Alkyne-Azide Cycloaddition Catalyzed by Fe-Cu Nanoparticles

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Received July 01, 2011: Revised November 07, 2011: Accepted December 15, 2011

Abstract: 1,2,3-triazoles were synthesized using several alkynes and azides as starting materials in the presence of catalytic amounts of Cu-Fe nanoparticles. The process represents many advantages because it does not require additional bases or reductants, and this is carried out under ambient pressure and temperature with good yields.

Keywords: 1,2,3-triazoles, alkynes, azides, nanoparticles.

INDTRODUCTION

Copper-catalyzed Alkyne-azide cycloaddition (CuAAC) has become one of the most important potent ligation methods developed in the 21st century [1, 2]. In addition, this reaction represents the main route to 1,2,3-triazoles which have demonstrated interesting biological activities [3]. One of the advantages of this reaction is the combination of mild conditions with high yields and regioselectivities joined to high efficiency in terms of atom economy, which makes CuAAC the most used “click” reaction.

Currently, there are two important protocols to perform these reactions, developed initially by the Meldal [4] and Sharpless-Fokin [5] groups. Although both procedures are widespread in application, research and developing in new copper catalysts is quite desirable, where the use of reducing agents or bases could be avoided.

On the other hand, the field of nanoparticles offers a new group of catalysts with many applications in chemical reactions [6]. In this regard, copper nanoparticles have been successfully used in CuAAC to synthesize 1,2,3-triazoles [7-9].

In connection with other studies, the group of Sanchez-Mendieta has developed a novel class of iron-copper nanoparticles which was initially used in waste water treatment [10]. In order to explore the catalytic ability of these compounds; we attempted to extend the use of the Fe-Cu nanoparticles to copper-catalyzed alkyne-azide cycloaddition. Herein is described a summary of our recent endeavors in this area.

In a model study, benzyl azide **1**, which in turn was prepared from benzyl bromide and sodium azide, was reacted with phenylacetylene **2** at room temperature using catalytic amounts of Cu-Fe nanoparticles in different solvents to afford 1-benzyl-4-phenyl-1,2,3-triazole **3** (Scheme **1**). The Cu-Fe nanoparticles catalysts were obtained from sodium borohydride reduction of $FeSO_4.7H_2O$ and $CuSO_4.5H_2O$ aqueous mixture [10, 11]. This last reduction provides a convenient method to prepare Fe-Cu nanoparticles with a grain size larger than 10 nm (average size: 10.47 nm, Fig. **2**), which are suitable for catalysis. Figs. (**1** and **2**) show HRTEM images of quasi-spherical nanoparticles, as well as the unimodal particle size distribution for the synthesized nanoparticles, in agreement with other studies [11].

Thus, Fe-Cu nanoparticles were tested as catalysts in CuAAC reaction in several solvents. The reaction yields are presented in Table **1**, and based on these results; methanol was selected as work solvent.

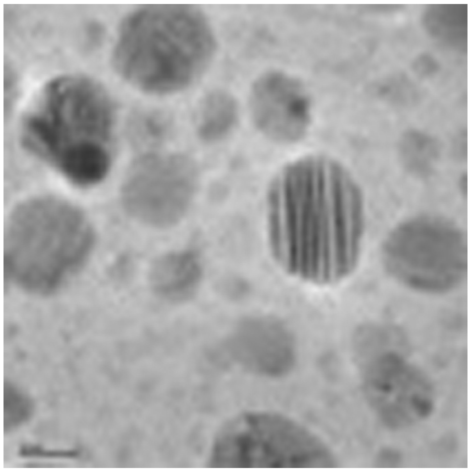

Fig. (1). TEM Micrograph of Fe-Cu nanoparticles, scale bar: 10 nm.

On the other hand, the use of base (sodium carbonate) [12] temperature and catalyst ratio in CuAAC was studied, and these results are presented in Table **2**. Optimal conditions were obtained when the reaction is carried out at room temperature using 10 mg/mmol of catalyst and sodium carbonate was not used as additive. Other catalytic systems were tested, such as $CuSO_4$-sodium ascorbate in *t*BuOH-water [5], CuI-DIPEA [4] and CuI-Et_3N [13] (entries 7-9, Table **2**). The results suggest that Cu-Fe nanoparticles are effective catalysts in these kind of processes.

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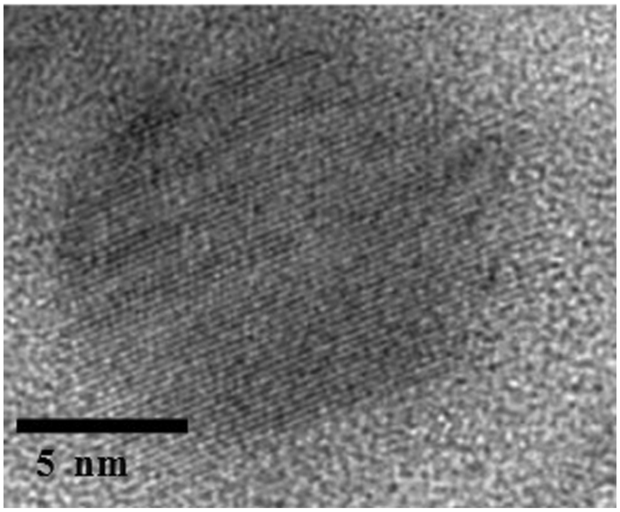
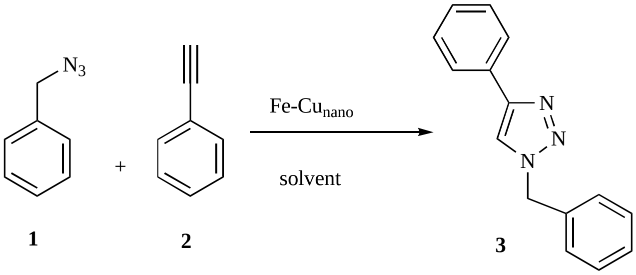


Fig. (2). TEM Micrograph of Fe-Cu nanoparticles, scale bar: 5nm.



Scheme 1. Reaction between benzyl azide and phenylacetylene using Fe-Cu nanoparticles.

Table 1. Solvent Effect in CuAAC Using Cu-Fe Nanoparticles Catalysts

Solvent	% Yield
methanol	82
Acetone	32
Ethyl acetate	42
Tetrahydrofuran	18
water	15
Acetonitrile	10
dichloromethane	4

In order to explore the reaction scope, several alkynes and azides were reacted under similar conditions (see Table **3**). In general, the results showed that 1,2,3-triazoles were the only products, and starting materials were recovered after 24 h when yields were moderated. The use of Cu-Fe nanoparticles catalysts represents many advantages in this process, because bases or reducing agents were not required and the reactions are performed in mild conditions (room pressure and temperature).

The Fe-Cu nanoparticles obtained in this work exhibit a paramagnetic behavior (average magnetic field: 40.57 T) which is unique in this kind of materials [11]. Some nanoparticles with similar properties have been used by other groups to design new catalytic systems [14-15], and in our case, we decide to investigate the feasibility to use these nanoparticles as recoverable heterogeneous catalysts in the synthesis of triazole **3**. The recycling experiments were carried out by applying an external magnet to the reaction flask. A separation of Fe-Cu nanoparticles was achieved and the supernatant containing the product can be decanted. The catalyst was re-dispersed in methanol and the magnetic decantation was repeated again. These nano-materials could be reused for the next cycle without further activation. The results (Table **4**) suggest a progressive lost of efficiency in the yield which is consistent with other studies. Thus, Fe-Cu nanoparticles represent a new class of catalysts that can be easily separated for reuse.

In conclusion, the appropriately constituted alkynes and azides are efficiently converted into 1,2,3-triazoles through a simple and mild method, using Cu-Fe nanoparticles as catalysts. In addition, the procedure is economic and environmentally benign. These elements suggest that this route will enjoy widespread application.

EXPERIMENTAL

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. The organic azides were prepared according to the literature [16, 17]. Solvents were distilled before use. 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 Bruker AVANCE 300, 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, 200^{o}C *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. TEM studies were performed on a JEM-100CX transmission electron microscope, operated at accelerating voltage of 200 kV.

The iron-copper nanoparticles were provided by the Advanced Materials Laboratory from Universidad Autónoma del Estado de Mexico and they were prepared using the method described by Sanchez-Mendieta and coworkers [10, 11].

Preparation of Iron-Copper Nanoparticles

According to the method described by Sanchez-Mendieta and coworkers [10, 11], a solution of $FeSO_4.7H_2O$ (2.30 g; 7.5 mmol) in H_2O (750 mL) was added to the solution of $CuSO_4.5H_2O$ (0.69 g; 2.5 mmol) in H_2O (250 mL). The resulting mixture was stirred with mechanical stirring (300 rpm) at room temperature. A solution of 0.5 M NaOH was added dropwise to pH=7. When pH was adjusted, a solution of $NaBH_4$ (0.757 g; 20 mmol) in H_2O (100 mL) was added, a vigorous evolution of hydrogen occurred, and the resulting dark mixture was stirred at room temperature for 15 min. The mixture was filtered, and the precipitate was washed

Table 2. Dependence of Temperature, Catalyst Ratio and Base in CuAAC

Entry	Temperature (°C)	Catalytic System	Catalyst ratio (mg/mmol)	Reaction Time (h)	Base	% Yield
1	R. T.	Cu-Fe nanoparticle	10	12	Na_2CO_3	43
2	60	Cu-Fe nanoparticle	10	12	Na_2CO_3	44
3	60	Cu-Fe nanoparticle	10	12	No base	53
4	R. T.	Cu-Fe nanoparticle	20	3	No base	81
5	R. T.	Cu-Fe nanoparticle	5	48	No base	82
6	R.T.	Cu-Fe nanoparticle	10	12	No base	82
7	R.T.	$CuSO_4$ Na ascorbate	10	12	No base	75
8	R.T.	CuI-DIPEA	10	12	DIPEA	85
9	R.T.	CuI-Et_3N	10	12	Et_3N	80

Table 3. 1,2,3-Triazoles Obtained from Alkyne-Azide Cycloaddition Catalyzed by Cu-Fe Nanoparticles

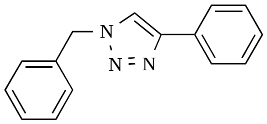
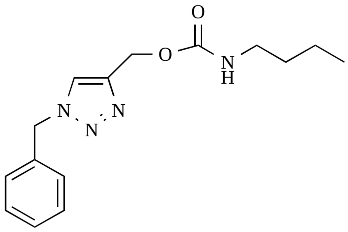
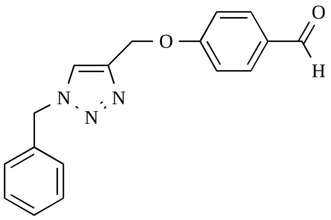
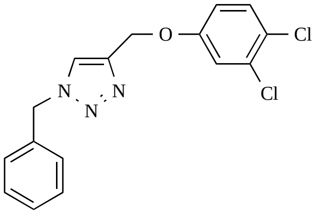
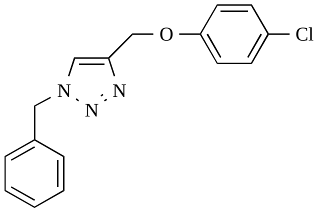
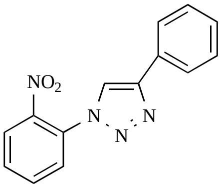
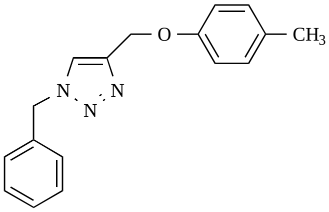
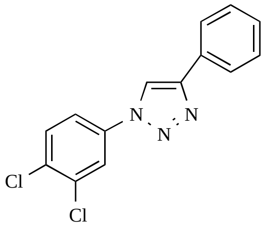
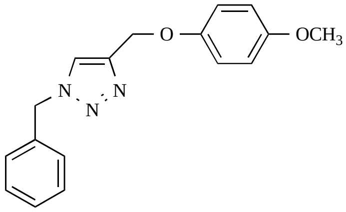
Entry	Triazole	% Yield	Entry	Triazole	% Yield
1		82	6		64
2		69	7		66
3		56	8		34
4		75	9		58
5		79			

Table 4. Recycling of Cu-Fe Nanoparticles in the Synthesis of Triazole 3

Cycle	Conversion (%)	Yield (%)	Purity (%)
1	95	82	98
2	87	73	98
3	75	64	98

successively with water and acetone. The nanoparticles were dried *in vacuo* at room temperature for 24 h.

Synthesis of Benzyl Azide

A solution of benzyl bromide (2.8 g; 16.5 mmol) in DMF (6mL) was added dropwise to a suspension of dry sodium azide (4.9 g, 75.3 mmol) in DMF (6 mL). The resulting mixture was stirred at 30 ° C under a nitrogen atmosphere for 12 h. Water (50mL) was added and the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 X 50mL). The organic layers were joined and dried over Na_2CO_3 and the solvent was removed *in vacuo* to yield a colorless oil (1.8 g, 80%) which was used without purification. IR (KBr, cm^{-1}) 2098, 1453. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.31 (s, 2H), 7.25-7.43 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ. 54.7, 128.2, 128.3, 129.3, 135.5 MS [EI+] m/z (%) 133 [M]+ (44), 91 [$C_6H_5CH_2$]+ (100).

Synthesis of 1,2,3-triazoles

Typical Procedure

To a stirring solution of benzyl azide (0.6g, 4.5 mmol) and Fe-Cu nanoparticles powder (45 mg) in anhydrous methanol (5 mL) at room temperature a solution of alkyne (4.7 mmol) was added dropwise, in methanol (2 mL). The resulting mixture was stirred at room temperature for 12 h and the solvent was removed *in vacuo*. Water (10 mL) and 10% EDTA (4 mL) were added and the mixture was stirred for additional 0.5 h. the product was filtered and purified by crystallization.

1-Benzyl-4-phenyl-1,2,3-triazole (Entry 1)

82% yield m.p. 130°C (MeOH, lit. 130-130.9ºC).[13] IR (KBr, cm-1) 1636, 1459, 1071. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.58 (s, 2H), 7.33-7.41 (m, 8H), 7.68 (s, 1H), 7.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 54.2, 119.5, 125.7, 128.0, 128.1, 128.2, 128.8, 128.8, 129.1, 130.5, 134.7, 148.2. MS [EI+] m/z (%) 235 [M]+ (20), 206 [M -HN_2]+ (50), 116 [M - $C_7H_7N_2$]+ (100), 91 [$C_6H_5CH_2$]+ (85).

4-(1-Benzyl[1,2,3]triazol-4-ylmethoxy)benzaldehyde (Entry 2)

69% yield m.p. 80°C (MeOH) [18]. IR (KBr, cm^{-1}) 1680, 1508, 1252. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.25 (s, 2H), 5.53 (s, 2H), 7.08(d, 2H, J= 8 Hz), 7.36 (m, 3H), 7.58(s, 1H), 7.80 (m, 2H), 7.83 (s, 2H, J= 8 Hz), 9.89(s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 55.9, 62.1, 115.1, 122.9,128.0, 128.9, 129.1, 130.3, 134.3, 143.5, 163.1, 163.14, 190.7. MS [EI+] m/z (%) 293 [M]+ (10), 172 [M - $C_7H_9N_2$]+ (75), 144 [M – $C_7H_7N_2O$]+ (80), 91 [$C_6H_5CH_2$]+ (100).). HRMS (EI+): for $C_{17}H_{15}N_3O_2$ calcd. 293.1164, found 299.1169.

1-Benzyl-4-(4´-chlorophenoxymethyl)-1,2,3-triazole (Entry 3)

56% yield m.p. 85°C (MeOH). IR (KBr, cm^{-1}) 1599, 1491, 1241. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.12 (s, 2H), 5.50 (s, 2H), 6.87 (d, 2H, J=8.2 Hz), 7.19 (d, 2H, J=8.2 Hz), 7.30 (m, 5H), 7.50 (s, 1H). ^{13}C-NMR (CDCl3, 75 MHz) δ. 55.6, 62.3, 115.1, 122.9, 128.0, 128.9, 129.1, 130.3, 134.3, 143.5, 153.1. MS [EI+] m/z (%) 301 [M +2]+ (5) 299 [M]+ (15), 144 [M – $C_6H_4ClN_2O$]+ (50), 91 [$C_6H_5CH_2$]+ (100). HRMS (EI+): for $C_{16}H_{14}ClN_3O$ calcd. 299.0825, found 299.0827.

1-Benzyl-4-(4-tolyloxymethyl)-1,2,3-triazole (Entry 4)

75% yield m.p. 76°C (MeOH).[18] IR (KBr, cm^{-1}) 1572, 1475, 1276. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 5.11(s, 2H), 5.45(s, 2H), 6.84 (d, 2H, J=8.5Hz), 7.03 (d, 2H, J=8.5Hz), 7.22- 7.32(m, 5H), 7.47(s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.51, 55.9, 62.2, 114.7, 122.6, 128.1, 128.7, 129.1, 129.9, 134.6, 144.8, 156.1. MS [EI+] m/z (%) 279 [M]+ (40), 144 [M – $C_7H_7N_2O$]+ (70), 91 [$C_6H_5CH_2$]+ (100). HRMS (EI+): for $C_{17}H_{17}N_3O$ calcd. 279.1372, found 279.1377.

1-Benzyl-4-[(4-methoxyphenoxy)methyl]-1,2,3-triazole (Entry 5)

79% yield m.p. 78°C (MeOH). IR (KBr, cm^{-1}) 1508, 1458, 1228. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H), 5.10 (s, 2H), 5.47 (s, 2H), 6.78 (d, 2H, J=8.5Hz), 6.89 (d, 2H, J=8.5Hz), 7.33(m, 5H), 7.49 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 55.5, 56.5, 62.8, 114.6, 115.9, 116.15, 122.6, 128.0, 128.7, 129.1, 134.5, 144.8, 154.2, 154.5. MS [EI+] m/z (%)MS [EI+] m/z (%) 295 [M]+ (20), 144 [M – $C_7H_7N_2O_2$]+ (35), 123 [M – C9H8N3]+ (100), 91 [$C_6H_5CH_2$]+ (50). HRMS (EI+): for $C_{17}H_{17}N_3O_2$ calcd. 295.1321, found 295.1327.

(1-Benzyl-1,2,3-triazol-4-yl)methyl butylcarbamate (Entry 6)

64% yield m.p. 82°C (MeOH). IR (KBr, cm^{-1}) 1710, 1610, 1536. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H), 2.57 (m, 4H), 3.31 (d, 2H), 5.26 (s, 2H), 5.54 (s, 2H), 7.26 (s, 2H), 7.28-7.37 (m, 5H), 7.56 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.9, 17.5, 31.3, 54.33, 55.6, 62.2, 115.2, 128.1, 128.9, 129.1, 134.28, 143.62, 163.13. MS [EI+] m/z (%) 288 [M]+ (10), 144 [M – $C_5H_{10}N_3O_2$]+ (20), 91 [$C_6H_5CH_2$]+ (100). HRMS (EI+): for $C_{15}H_{20}N_4O_2$ calcd. 288.1586, found 288.1583.

(1-Benzyl-4-[(3,4-dichlorophenoxy)methyl]-1,2,3-triazole (Entry 7)

66% yield m.p. 81°C (MeOH). IR (KBr, cm^{-1}) 1635, 1465, 1250. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.22 (s, 2H), 5.53 (s, 2H), 6.98 (m, 1H), 7.27-7.26 (m, 7H), 7.53 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 55.9, 62.4, 114.5, 115.7, 116.2, 122.6, 128.0, 128.7, 129.1, 129.3, 134.3, 144.5, 154.5. MS [EI+] m/z (%) 377 [M+4]+ (3), 335 [M+2]+ (9), 333 [M]+ (15), 144 [M – $C_6H_4ClN_2O$]+ (30), 91 [$C_6H_5CH_2$]+ (100). HRMS (EI+): for $C_{16}H_{13}Cl_2N_4O$ calcd. 233.0436, found 233.0433.

1-(2-Nitrophenyl)-4-phenyl-1,2,3-triazole (Entry 8)

34% yield m.p. 80°C (MeOH). IR (KBr, cm^{-1}) 1634, 1430, 1350. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.38 (m, 1H), 7.46 (m, 2H), 7.70 (m, 2H), 7.83 (m, 1H), 7.92 (m, 2H), 8.09 (s, 1H), 8.12 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 120.9, 125.6, 126.0, 128.6, 129.2, 130.3, 130.7, 133.8, 144.4, 148.4. MS [EI+] m/z (%) 266 [M]+ (100). HRMS (EI+): for $C_{14}H_{10}N_4O_2$ calcd. 266.0804, found 266.0809.

1-(3,4-Dichlorophenyl)-4-phenyl-1,2,3-triazole (Entry 9)

58% yield m.p. 79°C (MeOH). IR (KBr, cm^{-1}) 1640, 1420, 1150. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 1H), 7.46 (m, 2H), 7.62 (m, 1H), 7.68 (s, 2H), 7.89 (m, 2H), 8.17(s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 112.4, 115.8, 122.0, 123.9, 128.7, 129.1, 129,8, 133.2, 133.8, 135.6, 136.8, 146.7. MS [EI+] m/z (%) 293 [M +4]+ (10), 291 [M +2]+ (65), 289 [M]+ (100). HRMS (EI+): for $C_{14}H_9Cl_2N_3$ calcd. 289.0174, found 289.0176.

ACKNOWLEDGEMENTS

Financial support from SIEA-UAEMEX (project No. 2692-2008U) is gratefully acknowledged. The authors would like to thank Signa, S.A. de C.V. for some graciously donated solvents and reagents, and M. C. Nieves Zavala for the technical support.

CONFLICT OF INTEREST

Declared none.

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