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Synthesis of 1,2,3-triazoles from Alkyne-Azide Cycloaddition Catalyzed by a Bio-Reduced Alkynylcopper (I) Complex †

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Abstract: A small library of 1,2,3-triazoles was synthesized from diverse alkynes and azides using catalytic amounts of an alkynylcopper (I) complex which in turn was prepared from direct treatment of phenylacetylene with Fehling reagent in presence of glucose as reducing agent. The results suggest that CuAAC reaction requires only 0.5 mg/mmol copper (I) phenylacetylide without any further additives.

Keywords: 1,2,3-triazole; alkynylcopper(I) complex; click chemistry; bio-reduced catalyst

1. Introduction

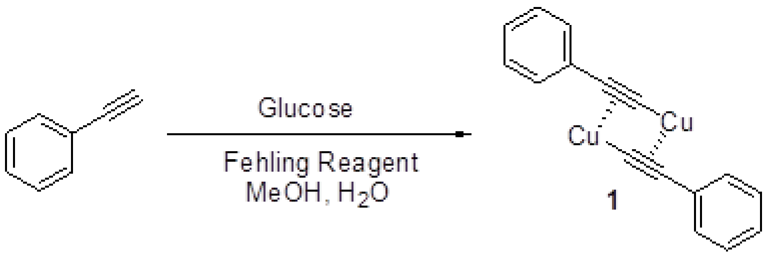
For more than 15 years copper catalyzed azide alkyne Cycloaddtion (CuAAC) has been the most extended "Click" reaction providing a successful method for molecular assembly as well as a growing approach for drug design and materials discovery [1]. In this reaction, the copper catalyst plays an essential role which drive the formation of 1,2,3-triazole recognized as main CuAAC product serving as molecular scaffold in these processes [2,3].

In this regard, diverse copper catalysts have been designed, prepared and used in CuAAC reactions for several reaction conditions; among these catalysts alkynylcopper (I) complexes, namely copper acetylides, have been identified as efficient catalysts in these reactions [4]. Although first reports described that metal acetylides are explosives [5], recent reports show some stable copper acetylides with excellent catalytic properties in CuAAC reactions [6–9].

In conjunction with other research, we observed in situ formation of 1,2,3-triazole copper complexes by a straightforward mixing of alkyne, azide and a copper (I) salt [10]. From these studies, we detected the formation of a copper acetylide and we decided to investigate in detail this process aimed to prepare efficient catalysts for the synthesis of 1,2,3-triazoles through CuAAC reactions. Herein is disclosed a summary of our recent findings about this challenge.

2. Results and Discussion

A particular chemical process that has drawn our attention is the bio-reduction of copper (II) sulfate promoted by glucose as reducing agent which has been used as catalytic source for CuAAC reactions [11]. Inspired by these features, we proceed to adapt the methodologies developed by our group to obtain exclusively copper acetylides. Thus, the successively addition of Fehling A and B solutions to a mixture glucose-phenylacetylene produced a characteristic yellow precipitate which was identified as phenylethynylcopper (I) **1** presenting the same physical data described in literature (Scheme 1) [12,13]. In addition, XPS analysis of compound **1** displays a signal 2p 3/2 at 935 eV corresponding to a copper species with oxidation number (I) in agreement to previous reports (Figure 1) [10,14], whereas a signal at 533.8 eV (spectrum b, Figure 1) suggests a Cu-C interaction [15,16]; moreover, C 1s bond energy at 285.8 eV assigned to aromatic carbons confirmed the formation of copper (I) phenylacetylide **1** which was used in following steps.



Scheme 1. Preparation of copper phenylacetylide **1**.

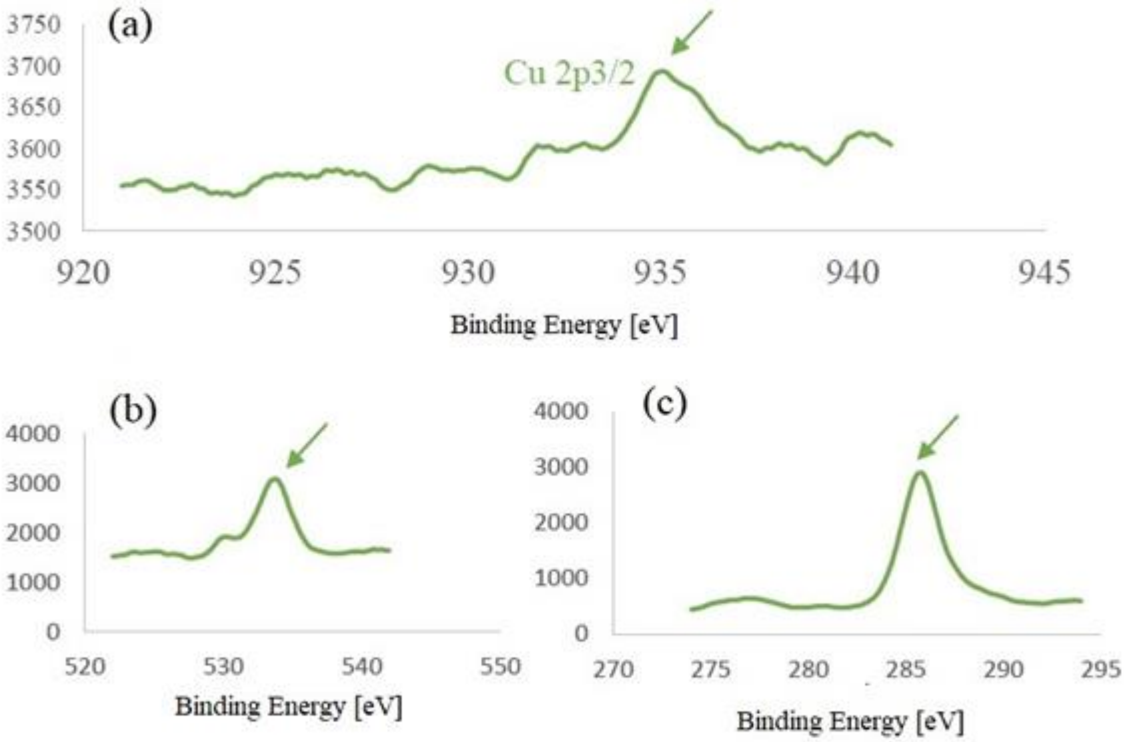
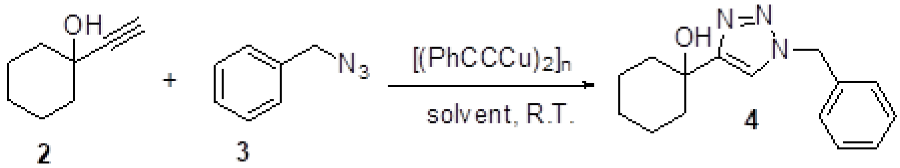


Figure 1. XPS narrow spectra of phenylacetylide **1** for (a) Cu 2p 3/2, (b) Cu-C at the O (1s) level, and (c) C 1s regions.

The reaction between 1-ethynylcyclohexanol **2** and benzylazide **3** was used as model to evaluate the catalytic activity of phenylacetylide **1** (Scheme 2). In all cases, 1-(1-benzyl-1,2,3-triazol-4-yl)cyclohexanol **4** was obtained as only reaction product. The results showed in Table 1 indicate that best conditions were obtained using 0.5 mg/mmol catalyst after 24 h using CH_2Cl_2 as solvent. The found conditions were extended to a series of diverse alkynes and both benzyl azide **3** and 1,3-diazidopropan-2-ol affording the corresponding 1,2,3-triazoles in 70–90 % yields (Table 2) with broad functional group tolerance and without other kind of additives.



Scheme 2. Synthesis of 1,2,3-triazole **4** catalyzed by copper phenylacetylide **1**.

Table 1. Synthesis of triazole **4** catalyzed by phenylacetylide **1**.

Entry	Catalyst Ratio (mg/mmol)	Solvent	Reaction Time (h)	%Yield
1	0.25	CH_3OH	24	50
2	0.25	Acetone	24	58
3	0.25	CH_2Cl_2	24	60
4	0.25	CH_3OH	48	51
5	0.25	Acetone	48	55
6	0.25	CH_2Cl_2	48	63
7	0.5	CH_3OH	24	72
8	0.5	Acetone	24	70
9	0.5	CH_2Cl_2	24	75
10	0.5	CH_3OH	48	71
11	0.5	Acetone	48	71
12	0.5	CH_2Cl_2	48	76
13	1	CH_3OH	24	74
14	1	Acetone	24	72
15	1	CH_2Cl_2	24	77
16	1.5	CH_3OH	24	74
17	1.5	Acetone	24	74
18	1.5	CH_2Cl_2	24	76

Table 2. 1,2,3-Triazole yields catalyzed by copper phenylacetylide **1**.

Compound	Alkyne	Azide	% Yield
4	$CH_2(CH_2CH_2)_2C(OH)C{\equiv}CH$	$PhCH_2N_3$	77
5	$PhC{\equiv}CH$	$PhCH_2N_3$	80
6	$4\text{-}ClC_6H_4OCH_2C{\equiv}CH$	$PhCH_2N_3$	70
7	$4\text{-}NO_2C_6H_4OCH_2C{\equiv}CH$	$PhCH_2N_3$	87
8	$4\text{-}BrC_6H_4OCH_2C{\equiv}CH$	$PhCH_2N_3$	72
9	$4\text{-}CH_3C_6H_4OCH_2C{\equiv}CH$	$PhCH_2N_3$	82
10	$C_{10}H_7OCH_2C{\equiv}CH$	$PhCH_2N_3$	80
11	$CH_2(CH_2CH_2)_2C(OH)C{\equiv}CH$	$N_3CH_2CH(OH)CH_2N_3$	83
12	$PhC{\equiv}CH$	$N_3CH_2CH(OH)CH_2N_3$	92
13	$4\text{-}ClC_6H_4OCH_2C{\equiv}CH$	$N_3CH_2CH(OH)CH_2N_3$	89

A particular group of triazoles synthesized by this protocol contains a 1,3-bis-(1,2,3-triazol-1-yl)-propan-2-ol core which has been recognized as a potential building block to antifungal compounds development due to its similarity to Fluconazole structure [17]. Thus, compounds **11–13** were obtained in 80–92 % through this simple and mild protocol opening possibilities to develop new potential antifungal drugs, hence, future studies are glimpsed to determine biological properties for these compounds.

3. Experimental

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were distilled before use. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Krüss Optronic melting point apparatus and they are uncorrected. 1H and 13C NMR spectra were recorded using a Bruker Avance 300-MHz; 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 Shimadzu GCMS-QP2010 Plus in the EI mode, 70 eV, 200 °C via direct inlet probe. Only the molecular and parent ions (*m*/*z*) are reported. IR spectra were recorded on a Bruker Tensor 27 equipment.

The XPS wide and narrow spectra were acquired with a JEOL JPS-9200, equipped with a Mg X-ray source (1253.6 eV) at 250 W over an analysis area of 3 mm2 under vacuum on the order of 1 × 10^{-8} Torr for all samples. The spectra were analyzed using the specsurf™ software included with the instrument and all spectra were charge corrected by means of the carbon signal (C1s) at 284 eV. The Shirley method was used for the background subtraction, whereas curve fitting was done with the Gauss-Lorentz method. Samples were directly deposited on the sample holder and analyzed without any further preparation.

*3.1. Copper (I) Phenylacetylide (**1**)*

Phenylacetylene (0.109 mL, 0.102 g, 1 mmol) was added to a solution of glucose (0.45 g, 2.5 mmol) in H_2O (5 mL) and MeOH (15 mL). The mixture was treated successively with tartrate-NaOH solution (Fehling B solution, 1.0 mL) and $CuSO_4$ solution (Fehling A solution, 2.5 mL, 1.0 mmol). The resulting mixture was stirred for 24 h at room temperature. The solid was filtered and washed with cold diethyl ether (10 mL), MeOH (20 mL), and H_2O (20 mL). The product was dried under reduced pressure. Yield: 0.156 g (95%), m.p. 290 °C. IR (ATR) νmax 3048, 2100 cm^{-1}. Elemental analysis calculated: C, 58.35; H, 3.06; found: C, 58.91; H, 3.19.

3.2. General Procedure for the Synthesis of 1,2,3-Triazoles Catalyzed by Copper Phenylacetylide

Copper (I) phenylacetylide **1** (0.05 g, 0.025mmol) was added to a stirred solution containing the corresponding alkyne (1.0mmol) and the appropriate azide (1.0 mmol) in CH_2Cl_2 (10 mL). The resulting reaction mixture was stirred at room temperature for 24 h. The mixture was filtered through celite. The solvent was removed under reduced pressure and the final product was purified by crystallization.

3.2.1. 1-(1-Benzyl-1,2,3-triazol-4-yl)cyclohexanol **4**

1-Ethynylcyclohexanol and benzyl azide afforded 1-(1-benzyl-1,2,3-triazol-4-yl)-cyclohexanol **4** as white solid, m.p. 150°C. Yield: 0.198 g (77%). IR (ATR) νmax 3386, 3291, 2930, 2855, 1604 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.39 (m, 5H), 5.60 (s, 1H), 4.92 (s, 1H), 1.92–1.46 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 136.2, 128.7, 128.5, 128.0, 121.1, 68.0, 52.7, 37.8, 25.224, 21.6. MS [EI^+] *m*/*z* (%): 257 $[M]^+$ (20), 91 $[C_6H_5CH_2]^+$ (100).

3.2.2. 1-Benzyl-4-phenyl-1,2,3-triazole **5**

Phenylacetylene and benzyl azide afforded 1-Benzyl-4-phenyl-1,2,3-triazole **5** as white solid. as white solid, m.p. 131 °C. Yield: 0.188 g (80 %). IR (ATR) νmax 3250, 2850, 1650, 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.68 (s, 1H), 7.41 (m, 4H), 7.33 (m, 1H), 5.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 134.6, 130.5, 129.1, 128.8, (2 X CH), 128.7, 127.9, 125.6, 119.5, 54.2. MS (EI^+) *m*/*z* (%): 235$[M]^+$ (21), 206 $[M - HN_2]^+$ (74), 116 $[M - C_6H_5N_3]^+$ (100).

3.2.3. 1-Benzyl-4-(4-chlorophenoxymethyl)-1,2,3-triazole **6**

1-Chloro-4-prop-2-ynyloxybenzene and benzyl azide afforded 1-benzyl-4-(4-chlorophenoxymethyl)-1,2,3-triazole **6** as white solid, m.p. 103 °C. Yield: 0.207 g (70 %). IR (ATR) νmax 1650, 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 3H), 7.27 (m, 2H), 7.22 (dd, 2H, *J* = 3Hz, *J* = 9Hz), 6.89 (dd, 2H, *J* = 2Hz, *J* = 9Hz), 5.54 (s, 2H), 5.16 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.2 (CH_2), 62.2(CH_2), 116.0 (2 X CH), 122.6 (CH), 126.1 (C), 128.0 (2 X CH), 128.8, 129.4 (2 X CH) 129.7 (2 X CH), 134.3 (C), 144.1 (C), 156.7 (C). MS (EI^+) *m*/*z* (%): 299 $[M]^+$ (15), 91 $[C_6H_5CH_2]^+$ (100).

3.2.4. 1-Benzyl-4-(4-nitrophenoxymethyl)-1,2,3-triazole **7**

1-Nitro-4-prop-2-ynyloxybenzene and benzyl azide afforded 1-benzyl-4-(4-nitrophenoxymethyl)-1,2,3-triazole **7** as white solid, m.p. 95 °C. Yield: 0.269 g (87 %). IR (ATR) νmax 3260, 3109, 3084, 2923, 2853, 2129, 1608, 1586, 1383, 1247 (m), 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9Hz, 2H) 7.38 (s, 1H) 7.25 (m, 2H), 7.16 (m, 4 H), 5.16 (s, 2H), 4.53; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 144.2, 140.1, 134.9, 129.7, 129.4, 128.8, 126.1, 116.0, 63.6, 53.7. MS (EI^+) *m/z* (%): 310 $[M]^+$ (5), 91 $[C_6H_5CH_2]^+$ (100).

3.2.5. 1-Benzyl-4-(4-bromophenoxymethyl)-1,2,3-triazole **8**

1-Bromo-4-prop-2-ynyloxybenzene and benzyl azide afforded 1-benzyl-4-(4-bromophenoxymethyl)-1,2,3-triazole 8 as white solid, m.p. 110 °C. Yield: 0.246 g (72 %). IR (ATR) νmax 3260, 3040, 2954, 2926, 2873, 1581, 1487 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.38 (m, 3H), 7.30 (m, 2H), 7.25 (d, 2H, *J* = 8.3Hz), 6.81 (d, 2H, *J* = 8.2 Hz), 5.52 (s, 2H), 5.14 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 144.2, 134.4, 132.3, 129.2, 128.9, 128.1, 122.7, 116.6, 113.5, 62.2, 54.3. MS (EI^+) *m/z* (%): 343 $[M]^+$ (5), 91 $[C_7H_7]^+$ (100).

3.2.6. 1-Benzyl-4-p-tolyloxymethyl-1,2,3-triazole **9**

1-Methyl-4-prop-2-ynyloxybenzene and benzyl azide afforded 1-benzyl-4-p-tolyloxymethyl-1,2,3-triazole as white solid, m.p. 111 °C. Yield: 0.228 g (82 %). IR (ATR) νmax 3212, 2954, 2919, 2869, 1607, 1287 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.34 (m, 3H), 7.24 (m, 2H), 7.04 (d, 2H, *J* = 8.2Hz), 6.83 (d, 2H, *J* = 8.2Hz), 5.50 (s, 2H), 5.54 (s, 2H), 5.15 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 144.9, 134.5, 130.1, 129.9, 129.1, 128.7, 128.1, 122.5, 114.7, 62.3, 54.2, 23.5. MS (EI^+) *m/z* (%): 279 $[M]^+$ (20), 91 $[C_7H_7]^+$ (100).

3.2.7. 1-Benzyl-4-(naphthalen-1-yloxymethyl)-1,2,3-riazole **10**

1-Prop-2-ynyloxynaphthalene and benzyl azide afforded 1-benzyl-4-(naphthalen-1-yloxymethyl)-1,2,3-riazole **10** as white solid, m.p. 76 °C. Yield: 0.252 g (80 %). IR (ATR) νmax 3126, 3084, 3066, 3040, 2956, 2924, 2874, 2854, 1579, 1460, 1378, 1267, 1240 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 1H), 7.82 (m 2H), 7.65 (m, 2H), 7.59 (s, 1H), 7.38 (m, 3H), 7.30 (m, 3H), 6.95 (d, 1H), 5.55 (s, 2H), 5.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 143.1, 132.8, 127.4, 127.0, 126.3, 125.7, 124.1, 124.0, 123.5, 120.7, 120.2, 119.1, 103.7, 60.8, 52.5. MS (EI^+) m/z (%): 315 $[M]^+$ (10), 91 $[C_7H_7]^+$ (100).

3.2.8. 1,3-Bis-[4-(1-hydroxy)cyclohexyl-1,2,3-triazol-1-yl]propan-2-ol **11**

1-Ethynylcyclohexanol 2 and 1,3-diazidopropan-2-ol afforded 1,3-Bis-[4-(1-hydroxy)cyclohexyl-1,2,3-triazol-1-yl]propan-2-ol 11 as a white solid, m.p. 100 °C. Yield: 0.319 g (82 %). IR (ATR) νmax 3270, 3143, 3094, 2915, 2874, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 2H), 5.04 (s, 1H), 4.60–4.51 (m), 4.20–3.89 (m), 2.22 -2.00 (m), 1.87–1.71 (m), 1.60–1.44 (m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 120.3, 72.8, 71.9, 52.9, 36.6, 25.5, 22.6. MS $[EI^+]$ *m/z* (%): 390 $[M]^+$ (5), 210 $[C_{10}H_{16}N_3O]^+$ (100).

3.2.9. 1,3-Bis-(4-phenyl-1,2,3-triazol-1-yl)-propan-2-ol **12**

Penylacetylene and 1,3-diazidopropan-2-ol afforded 1,3-bis-(4-phenyl-1,2,3-triazol-1-yl)-propan-2-ol 12 as a white solid, m.p. 200 °C. Yield: 0.318 g (92 %). IR (ATR) νmax 3368, 3123, 3094, 2936, 1610, 1579, 1557, 1147, 1126 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 2H), 7.85 (d, *J* = 7.5 Hz, 4H), 7.43 (t, *J* = 8 Hz, 4H), 7.31 (t, *J* = 7.5 Hz, 2H), 5.78 (d, *J* = 5 Hz, 1H), 4.60 (d, *J* = 10.5 Hz, 2H), 4.41 (d, *J* = 10.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 130.8, 128.8, 127.7, 125.0, 122.4, 68.2, 53.2. MS $[EI^+]$ *m/z* (%): 346 $[M]^+$ (100).

3.2.10. 1,3-Bis-[4-(4-chlorophenoxymethyl)-1,2,3-triazol-1-yl]-propan-2-ol **13**

1-Chloro-4-prop-2-ynyloxybenzene and 1,3-diazidopropan-2-ol afforded 1,3-bis-[4-(4-chlorophenoxymethyl)-1,2,3-triazol-1-yl]-propan-2-ol **13** as a white solid, m.p. 119 °C. Yield: 0.421 g (89 %). IR (ATR) νmax 3397, 3128, 3095, 2923, 2853, 1578, 1487, 1386 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.38 (d, *J* = 8.3 Hz, 3H), 7.26 (d, *J* = 1.4 Hz, 3H), 6.87 (d, *J* = 8.0 Hz, 3H), 5.18 (s, 2H), 4.53 (d, *J* = 14.9 Hz, 1H), 4.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158., 134.9, 130.3, 124.8, 121, 6, 68.5, 61.9, 53.1. MS [EI^+] *m*/*z* (%) 474 $[M]^+$ (100).

4. Conclusions

1,3-Bis-1,2,3-triazol-1-yl-propan-2-ol based compounds are easily available from CuAAC reaction using phenylacetylide **1** as an inexpensive catalyst obtained from glucose promoted bio-reduction of Fehling reagent in presence of phenylacetylene through a mild synthetic protocol which does not requires other additives with high functional group tolerance. The simplicity of this synthetic method suggests that this route to 1,2,3-triazoles will enjoy widespread application.

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