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Reaction of (*Z*)-1-Aryl-3-hexen-1,5-diynes with Sodium Azide: Synthesis of 1-Aryl-1*H*-benzotriazoles

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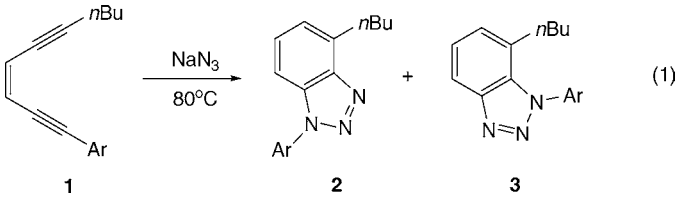
ABSTRACT



A novel tandem cascade reaction involving 1,3-dipolar cycloaddition reaction, anionic cyclization, and sigmatropic rearrangement for the synthesis of 1-aryl-1*H*-benzotriazoles 2 and 3 was accomplished by treatment of the (*Z*)-1-aryl-3-henen-1,5-diynes (1) with sodium azide in DMF or DMSO at 80 °C for 12 h and gives 65–91% yields.

The 1*H*-benzotriazoles are an important class of compounds because of their wide use in synthetic organic chemistry and pharmaceutical science. They are useful synthons for the Graebe−Ullmman reaction[1] in some versions of the synthesis of Ellipticine[2] and pyridoacridine[1g] for preparations of tetraazapentalenes[3] and 1,1′-carbonylbisbenzotriazoles.[4] 1*H*-Benzotriazoles are also found to exhibit a broad spectrum of pharmacological activities such as antiinflammatory, antifungal, antitumor, antineoplastic, and antidepressant activities.[5]

They also serve as synthetic auxiliaries in insertion, amidoalkylation, and imidoylation that have been applied in many heterocyclic compound syntheses.[6] Furthermore, 1*H*-benzotriazole moieties are emerging as powerful RNA and DNA labels in SERRS detectors.

1,3-Dipolar cycloaddition reactions are powerful methods for the preparation of a variety of cyclic compounds. It is well-known that the 1,3-dipolar cycloaddition of an azide with an alkyne leads to the formation of 1,2,3-triazoles.[8]

Recently, we reported nucleophile-promoted anionic cycloaromatization reactions of enediynes that would allow us to prepare a variety of aromaric compounds such as phenanthridinones, biphenyls, dibenzofurans, and carbazoles.[9] In

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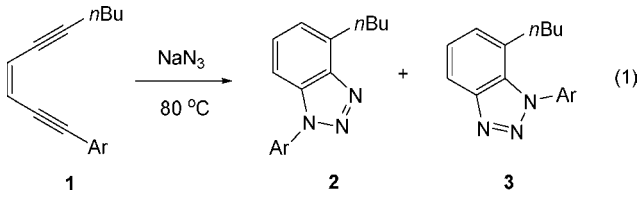
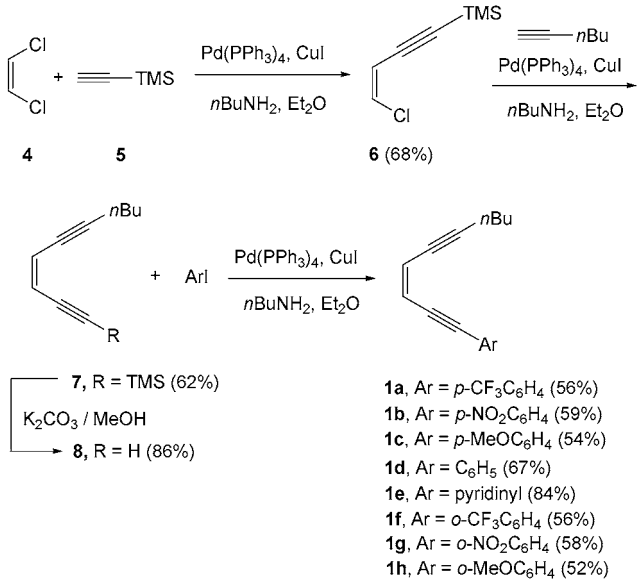
continuation of our interest in the chemistry of enediynes, we now report a novel one-pot reaction of (*Z*)-1-aryl-3-hexen-1,5-diynes (**1**) with sodium azide to give 4-butyl-1-aryl-1*H*-benzotriazoles (**2**) and 7-butyl-1-aryl-1*H*-benzotriazoles (**3**).



The preparation of the precursors, (*Z*)-1-aryl-3-hexen-1,5-diynes **1a**−**h**, is outlined in Scheme 1. The Sonogashira

Scheme 1. Synthesis of the Precursors (*Z*)-1-Aryl-3-hexen-1,5-diynes **1a**−**h** from *cis*-1,2-Dichloroethene



cross-coupling reaction of *cis*-1,2-dichloroethene (**4**) with trimethylsilylacetylene (**5**) using palladium as a catalyst gave enyne **6** in 68% yield. Palladium-catalyzed coupling reaction of **6** with 1-hexyne provided enediyne **7** in 62% yield. Desilylation of **7** with potassium carbonate in methanol gave **8** in 86% yield. Finally, reaction of aryl iodides with **8** using palladium as a catalyst gave (*Z*)-1-aryl-3-hexen-1,5-diynes **1a**−**h** in 52−84% yields, respectively.

Our first attempt of the new type of cyclization reaction was carried out by treatment of (*Z*)-1-aryl-3-hexen-1,5-diynes **1a** with sodium azide in DMF at 25 °C for 48 h. No reaction took place. However, when the reaction was heated to 80 °C and stirred for 12 h, 4-butyl-1-(4-trifluoromethylphenyl)-1*H*-benzotriazole (**2a**) was obtained in 54% yield along with 20% yield of 7-butyl-1-(4-trifluoromethylphenyl)-1*H*-benzotriazole (**3a**). The structure of **2a** was unambiguously determined by single-crystal X-ray analysis (Figure 1). Other

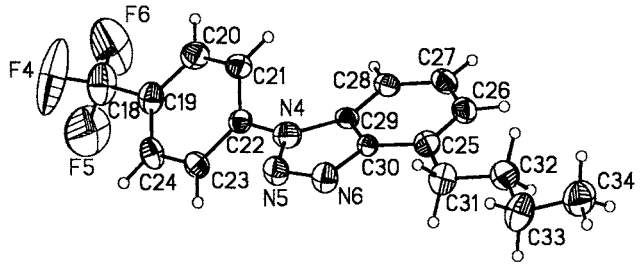
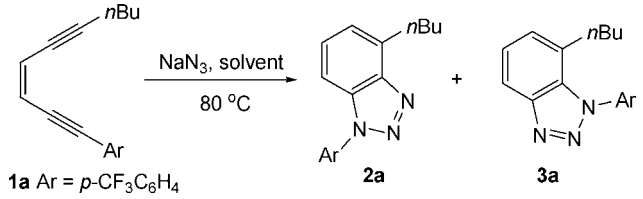


Figure 1. ORTEP Plots for X-ray Crystal Structures of **2a**.

solvents were also examined, and the results are summarized in Table 1. Replacing the solvent from DMF to DMSO afforded **2a** in 19% yield and **3a** in 72% yield. Using HMPA as the solvent afforded **2a** in 25% yield and **3a** in 70% yield. No product was obtained using CH_3CN, THF, CH_2Cl_2 and toluene as the solvent in this reaction.

Table 1. Solvent Effects on the Synthesis of 1-Aryl-1*H*-benzotriazole

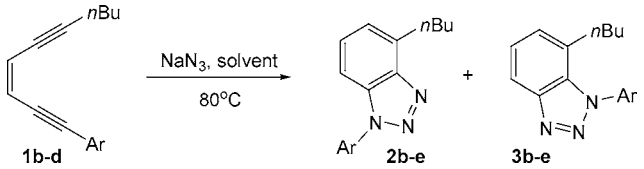


			isolated yields [%]	
entry	solvent	time [h]	**2a**	**3a**
1	DMF	12	54	20
2	DMSO	24	19	72
3	HMPA	32	25	70
4	NMP	144	19	62
5	THF	52	no reaction	
6	CH_3CN	52	no reaction	
7	CH_2Cl_2	46	no reaction	
8	toluene	56	no reaction	

Various (*Z*)-1-aryl-3-hexen-1,5-diynes **1b**−**e** bearing electron-withdrawing or -donating groups have also been carried out for the reaction with sodium azide, and the results are summarized in Table 2. The results indicated that the substituent effect has no influence on this reaction. However, the solvent plays an important role in this cyclization reaction. When DMF was employed in this reaction, compounds **2b**−**e** were obtained as the major products, and using DMSO as the solvent, compounds **3b**−**e** became the major products. However, when (*Z*)-1-aryl-3-hexen-1,5-diynes **1f**−**h** bearing a substituent at the ortho position on the aryl group were used, compounds **2f**−**h** were obtained as the major products either in DMF or in DMSO. (Table 3)

A plausible mechanism for the formation of compounds **2** and **3** is proposed as shown in Scheme 2. The [3 + 2]

Table 2. Direct Synthesis of 1-Aryl-1*H*-benzotriazoles by the Reaction of 1-Aryl-3-(*Z*)-hexen-1,5-diynes with Sodium Azide

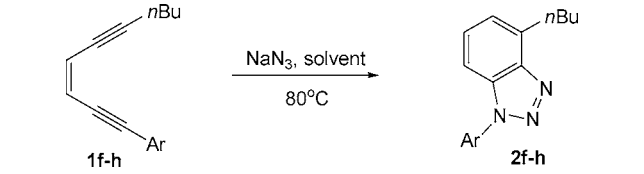


entry	Ar	solvent	time [h]	product, yield [%]	
1	**1b**, *p*-$NO_2C_6H_4$	DMF	12	**2b**, 70	**3b**, 19
2	**1c**, *p*-$MeOC_6H_4$	DMF	72	**2c**, 54	**3c**, 18
3	**1d**, C_6H_4	DMF	72	**2d**, 56	**3d**, 20
4	**1e**, pyridinyl	DMF	14	**2e**, 65	**3e**, 19
5	**1b**, *p*-$NO_2C_6H_4$	DMSO	24	**2b**, 19	**3b**, 61
6	**1c**, *p*-$MeOC_6H_4$	DMSO	64	**2c**, 22	**3c**, 43
7	**1d**, C_6H_4	DMSO	52	**2d**, 19	**3d**, 56
8	**1e**, pyridinyl	DMSO	16	**2e**, 16	**3e**, 67

cycloaddition between (*Z*)-1-aryl-3-hexen-1,5-diyne **1** and sodium azide would produce the triazole **9**. An anionic cascade cyclization of **9** would lead to the formation of the corresponding 3a-arylbenzo[*d*][1,2,3]triazole **10**. The intermediate **10** could undergo a 1,5-aryl-shift to give **11** or undergo another 1,5-shift followed by protonation during the workup to produce the 1-aryl-7-butyl-1*H*-benzotriazole **3**. On the other hand, intermediate **11** would undergo a 1,5-aryl-shift, and then protonation to give the 1-aryl-4-butyl-1*H*-benzotriazole **2**.

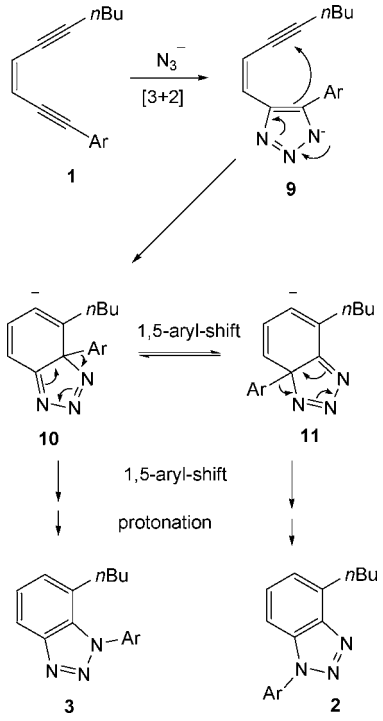
We believe that upon using a polar solvent such as DMSO, intermediate **10** would undergo a fast 1,5-aryl-shift to form the kinetic product **3**. However, under a less polar solvent such as DMF, intermediate **10** could form an equilibration

Table 3. Substituent Effect on the Synthesis of 4-Butyl-1-aryl-1*H*-benzotriazoles



entry	Ar	solvent	time [h]	product, yield [%]
1	**1f**, *o*-$CF_3C_6H_4$	DMF	48	**2f**, 85
2	**1g**, *o*-$NO_2C_6H_4$	DMF	44	**2g**, 82
3	**1h**, *o*-$MeOC_6H_4$	DMF	72	**2h**, 76
4	**1f**, *o*-$CF_3C_6H_4$	DMSO	42	**2f**, 68
5	**1g**, *o*-$NO_2C_6H_4$	DMSO	44	**2g**, 68
6	**1h**, *o*-$MeOC_6H_4$	DMSO	66	**2h**, 65

Scheme 2. Proposed Mechanism for the Formation of 1-Aryl-1*H*-benzotriazoles.



with intermediate **11**. Since intermediate **11** is considered to be a more stable intermediate, the equilibration would lead to the more stable intermediate **11**. After the 1,5-aryl shift, the thermodynamic product **2** would form as the major product.

In conclusion, we have developed an efficient as well as novel example of the construction of 1-ary-1*H*-benzotriazoles from enediynes. This reaction not only produces the products in high yield but also involves a tandem anionic cascade cyclization reaction and sigmatropic rearrangement in the benzotriazole systems. We believe that this finding would have a great impact to the chemistry of enediynes. Further study of the reaction mechanism and the application of this methodology to the synthesis of biological active 1-aryl-1*H*-benzotriazoles are currently under investigation.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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