and trimethylsilyl azide under a catalytic amount of $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %) and tri(2-furyl)phosphine (10 mol %) gave various kinds of 2-allyltetrazoles in good to excellent yields. A π-allylpalladium azide complex is proposed as a key intermediate in the TCC reaction.

Introduction

The synthesis of tetrazoles[1] from cyanides has received much attention recently, and new preparation methods have appeared.[2] Tetrazoles are regarded as a biological equivalent for carboxylic acid group, and extensive works have been carried out in a field of medicinal chemistry.[3] Tetrazoles are also found as a precursor of carbenes in flash vacuum pyrolysis.[4] Although tetrazoles are an important class of chemicals, the synthetic approaches starting from cyano compounds are quite limited and have several disadvantages. The following are the classical synthetic methods:[1] (1) the reaction of cyanides with hydrogen azide or MN_3 species and (2) the reaction of cyanides with organic azide compounds. Usually, long reaction times and high temperatures are required for reactions of category 1. Moreover, we often have difficulties choosing azide sources and solvents; very narrow ranges of the solvents and substrates have to be used. In the reaction type 2, only activated cyanides with strong electron-withdrawing groups can be used as a substrate. Furthermore, the alkylation of tetrazoles under basic conditions generally affords a mixture of regioisomers.[5] It occurred to us that the employment of a transition metal catalyst may overcome the above-mentioned problems: both the acceleration of the reaction between an azide and cyano compounds and the selective allylation of the tetrazoles might be achieved via the use of a transition metal catalyst. The selective synthesis of 2-allyltetrazoles starting from malononitrile derivatives via the palladium-catalyzed three-component coupling reaction was reported in 2000 (eq 1).[6] We now report that the palladium-catalyzed TCC reaction of the cyano compounds **1**, allyl methyl carbonate, and trimethylsilyl azide produces the 2-allyltetrazoles **2** selectively in good to excellent yields (eq 2).





Results and Discussion

The cyano compounds, shown in eq 1, were limited to alkyl- and arylidenemalononitriles, and therefore the

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(1) (a) For reviews on the chemistry of tetrazoles, see: Meier, H. R.; Heimgartner, H. In *Methoden der Organischen Chemie (Houben-Weyl)*; Schumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1994; Vol. E8d, pp 664−795. (b) Butler, R. N. In *Comprehensive Heterocyclic Chemistry;* Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, pp 791−838.

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(5) See: (a) ref 1a, pp 736−748; (b) ref 1b, pp 817−819.

(6) For a preliminary communication, see: Gyoung, Y. S.; Shim, J.-G.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 4193−4196.

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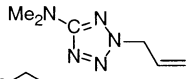
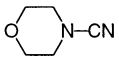
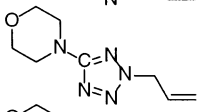
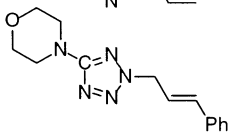
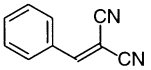
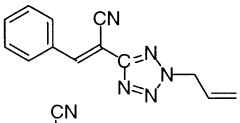
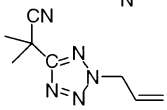
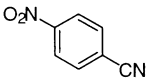
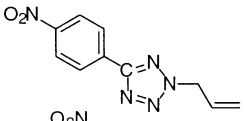
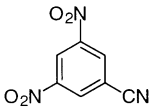
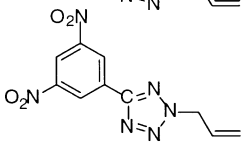
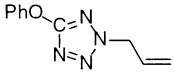
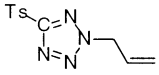
TABLE 1. Palladium-Catalyzed Formation of 2-Allyltetrazoles from Various Cyanides[a]

entry	1		reaction time, h	2		yield, %[b]
1	**1a**	Me_2N–CN	2	**2a**		52
2	**1b**		24	**2b**		77
3[c]	**1b**		24	**2c**		66
4[d]	**1b**		24	**2c**		58
5	**1d**		10	**2d**		68
6	**1e**		10	**2e**		87
7	**1f**		24	**2f**		40
8	**1g**		24	**2g**		72
9	**1h**	PhO–CN	24	**2h**		77
10	**1i**	Ts–CN	24	**2i**		45

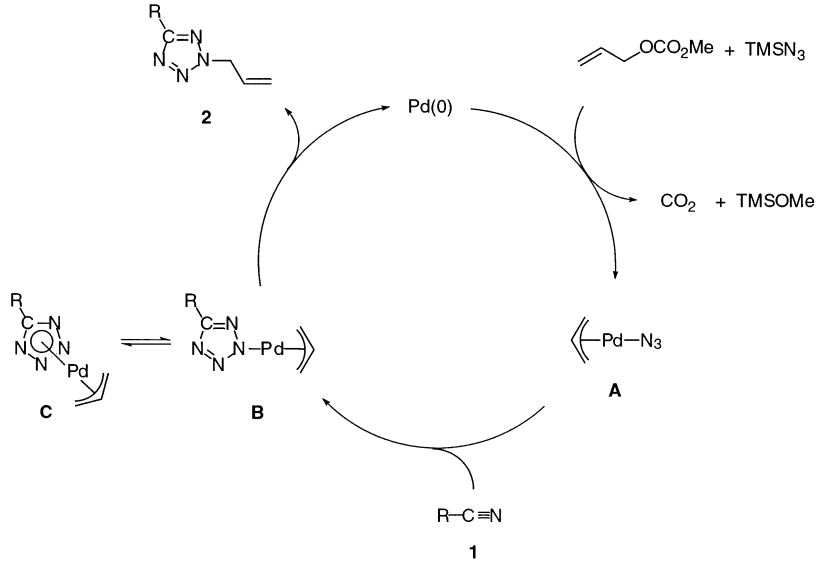
[a] To a mixture of **1** (0.5 mmol), allyl methyl carbonate (0.6 mmol), and $TMSN_3$ (0.6 mmol) were added $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %) and $(2\text{-furyl})_3P$ (10 mol %) in octane (0.5 M). The mixture was stirred at room temperature for 10 min and then at 100 °C for the time shown in Table 1. [b] Isolated yield. [c] Methyl (3-phenyl-2-propenyl) carbonate was used. [d] Methyl (1-phenyl-2-propenyl) carbonate was used.

synthetic scope was very narrow. To find a more general procedure, we carried out a number of trials and finally reached the TCC reaction shown in eq 2. The optimized reaction conditions are shown in eq 2. The results are summarized in Table 1. To an octane solution (0.5 M) of $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol %) and $(2\text{-furyl})_3P$ (10 mol %) were added dimethylcyanamide **1a**, allyl methyl carbonate (1.2 equiv), and trimethylsilyl azide (1.2 equiv). The mixture was stirred at room temperature for 10 min and heated at 100 °C for 1 h. 2-Allyl-5-(dimethylamino)-tetrazole **2a** was obtained in 52% isolated yield (entry 1). Octane was the solvent of choice; other solvents such as toluene, THF, and 1,2-dichloromethane gave the desired product **2a** in lower yields. As for the phosphine ligand, $(2\text{-furyl})_3P$ showed the best catalytic activity when combined with $Pd_2(dba)_3 \cdot CHCl_3$ complex. Other phosphine ligands such as $(p\text{-}CF_3{-}C_6H_4)_3P$, $(p\text{-}MeO{-}C_6H_4)_3P$, and dppe (1,2-bis(diphenylphosphino)ethane) were less effective. Addition of 2 equiv of allyl methyl carbonate and 2 equiv of trimethylsilyl azide did not increase the yield of tetrazole **2a**. Allyl acetate showed a reactivity similar to that of allyl methyl carbonate. However, when we carried out the TCC reaction of **1a**, allyl acetate, and $TMSN_3$ under the reaction conditions shown in eq 1, only a small amount of **2a** was obtained.[7] In the absence of the palladium and phosphine catalysts, no reaction took place even after 24 h at 100 °C and the recovery of dimethylcyanamide **1a** was observed.

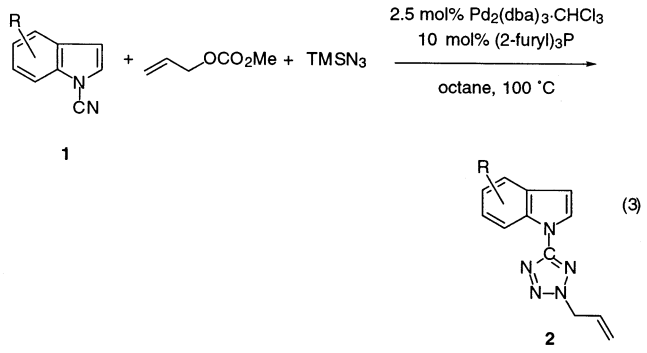
We investigated the scope and limitations of the new TCC reaction using various kinds of cyano compounds. The reaction of *N*-cyanomorpholine **1b** afforded the desired tetrazole **2b** in 77%, although a longer reaction time was needed (entry 2). The reaction of **1b** with methyl

(7) The reaction of dimethylcyanamide **1a**, allyl acetate (2 equiv), and $TMSN_3$ (1.2 equiv) was conducted at 100 °C for 24 h in the presence of $Pd(PPh_3)_4$ (5 mol %) catalyst in THF. The corresponding tetrazole **2a** was obtained only in 17% NMR yield, and the recovery of dimethylcyanamide **1a** was observed.

SCHEME 1. Proposed Mechanism for the Formation of 2-Allyltetrazoles



(3-phenyl-2-propenyl) carbonate or with methyl (1-phenyl-2-propenyl) carbonate afforded the same tetrazole **2c** (entries 3 and 4), clearly indicating that a π-allylpalladium species intervenes in the catalytic cycle (see Scheme 1, vide post). The reaction of benzylidenemalononitrile **1d** proceeded smoothly to give the corresponding tetrazole **2d** in 68% yield (entry 5).[8] Dimethylmalononitrile **1e** produced the tetrazole **2e** in 87% yield (entry 6). Only one of the two cyano groups can participate in the tetrazole-forming reaction in the malononitrile derivatives. We then examined the reactivity of aryl nitriles. Activated benzonitriles such as 4-nitrobenzonitrile **1f** and 3,5-dinitrobenzonitrile **1g** afforded the desired tetrazoles **2f** and **2g** in 40 and 72% yields, respectively (entries 7 and 8). The reaction of benzonitrile and 4-methoxybenzonitrile did not proceed at all, and starting materials were recovered. Alkyl cyanides such as valeronitrile did not afford the corresponding tetrazole. The heteroatom-bounded cyano compounds such as phenyl cyanate **1h** and tosyl cyanide **1i** gave the corresponding tetrazoles **2h** and **2i** in 77 and 45% yields, respectively (entries 9 and 10).



We next investigated the TCC reaction of monosubstituted *N*-cyanoindoles[9,10] (eq 3). The results are summarized in Table 2. The reaction of *N*-cyanoindole **1j** was completed in 2 h to produce the tetrazole **2j** in an excellent yield (entry 1). We carried out reactions of *N*-cyanoindoles, which have a substituent on the five-membered ring of the indole skeleton. The *N*-cyanoindoles having methyl (**1k**) and phenyl groups (**1l**) at the 2-position on the indole skeleton afforded the corresponding tetrazoles **2k** and **2l** in high yields, although a longer reaction time was needed (entries 2 and 3). The 3-substituted *N*-cyanoindoles with an electron-donating methyl group (**1m**) and an electron-withdrawing methoxycarbonyl group (**1n**) gave the desired tetrazoles **2m** and **2n** in excellent yields, respectively (entries 4 and 5). We carried out the reactions of *N*-cyanoindoles **1o**−**t**, which have a substituent on the six-membered ring. The reaction of 4-methyl-*N*-cyanoindole **1o** was completed in 2 h to afford the corresponding tetrazole **2o** in high yield (entry 6). Several *N*-cyanoindoles having a substituent at the position para to the nitrogen atom of the indole skeleton were investigated. The reactions of *N*-cyanoindoles substituted with electron-donating groups such as methyl (**1p**) and methoxy groups (**1q**) were completed in 5 h to afford the corresponding tetrazoles **2p** and **2q** in 81 and 78% yields, respectively (entries 7 and 8). The reactions of *N*-cyanoindoles substituted with electron-withdrawing groups such as methoxycarbonyl (**1r**) and nitro groups (**1s**) were completed only in 1 h to produce the desired tetrazoles **2r** and **2s** in 90 and 99% yields, respectively (entries 9 and 10). The above results indicate that *N*-cyanoindoles having an electron-withdrawing group are more reactive than those having an electron-donating group. The reactions of electron-deficient *N*-cyanoindoles usually proceed faster and give higher yields of the desired tetrazoles. The reaction of 7-methyl-*N*-cyanoindole **1t** was not complete even after 24 h (entry 11). The

(8) The structure of the 2-allyltetrazole **2c** was unambiguously confirmed by X-ray crystallographic analysis, and detailed data were reported in ref 6.

(9) For the synthesis of *N*-cyanoindoles via the palladium-catalyzed three-component coupling reaction, see: Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, in press.

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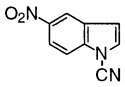
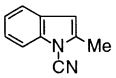
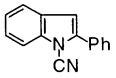
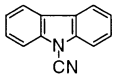
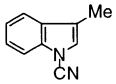
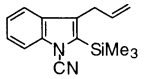
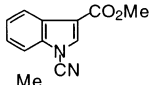
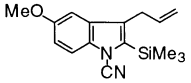
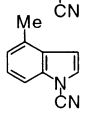
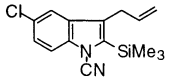
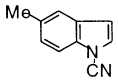
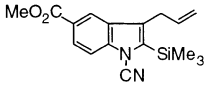
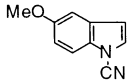
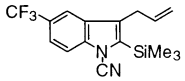
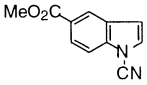
TABLE 2. Palladium-Catalyzed Formation of 2-Allyltetrazoles from *N*-Cyanoindoles[a]

entry	1	R	reaction time, h	2	yield, %[b]	entry	1	R	reaction time, h	2	yield, %[b]
1	**1j**		2	**2j**	96	10	**1s**		1	**2s**	99
2	**1k**		24	**2k**	80	11	**1t**		24	**2t**	67[c]
3	**1l**		24	**2l**	71	12	**1u**		24	**2u**	86
4	**1m**		4	**2m**	91	13	**1v**		24	**2v**	54[d]
5	**1n**		2	**2n**	90	14	**1w**		24	**2w**	51[e]
6	**1o**		2	**2o**	81	15	**1x**		24	**2x**	62
7	**1p**		5	**2p**	78	16	**1y**		24	**2y**	75
8	**1q**		6	**2q**	89	17	**1z**		24	**2z**	72
9	**1r**		7	**2r**	90						

[a] To a mixture of **1** (0.5 mmol), allyl methyl carbonate (0.6 mmol), and $TMSN_3$ (0.6 mmol) were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and $(2\text{-furyl})_3P$ (10 mol %) in octane (0.5 M). The mixture was stirred at room temperature for 10 min and then at 100 °C for the time shown in Table 2. [b] Isolated yield. [c] Starting material **1t** was recovered in 13% yield. [d] Starting material **1v** was recovered in 29% yield. [e] Starting material **1w** was recovered in 28% yield.

corresponding tetrazole **2t** was obtained in 67% yield along with the starting *N*-cyanoindole **1t** recovered in 13% yield. The reactions of *N*-cyanoindoles with sterically congested substituents around the reaction site take a longer reaction time to complete, and sometimes starting material is recovered (entries 2, 3, and 11). The reaction of the cyano compound **1u** derived from carbazole afforded the corresponding tetrazole **2u** in a high yield (entry 12). We further investigated the applicability for the highly functionalized and sterically congested multisubstituted *N*-cyanoindole systems. The *N*-cyanoindoles **1v** and **1w** showed a similar reactivity, and the reactions were not complete even after 24 h at 100 °C. The desired products **2v** and **2w** were obtained in 54 and 51% yields together with the recovery of the starting materials **1v** and **1w**, respectively (entries 13 and 14). On the other hand, the installation of electron-withdrawing groups on the indole skeleton such as chloro (**1x**), methoxycarbonyl (**1y**), and trifluoromethyl groups (**1z**) increased the reactivity of the *N*-cyanoindoles, and the reactions were completed in 24 h to afford the corresponding tetrazoles **2x**−**z** in moderate to good yields (entries 15−17).

A proposed mechanism is shown in Scheme 1. Initially, Pd(0) reacts with allyl methyl carbonate and $TMSN_3$ to give the π-allylpalladium azide complex **A**;[11,12] CO_2 and TMSOMe are eliminated at this stage. The [3 + 2] cycloaddition between the cyanides **1** and the π-allylpalladium azide complex **A** would take place to form the π-allylpalladium tetrazole intermediate **B**. Precoordination of palladium to heteroatoms such as N, O, and S exists in the substituent R of **1**, or precoordination to the nitrogen atom of CN group of **1** would accelerate this cyclization step. The intermediate **B** could be in equilibrium with (η^3-allyl)(η^5-tetrazoyl)palladium complex **C**, an analogue of (η^3-allyl)(η^5-cyclopentadienyl)palladium complex.[13] Involvement of the palladium catalyst determines the position of allyl group on the tetrazole ring. Reductive elimination of the palladium catalyst would produce the tetrazoles **2** and Pd(0). We further conducted the reactions of *N*-cyanomorpholine **1b** with cinnamyl azide. The reaction proceeded smoothly under $Pd_2(dba)_3{\cdot}CHCl_3$−$(2\text{-furyl})_3P$ catalyst to give the corresponding tetrazole **2c** in 96% NMR yield, whereas the reaction did not take place without the addition of the palladium catalyst. The staritng material **1b** was recoverd in 94% NMR yield. These results clearly indicate that the generation of the π-allylpalladium azide complex **A** is a key intermediate in the catalytic cycle shown in Scheme 1.

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Conclusions

We are now in a position to synthesize the 2-allyltetrazoles **2** selectively in good to excellent yields through the palladium-catalyzed TCC reaction of the cyano compounds **1**, allyl methyl carbonate, and trimethylsilyl azide. Mechanistically, a new type of [3 + 2] cycloaddition between the π-allylpalladium azide complex **A** and **1** (R−C≡N) is proposed.

Experimental Section

Typical Procedure for the Synthesis of 2a via Palladium-Catalyzed TCC Reaction. To an octane solution (1.0 mL) of $Pd_2(dba)_3 \cdot CHCl_3$ (13.0 mg, 0.0125 mmol) and $(2\text{-furyl})_3P$ (12.0 mg, 0.05 mmol) were added dimethylcyanamide **1a** (41 μL, 0.5 mmol), trimethylsilyl azide (80 μL, 0.6 mmol), and allyl methyl carbonate (70 μL, 0.6 mmol) under an argon atmosphere. The solution was stirred at room temperature for 10 min and then at 100 °C for 2 h. The reaction mixture was cooled to room temperature and filtered through a short Florisil pad using ether as an eluent. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, from 20/1 to 1/1 hexane−ether) to afford 2-allyl-5-(dimethylamino)tetrazole **2a** in 52% yield (40.0 mg).

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Supporting Information Available: Characterization data of relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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