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Azide-Alkyne Cycloaddition Catalyzed by a Glucose/Benedict Reagent System †

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Abstract: Benedict's Reagent is commonly used in identifying reducing sugars through a redox process where a Cu(I) species is generated. Despite the simplicity of this reaction, this has barely been investigated as a copper (I) source for catalytic processes. In this report, diverse organic azides and alkynes were reacted in presence of catalytic amounts of a Glucose-Benedict Reagent system, obtaining the corresponding 1,2,3-triazoles through a simple and environmentally friendly synthetic procedure.

Keywords: click chemistry; Benedict reagent; glucose; alkyne; azide; 1,2,3-triazole

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1. Introduction

The notion of Click Chemistry was initially conceived by Sharpless 20 years ago [1] and shortly thereafter this group, together to Meldal group [2], developed the copper-catalyzed azide-alkyne cycloaddition (CuAAC), the first click reaction. This was the departure point for an amazingly rapid growth of CuAAC reaction including its applications in diverse fields as materials science, catalysis, or medicinal chemistry [3–6].

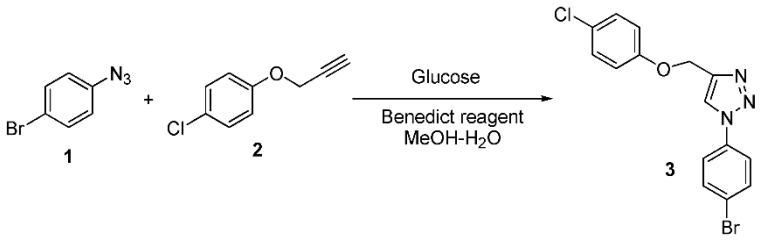
Since its discovery, copper catalyst represents a fundamental part of CuAAC reaction. Therefore, a considerable number of copper based catalytic systems have been devised to catalyze this reaction. A widely used copper catalytic system is based on the bioreduction of a copper(II) salt. Seminal reports describe the use of sodium ascorbate as reducing agent to provide a copper(I) catalyst from copper(II) sulfate which efficiently catalyzes CuAAC reaction using a mixture tBuOH-H_2O as solvent [7].

From these original conditions which served as model, many adaptations were made to prepare alternative copper catalytic systems. For instance, the well-known Fehling reagent was reduced by hydrazine to give in situ a copper(I) system which catalyzes CuAAC reaction yielding the corresponding 1,2,3-triazoles [8]. In this regard, our group observed that reducing sugars can also be used as reducing agents in combination with Fehling reagent to generate a Cu(I) catalyst for the synthesis of both 1,2,3-triazoles and bi-1,2,3-triazoles through Click Chemistry approach [9,10]. On the other hand, analogue Benedict reagent was reduced by ascorbic acid affording a Cu_2O catalyst which was used as catalytic system in the preparation of a series of 1,2,3-triazoles [11].

This background prompted us to propose that a combination of Benedict reagent and a reducing sugar would provide an efficient copper(I) source to catalyze the CuAAC reaction. In this report we disclose our most recent findings in this area.

2. Results and Discussion

Preliminary studies were carried out to find optimal reaction conditions and glucose was selected as reducing sugar in these studies. An initial mixture of Benedict reagent, glucose, 1-Azido-4-bromobenzene **1** and 1-chloro-4-prop-2-ynyloxybenzene **2** according to Scheme 1 remained unreactive at room temperature presumably due to Cu(I) species is not formed under these conditions, which was evident by the blue-colored solution in the reaction mixture indicating the presence of Cu(II) ion.



Scheme 1. Synthesis of 1,2,3-triazole **3** catalyzed by Glucose/Benedict Reagent System.

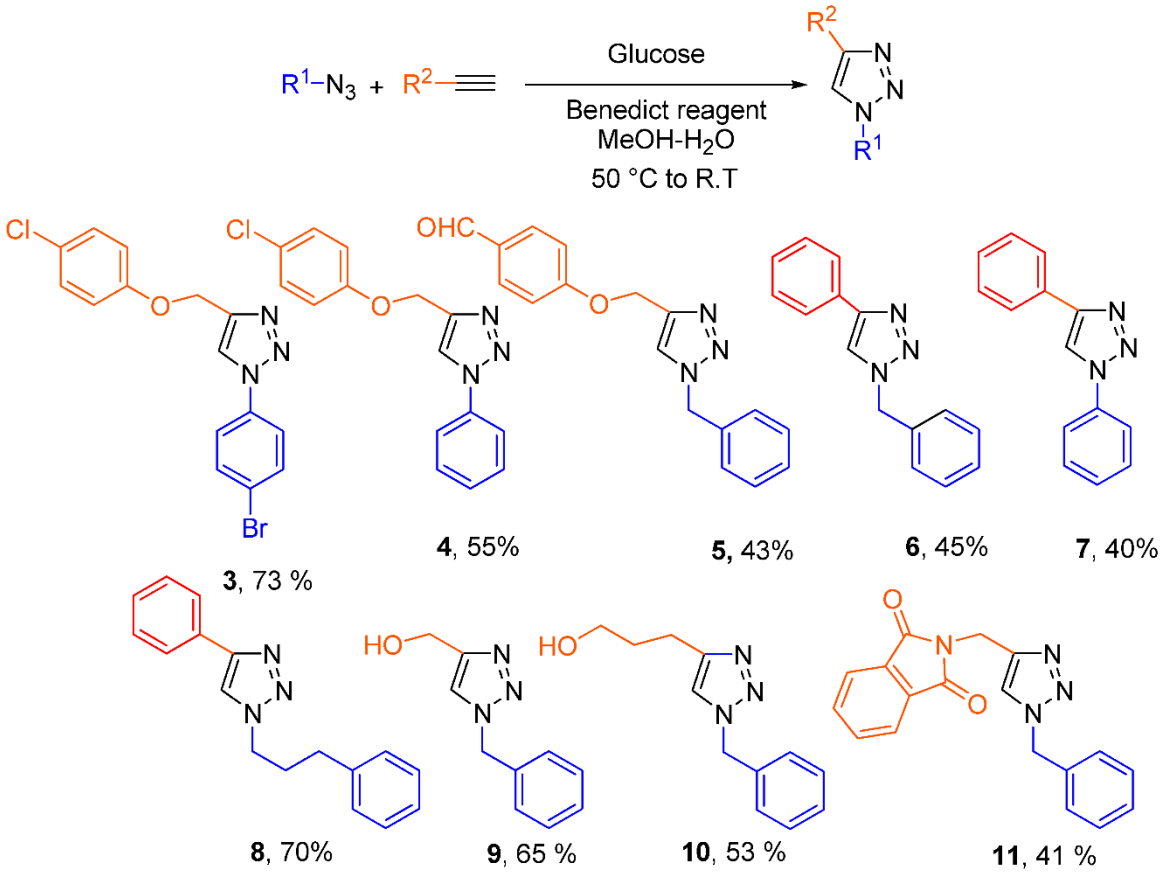
Table 1. Synthesis of triazole **3** catalyzed by Glucose/Benedict Reagent System.

Entry	Catalyst Ratio (% mmol)	Temperature (°C)	Reaction Time (h)	%Yield
1	2.5	R.T.	24	0
2	5	R.T.	24	0
3	10	R.T.	24	0
4	2.5	reflux	24	30
5	5	reflux	24	44
6	10	reflux	24	53
7	2.5	50	24	67
8	5	50	24	67
9	10	50	24	68
10	2.5	50 °C to R.T.	12	32
11	5	50 °C to R.T.	12	49
12	10	50 °C to R.T.	12	51
13	2.5	50 °C to R.T.	24	70
14	5	50 °C to R.T.	24	73
15	10	50 °C to R.T.	24	74
16	2.5	50 °C to R.T.	48	71
17	5	50 °C to R.T.	48	74
18	10	50 °C to R.T.	48	75

This fact drove to perform the following experiments at higher temperatures. Reactions heated to reflux temperature gave triazole **3** together with traces of other side products identified as bis-acetylenes. In order to avoid this kind of compounds, an adaptation was accomplished. A premixed glucose-Benedict reagent solution was heated to 50 °C for 5 min and cooled to room temperature and the resulting red Cu_2O suspension was treated successively with azide **1** and alkyne **2** obtaining the corresponding triazole **3** with a yield up to 73%.

The success of this process promoted an in-depth study to determine the scope of this reaction. Thus, an arrange of organic azides and alkynes were reacted in presence of

catalytic amounts of glucose/Benedict reagent system giving the triazoles **3**-**11** in yields ranged from 40 to 73 % (Scheme 2).



Scheme 2. Synthesized 1,2,3-triazoles catalyzed by Glucose/Benedict Reagent System.

An outstanding feature of this procedure is related to the high selectivity displayed, due to only 1,2,3-triazole was obtained, whereas bi-1,2,3-triazole formation was not detected unlike the use of Fehling-glucose catalytic system which promotes the generation of these compounds [9,10]. An explanation of this behavior might be found in the strong dependence on the alkalinity of the solution often observed in these processes. Previous reports emphasize that an excess of NaOH contributes to the formation of bi-1,2,3-triazole [12]. In this case, the pH is controlled by the concentration of less basic Na_2CO_3 and the Cu (I) ion is stabilized by the citrate ligand. These conditions provide a convenient source of Cu (I) ion but also avoid the triazolide oxidative coupling to bi-1,2,3-triazole. Hence, glucose/Benedict reagent system exhibits catalytic activity which is useful for the synthesis of 1,2,3-triazoles.

As far we know, these are the first examples about the use of the glucose/Benedict reagent system as a copper source for CuAAC reaction which represents an alternative catalytic system for the synthesis of 1,2,3-triazoles through a simple and environmentally friendly methodology.

3. Experimental

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Benedict's reagent was prepared by mixing sodium citrate (17.3 g), Na_2CO_3 (5.0 g) and $CuSO_4{\cdot}5H_2O$ (17.3 g) in distilled H_2O (50 mL). The 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 were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker

Avance 300-MHz; the chemical shifts (δ) are given in ppm relative to TMS as an internal standard (0.00). For analytical purposes, the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus in the EI mode, 70 eV, and 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.

3.1. General Procedure for the Synthesis of 1,2,3-Triazoles Catalyzed by Glucose/Benedict Reagent System

Glucose (0.045 g, 0.25 mmol) was added to a solution of Benedict reagent (0.75 mL, 0.005 mmol) in MeOH (10 mL) and H_2O (4 mL). The resulting mixture was heated at 50 °C for 5 min and cooled to room temperature. The mixture was treated successively with a solution of azide (1 mmol) in MeOH (2 mL) and alkyne (1 mmol) in MeOH (2 mL). The reaction mixture was stirred for 24 h at room temperature. A 2% EDTA.2Na aqueous solution (10 mL) was added and the stirring was continued for additional 12 h. Charcoal (0.5 g) was added, the mixture was filtered through celite and the solvent was removed under reduced pressure. The final product was purified by crystallization.

3.1.1. 1-(4-Bromophenyl)-4-(4-chlorophenoxymethyl)-1,2,3-triazole 3

1-Azido-4-bromobenzene **1** and 1-chloro-4-prop-2-ynyloxybenzene **2** afforded 1-(4-Bromophenyl)-4-(4-chlorophenoxymethyl)-1,2,3-triazole **3** as a white solid, m.p. 112 °C (73%). IR (ATR) νmax 3140, 3102, 2925, 2859, 1485, 823, 799 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.68 (m, 4H), 7.27 (d, 2H), 6.96 (d, 2H), 5.26 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 144.9, 135.9, 133.0, 129.5, 126.4, 122.63, 122.0, 120.8, 116.1, 62.16. MS [EI+] m/z (%): 363 $[M]^+$ (5), 141 $[C_7H_6Cl]^+$ (100).

3.1.2. 4-(4-Chlorophenoxymethyl)-1-phenyl-1,2,3-triazole 4

Phenyl azide and 1-chloro-4-prop-2-ynyloxybenzene **2** afforded 4-(4-Chlorophenoxymethyl)-1-phenyl-1,2,3-triazole **4**, m.p. 97 °C (55%). IR (ATR) νmax 3050, 1500, 1250, 825 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.63 (m, 2H), 7.49 (m, 2H), 7.26 (m, 2H), 6.97 (m, 2H), 5.28 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 142.1, 133.5, 129.7, 128.2, 126.8, 123.8, 119.4, 115.0, 74.64. MS [EI+] m/z (%): 285 [M]+ (5), 77 ($[C_6H_5]^+$ 100).

3.1.3. (1-Benzyl-1,2,3-triazol-4-ylmethoxy)-benzaldehyde 5

Benzyl azide and 4-Prop-2-ynyloxybenzaldehyde afforded (1-Benzyl-1,2,3-triazol-4-ylmethoxy)-benzaldehyde **5** as a white solid, m.p. 79 °C (43%). IR (ATR) νmax 1660, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.54 (s, 1H), 7.82–7.83 (dd, 2H, *J* = 3 Hz, *J* = 9 Hz), 7.36–7.38 (m, 3H), 7.26–7.29 (m, 2H), 7.07–7.09 (dd, 2H, *J* = 3 Hz, *J* = 9 Hz), 5.54 (s, 2H), 5.26 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 163.3, 143.6, 134.3, 130.3, 129.2, 128.9, 128.1, 122.7, 115.0, 62.2, 54.3, MS [EI+] m/z (%): 293 $[M]^+$ (5), 91 ($[C_6H_5CH_2]^+$ (100).

3.1.4. 1-Benzyl-4-phenyl-1,2,3-triazole 6

Phenylacetylene and benzyl azide afforded 1-Benzyl-4-phenyl-1,2,3-triazole **6** as a white solid, m.p. 131 °C (45%). IR (ATR) νmax 3250, 2850, 1650, 1600 cm^{-1}. ^1H 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).

3.1.5. 1,4-. diphenyl-1,2,3-triazole 7

Phenylacetylene and phenyl azide afforded 1,4-diphenyl-1,2,3-triazole **7** as a white solid, m.p. 97 °C (40%). IR (ATR) νmax 3050, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.92 (m, 10H), 8.20 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.5, 121.5, 125.8, 128.2, 128.4, 128.5, 128.7, 128.9, 128.9, 129.7, 130.7, 130.8, 134.9, 147.6. MS [EI+] m/z (%): 222 $[M + 1]^+$ (5), 193 $([M - N_2]^+$ (95), 165 (100).

3.1.6. 4-phenyl-1-(3-phenylpropyl) -1,2,3-triazole 8

Phenylacetylene and 3-Azidopropyl benzene afforded 4-phenyl-1-(3-phenylpropyl) -1,2,3-triazole **8** as a white solid, m.p. 238 °C (70%). IR (ATR) νmax 1380, 1450, 1696, 3071 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.85 (d, J = 7.5 Hz, 4H), 7.43 (m, 4H), 7.31 (m, 2H), 5.81 (s, 2H), 4.62 (d, J = 9 Hz, 2H), 4.43 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 130.8, 128.9, 127.8, 125.1, 122.5, 58.3, 53.2. MS [EI+] m/z (%): 263 $[M]^+$ (100), 116 $[M - C_9H_{11}N_2]^+$ (30).

3.1.7. (1-Benzyl-1,2,3-triazol-4-yl)-methanol 9

Propargyl alcohol and benzyl azide afforded 1-Benzyl-1,2,3-triazol-4-yl)-methanol 9 as a white solid, m.p. 76–77 °C (65%). IR (ATR) νmax , 3330, 1572, 1475, 1276 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47(s, 1H), 7.32 (m, 3H), 7.21 (m, 2H), 5.44 (s, 2H), 4.68 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 134.5, 129.0, 128.7, 128.0, 121.9, 55.9, 54.0. MS [EI+] m/z (%): 189 [M]+ (40), 91 $[C_6H_5CH_2]^+$ (100).

3.1.8. 3-(1-Benzyl-1,2,3-triazol-4-yl)-propan-1-ol 10

Pent-4-yn-1-ol and benzyl azide afforded 3-(1-Benzyl-1,2,3-triazol-4-yl)-propan-1-ol **10** as a white solid, m.p. 90 °C (53%). IR (ATR) νmax 3350, 3050, 1600 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.31 (m, 3H), 7.23 (m, 2H), 5.44 (s, 2H), 4.32 (s, 1H), 3.61 (t, 2H), 2.75 (t, 2H), 1.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 134.9, 129.0, 128.5, 127.9, 121.3, 61.1, 53.9, 32.0, 21.90. MS [EI+] m/z (%): 217 $[M + 1]^+$ (5), 91 $[C_6H_5CH_2]^+$ (100).

3.1.9. 2-(1-Benzyl-1,2,3-triazol-4-ylmethyl)-isoindole-1,3-dione 11

2-Prop-2-ynyl-isoindole-1,3-dione and benzyl azide afforded 2-(1-Benzyl-1,2,3-triazol-4-ylmethyl)-isoindole-1,3-dione **11** as a white solid, m.p. 140 °C (41%). IR (ATR) νmax 3112, 3072, 3043, 1702 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 4H), 7.51 (s, 1H), 7.36 (m, 5H), 129.1, 5.48 (s, 2H), 4.97 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 143.2, 134.4, 33.06, 134.1, 132.0, 129.1, 128.7, 128.1, 123.4, 122.7, 54.2, 33.1. MS [EI+] m/z (%): 318 $[M]^+$ (5), 91 ($[C_6H_5CH_2]^+$ (100).

4. Conclusions

Diverse 1,2,3-triazoles were obtained as only reaction product using glucose/Benedict reagent system as catalyst through a mild synthetic protocol which does not requires other additives with high functional group tolerance developed from easily available reagents. The simplicity of this synthetic method suggests that this route to 1,2,3-triazoles will enjoy widespread application.

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