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Microwave-assisted benzyne-click chemistry: preparation of 1*H*-benzo[*d*][1,2,3]triazoles

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ABSTRACT

The benzotriazoles were prepared by three-component and two-component microwave-assisted [3+2] cycloadditions of various azides to benzyne, 3-methoxybenzyne, and 4,5-difluorobenzyne. In the three-component reaction, the aryne is generated, in the presence of an azide prepared in situ, by the reaction of an *o*-(trimethylsilylaryl) triflate with either CsF or KF/18-Crown-6. However, in the two-component reactions, a freshly prepared azide is added to the reaction vessel prior to aryne generation. Good to excellent yields of benzotriazoles were obtained in 15–20 min when the microwave-assisted reactions were carried out at 125 °C. These reaction times are significantly faster than similar reactions carried out using conventional heating.

1. Introduction

The [3+2] cycloaddition of azides with alkynes,[1] termed 'click' chemistry,[2] has been extensively studied and applied to several areas of chemistry. Recently, Larock et al.[3] reported the first benzyne click chemistry which involved the room temperature reaction of an azide with benzyne, generated by the reaction of *o*-(trimethylsilyl)-aryl triflate and CsF,[4] to give the corresponding 1*H*-benzo[*d*][1,2,3]triazoles (hereafter referred to as benzotriazoles). The benzotriazoles were obtained in 51–100% yields, but reaction times ranging from 18 to 24 h were required. Subsequently, Campbell-Verduyn et al.[5] developed a copper-free 'click' 1,3-dipolar-cycloaddition of azide and arynes (also generated by the reaction of *o*-(trimethylsilyl)-aryl triflate and KF in the presence of 18-crown-6) in which benzotriazoles were formed rapidly (0.5–2 h) at room temperature in yields ranging from 59% to 82%.

In our continuing interest in microwave-assisted reactions, we recently reported the first microwave-assisted reaction[6] involving benzyne, namely, the copper-catalyzed benzyne-acetylene coupling reaction. We have extended the use of microwave heating to benzyne click chemistry and report the results herein. To our knowledge this is the first example of a microwave-assisted benzyne click reaction.[7]

2. Results

Initially, benzotriazoles were prepared by benzyne-click chemistry using a microwave-assisted three-component reaction involving a [3+2] cycloaddition of an azide to an aryne. Accordingly, various azides were first prepared in situ, which was followed by the generation of benzyne, 3-methoxybenzyne, or 3,4-difluorobenzyne by the reaction of an *o*-trimethylsilylaryl triflate with either CsF or KF/18-crown-6. The reagents were charged into a sealed tube which was placed in a CEM Discover Model and subjected to microwave radiation at a power of 200 W while being rapidly stirred. By varying the solvent, temperature, and reaction time, best yields were obtained when the two successive reactions were run in MeCN at 125 °C for 10 min each. The reaction scheme and results are listed in Table 1 (see Ref. [8] for typical example). As shown, 1-benzyl and 1-substituted benzotriazoles are formed via benzyne itself (entries 1–10) in yields ranging from 51% to 85% (CsF) and 63% to 88% (KF/18-crown-6). In most cases, the yields were slightly higher when benzyne was generated from KF/18-crown-6. Similar treatment of the unsymmetric 3-methoxybenzyne intermediate gave 4-methoxy-1-substituted benzotriazoles (entries 11–14) in yields ranging from 63% to 77% using CsF as benzyne inducer and from 69% to 79% using KF/18-crown-6 as benzyne inducer. The structures of these products were confirmed by 1D and 2D NOE experiments. Presumably the 4-methoxy group sterically hinders the formation of the 7-methoxy-1-substituted product. As expected the symmetric 4,5-difluorobenzyne gave 1-benzyl-5,6-di-fluorobenzotriazole (entries 15 and 16) as sole product in very similar yields, that is, 76–79% versus 78–80%. Importantly, the, C=O, CF_3, NO_2, CN, OMe, and COOH groups tolerated microwave heating. Further, the reaction times of the CsF and KF/18-crown-6-induced benzyne reactions were significantly faster than similar reactions carried out using conventional heating. Interestingly, attempts to prepare aryl azides by various in situ aryl amine diazotization reactions prior to benzyne formation gave complex mixture of products.

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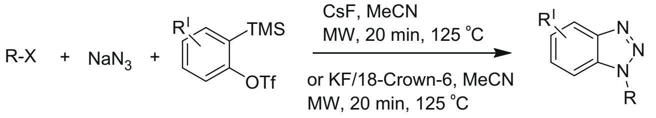
Table 1
Three-component microwave-assisted benzyne click chemistry



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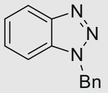
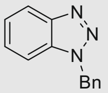
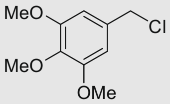
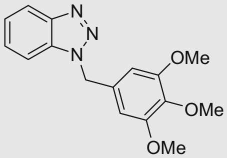
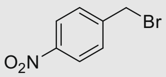
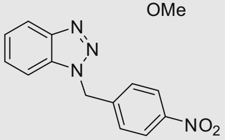
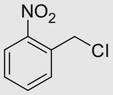
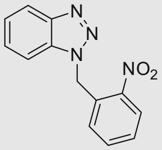
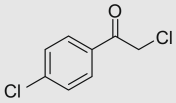
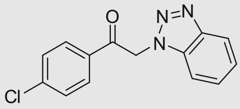
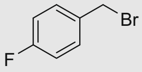
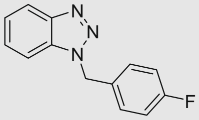
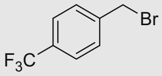
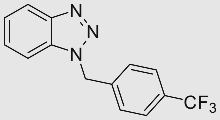
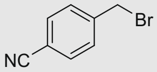
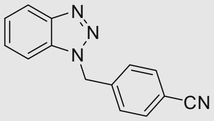
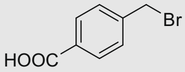
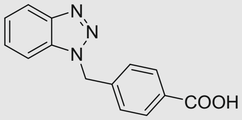
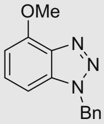
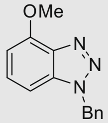
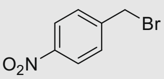
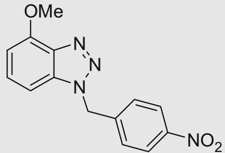
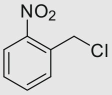
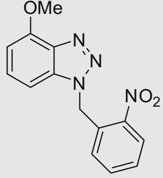
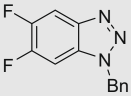
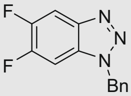
1	BnBr	H		79	86
2	BnCl	H		80	88
3		H		85	88
4		H		76	78
5		H		62	66
6		H		51	63
7		H		78	81
8		H		81	83
9		H		75	78
10		H		68	71
11	BnBr	3-OMe		70	76

Table 1 (*continued*)

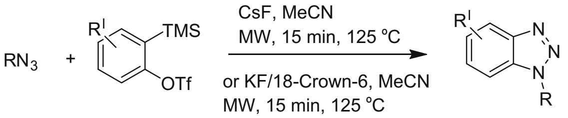
Entry	RX	R^1	Product[a]	CsF % yield[b]	KF/18-Crown-6 % yield[b]
12	BnCl	3-OMe		72	79
13		3-OMe		77	79
14		3-OMe		63	69
15	BnBr	4,5-F_2		76	78
16	BnCl	4,5-F_2		79	80

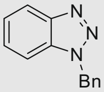
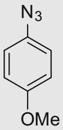
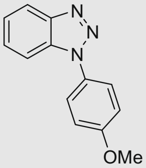
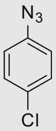
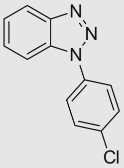
[a] All the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopies.

[b] Isolated yields.

We next studied the microwave-assisted 2-component benzyne click synthesis of benzotriazoles in which freshly prepared aliphatic and aryl azides were added to the reaction vessel prior to aryne generation. The aliphatic azides were prepared by the microwave-assisted reaction of primary halides with NaN_3 and catalytic amount of 18-Crown-6, in nearly quantitative yields (see Ref. 9 for typical example) whereas the aryl azides were synthesized by

Table 2
Two-component microwave-assisted benzyne click reaction



Entry	RN_3[a]	R^1	Product[b]	CsF % yield[c]	KF/18-Crown-6 % yield[c]
1	BnN_3	H		81	89
2		H		83	92
3		H		81	85

(continued on next page)

Table 2 (*continued*)

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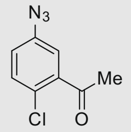
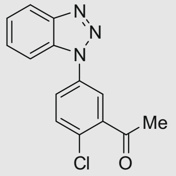
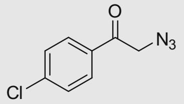
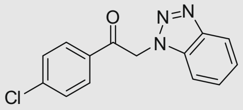
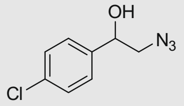
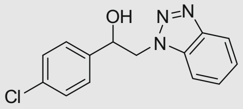
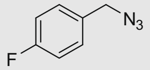
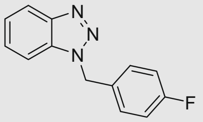
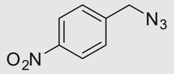
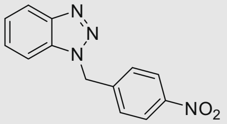
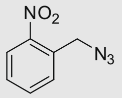
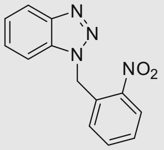
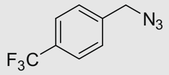
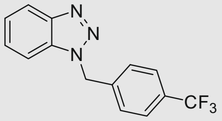
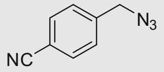
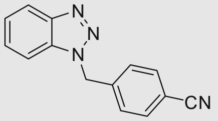
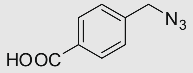
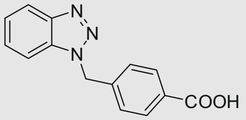
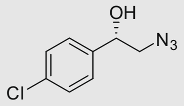
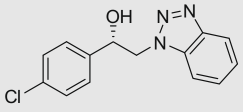
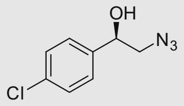
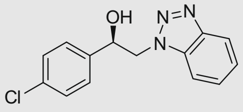
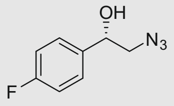
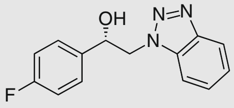
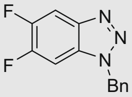
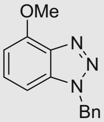
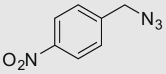
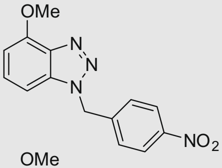
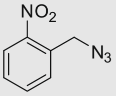
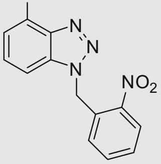
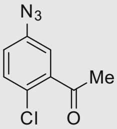
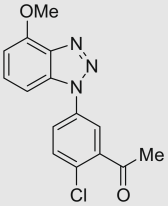
4		H		69	78
5		H		68	73
6		H		66	71
7		H		81	83
8		H		82	87
9		H		69	73
10		H		83	86
11		H		76	77
12		H		72	79
13		H		73	75
14		H		71	74
15		H		71	76

Table 2 (*continued*)

Entry	RN_3[a]	R^1	Product[b]	CsF % yield[c]	KF/18-Crown-6 % yield[c]
16	BnN_3	4,5-F_2		73	75
17	BnN_3	3-OMe		86	89
18		3-OMe		81	88
19		3-OMe		74	79
20		3-OMe		73	79

[a] All the aliphatic azides were prepared in a CEM microwave synthesizer at 125 °C except entry 6 which was prepared by sodium borohydride reduction of ketone at 0 °C and all the aryl azides were prepared by diazonium reaction of aromatic amines using *t*-BuONO followed by treatment with $TMSN_3$.[8]

[b] All the compounds were characterized by ^1H and ^{13}C NMR spectroscopies.

[c] Isolated yields.

a newly reported novel diazonium reaction of aromatic amines with *t*-BuONO followed by treatment with $TMSN_3$.[10]

As shown in Table 2, good to excellent yields of both 1-aryl-(entries 2–4) and 1-benzylbenzotriazoles (entries 1, 5–15) were obtained in 15 min at 125 °C using either CsF and KF/18-Crown-6 to generate the aryne intermediates (see Ref. [11] for typical example). As in the case of the 3-component reactions, the yields of the KF/18-Crown-6-initiated reactions were higher than those of the CsF-initiated reactions. For example, the reaction of benzyne with aryl azides (entries 2–4) gave the corresponding 1-arylbenzotriazoles in yields ranging from 69% to 83% and from 78% to 92% when benzyne was generated by CsF and KF/18-Crown-6, respectively. Additionally, 1-benzylbenzotriazoles were prepared in yields ranging from 66% to 83% and from 74% to 89% when benzyne was generated by the respective fluoride-generating bases. Interestingly, (*S*)-2-azido-1-(4-fluorophenyl)ethanol (entry 15) was converted to (*S*)-2-(1*H*-benzo[*d*][1,2,3triazol-1yl)-1-(4-fluorophenyl)-ethanol in 71% and 74% yields demonstrating that the chiral carbon is retained and the alcohol functional group tolerated microwave heating. Additionally, 3-methoxybenzyne (entries 17–20) gave the corresponding 4-methoxybenzotriazoles in 73–86% and 79–89% yield, respectively, and 4,5-di fluorobenzyne (entry 16) reacted with benzyl azide to give the 4,5-difluoro 1-benzylbenzotriazole in 73% and 75% yield, respectively. Again the yields from the KF/18-Crown-6 reactions were higher than those from the CsF. However, the convenience of the 3-component method in which the aliphatic azides are prepared in situ, may justify its use in certain cases.

In conclusion, we have developed a rapid (15–20 min) microwave-assisted, two-component (aryne precursor and freshly prepared primary or aryl azide) and three-component benzyne (primary halide, NaN_3, and benzyne precursor) click reaction for the preparation of 1-substituted benzotriazoles. In each case, benzyne intermediates were generated by either CsF or KF/18-Crown-6. Benzotriazoles possessing a 1-primiary azide group can be prepared by either method with best yields and fastest reaction times (15 min) being achieved by the 2-component reaction in which benzyne is generated by KF/18-Crown-6. On the other hand 1-aryl benzotriazoles are best prepared by the 2-component reaction in which the benzynes are generated by KF/18-Crown-6. The C=O, CF_3, NO_2, CN, OMe, OH, and COOH functional groups tolerate the conditions of the microwave reactions. Further, it has been shown that the rate determining step in the fluoride ion-induced aryne formation from *o*-trifluoromethysilylaryl triflates involves the very slow loss of triflate from the anionic phenyl triflate intermediate.[4] Under mild, conventional conditions, these arynic reactions can take as long as 15–22 h. That the arynic reactions reported here are complete within 15–20 min under microwave heating is truly remarkable.

Acknowledgment

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Supplementary data

Supplementary data (preparation of azide starting materials, experimental details, and characterization of the products by ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.004.

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8. *General procedure for the preparation of benzotriazoles by a three-component system using CsF*: Substituted benzyl halide (0.30 mmol), sodium azide (0.45 mmol), and 18-Crown-6 (0.03 mmol) acetonitrile (3 mL) were placed in a microwave test tube. The tube was then capped and charged into a CEM microwave instrument. The mixture was irradiated with 250 psi pressure at a temperature of 125 °C for 10 min. Then *o*-trimethylsilylphenyl triflate (0.35 mmol) and cesium fluoride (0.6 mmol) were added and the reaction mixture was stirred for 10 min under microwave heating at 125 °C and 250 psi pressure. The reaction mixture was then washed with saturated $NaHCO_3$ solution followed by saturated brine solution. The organic layer was removed, dried over Na_2SO_4, and concentrated under reduced pressure to obtain a crude product that was purified by preparative TLC using ethyl acetate/hexane (2:8) system to get the pure compound. Physical and Spectra properties of a typical benzotriazole produced by this method, that is, 1-benzyl-1*H*-benzo[*d*][1,2,3]-triazole (entry 1**,** Table 1) is given here**.** Light yellow compound, mp 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.05 (d, 1H, *J* = 8.05 Hz). 7.27–7.35 (m, 8H), 5.83 (s, 2H), ^{13}C NMR (125 MHz, $CDCl_3$): 146.4 (C), 134.8 (C), 132.9 (C), 129.0 (CH), 128.5 (CH), 127.7 (CH), 127.5 (CH), 124.0 (CH), 120.2 (CH), 109.8 (CH), 52.3 (CH_2).
9. *Preparation of (azidomethyl)benzene*: Benzyl chloride (0.252 mg, 2 mmol), sodium azide (0.162 mg, 2.5 mmol), 18-crown-6 (5.28 mg, 0.2 mmol), and acetonitrile (3 mL) were placed in a microwave test tube. The tube was then capped and charged into a CEM microwave instrument. The mixture was irradiated with 250 psi pressure at a temperature of 125 °C for 10 min. At this time, the product in the reaction mixture was confirmed by GC/MS. Then the reaction mixture was diluted with ethyl acetate then washed with water followed by brine solution. The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a yellow oily liquid product (0.253 mg, 95% yield) that was directly used for the preparation of triazole reaction. ^{1}H NMR (500 MHz, $CDCl_3$): 7.40–7.49 (m, 5H), 4.37 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 135.6 (C), 129.0 (CH), 128.8 (C), 128.5 (CH), 128.4 (CH), 54.9 (CH_2): IR (cm^{-1}): 3033.5, 2934.0, 2098.3, 1605.0, 1496.5, 1455.2, 1265.6, 1202.5, 877.0, 734.6, 701.6; GC/MS: 133 [M^{+}].
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11. *General procedure for the preparation of benzotriazoles by the two-component method using KF/18-Crown-6*: Substituted azide (0.30 mmol), 2-(trimethylsilyl)phenyl triflate (0.35 mmol), potassium fluoride (0.60 mmol), and 18-crown-6 (0.30 mmol) in acetonitrile (3 mL) were placed in a microwave test tube. The tube was then capped and charged into a CEM microwave instrument. The mixture was irradiated with 250 psi pressure and at a temperature of 125 °C for 15 min. Then the reaction mixture was washed with saturated $NaHCO_3$ solution followed by brine solution. The separated organic layer was dried on Na_2SO_4 and concentrated under reduced pressure and thus the obtained solid was purified by preparative TLC using ethyl acetate/hexane (2:8) system to get the pure compound. A typical compound produced by this method, that is, 1-(2-chloro-5-(4-methoxy-1*H*-benzo[*d*][1,2,3-triazol-1-yl)phenyl)ethanone (entry 20, Table 2): yellow compound; mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.99 (d, 1H, *J* = 2.5 Hz), 7.86 (dd, 1H, *J* = 8.60, 2.30 Hz), 7.66 (d, 1H, *J* = 8.0 Hz), 7.48 (t, 1H, *J* = 8.0 Hz), 7.25 (d, 1H, *J* = 7.45 Hz), 6.78 (d, 1H, *J* = 7.45 Hz), 4.14 (s, 3H), 2.73 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$): 199.1 (CO), 152.1 (C), 140.4 (C), 138.5 (C), 136.0 (C), 132.3 (CH), 131.2 (C), 130.2 (CH), 125.8 (CH), 123.2 (CH), 104.3 (CH), 102.1 (CH), 56.5 (OCH_3), 30.8 (CH_3).