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Benzyne Click Chemistry with in Situ Generated Aromatic Azides

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ABSTRACT

An efficient synthesis of substituted benzotriazoles using an azide−alkyne 1,3-dipolar cycloaddition "click reaction" is described. Key to the procedure is the in situ generation of the reactive aromatic azide and benzyne reaction partners.

The recent discovery of Cu(I)-catalyzed advancement[1] of the Huisgen 1,3-dipolar cycloaddition between azides and terminal alkynes has brought about a renaissance of interest in this useful and reliable bond-forming "click" reaction.[2] This chemistry has found wide application in various disciplines including materials science,[3] chemical biology,[4] and medicinal chemistry.[5] In the absence of Cu(I) catalysis, the Huisgen cyloaddition reaction is generally sluggish due to the kinetic stability of the azide and alkyne functionality. In such instances, elevated temperature or pressure are often required to drive the process. This inertness renders the azide and alkyne functional groups bioorthogonal and, as such, highly attractive motifs for bioconjugation applications.

Strategies aimed at avoiding Cu(I) catalysis or harsh reaction conditions have been developed in recent times. These methods involve activated alkynes which readily react with azides at ambient temperature, including alkynes in conjugation with electron-withdrawing groups[6] and strained internal alkynes such as cyclooctyne.[7] One particularly important class of activated alkynes, arynes, have long been known to undergo facile annulation with organic azides to yield benzotriazoles.[8] This pharmacologically significant structural motif is found in many biologically active compounds, including anticancer, antifungal, anti-inflammatory, and antidepressant agents.[9]

The reactive aryne intermediates must be generated in situ, and several methods have been developed for this purpose. Early procedures utilized diazotized anthranilic acid as the benzyne precursor,[10] which is a reliable and convenient strategy, especially considering the ready availability of the starting materials. However, the diazo intermediates are considered to be potentially explosive, and milder alternative conditions have since been developed, including the use of

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o-(trimethylsilyl)aryliodonium salts[11] and two-step deprotonation−dehalogenation of aromatic halogen compounds.[12] These days, arynes are commonly prepared in situ by fluoride-promoted *ortho*-elimination of *o*-(trimethylsilyl)aryl triflates.[13] Using this procedure, Larock et al.[14] and others[15,16] have reported the synthesis of a range of benzotriazoles by the [3 + 2] cycloaddition of benzyne and organic azides.

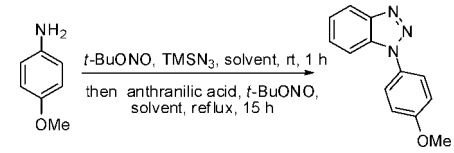
Perhaps safer in terms of the preparation of the benzyne component, these procedures still require the use of preformed organic azides. Despite being stable under most reaction conditions, organic azides with low molecular weight can sometimes be explosive, and so-called "azidophobia" may hinder the uptake of these potentially useful methodologies.[17] Procedures which enable the in situ generation of organic azides followed by their immediate reaction minimize such hazards. In the context of "click" chemistry,[18] several procedures have already been reported, where in situ azide formation is immediately followed by Cu(I)-catalyzed cycloaddition with terminal alkynes to give the corresponding 1,4-triazole linkage.[19]

Building upon our recent success in the development of in situ "click" chemistry with aromatic azides,[20] we envisioned extending the scope of this methodology to include in situ benzyne annulation. Herein we report a one-pot synthesis of benzotriazoles using benzyne click chemistry without the need for isolation of the aromatic azide substrate.

For convenience, we considered using a common alkyl nitrite reagent for the in situ generation of both benzyne from anthranilic acid and an aromatic azide fragment from aniline. With this in mind, 1-azido-4-methoxybenzene was prepared in situ from 4-methoxyaniline using an excess of *t*-BuONO (2.0 equiv) and $TMSN_3$ (1.1 equiv) in acetone.

This was followed by the addition of 2 equiv of anthranilic acid at reflux (Table 1). Unfortunately, under these conditions, the desired product was not observed (entry 1). However, when additional *t*-BuONO (2.0 equiv) and anthranilic acid (2.0 equiv) were simultaneously added (over 25 min) to a mixture containing the in situ generated azide, the target benzotriazole product was isolated in 34% yield

Table 1. Reaction Optimization



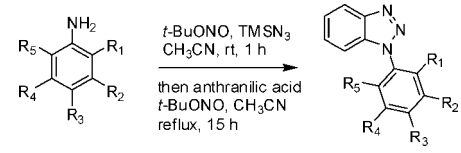
entry[a]	*t*-BuONO (equiv)	$TMSN_3$ (equiv)	anthranilic acid (equiv)	solvent (*T*, °C)	yield[b] (%)
1	2	1.1	2	acetone (57)	
2	2 + 2	1.1	2	acetone (57)	34
3	2 + 2	1.1	2	THF (66)	60
4	2 + 2	1.1	2	CH_3CN (82)	88

[a] All reactions were carried out at 1.0 mmol. [b] Isolated yield.

(entry 2). Changing the solvent from acetone to THF improved the yield to 60% (entry 3). Gratifyingly, we found if the solvent was changed to acetonitrile the yield could reach 88%. These optimized conditions were chosen for all subsequent work.[21]

In order to explore the scope of this reaction, a range of aromatic amines were reacted under the optimized conditions with anthranilic acid (Table 2). Simple aromatic amines such

Table 2. One-Pot Reaction with Different Aromatic Azides



entry[a]	R_1	R_2	R_3	R_4	R_5	yield[b] (%)
1	H	H	H	H	H	71
2	H	H	$CH(CH_3)_2$	H	H	79
3	CH_2CH_3	H	H	H	CH_2CH_3	83
4	H	H	I	H	H	51
5	H	H	CF_3	H	H	56
6	H	H	NO_2	H	H	32
7	H	H	CN	H	H	64
8	OMe	H	H	OMe	H	52
9	H	OMe	OMe	H	H	72

[a] All reactions were carried out on a 1.0 mmol scale with 2.0 equiv of benzyne precursor. [b] Isolated yield.

as aniline and 4-isopropylaniline reacted smoothly to give the benzotriazole products in 71% and 79% yields, respectively (entries 1 and 2). Lower yields were observed with stabilized aromatic amines containing deactivating substituents (entries 4−7). These lower yields may be due to a decrease in the rate of cycloaddition, thus enabling competing reaction pathways of benzyne to occur. Indeed, these reactions were generally more complex, with several unidentified products obtained. Electron-rich substrates (entries 8 and 9), as well as sterically demanding anilines (entries 3

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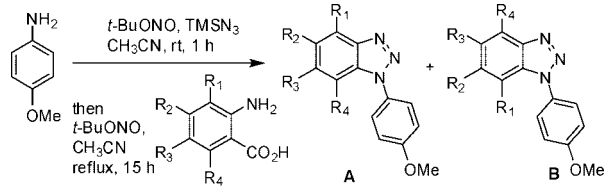
and 8), reacted efficiently to give the desired products with good yields.

We next tested several substituted anthranilic acid benzyne precursors using this one-pot "click" procedure (Table 3).

Table 3. One-Pot Reaction with Different Substituted Anthranilic Acids



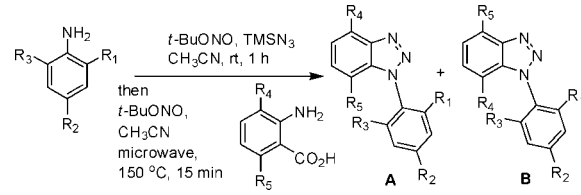
entry[a]	R_1	R_2	R_3	R_4	yield (%) (A:B)[c]
1	H	−CHCHCHCH−		H	36
2	H	H	Cl	H	34 (3:1)
3	H	H	H	F	33 (1:1)
4	CF_3	H	H	H	61 (>95:1)
5	H	H	NO_2	H	
6	Me	H	H	H	74 (1:1)
7	H	H	H	Me	77 (1:1)
8	OMe	H	H	H	75 (1:0)[d]

[a] All reactions were carried out at 1.0 mmol with 2.0 equiv of benzyne precursor. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [d] Regiochemistry determined by NOE.

When 4-methoxyaniline and 3-amino-2-naphthoic acid were used as the substrates, the corresponding napthotriazole product was isolated in 36% yield (entry 1). With a chlorine substituent at R_3, or fluorine at R_4, the unsymmetrical aryne intermediates resulted in a 3:1 and 1:1 mixture of regioisomers, respectively, with moderate yields (entries 2 and 3). With deactivating CF_3 at R_1, a >95:1 mixture of regioisomers was obtained in 61% yield (entry 4). However, when 2-amino-5-nitrobenzoic acid was used as the benzyne precursor, no product formation was observed (entry 5). With a methyl substituent at R_4 or R_1, the reactions gave a 1:1 mixture of separable regioisomers (entries 6 and 7). In the case of 2-amino-3-methoxybenzoic acid, a single regioisomer was obtained (entry 8) with the aromatic ring on nitrogen remote to the substituent, which is consistent with Larock's observations.[1]

Interestingly, reaction times could be significantly reduced (15 h to 15 min) using microwave conditions without significant change in the product yields (Table 4).[20b,22] Following in situ formation of the aromatic azide fragment, the corresponding anthranilic acid−benzyne precursor and *t*-BuONO were added to the same flask. The reaction mixture was placed in a microwave reactor and irradiated for 15 min at 150 °C. These conditions favored electron-rich azides (entries 1−3), whereas lower yields were observed with electron-poor substrates (entries 5−7).

Table 4. One-Pot Reaction under Microwave Conditions

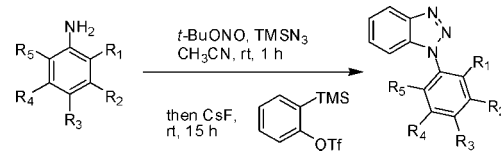


entry[a]	R_1	R_2	R_3	R_4	R_5	yield (%) (A:B)[c]
1	H	OMe	H	H	H	86
2	H	OMe	H	H	Me	69 (1:1)
3	H	OMe	H	CF_3	H	65 (>95:1)
4	H	OMe	H	H	F	52 (1:1)
5	Cl	NO_2	Cl	H	H	41
6	H	NO_2	H	H	H	29
7	H	CN	H	H	H	42

[a] All reactions were carried out at 0.5 mmol with 2.0 equiv of benzyne precursor. [b] Isolated yield. [c] The regioisomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product.

We were intrigued to investigate alternative strategies for benzyne generation and determine the compatibility with our in situ protocol. We turned to the popular method of fluoride promoted *ortho*-elimination of *o*-(trimethylsilyl)phenyl triflates (Table 5), recently utilized by Larock[14] and Ferringa.[15]

Table 5. One-Pot Reaction with *o*-(Trimethylsilyl)phenyl Triflate as Benzyne Precursors



entry[a]	R_1	R_2	R_3	R_4	R_5	yield[b] (%)
1	H	H	H	H	H	89
2	H	Me	H	Me	H	64
3	H	H	OMe	H	H	67
4	OMe	H	H	OMe	H	59
5	H	H	Br	H	H	53
6	Cl	H	H	Cl	H	73
7	H	H	NO_2	H	H	76

[a] All reactions were carried out at 1.0 mmol with 1.5 equiv of benzyne precursor. [b] Isolated yield.

Following in situ formation of the azide fragment, the benzyne precursor *o*-(trimethylsilyl)phenyl triflate and CsF

(21) **General Procedure.** The corresponding amine (1.0 mmol) was dissolved in CH_3CN (3.0 mL) in a 25 mL round-bottomed flask. To this stirring mixture was added *t*-BuONO (0.24 mL, 2.0 equiv) followed by $TMSN_3$ (0.14 mL, 1.05 equiv) dropwise. The resulting solution was stirred at room temperature for 1 h. Two solutions, *t*-BuONO (0.24 mL, 2 equiv) in CH_3CN (1.0 mL) and the corresponding anthranilic acid benzyne precursor (2 equiv) in CH_3CN (3.0 mL), were prepared. Over a period of 25 min, these two solutions were simultaneously added dropwise to the refluxing reaction. When the addition was complete, the mixture was stirred under reflux overnight. The reaction mixture was allowed to cool to room temperature. Saturated $NaHCO_3$ solution (10 mL) was then added. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the crude residue purified by silica gel chromatography (PE/EtOAc).

were added to the same flask, and the reaction mixture stirred at rt for 15 h. A range of aromatic amines, including electron rich (entries 2−4), electron poor (entries 5−7), and sterically hindered (entries 4 and 6), were tested. All of the substrates gave clean reactions under mild conditions and offered yields comparable to or better than those previously reported.[14]

In summary, a simple and efficient one-pot benzyne click reaction has been described that enabled access to a range of functionalized benzotriazoles. The method avoids isolation and handling of potentially explosive aromatic azides and uses readily available and inexpensive substituted anthranilic acid or *o*-(trimethylsilyl)phenyl triflate as benzyne precursor. Heating the reaction using microwave irradiation dramatically decreased reaction times from hours to minutes with increased yields in some case. This procedure offers advantages over current methodologies in terms of safety, ease of execution, and efficiency.

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Supporting Information Available: Full characterization data and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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