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Benzyne Click Chemistry: Synthesis of Benzotriazoles from Benzynes and Azides

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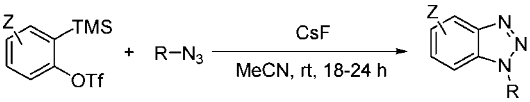
ABSTRACT



A variety of substituted benzotriazoles have been prepared by the [3 + 2] cycloaddition of azides to benzynes. The reaction scope is quite general, affording a rapid and easy entry to substituted, functionalized benzotriazoles under mild conditions.

Recent years have seen rapid development of the Cu-catalyzed [3 + 2] cycloaddition[1] reaction between terminal alkynes and azides, commonly referred to as "click chemistry".[2] Such chemistry has found wide applications not only in synthetic organic chemistry[3] but also in dendrimer and polymer chemistry,[4] the material sciences,[5] bioconjugation chemistry,[6] and the pharmaceutical sciences.[7]

Although there have been several reports on the annulation of arynes by azides,[8] efforts to modernize this reaction are certainly necessary. Early examples utilizing potentially explosive diazotized anthranilic acid as the benzyne precursor[8a–c] suffer from the use of a potentially explosive reagent and dangerous reaction conditions, and more recent examples utilizing *o*-(trimethylsilyl)aryliodonium salts[8e,f] suffer from the limited availability and difficulties in preparation of these reagents. Nowadays, arynes are more readily and conveniently generated in situ by the fluoride-promoted *ortho*-elimination of commercially available or easily prepared *o*-(trimethylsilyl)aryl triflates.[9] Arynes generated in this way retain their high reactivity toward nucleophilic additions and annulations.[10]

With our recent success in the development of benzyne annulation chemistry,[11] particularly the [3 + 2] cycloaddition reaction between benzynes and diazo compounds,[11a,12] we envisioned the [3 + 2] annulation of benzynes by azides as a very promising extension of the current click chemsitry. Such chemistry should not only expand the scope and utility

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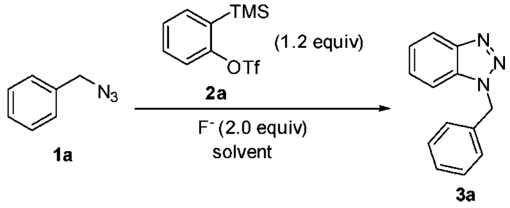
of the present click chemistry but also potentially provide a rapid entry to substituted, functionalized benzotriazoles, which are known to possess important biological activity[13] and exhibit utility as synthetic auxiliaries.[14] Herein, we report our preliminary results on the [3 + 2] annulation reaction of benzynes and azides, new benzyne click chemistry.

We started our investigation using commercially available benzyl azide (**1a**) and *o*-(trimethylsilyl)phenyl triflate (**2a**) under a variety of different reaction conditions (Table 1). TBAF and CsF were chosen as fluoride sources, and the reaction was examined in several dipolar aprotic solvents. While most reaction conditions gave low yields (entries 1−4), the reaction carried out in acetonitrile using CsF as the fluoride source afforded a superior yield of 76% (entry 5). These optimized conditions are identical to the optimal conditions observed previously by us for the synthesis of indazoles by the cycloaddition of diazo compounds to arynes.[11a] We have thus chosen these conditions as our general procedure for all subsequent work.[15]

Table 1. Reaction Optimization[a]

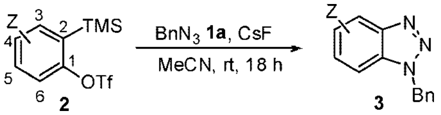


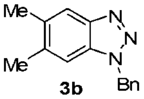
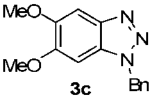
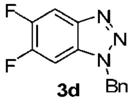
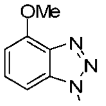
entry	fluoride source	solvent	*T* (°C)	time (h)	yield[b] (%)
1	TBAF	THF	0 to rt	3	37
2	TBAF	MeCN	0 to rt	3	45
3	TBAF	DCM	0 to rt	5	34
4	CsF	THF	rt	18	37
5	**CsF**	**MeCN**	**rt**	**18**	**76**

[a] All reactions were carried out on a 0.3 mmol scale in 0.1 M concentration. [b] Isolated yield.

We next tested different benzyne precursors in this reaction (Table 2). As can be seen, the reaction shows good compatibility with a range of different benzyne precursors. Thus, benzyne precursors **2b** and **2c** gave comparable yields of the desired benzotriazole products (entries 1 and 2). However, the electron-poor benzyne precursor **2d** gave only a 56% yield (entry 3). An unsymmetrical benzyne precursor **2e** afforded a single regioisomer in a 78% yield (entry 4), which is consistent with our previous results.[11a]

Table 2. Reaction with Different Benzyne Precursors[a]



entry	benzyne precursor	Z	product	yield (%)[b]
1	**2b**	4,5-Me_2	 **3b**	71
2	**2c**	4,5-$(OMe)_2$	 **3c**	71
3	**2d**	4,5-F_2	 **3d**	56
4	**2e**	3-OMe	 **3e**	78[c]

[a] All reactions were carried out on a 0.3 mmol scale with 1.2 equiv of benzyne precursor and 2.0 equiv of CsF. [b] Isolated yield. [c] The product was assigned by a 2D-NOESY experiment; see the Supporting Information for details.

A wide range of azides have also been screened (Table 3). Among them, aryl and heteroaryl azides are generally good substrates, affording the desired benzotriazole products in 83−90% yields (entries 1−8). The substrate scope includes electron-rich (entries 2 and 3), electron-poor (entries 4−7), sterically hindered (entries 2, 4, and 7), and heterocyclic (entry 8) aryl azides. All of these substrates gave clean reactions under mild conditions and tolerated functional groups, such as ester, ether, cyano, and halogen groups. Alkyl

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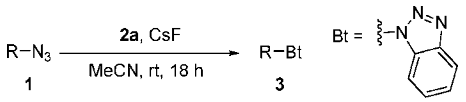
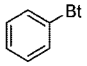
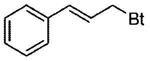
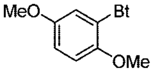
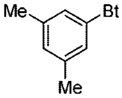
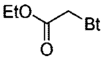
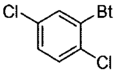
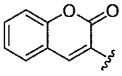
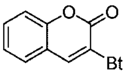
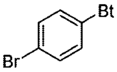
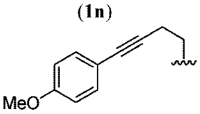
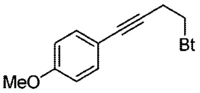
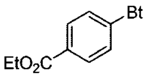
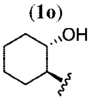
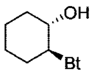
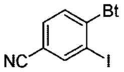
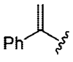
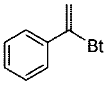
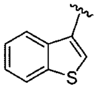
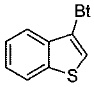
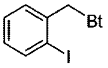
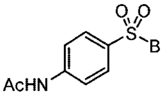
(15) **General Procedure.** To a solution of benzyne precursor (0.35 mmol) and azide (0.30 mmol) in 3 mL of dry MeCN was added CsF (0.60 mmol). The reaction vial was sealed, and the reaction mixture was stirred at room temperature for 18−24 h before being poured into saturated aqueous $NaHCO_3$. The resulting mixture was extracted with EtOAc or DCM, and the combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by silica gel chromatography.

Table 3. Reaction Scope with Different Azides[a]



entry	R (compound)	product	yield (%)[b]	entry	R (compound)	product	yield (%)[b]
1	Ph (**1b**)	 **3f**	87	10	cinnamyl (**1k**)	 **3o**	91
2	2,5-(MeO)$_2$C$_6$H$_3$ (**1c**)	 **3g**	88	11[c]	1-adamantyl (**1l**)	 **3p**	78
3	3,5-Me$_2$C$_6$H$_3$ (**1d**)	 **3h**	85	12	EtO$_2$CCH$_2$ (**1m**)	 **3q**	100
4	2,5-Cl$_2$C$_6$H$_3$ (**1e**)	 **3i**	87	13	 (**1n**)	 **3r**	51
5	4-BrC$_6$H$_4$ (**1f**)	 **3j**	83	14	 (**1o**)	 **3s**	93
6[c,d]	4-EtO$_2$CC$_6$H$_4$ (**1g**)	 **3k**	90	15[e]	 (**1p**)	 **3t**	68
7	4-(NC)-2-IC$_6$H$_3$ (**1h**)	 **3l**	86	16[e]	 (**1q**)	 **3u**	20
8	 (**1i**)	 **3m**	85	17[f]	TMS (**1r**)	**3f**	58
9	2-IC$_6$H$_4$CH$_2$ (**1j**)	 **3n**	100	18	4-AcNHC$_6$H$_4$SO$_2$ (**1s**)	 **3v**	0

[a] All reactions were carried out on a 0.3 mmol scale with 1.2 equiv of **2a** and 2.0 equiv of CsF. [b] Isolated yield. [c] The reaction was allowed to run for 24 h. [d] A trace of unreacted starting azide remained even after 24 h. [e] Other unidentified products were present. [f] The reaction was carried out using 2.4 equiv of **2a** and 5.0 equiv of CsF.

azides are also good substrates. Other than benzyl azide (**1a**), functionalized benzylic (entry 9) and allylic (entry 10) azides also have afforded excellent yields of the desired products. Sterically demanding adamantyl azide (**1l**) (entry 11) reacted smoothly to afford a 78% yield as well. Azides with functional groups can be easily transformed into the corresponding benzotriazoles. Thus, ethyl azidoacetate (**1m**) reacted cleanly to give a quantitative yield of the corresponding benzotriazole (entry 12). Coumarin-derived azide **1n** also afforded the desired product in a moderate 51% yield (entry 13). An alkyne moiety is well tolerated under the reaction conditions, as seen in the smooth reaction of alkyne **1o** with benzyne, affording the alkynyl benzotriazole **3s** (entry 14). A free hydroxyl group is tolerated, although an additional, unidentified side product was observed (entry 15). Although the reaction tolerates alkenes quite well (see entries 10 and 13), the vinylic azide **1q** was not a suitable substrate in this annulation process (entry 16). After the reaction was complete, a complex mixture was obtained. After isolation, purification, and identification, the product was found in only a 20% yield, and we were unable to identify the rest of the products. Trimethylsilyl azide (**1r**) was also examined in this reaction (entry 17). Surprisingly, the reaction did not stop at the [3 + 2] cycloaddition stage but underwent further desilylation, followed by phenylation with another equivalent of **2a** to afford **3f** as the final product. The same reaction afforded unidentified products when MeOH was used as a cosolvent.[16] The current limitation on the scope of the azide substrate is that azides bearing electron-withdrawing groups directly attached to the azide moiety do not work in this annulation. Thus, the reaction of sulfonyl azide **1s** did not give any annulation product.[17]

In conclusion, we have developed a facile, efficient, and general method for the synthesis of substituted, functionalized benzotriazoles by the 1,3-dipolar cycloaddition of benzynes with azides under very mild reaction conditions. The reaction has good substrate scope and tolerates a board range of functional groups. It provides a useful new route to benzotriazoles in much the same manner as present “click” chemistry affords triazoles. We believe that this methodology should find broad applications in synthetic organic chemistry, as well as the combinatorial, pharmaceutical, and polymer sciences.

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Supporting Information Available: Preparation of azide starting materials, experimental details, and characterization of the final products, including full ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In a similar reaction between benzyne **2a** and TMS diazomethane to form indazole, MeOH was needed as a co-solvent; see ref 11a.

(17) We have also unsuccessfully carried out a reaction with an acyl azide (2-iodobenzoyl azide). However, we observed severe spontaneous decomposition of this azide simply upon standing. Thus, not surprisingly, under our reaction conditions, the reaction between this azide and **2a** afforded a complex mixture. Other acyl azides will be investigated, and results will be published in due course.