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Regiospecific synthesis of 2-allyl-1,2,3-triazoles by palladium-catalyzed 1,3-dipolar cycloaddition

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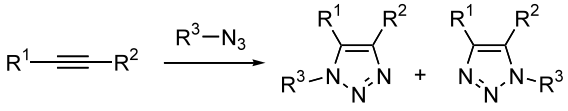
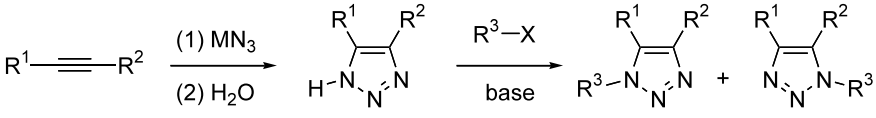
Abstract—2-Allyl-1,2,3-triazoles were prepared by the palladium-catalyzed three component coupling (TCC) reaction of alkynes, allyl methyl carbonate and trimethylsilyl azide. A π-allylpalladium azide complex, which undergoes the 1,3-dipolar cycloaddition with alkynes, is proposed as a key intermediate in the TCC reaction. © 2002 Published by Elsevier Science Ltd.

1,2,3-Triazoles are important substrates because of their wide use.[1] They have been considered as an interesting component in terms of biological activity and are seen in many drugs.[2] 1,2,3-Triazole heterocycles have also found broad use in industrial applications[1b] such as dyes and brighteners for fibers, corrosion inhibitors for many metals and alloys, light stabilizers for organic materials and polymers, and agrochemicals as herbicides, fungicides and antibacterial agents. More recently, 1,2,3-triazoles have been used as a backbone of a bidentate phosphine ligand and several new complexes have been synthesized.[3]



(1)



(2)

1,3-Dipolar cycloadditions are well-studied reactions and a wide variety of 1,3-dipoles have been developed.[4] It is well known that the 1,3-dipolar cycloaddition between azides and alkynes is a useful procedure for the preparation of 1,2,3-triazoles. However, we encountered difficulty when we planned to synthesize regioselectively *N*-alkyl-substituted 1,2,3-triazoles through this procedure, although several new and useful methodologies have been developed quite recently.[5] Usually, when an organic azide is reacted with a nonsymmetrical acetylene as the dipolarophile, a mixture of 1-substituted and 3-substituted-1,2,3-triazoles is obtained as shown in Eq. (1).[1,4c] An alternative procedure for the preparation of *N*-substituted-1,2,3-triazoles is shown in Eq. (2), in which the introduction of the substituent is carried out after the formation of the 1,2,3-triazole.[1,4c] However, the reaction of organic halides with 1,2,3-triazoles under basic conditions gives a mixture of 1-substituted and 3-substituted-1,2,3-triazoles in most cases.[6]

We now report that the palladium-catalyzed three component coupling (TCC) reaction of alkynes, allyl carbonate and trimethylsilyl azide results in the regiospecific formation of 2-allyl-1,2,3-triazoles (Eq. (3)). This palladium-catalyzed TCC reaction allows us to prepare 2-allyl-1,2,3-triazoles selectively, which are not easily obtained via known methods.

The results of the palladium-catalyzed TCC reaction for the regioselective formation of 2-allyl-1,2,3-triazoles

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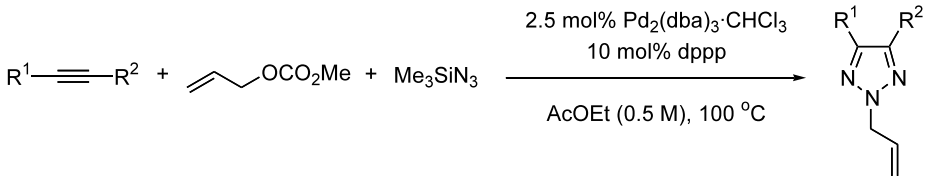


1 2 (3)

are summarized in Table 1. We first found that the TCC reaction with the electron-deficient alkyne **1a**, which is conjugated with a cyano group, gave the allyltriazole **2a**. Encouraged by this result, we optimized the reaction conditions. A representative procedure is as follows. Allyl methyl carbonate (1.2 equiv.) and trimethylsilyl azide (1.2 equiv.) were added to a solution of cyano phenyl acetylene **1a**, $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%) and dppp (1,3-bis(diphenylphosphino)propane) (10 mol%) in AcOEt (0.5 M). The mixture was stirred at 100°C for 2 h. After the starting acetylene was consumed, the mixture was cooled down to rt and filtered through a Florisil short column. Purification on a silica gel column (hexane/toluene 1:1–1:2) afforded 2-allyl-4-cyano-5-phenyl-1,2,3-triazole **2a** in 50% yield (entry 1). We further carried out the reactions of alkynes **1b–f** conjugated with various electron-withdrawing groups. The reaction of the alkynyl aldehyde **1b** and ketone **1c** proceeded smoothly to afford the corresponding allyltriazoles **2b** and **2c**, respectively, in moderate yields (entries 2 and 3). The reaction of the alkynyl ester **1d** and phosphonate **1e** also produced the allyltriazoles **2d** and **2e**, respectively, in moderate yields though longer reaction times were needed (entries 4 and 5). The reaction of the alkynyl sulfone **1f** proceeded smoothly and was complete in 3 h; however, the allyltriazole **2f** was obtained in a lower yield (entry 6). An alkyne having an electron-donating group such as the diethylamino group **1g** also underwent the cycloaddition, but the corresponding allyltriazole **2g** was obtained in only 33% yield (entry 7). We next investigated the reaction of various alkynyl methyl ketones **1h–k** in which R^1 is H, Et, cyclohexenyl, or *t*-Bu. The reaction of the terminal alkyne **1h** and ethyl-substituted internal alkyne **1i** produced the allyltriazoles **2h** and **2i**, respectively, in moderate to good yields (entries 8 and 9). In the case of an alkyne conjugated with an alkenyl group **1j**, the reaction took place chemoselectively at the alkyne moiety to produce the corresponding allyltriazole **2j** (entry 10). Even the sterically hindered *tert*-butyl-substituted alkyne **1k** gave the allyltriazole **2k** in good yield (entry 11). The above results indicate that the reaction proceeds irrespective of the substituent R^1. On the contrary, the yields of the allyltriazoles **2l** and **2m** were less in the cases of the alkynes **1l** and **1m** having an ester as an electron-withdrawing group (entries 12 and 13). However, the introduction of two ester groups at both termini of the triple bond resulted in enhancement of the reactivity; the reaction of dimethyl acetylenedicarboxylate **1n** gave the corresponding allyltriazole **2n** in 60% yield within 2 h (entry 14). The alkyl-substituted alkynyl aldehyde **1o** afforded the corresponding allyltriazole **2o** in moderate yield (entry 15).

The structures of the products were determined by the detailed analyses of the spectroscopic data of the allyltriazoles **2**. The ^1H and ^{13}C NMR data of allyltriazole

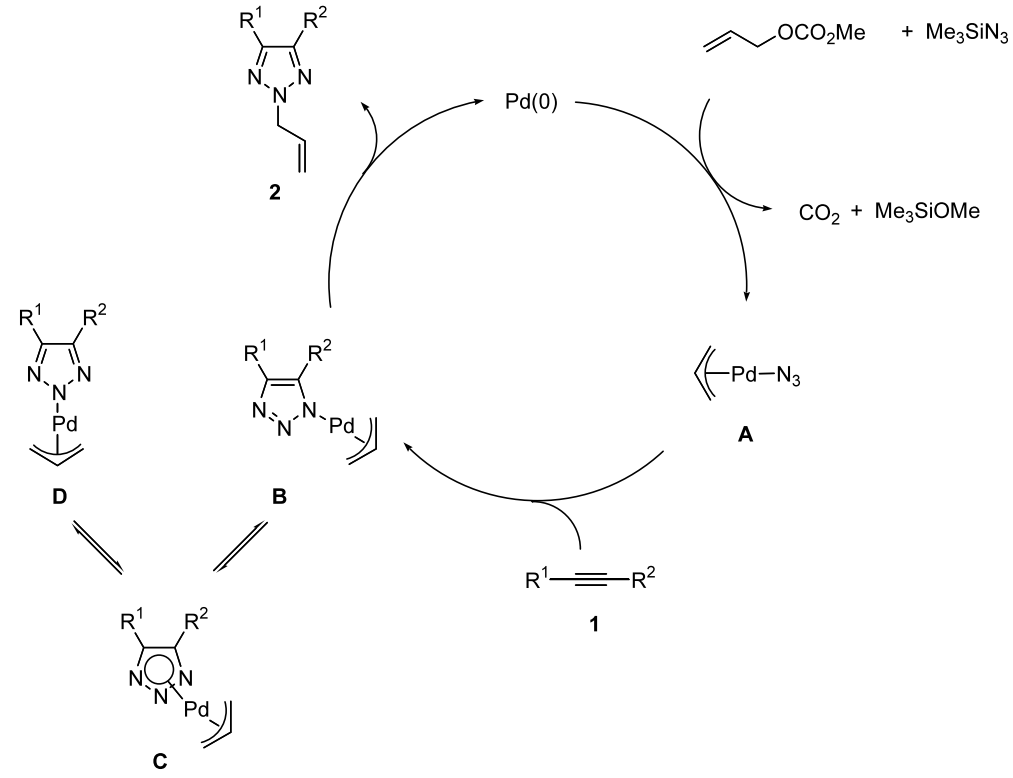
Table 1. Palladium-catalyzed formation of 2-allyl-1,2,3-triazoles[a]

Entry	R^1	R^2	**1**	Reaction time (h)	**2**	Yield (%)[b]
1	Ph	CN	**1a**	2	**2a**	50
2	Ph	CHO	**1b**	2	**2b**	55
3	Ph	COMe	**1c**	2	**2c**	56
4	Ph	CO_2Me	**1d**	24	**2d**	53
5	Ph	$P(O)(OEt)_2$	**1e**	24	**2e**	53
6	Ph	SO_2Ph	**1f**	3	**2f**	29
7	Ph	NEt_2	**1g**	2	**2g**	33
8	H	COMe	**1h**	2	**2h**	66
9	Et	COMe	**1i**	2	**2i**	56
10	1-Cyclohexenyl	COMe	**1j**	4	**2j**	61
11	^{t}Bu	COMe	**1k**	4	**2k**	65
12	H	CO_2Me	**1l**	24	**2l**	24
13	$CH_3(CH_2)_5$	CO_2Me	**1m**	24	**2m**	15[c]
14	CO_2Me	CO_2Me	**1n**	2	**2n**	60
15	$CH_3(CH_2)_4$	CHO	**1o**	3	**2o**	53

[a] Allyl methyl carbonate and Me_3SiN_3 were added to a solution of the alkyne **1**, $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%) and dppp (10 mol%) in AcOEt. The mixture was stirred at 100°C for the time shown in Table 1.

[b] Isolated yields.

[c] The starting alkyne **1i** was recovered in 13% yield.



Scheme 1. Proposed mechanism for the formation of 2-allyl-1,2,3-triazoles.

2n indicated that the product had a symmetrical structure.[7] Furthermore, the position of the allyl group was unambiguously confirmed by conducting NOE experiments on compound **2h**.[8]

A proposed mechanism for the formation of 2-allyl-1,2,3-triazoles via the palladium-catalyzed TCC reaction is shown in Scheme 1. The reaction of allyl methyl carbonate, trimethylsilyl azide and Pd(0) produces the π-allylpalladium azide complex **A**[9,10] with concomitant evolution of CO_2 and trimethylsilyl methoxide in the first step of the catalytic cycle. Then, the 1,3-dipolar cycloaddition of the azide moiety of the complex **A** with the alkyne **1** forms the 1-(η^3-allylpalladium)-1,2,3-triazole complex **B**. The complex **B** will be in equilibrium with the 2-(η^3-allylpalladium)-1,2,3-triazole **D** through the formation of the (η^3-allyl)(η^5-triazoyl)palladium complex **C**, an analogue of the (η^3-allyl)(η^5-cyclopentadienyl)palladium complex.[11] Regeneration of Pd(0) by reductive elimination from the complex **D** affords the 2-allyltriazole **2**.

We have developed a new synthetic method for the synthesis of 2-allyl-1,2,3-triazoles **2** via the palladium-catalyzed three component coupling (TCC) reaction of alkynes **1**, allyl methyl carbonate and trimethylsilyl azide. The 1,3-dipolar cycloaddition between the π-allylpalladium azide complex **A** and alkynes is a key step in the catalytic cycle. One of the characteristic points of this TCC reaction is that 2-allyl-1,2,3-triazoles are formed regioselectively and no other isomers are obtained at all. Further studies on the reactivity and the synthetic applications of π-allylpalladium azide complexes are in progress in our laboratory.

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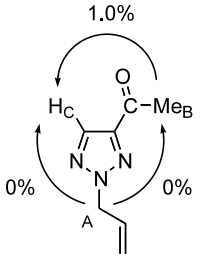
7. Analytical data for 2-allyl-4,5-di(methoxycarbonyl)-1,2,3-triazole **2n**; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (6H, s), 5.12 (2H, br d, $J=6.5$ Hz), 5.37 (1H, br d, $J=17.0$ Hz), 5.39 (1H, br d, $J=10.0$ Hz), 6.09 (1H, ddt, $J=17.0$, 10.0, 6.5 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.77, 58.44, 121.08, 129.66, 139.84, 160.04; IR (neat) 1735, 1460, 1307, 1226, 1097, 993 cm^{-1}; HRMS (EI) Calcd for $C_9H_{11}N_3O_4$ (M^+) 225.0750. Found 225.0749.
8. The geometry of 2-allyl-4-acetyl-1,2,3-triazole **2h** was established by NOE experiments. Neither H_B nor H_C protons showed enhancement with the allylic protons (H_A) in the 2,4-isomer, which is observed for 1,4- and 1,5-isomers.[5a]



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