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Effect of the Ligand in the Synthesis of 1-Sulfonyl-1,2,3-triazoles Through Copper-Catalyzed Alkyne-Azide Cycloaddition

Rocío A. Valencia, David Corona and Erick Cuevas-Yañez*

Centro Conjunto de Investigación en Química Sustentable UAEM-UNAM. Carretera Toluca-Atlacomulco Km 14.5, Toluca, Estado de México, 50200, Mexico. Universidad Autónoma del Estado de México. ecuevasy@uaemex.mx.

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Abstract. Copper-catalyzed alkyne-azide cycloaddition of *p*-toluenesulfonylazide and phenylacetylene was investigated, using catalytic amounts of copper (I) chloride and diverse additives which were tested as copper ligands. The best results were obtained using a catalytic amount of diphenyl disulfide.
Key words. Triazol, sulfonylazide, ligand, copper.

Resumen. La cicloadición alquino-azida catalizada por cobre entre la *p*-toluensulfonilazida y el fenilacetileno fue investigada, usando cantidades catalíticas de cloruro de cobre (I) y diversos aditivos que fueron utilizados como ligantes para el cobre. Los mejores resultados se obtuvieron utilizando una cantidad catalítica de disulfuro de difenilo.
Palabras clave: Triazol, sulfonilazida, ligante, cobre.

Introduction

The chemistry of 1,2,3-triazoles has grown exponentially in the last years as a consequence of the re-discovery of the old Huisgen [3+2] cycladdition under catalytic conditions [1]. Currently, many groups have thoroughly studied this process, finding catalysts as well as searching mechanistic aspects [2]. In a beginning, copper-catalyzed alkyne-azide cycloaddition (CuAAC) was established as a process that was unaffected by the electronic nature of substituent on both alkyne and azide precursors [3]. However, recent reports by Fokin and coworkers showed that electron-withdrawing groups on azide component dramatically change the reaction pathway. In the case of sulfonylazides, the major products obtained from these reactions were *N*-acylsulfonylamides instead of the corresponding 1-sulfonyl-1,2,3-triazoles [4].

In this regard, 1-sulfonyl-1,2,3-triazoles have attracted the interest of research groups due to these compounds represent alternative and safe precursors of matallocarbenes intermediates, which have been used in cyclopropanations [5], insertions to nitriles [6], and cycloadditions to alkynes [7, 8].

One of the challenges in the synthesis of 1-sulfonyl-1,2,3-triazoles from CuAAC is the design of a catalytic system for the selective formation of sulfonyltriazol moiety. Investigations have demonstrated that ligands coordinated to copper (I) ion play an important role in conjunction with the temperature control [9]. For example, Raushel and Fokin found that 2,6-lutidine and thiophene-2-carboxylate can modulate the selective synthesis of sulfonyltriazoles [10]. In addition, the group of Fu reported that thioanisole is an effective copper ligand for the synthesis of sulfonyltriazoles using water as solvent [11].

Motivated by these last reports, we decided to investigate the influence of diverse ligands in the CuAAC of *p*-toluenesulfonyl azide with the aim of synthesize sulfonyltriazoles. Herein is described a summary of our successful endeavors in this area.

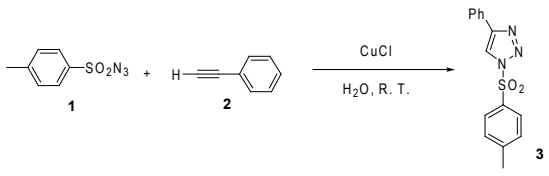
Results and Discussion

In a model reaction, phenylacetylene (**1**) reacted with *p*-toluenesulfonyl azide (**2**) in the presence of catalytic amounts of copper (I) chloride at room temperature, without any other additive, using water as solvent. After a week, the 1-sulfonyl-1,2,3-triazole **3** was obtained in 96 %yield (Scheme 1).

In order to reduce the reaction time, diverse additives were selected and tested as potential copper ligands in this process, these compounds contain nitrogen or sulfur atoms and some are derivatives of thioanisole [11], and have been used as ligands for other metals [12]. The results are presented in table 1 and they show that after 24 h, moderate yields of the triazole **3** are obtained. A noteworthy feature is that sulfur ligands afforded higher yields in less time. For example, the use of hydroxymethyl thioanisol (Table 1, entry 8) gave the triazole **3** in 77% yield. In addition, using diphenyl disulfide (table 1, entry 9) the yield of compound 3 is increased to 93%.

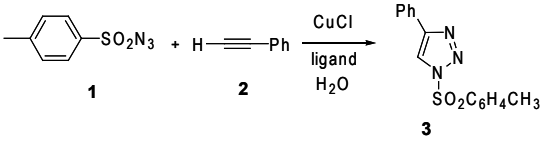
This last result motivated us to explore the reaction scope. Thus, sulfonyl triazoles in Table 2 (entries 2 and 3) were synthesized in high yield from the corresponding alkynes derivatives of prostaglandin analogs [13].

On the other hand, we observed that certain alkynes gave a mixture of sulfonyl triazoles and *N*-acyl-sulfonylamides (scheme 2 and table 3). This behavior has been previously described by Wang [11], Yoo [9], and Fokin [10], and we

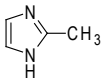
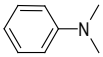
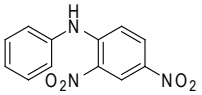
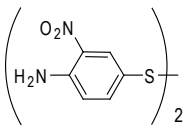
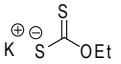
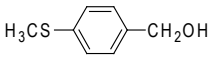


Scheme 1. Synthesis of triazole **3** from phenylacetylene and sulfonylazide **1**.

Table 1. Effect of the ligand in the synthesis of triazole **3**.



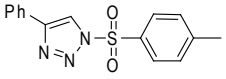
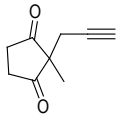
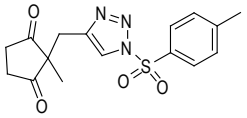
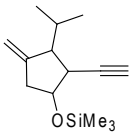
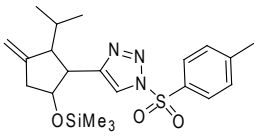
1 **2** **3**

Entry	Ligand	Time (h)	Yield (%)
1		24	41
2		24	31
3		24	43
4		24	31
5		24	36
6		24	23
7		24	40
8		16	77
9	$(PhS)_2$	16	93
10	none	168	96

found that major products were sulfonyl triazoles in all cases. According to these authors [11,9,10] *N*-acyl-sulfonylamides are derived from the corresponding copper triazolide fragmentation with subsequent loss of nitrogen.

Other relevant feature is the use of water as solvent in this process, which creates a heterogeneous system and facilitates the product separation. In conclusion, alkynes and sulfonyl azide are efficiently converted into 1-sulfonyl-1,2,3-triazoles through a simple and mild method. In addition, this procedure is economic and environmentally benign. These elements suggest that this route will enjoy widespread application.

Table 2. Synthesized sulfonyl triazoles.

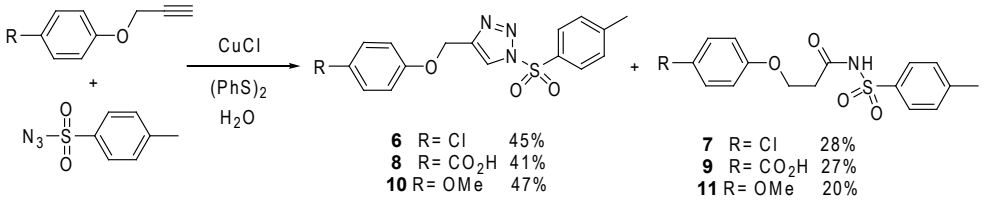
Compound	Alkyne	Triazole	Yield (%)
3			93
4			72
5			62

Experimental

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were distilled before using. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher-Johns melting point apparatus and they are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Varian 500, the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a JEOL JMS-5X 10217 in the EI mode, 70 eV, 200ºC via direct inlet probe. Only the molecular and parent ions (m/z) are reported. IR spectra were recorded on a Nicolet Magna 55-X FT instrument.

Synthesis of 1-sulfonyl-1,2,3-triazoles. *General Procedure*. The corresponding alkyne (1.3 mmol) was added to a suspension of *p*-toluenesulfonyl azide (0.19g, 1mmol), CuCl (0.011g, 0.1 mmol) and $(PhS)_2$ (0.047g, 0.2 mmol) in H_2O (1 mL). The resulting mixture was stirred 16 h at room temperature. The solid was filtered and purified by column chromatography (SiO_2, hexane/AcOEt 8:2).

4-Phenyl-1-(toluene-4-sulfonyl)-1,2,3-triazole (3). 93% yield, mp. 108-109 °C. IR (KBr, cm^{-1}): 1371, 1028, 461. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ**:** 2.44 (s, 3H), 7.39-7.43 (m, 5H), 7.82 (d, 2H, *J* = 8.5 Hz), 8.07 (d, 2H, *J* = 8.5 Hz), 8.32 (s, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ**:** 21.9 (CH_3), 119.1 (CH), 126.2 (2 X CH), 128.0 (CH), 128.8 (2 X CH), 129.2 (2 X CH), 129.4 (C), 130.3 (2 X CH), 133.2 (C), 135.9 (C), 147.5 (C). MS [EI^+] m/z (%): 299 $[M]^+$ (10), 155 $[M\text{-}C_8H_6N_2]^+$ (40), 145 $[M\text{-}C_7H_6SO_2]^+$ (100), 91 $[M\text{-}C_8H_6N_3SO_2]^+$ (70).



6 R= Cl 45%
8 R= CO_2H 41%
10 R= OMe 47%

7 R= Cl 28%
9 R= CO_2H 27%
11 R= OMe 20%

Scheme 2. Formation of triazoles and *N*-sulfonylamides.

2-Methyl-2-[1-(toluene-4-sulfonyl)-1,2,3-triazol-4-yl-methyl]-cyclopentane-1,3-dione (4). 72 % yield, mp. 154-155 °C (MeOH). IR (KBr, cm^{-1}): 1760, 1690, 1371, 1028, 461. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.25 (s, 3H), 2.44 (s, 3H), 2.80-2.86 (m, 4H), 3.12 (s, 2H), 7.37 (d, 2H, *J* = 8.2 Hz), 7.83 (s, 1H), 7.93 (d, 2H, *J* = 8.2 Hz). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ**:** 21.8 (CH_3), 22.0 (CH_3), 29.4 (CH_2), 34.9 (2 X CH_2), 53.0 (C), 121.0 (CH), 128.9 (2 X CH), 130.6 (2 X CH), 132.9 (C), 142.8 (C), 147.6 (C), 216.2 (2 X C). MS m/z (%): 347 $[M]^+$ (20), 155 $[C_7H_7SO_2]^+$ (65), 91 $[C_7H_7]^+$ (100).

4-(2-Isopropyl-3-methylene-5-trimethylsilanyloxy-cyclopentyl)-1-(toluene-4-sulfonyl)-1,2,3-triazole (5). 62 % yield, mp. 57-58 °C (MeOH). IR (KBr, cm^{-1}): 3066, 1371, 1028, 737, 461. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 0.65 (d, 6H, $2CH_3$), 0.86 (s, 9H, $3CH_3$), 1.33 (m, 1H), 2.32 (m, 1H), 2.44 (s, 3H), 2.63 (m, 1H), 3.21 (m,1H), 4.05 (m, 1H), 4.90 (d, 1H, *J* = 3Hz), 5.0 (d, 1H, *J* = 3Hz), 7.20 (d, 2H, *J* = 8.5 Hz), 7.36 (d, 2H, *J* = 8.5 Hz), 8.00 (s, 1H). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 0.34 (3 X CH_3), 23.9 (CH_3), 27.1 (2 X CH_3), 30.9 (CH), 36.5 (CH_2), 49.3 (CH), 51.9 (CH), 57.8 (CH), 113.5 (CH_2), 132.8 (2 X CH), 133.8 (CH), 133.9 (2 X CH), 135.8 (C), 140.8 (C), 151.7 (C), 154.2 (C). MS m/z (%): 433 $[M]^+$ (20), 155 $[C_7H_7SO_2]^+$ (40), 91 $[C_7H_7]^+$ (100).

4-(4-Chloro-phenoxymethyl)-1-(toluene-4-sulfonyl)-1,2,3-triazole (6) 45 % yield, mp. 107-108 °C (MeOH). IR (KBr, cm^{-1}): 1571, 1329, 1128, 737. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.49 (s, 3H), 5.85 (s, 2H), 7.10-7.22 (m, 4H), 8.55 (d, 2H, *J* = 8.2 Hz), 8.90 (d, 2 H, *J* =8.2 Hz), 8.97 (s, 1H). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 20.4 (CH_3), 62.9 (CH_2), 115.6 (CH), 117.1 (2 X CH), 124.0 (C), 127.9 (2 X CH), 129.9 (2 X CH), 130.3 (2 X CH), 136.8(C) , 138.9 (C), 145.0 (C), 157.8 (C). MS m/z (%) 363 $[M]^+$ (10), 183 $[M\text{-}C_7H_8NSO_2]^+$ (45), 91 $[C_7H_7]^+$ (100).

The column chromatography (SiO_2, hexane/AcOEt 8:2) of this reaction also afforded the *N*-[3-(4-Chloro-phenoxy)-propionyl]-4-methyl-benzenesulfonamide **(7)** in 28 % yield, mp. 117-118 °C. (MeOH). IR (KBr, cm^{-1}): 3066, 1571, 1028, 737. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.49 (s, 3H), 4.00 (t, 2H), 4.25 (t, 2H), 7.10-7.22 (m, 4H), 8.55 (d, 2H, *J* = 8.3 Hz), 8.90 (d, 2H, *J* = 8.2 Hz). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 21.3 (CH_3), 35.2 (CH_2), 55.3 (CH_2), 117.1 (2 x CH), 125.1 (C), 125.9 (2 x CH), 128.6 (2 x CH), 129.9 (2 x CH), 136.8 (C), 144.8 (C), 157.1 (C), 169.5 (C). MS m/z (%): 353 $[M]^+$ (15), 183 $[M\text{-}C_7H_8NSO_2]^+$ (45), 91 $[C_7H_7]^+$ (100).

4-[1-(Toluene-4-sulfonyl)-1,2,3-triazol-4-ylmethoxy]-benzoic acid (8). 41 % yield, mp. 83 °C (MeOH). IR (KBr, cm^{-1}): 3400, 3066, 1725, 1371, 1132, 737. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.48 (s, 3H), 6.22 (s, 2H), 6.66 (d, 2H, *J* = 8Hz), 7.00 (d, 2H, *J* = 8Hz), 7.36 (d, 2H, *J* = 8Hz), 7.80 (d, 2H, *J* = 8Hz), 8.2 (s, 1H), 10.9 (s, 1H). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 21.6 (CH_3), 79.9 (CH_2), 114.8 (CH), 125.3 (C), 128.1 (2 x CH), 129.9 (2 x CH), 130.0 (2 x CH), 130.3 (2 x CH), 137.0 (C), 144.7 (C), 156.6 (C), 159.2 (C), 169.8 (C). MS m/z (%): 373 $[M]^+$ (15), 91 $[C_7H_7]^+$ (100).

The column chromatography (SiO_2, hexane/AcOEt 8:2) of this reaction also afforded the 4-[3-Oxo-3-(toluene-4-sulfonyl-amino)-propoxy]-benzoic acid **(9)** in 21% yield, mp. 56-57 °C (MeOH). IR (KBr, cm^{-1}): 3400, 3066, 1725, 1660, 1371, 1028, 737. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.48 (s, 3H), 2.68 (t, 2H), 4.03 (t, 2H), 6.67 (d, 2H, *J* = 8Hz), 7.01 (d, 2H, *J* = 8Hz), 7.38 (d, 2H, *J* = 8Hz), 7.77 (d, 2H, *J* = 8Hz), 8.0 (s, 1H), 10.9 (s, 1H). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 21.6 (CH_3), 35.9 (CH_2), 63.3 (CH_2), 114.8 (2 x CH), 123.1 (C), 127.9 (2 x CH), 128.1 (2 x CH), 129.9 (2 x CH), 130.2 (C), 136.9 (C), 144.6 (C), 156.4 (C), 169.7 (C). MS m/z (%): 363 $[M]^+$ (15), 155 $[C_7H_7SO_2]^+$ (60), 91 $[C_7H_7]^+$ (100).

4-(4-Methoxy-phenoxymethyl)-1-(toluene-4-sulfonyl)-1,2,3-triazole (10). 62 % yield, mp. 95 °C (MeOH). IR (KBr, cm^{-1}): 1565, 1329, 1128, 737. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.27 (s, 3H), 3.89 (s, 3H), 5.71 (s, 2H), 7.08-7.12 (m, 4H), 7.46 (d, 2H, *J* = 8.2 Hz), 7.86 (d, 2 H, *J* = 8.2 Hz), 7.98 (s, 1H). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 20.9 (CH_3), 54.9 (CH_3), 78.7 (CH_2), 114.3 (2 x CH), 123.4 (CH), 127.6 (2 x CH), 129.0 (2 x CH), 129.6 (2 x CH), 131.4 (C), 138.0 (C), 141.5 (C), 145.0 (C), 161.1 . (C) MS m/z (%): 359 $[M]^+$ (10), 91 $[C_7H_7]^+$ (100).

The column chromatography (SiO_2, hexane/AcOEt 8:2) of this reaction also afforded the *N*-[3-(4-Methoxy-phenoxy)-propionyl]-4-methyl-benzenesulfonamide **(11)** in 20 % yield, mp. 120 °C (MeOH). IR (KBr, cm^{-1}): 3260, 1570, 1329, 1128, 737. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ: 2.49 (s, 3H), 3.89 (s, 3H), 4.00 (t, 2H), 4.25 (t, 2H), 7.08-7.13 (m, 4H), 7.46 (d, 2H, *J* = 8 Hz), 7.86 (d, 2 H, *J* = 8 Hz). ^{13}C-NMR (DMSO-d_6, 125 MHz) δ: 21.2 (CH_3), 35.4 (CH_2), 55.7 (CH_3), 61.1 (CH_2), 114.7 (2 x CH), 125.6 (2 x CH), 128.2 (2 x CH), 129.6 (2 x CH), 138.1 (C), 141.6 (C), 145.4 (C), 167.1 (C). MS m/z (%): 349 $[M]^+$ (20), 170 $[M\text{-}C_7H_8NSO_2]^+$ (40), 91 $[C_7H_7]^+$ (100).

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