Phenylboronic Acid/CuSO$_4$ as an Efficient Catalyst for the Synthesis of 1,4-Disubstituted-1,2,3-Triazoles from Terminal Acetylenes and Alkyl Azides

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Abstract. The synthesis of 1,4-disubstituted-1,2,3-triazoles from alkyl azides and terminal alkynes at room temperature and under microwave heating was attained using Cu(I), generated *in-situ* from copper(II) sulfate and phenylboronic acid, as catalyst. Twelve new triazoles were obtained in moderate to good yields (53-98%), and the products were obtained by crystallization from the mixture reaction without further purification.
Key words: triazoles, phenylboronic acid, CuSO$_4$, Microwave irradiation.

Resumen. Se describe la síntesis de 1,2,3-triazoles-1,4-disustituidos a partir de alquilazidas y alquinos terminales a temperatura ambiente y calentamiento por microondas empleando Cu(I) generado *in-situ* a partir de sulfato de cobre(II) y ácido fenilborónico, como catalizador. Bajo estas condiciones se prepararon doce triazoles nuevos en rendimientos de moderados a buenos (53-98%), que cristalizan de la mezcla de reacción sin purificación adicional.
Palabras clave: triazoles, ácido fenilborónico, CuSO$_4$, irradiación de microondas.

Introduction

The Cu(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) has become the preferred synthetic route to 1,4-disubstituted 1,2,3-triazoles, some of which have interesting biological properties and/or applications in drug design [1-3]. Because of the thermodynamic instability of Cu(I), Cu(II) is usually reduced *in situ*, by the addition of reducing agents such as sodium ascorbate [4], glucose in the presence of Fehling's reagent [5], or NaN$_3$ [6], and NaCN [7]. In general, longer reaction times are required when the Cu(II)/ascorbate process is used, therefore we believe there is still potential for further development in this reaction.

The readily available phenylboronic acid [8] is stable to heat, air, and moisture, making it an attractive and valuable precursor of phenol by its oxidation with CuSO$_4$ [9-10]. Thus, stirring phenylboronic acid in a solvent, followed by addition of CuSO$_4$ produces Cu(I). We employed this reaction to develop an efficient, synthesis of 1,4-disubstituted-1,2,3-triazoles from alkyl acetylenes that can be effected at room temperature, or more rapidly upon microwave irradiation.

The assistance of aryl boronic acid in the synthesis of triazoles by this route using Cu-catalysts in H$_2$O and other solvents has been reported earlier [6, 11]. However, Cu(I) generated in this manner has not been used to catalyze the formation of 1,4-disubstituted-1,2,3-triazoles from alkyl azides and mono-substituted acetylenes therefore we describe herein the application of this methodology to the synthesis of new six new triazole derivatives.

Results and discussion

Initially, studies were carried out using phenyl acetylene and benzyl azide in the presence of varying amounts of CuSO$_4$ and PhB(OH)$_2$ at room temperature. Therefore, a 1:1 mixture of H$_2$O/^{i}PrOH was chosen as the solvent, and several experiments were carried out (see table 1). The data (Table 1) clearly show that the best conditions for the formation of **3a** involved the use of 10 mol % CuSO$_4$ and 20 mol % PhB(OH)$_2$ (Table 1, entry 5). We also evaluated the solvent effect, although previous studies from our laboratory have documented the advantage of a H$_2$O/^{i}PrOH (1:1) solvent mixture [7,12]. In addition, the influence of different bases was investigated finding that the highest yields were obtained using a molar excess of Et$_3$N. Under his conditions, the cycloaddition reaction is favored by minimizing the formation of by products, also it prevents degradation of Cu(I) by oxidation or switching and helps to solubilize the copper in the reaction medium [13].

After optimization of the conditions, the scope of the reaction in regard to alkyne and azide structures was explored by reacting various azides with terminal alkynes in the presence of CuSO$_4$ (10 mol%) and PhB(OH)$_2$ (20 mol%). The results are summarized in Table 3. It is obvious from these data that a wide variety of azides possessing different functional groups are tolerated. The reaction also showed considerable tolerance for substituents in the phenyl alkynes (Table 3). Both electron donating and electron withdrawing substituents in the phenyl alkynes led to the desired products in high yields with little differences in reaction times. In contrast, both the reaction of
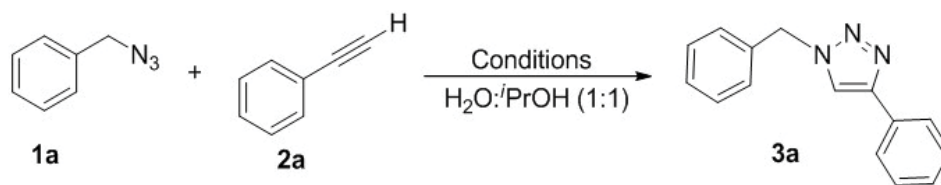
Scheme 1. Search for optimal conditions.
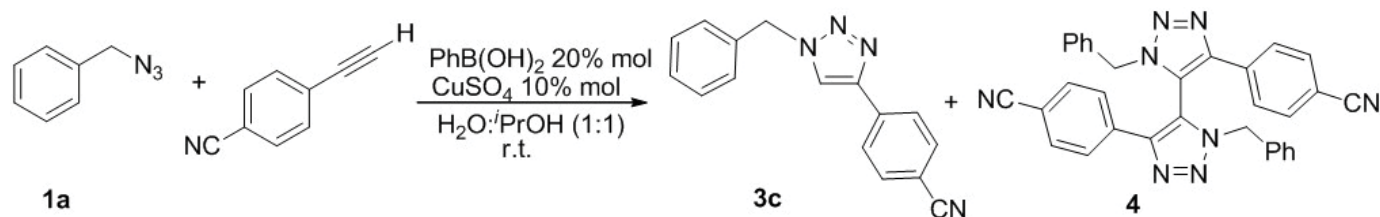
Scheme 2. Synthesis of compound **3c** and bistriazole **4**.

Table 1. Catalyst screening for the synthesis of **3a**.

| Entry	Conditions		Yield (%)[b]
	CuSO$_4$ (mol%)	PhB(OH)$_2$ (mol%)	
1	10	10	NR[c]
2	10	5	14[b]
3	10	7	29[b]
4	10	10	54[b]
5	10	20	85[b]
6	10	-----	NR

[a] All reactions were carried out using 0.75 mmol of benzyl azide, 0.75 mmol of phenylacetylene and 1 mL of Et$_3$N in 2 mL of ^{i}PrOH/H$_2$O (1:1) at room temperature during 5 h.

[b] isolated yield after purification via flash chromatography.

[c] without Et$_3$N

phenylacetylene and 1-chloro-4-ethynylbenzene with 5-azido-2-(2-methoxyphenyl)benzoxazole gave modest yields of the expected products **3g** and **3h** respectively, in spite of increased reactions times (Table 3, entries 7-8). However, when reactions with benzyl azide and 4-ethynylbenzonitrile were carried out using catalytic CuSO$_4$ in the presence of phenylboronic acid, a mixture of triazole and bistriazole was obtained in agreement with the observations of Burgess [14] and Cuevas-Yañez [15] (Scheme 2). We rationalized the formation of this by-product on the basis of the reducing power of PhB(OH)$_2$ at room temperature. The structures of most of the 1,2,3-triazoles was supported by the usual spectroscopic data. In contrast, the structures of triazole **3h** and bistriazole **4** were unequivocally established by X-ray crystallography (Fig. 1) [16].

Microwave irradiation has revolutionized modern organic synthesis due the energy saving, shortened reaction times, and the formation of fewer side products [17]. Accordingly, the
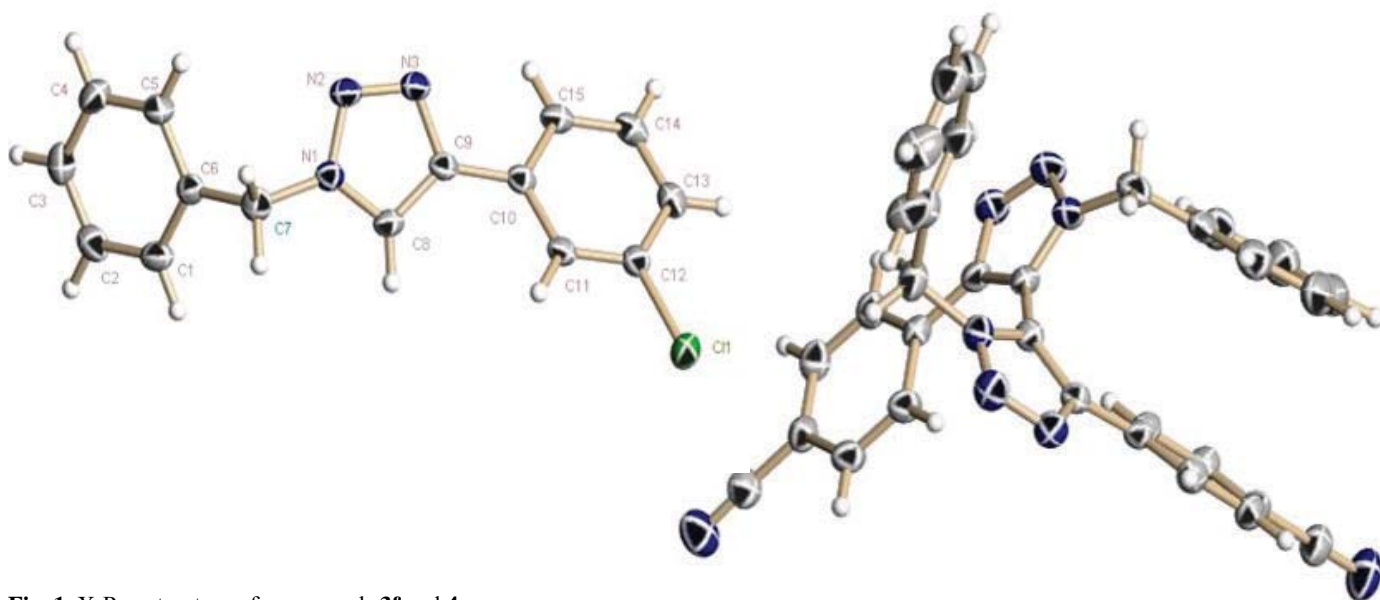
Fig. 1. X-Ray structure of compounds **3f** and **4**.

methodology already described above was explored under microwave irradiation. Thus, the same reactions between azides and terminal alkynes using Cu(I) generated with $CuSO_4$ and phenylboronic acid were run in water/^{i}PrOH (1:1) using microwave irradiation at 100 W and 125 ºC (Table 2). The data clearly show that the best conditions for the formation of **3a** involved the use of $CuSO_4$ (10 mol%) and $PhB(OH)_2$ (20 mol%) at 100 W and 125 ºC for 10 min (Table 2, entry 3). Increasing the reaction time to 30 min led to a decrease in yield. With these optimized reaction conditions in hand, the scope and generality of this protocol was examined employing benzyl azide and various aromatic azides with terminal alkynes (Table 3). When we used benzyl azide with different phenylalkynes the reaction took only 10 min (Table 3, entries 1-6). However, the reaction of phenylacetylene, 1-chloro-4-ethynylbenzene and 4-ethynylanisole with 5-azido-2-(2-methoxyphenyl)benzoxazole required 15 min to give good product yields (Table 3, entries 7-9). In contrast to the room temperature results described above, no diyne or bis-triazole formation was observed under these conditions.

The role of phenylboronic acid is to reduce copper(II) sulfate to Cu(I), which is responsible for catalyzing the reaction, obtaining only the 1,4-disubstituted-1,2,3-triazoles in excellent yields. A possible mechanism for the catalytic $CuSO_4$/$PhB(OH)_2$ reaction is depicted in Scheme 3 [18].

The structure of most 1,2,3-triazoles was supported by the usual spectroscopic data and by X-ray crystallography.

Conclusions

In summary, a very efficient and straightforward procedure for the regioselective synthesis of alkyl and aryl-1,2,3-triazoles has been developed using commercially available $CuSO_4$ (10 mol%) and $PhB(OH)_2$ (20 mol%), at room temperature or at 125 ºC by microwave irradiation at 100 W. Microwave irradiation dramatically decreases reaction time from hours to minutes with excellent yields. 1,2,3-Triazoles thus produced often crystallize from the reaction mixture and do not require any further purification.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Thin

Table 2. Catalyst screening for the synthesis of **3a** in MW irradiation.[a]

Entry	Conditions		Time (min.)	Yield (%)[b]
	$CuSO_4$ (mol%)	$PhB(OH)_2$ (mol%)		
1	--	--	10	NR
2	5	10	10	89
3	10	20	10	97
4	10	--	10	53
5	--	20	10	NR
6	10	20	30	96

[a] All reactions were carried out using 0.75 mmol of benzyl azide, 0.75 mmol of phenylacetylene and 1 mL of Et_3N in 2 mL of ^{i}PrOH:H_2O (1:1) at 100W and 125ºC.
[b] isolated yields purified by crystallization.
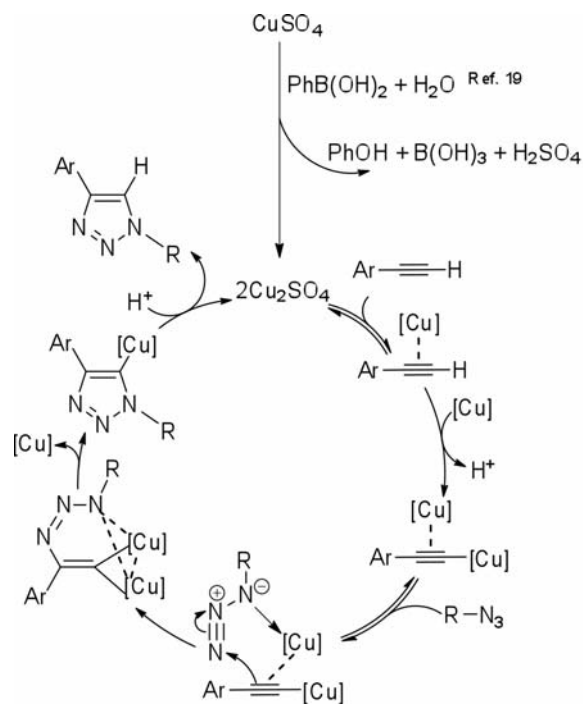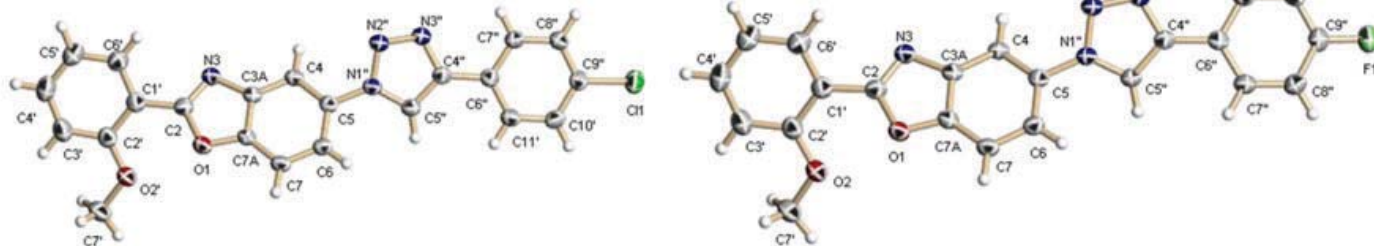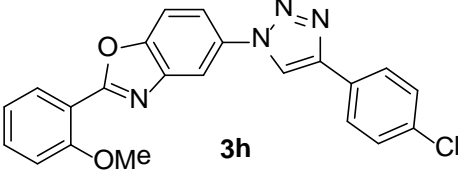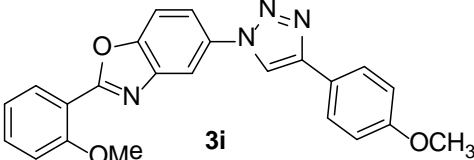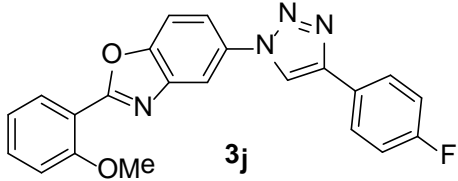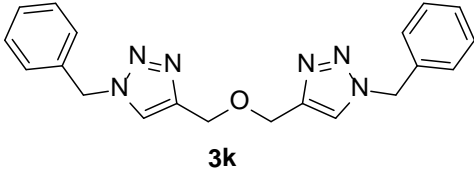

Scheme 3. Postulated Mechanism.
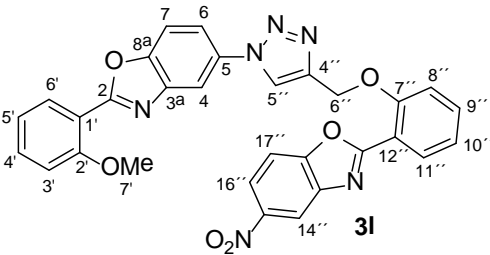
Fig. 2. X-Ray structure of compounds **3h** and **3j**.

Table 3: Synthesis of 1,4-disubstituted-1,2,3-triazoles from alkyl or aryl azides and terminal alkynes at room temperature or using MW.

Entry	Product	Yield (%)[c]		Time (min.)		m.p. (°C)
		MW[a]	r.t.[b]	MW	r.t.	[Ref.]
1	**3a**	97	85	10	300	129-131 [7]
2	**3b**	96	93	10	300	181-182 [7]
3	**3c**	89	78	10	300	144-146 [7]
4	**3d**	93	88	10	280	144-146 [7]
5	**3e**	97	97	10	240	117-119 [7]
6	**3f**	93	75	10	300	102-104 [7]

Entry	Product	Yield (%)[c]		Time (min.)		m.p. (°C) [Ref.]
		MW[a]	r.t.[b]	MW	r.t.	
8	**3h**	91	53	15	24h	211-213 [7]
9	**3i**	93	85	15	24h	164-166 [7]
10	**3j**	73	67	15	24h	222-223 [7]
11	**3k**	98	95	10	300	127-128 [12]
12	**3l**	98	-----	15	-----	251-253

[a] All reactions were carried out using 0.75 mmol of benzyl azide, 0.75 mmol of phenylacetylene and 1 mL of Et_3N in 2 mL of ^{i}Pr-OH/H_2O (1:1) at 100W and 125ºC.

[b] All reactions were carried out using 0.75 mmol of benzyl azide, 0.75 mmol of phenylacetylene and 1 mL of Et_3N in 2 mL of ^{i}Pr-OH/H_2O (1:1) at room temperature.

[c] isolated yields.

layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F254 and visualized by UV (254 nm). Flash column chromatography was performed using Merck silica gel (230-240 mesh). Melting points were measured in open capillary tubes on a Büchi Melting Point B-540 apparatus and have not been corrected. ^1H and ^{13}C NMR spectra were recorded on Varian VNMRS 400 (400 and 100 MHz) spectrometer. Chemical shifts (δ) are indicated in ppm downfield from inter- nal TMS used as a reference; coupling constants (J) are given in Hz. IR spectra were measured on a Perkin Elmer GX FT-IR. High resolution mass spectra were obtained with an Agilent G1969A spectrometer. All microwave irradiation experiments were carried out in a CEM-Discover mono-mode microwave apparatus, operating at a frequency of 2.45 GHz with continu- ous irradiation power from 0 to 100 W utilizing the standard absorbance level of 300 W maximum power.

General procedure for the preparation of 1,2,3-triazoles at room temperature

In a 50 mL round-bottomed flask containing a magnetic stirring bar was placed 1 equiv. of azide in 2 mL of a mixture of 1 mL of H_2O and 1 mL of isopropanol as solvent, followed by the addition of 1 equiv. of alkyne, 0.10 equiv. of $CuSO_4$, 0.20 equiv. of phenylboronic acid, and 1.0 mL of Et_3N. The resulting solution was stirred at room temperature for 5-24 h, followed by extraction with EtOAc (3 x 25 mL). The collected organic layers were dried with $MgSO_4$ and the solvent was removed under vacuum to give the corresponding triazole. After removal of ethyl acetate, the crude residue was purified by column chromatography (EtOAc/hexane) to afford 1,2,3-triazoles.

General procedure for the preparation of 1,2,3-triazoles by microwave irradiation

In a MW tube equipped with a magnetic stirrer was placed 1 equiv. of azide in 2 mL of a mixture of 1 mL of H_2O and 1 mL of isopropanol as solvent, followed by the addition of 1 equiv. of alkyne, $CuSO_4$ (10 mol%), phenylboronic acid (20 mol%), and 1.0 mL of Et_3N. This tube was sealed, and the content was subjected to focused microwave irradiation at 100 W for 10 or 15 min at 125 °C. Then the reaction mixture was diluted with ethyl acetate and washed with a saturated solution of NH_4Cl, the organic phase was collected, dried with $MgSO_4$, filtered and the solvent was vacuum removed. The crude product was purified by crystallization to afford 1,2,3-triazoles.

Compound **3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j** and **3k** are known, and their spectra are consistent with the literature data (Table 3).

2-(2-methoxyphenyl)-5-(4-((2-(5-nitrobenzoxazol-2-yl) phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzoxazole (3l). White solid: mp 251-253 °C; yield: 0.11 g (98%). IR (KBr); v_{max} 2925, 1603, 1532, 1494, 1263, 1352, 1021, 746 cm⁻¹; ¹H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H, H-5"), 8.65 (d, 1H, J = 2.4 Hz, H-14"), 8.30 (m, 2H, H-4, H-6), 8.07 (m, 2H, H-16", H-17"), 7.97 (m, 2H, H-7, H-10"), 7.62 (m, 3H, H-6', H-8", H-11"), 7.29 (d, 1H, J = 8.4 Hz, H-3'), 7.21 (t, 1H, J = 7.5 Hz, H-5'), 7.15 (td, 1H, J = 8.0 Hz, J = 2.5 Hz, H-9"), 5.73 (s, 2H, H-6"), 3.93 (s, 3H, H-7'); ¹³C NMR (DMSO-d_6, 100 MHz) δ 163.5 (C-2), 162.7 (C-13"), 157.3 (C-7"), 157.1 (C-2'), 156.1 (C-17a"), 150.4 (C-8a), 150.0 (C-13a"), 144.4 (C-4"), 142.4 (C-3a), 141.5 (C-6'), 137.7 (C-11"), 133.6 (C-4'), 132.4 (C-9"), 129.7 (C-5), 123.1 (C-6), 121.7 (C-16"), 121.5 (C-10"), 121.0 (C-5"), 120.3 (C-15"), 119.9 (C-4), 119.1 (C-3'), 117.3 (C-8"), 116.6 (C-14"), 115.2 (C-17"), 111.5 (C-7), 110.6 (C-12"), 109.2 (C-1'), 72.6 (C-6"), 56.1 (C-7'); HRMS (ESI) calcd for $C_{30}H_{20}N_6O_6$ (M + H)⁺ 561.1444, found 561.1521.

Acknowledgements

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16. X-ray crystallographic data (excluding structure factors) for the structures in this paper has been deposited with the Cambridge

Crystallographic Data Centre as a Supplementary Publication Numbers, CCDC 1007167 No. for **3f**, CCDC 1007170 No. for **4**, CCDC 1007168 No. for **3h**, and CCDC 1007169 No for **3j**. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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