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Metal-free intermolecular azide-alkyne cycloaddition promoted by glycerol

Marta Rodríguez-Rodríguez,^[a,b] Emmanuel Gras,^[c] Miquel A. Pericàs,^{*[b]} and Montserrat Gómez^{*[a]}

Abstract: Metal-free intermolecular Huisgen cycloadditions using non-activated internal alkynes have been successfully performed in neat glycerol, under microwave dielectric heating. Surprisingly other protic solvents (such as water, ethanol or propane-diols) did not favor the reaction, probably due to their lower relaxation times than that exhibited by glycerol, thanks to the extensive hydrogen bonds formed in this latter case. DFT calculations have shown that the BnN₃/glycerol adduct causes a more important stabilization of the corresponding LUMO than that produced in the analogous BnN₃/alcohol adducts, increasing then the reactivity with the alkyne. The presence of copper salts in the medium did not change the reaction pathway (actually Cu(I) acts out as spectator), except for disubstituted silyl-alkynes, for which desilylation takes place in contrast to the metal-free system.

Introduction

Azide-alkyne cycloadditions (AAC) represent a powerful tool for the synthesis of 1,2,3-triazoles, valuable heterocycles involved in diverse fields, such as biochemistry, organic synthesis or materials science.^[1] Although this reaction was first reported in 1893 by Michael^[2] and particularly developed by Huisgen in the 1960s,^[3] it was not up to the beginning of 21st century that the reaction found widespread practical interest after overcoming kinetic and regioselective concerns, by transforming the thermal activated process into a catalytic reaction, mainly using copper-based systems.^[1,4] Since then many catalytic systems have been described, also including metals other than copper (such as Ag,^[5] Ru,^[6] Ir^[7] or Ni^[8]), which allow access to substituted-1,2,3-triazoles from organic azides and alkynes. The use of internal alkynes to lead to the formation of 1,4,5-trisubstituted 1,2,3-triazoles generally requires harsher conditions, electron-deficient reagents (such as halo- and carboxylate-alkynes) and/or strained alkynes.

For biological and pharmacological applications, metal-free AAC methodologies (back to origins) still remain attractive approaches.^[9] Bertozzi and coworkers first used the strained-promoted strategy involving substituted cycloalkynes for bioconjugation purposes.^[10] Another elegant method is through intramolecular AAC reactions, taking advantage of the favorable entropy effects.^[11] However to the best of our knowledge, intermolecular cycloadditions between organic azides and non-activated internal alkynes under metal-free conditions remain an important challenge to be solved.

In the last years, with the purpose of using eco-friendly solvents, we have developed glycerol catalytic phases. They exhibit appealing properties mainly concerning the immobilization of metal species, probably due to the supramolecular arrangement shown by glycerol.^[12] In particular, Cu₂O nanoparticles prepared in neat glycerol led to the synthesis of 1,4-disubstituted-1,2,3-triazoles permitting an easy recycling of the catalytic phase.^[13] With the suspicion of the non-innocent role of glycerol in this process, we decided to investigate the metal-free AAC in glycerol for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles.

Results and Discussion

We chose as benchmark reaction the intermolecular azide-alkyne cycloaddition (AAC) between diphenylacetylene (**1**) and benzyl azide (**a**) in neat glycerol under microwave dielectric heating for 30 minutes, affording 1-benzyl-4,5-diphenyl-1,2,3-triazole, **1a** (Table 1).^[14] The organic products were isolated by means of a biphasic liquid-liquid extraction after adding dichloromethane to the reaction mixture. The triazole **1a** was exclusively obtained in high yield (85%, entry 1, Table 1). With the aim of checking the effect of copper in this reaction,^[15] we carried out the synthesis in the presence of a copper salt (2.5 mol% of CuCl), obtaining **1a** with almost the same isolated yield (entry 2, Table 1). This evidences the spectator role of copper (see Table S1 in the Supporting Information).^[16] A similar trend could be observed under classical thermal-promoted conditions (entries 3 and 4, Table 1), albeit in lower yields (<35%) after 20h course time. In the absence of glycerol (*i.e.* under solvent-free conditions), only 18% yield was observed (entry 5, Table 1).

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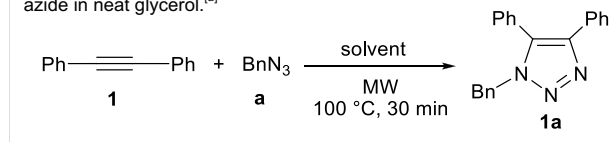
No copper was detected by ICP-AES analyses of neat glycerol (< 3 ppm).

With the aim to better control the temperature (we worked under constant temperature mode using an external infrared temperature sensor),^[17] we employed a MW instrument equipped with both internal fiber-optic and external infrared temperature sensors (Fig. S1 in the Supporting Information). We carried out the cycloaddition at different temperatures (100, 140 and 180 °C) and we could observe that the yield obtained at 180 °C was comparable to that obtained working with the instrument equipped only with infrared sensor (Table S2 in the Supporting Information).

Then, we decided to study the influence of the solvent nature under metal-free conditions. Surprisingly no reaction took place using other alcohol-based solvents, including ethanol and diols such as ethylene glycol, propane-1,2-diol and propane-1,3-diol (entry 6, Table 1). Water gave very low conversion of benzyl azide (13% conversion, entry 7, Table 1). Aprotic polar solvents as 1,4-dioxane and fluorobenzene also disfavored the cycloaddition (entries 8-9, Table 1). The unlike reactivity observed using different protic solvents can be explained by the solvent interaction with an external electric field. Alcohols, in particular polyols, form extensive hydrogen bonds, which in turn correlate with long relaxation times (the time taken to achieve the random state after being submitted to an external electric field).^[18] Therefore, water (9.2 ps), ethanol (170 ps), ethylene glycol (170 ps) or propane-1,3-diol (340 ps) exhibit shorter relaxation times than glycerol (1,215 ps), making it more relevant than other protic solvents for synthetic purposes under microwave conditions, as illustrated here for the AAC reaction.

Under thermal conditions (Table S3 in the Supporting Information), the reactivity in the different solvents follows the same trend, except for ethylene glycol and water, for which **1a** was obtained in 25 and 31% yield respectively (in glycerol, 33% yield; entry 3, Table 1) after 20h at 100 °C. This clearly contrasts with the practically lack of reaction under microwave heating (entries 6-7, Table 1), taking into account the high temperature achieved under MW activation (see above).

Table 1. Azide-alkyne cycloaddition of diphenylacetylene and benzyl azide in neat glycerol.^[a]



Entry	Solvent	Conversion (%) ^{[b][c]}	Isolated Yield (%) ^[d]
1	Glycerol	85	85 (85)
2 ^[e]	Glycerol	86	82 (80)
3 ^[f]	Glycerol	37	33 (33)
4 ^{[e][f]}	Glycerol	42	28 (27)
5	-	20	18 ^[g]
6 ^[j]	Protic solvent	n.r.	-
7	H ₂ O	13	n.d.
8	1,4-Dioxane	n.r.	-
9	Fluorobenzene	n.r.	-

[a] Results from duplicate experiments. Reaction conditions: 0.4 mmol of benzyl azide and 0.6 mmol of diphenylacetylene in 1 mL of solvent under microwaves activation (250 W) at 100 °C for 30 minutes (temperature controlled by external infrared sensor). [b] Based on benzyl azide. [c] Determined by ¹H NMR using 2-methoxynaphthalene as internal standard. [d] In brackets, yields determined by ¹H NMR using 2-methoxynaphthalene as internal standard. [e] In the presence of 2.5% mol of CuCl. [f] Reaction in a sealed tube under thermal activation at 100 °C for 20h. [g] Determined by ¹H NMR using 2-methoxynaphthalene as internal standard. [j] Results obtained with the following alcohols: ethanol, ethylene glycol, propane-1,2-diol and propane-1,3-diol used as solvents.

With these results in hands, we decided to study the scope of the process to other internal alkynes (Table 2). For the symmetrical disubstituted alkynes **2-5** (entries 1-4, Table 2), moderate to high yields were obtained (32 – 90%). No transesterification reactions between the alkyne **2** or the triazole **2a** and glycerol were observed, opposite to the reaction in ethanol (see Tables S4 and S5 in the Supporting Information). It is important to underline that the non-activated 4-octyne reacted with BnN₃ to give 1-benzyl-4,5-dipropyl-1,2,3-triazole, **5a**, in 71% isolated yield (after 1h under microwave irradiation; entry 4).

Unsymmetrical substituted alkynes **6** and **7** led to an almost equimolar mixture of both regioisomers (entries 5-6, Table 2). Considering synthetic applications as well as a need to explore the role of silyl as directing group during the cycloaddition,^[19] we carried

out the synthesis of triazoles **8-10** from the corresponding alkynes containing silyl-based groups, SiMe₃ (alkynes **8** and **9**; entries 7-8, Table 2) and Si(*t*Bu)Me₂ (**10**; entry 9, Table 2). As expected, we obtained the 4-silyl substituted heterocycle as the major regioisomer,^[20] and as the sole product for the bulky TBDMS derivative (entry 9, Table 2).

Phenyl (**b**) and *n*-octyl (**c**) azides also gave the expected triazoles; conversions and yields were lower than those obtained using benzyl azide (Figure 1).^[21] In contrast to benzyl and *n*-octyl azides, PhN₃ tends to decompose under the reaction conditions employed.^[22]

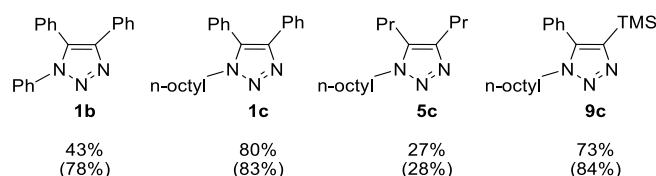
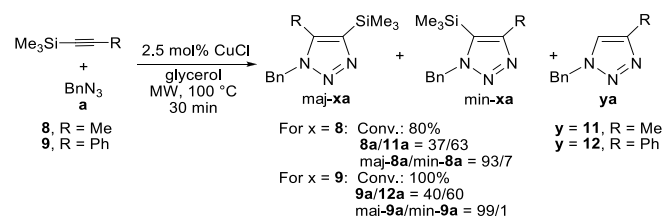


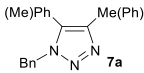
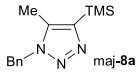
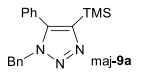
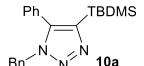
Figure 1. 1,4,5-Trisubstituted 1,2,3-triazoles from phenyl (**1b**) and *n*-octyl azides (**1c**, **5c**, **9c**). Figures indicate yields (conversions are given in brackets).

We studied the effect of Cu(I) in the synthesis of silyl-based triazoles, **8a-10a**. For the synthesis of **10a**, bearing a TBDMS group, the reactivity was similar to the one observed in the absence of Cu(I). However for TMS substituted ones (**8a**, **9a**), a mixture of two triazoles was obtained, the expected **8a** or **9a** and the desilylated one, obtained as a single regioisomer, 1-benzyl-4-R-1,2,3-triazole (R = Me (**11a**), Ph (**12a**)) (Scheme 1). Under classical thermal conditions, the same behavior was observed (Scheme S1 in the Supporting Information).



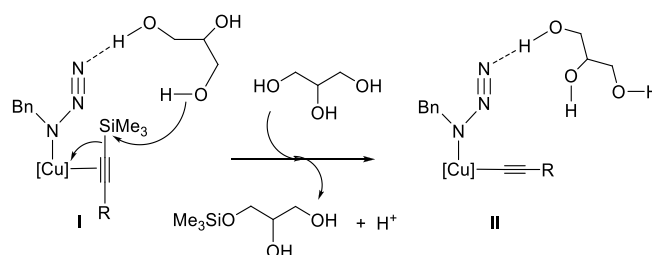
Scheme 1. Reactivity of silyl-based alkynes in the presence of CuCl under microwave activation. Data from NMR analysis.

Entry	Alkyne (R, R')	Product	Conv. (%) ^{[b][c]}	Yield (%) ^[c]
1 ^[d]	2 (CO ₂ Me)		100	78
2	3 (CH ₂ OMe)		96	90
3	4 (CH ₂ OH)		56	32
4 ^[e]	5 (Pr)		73	71
5	6 (Ph, CO ₂ Me)		91	83 ^[f]

6	7 (Ph, Me)		49	49 ^[f]
7	8 (Me, TMS)		65	62 (9:1) ^[g]
8	9 (Ph, TMS)		92	85 (9:1) ^[g]
9	10 (Ph, TBDMS)		85	84 ^[h]

[a] Results from duplicate experiments. Reaction conditions: 0.4 mmol of benzyl azide and 0.6 mmol of the corresponding alkyne in 1 mL of solvent under microwaves activation (250 W) at 100 °C for 30 minutes (temperature controlled by external infrared sensor).. [b] Based on benzyl azide. [c] Determined by ¹H NMR using 2-methoxynaphthalene as internal standard. [d] Reaction time: 15 min. [e] Reaction time: 60 min. [f] Regioisomer ratio: 1/1. [g] In brackets, regioisomer ratio (major isomer: 1-benzyl-4-trimethylsilyl-5-R-1,2,3-triazole (for R = Me, maj-**8a**; for R = Ph, maj-**9a**); minor isomer: 1-benzyl-5-trimethylsilyl-4-R-1,2,3-triazole (for R = Me, min-**8a**; for R = Ph, min-**9a**). [h] Only one isomer was obtained (1-benzyl-4-*t*-butyldimethylsilyl-5-phenyl-1,2,3-triazole); see [20].

Control tests established that the desilylation took place neither on the alkyne **8** or **9** nor on the triazole **8a** or **9a** (Scheme S2 in the Supporting Information). In addition when the AAC reaction was carried out in dioxane, no corresponding desilylation occurred. Monitoring the reaction by GC-MS demonstrated that the formation of **9a** is faster than that corresponding to **12a** (after 5 min, the ratio **9a/12a** was ca. 3.4/1; after 15 min, it was ca. 1.2/1, with full consumption of BnN₃). Once BnN₃ was totally consumed, desilylation of the alkyne **9** could be observed (Figure S4 in the Supporting Information). These facts lead us to propose that the desilylation leading to **12a** (and **11a**) occurs upon coordination of the alkyne to copper (intermediate **I** in Scheme 2), promoted by glycerol, which is undoubtedly close to the coordination sphere, thanks to its interaction with BnN₃ through hydrogen bonds (see below). Intermediate **II** evolves then to give the favored regioisomer 1-benzyl-4-R-1,2,3-triazole, accordingly to the accepted Cu-catalyzed mechanisms.^[23] The formation of the corresponding silyl-derivative of glycerol could be proved by NMR (see Figures S5 and S6 in the Supporting Information).^[24] Alkyne **10** did not give the corresponding desilylated triazole probably as a consequence of the steric hindrance triggered by the TBDMS group around the metal center.



Scheme 2. Plausible Cu-mediated desilylation of SiMe₃-based alkynes promoted by glycerol.

With the aim of rationalizing the effect of glycerol in AAC reactions, we studied the interaction of glycerol with benzyl azide by means of theoretical calculations (DFT B3LYP, 6-31G*), taking into account the ability of glycerol to form hydrogen bonds.^[25,26] For comparative purposes, we also analyzed this effect with ethanol and diols (ethylene glycol, 1,2- and 1,3-propanediol). The resulting BnN₃/alcohol adducts increase the dipolar character of BnN₃ in relation to neat benzyl azide (see calculated charges in Figure S7 in the Supporting Information). It is important to underline that in the case of polyols (ethylene glycol, 1,2-propanediol and glycerol) the intramolecular hydrogen bonds trigger an additional stabilization of the corresponding BnN₃/alcohol adduct (see Figure S8 in the Supporting Information). The analyses of the relative energies of frontier orbitals for the different BnN₃/alcohol adducts (see Figure S9 in the Supporting Information) showed that the BnN₃/glycerol LUMO, which overlaps with the dipolarophile HOMO (diphenylacetylene was chosen for the calculations), is more stable than the ones obtained for the other adducts (see Table S6 in the Supporting Information). In consequence, the reactivity should be enhanced as observed in this work for a range of alkynes.

Conclusions

To sum up, we have shown that glycerol acts as a non-innocent solvent for metal-free azide-alkyne cycloadditions, promoting the reaction between internal alkynes and organic azides in contrast to other protic solvents, both under classical and dielectric heating. Moreover, the reactivity in glycerol was particularly enhanced by microwave activation, probably due to the long relaxation time of glycerol in comparison with other protic solvents related to the supramolecular arrangement through intermolecular hydrogen bonds. At molecular level, an analysis of the frontier orbitals for the $\text{BnN}_3/\text{glycerol}$ adduct pointed to a higher stabilization of the corresponding LUMO than that for comparable adducts involving ethanol and diols. This trend justifies the increase of the reaction rate according to a concerted pathway for the metal-free cycloaddition.

These results permit us to envisage the formation of fully substituted 1,2,3-triazoles using a metal-free methodology, in particular interesting for synthesis of drugs and natural products.

Experimental Section

General: All manipulations were performed using standard Schlenk techniques under argon atmosphere. Unless stated otherwise, commercially compounds were used without further purification. Glycerol was treated under vacuum at 70 °C overnight prior to use. NMR spectra were recorded on a Bruker Avance 300, 400 and 500 spectrometers at 293 K. GC analyses were carried out on an Agilent GC6890 with a flame ionization detector, using a SGE BPX5 column composed by 5% of phenylmethylsiloxane. Reactions under microwave activation were carried out on single-mode microwave CEM Explorer SP 48, 2.45GHz, Max Power 300W Synthesis System, CEM Focused MicrowaveTM Synthesis System Model Discover, and Anton Paar Monowave 300 instruments. Theoretical studies were carried out using the following software: SPARTAN'14 for Windows and Linux. Wavefunction, Inc. 18401 Von Karmaan Avenue, suite 307. Irvine, CA 92612, USA. Calculations were carried out with Density Functional B3LYP using the basis set 6-31G*.

General AAC procedure in glycerol under microwave activation.

A sealed tube equipped with a stirring bar was successively charged with the corresponding alkyne (0.6 mmol) and glycerol (1 mL); the mixture was stirred at room temperature for 5 min. Benzyl azide (0.4 mmol, 532 mg) was then added and the sealed tube introduced in the microwave reactor (100 °C, 250 W) for 30 min (or the appropriate time). The organic products were extracted with dichloromethane (6 x 2 mL). The combined chlorinated organic layers were filtered through a Celite pad. The resultant filtrate was concentrated under reduce pressure. Products were purified by chromatography (silica short-column) in order to determine the isolated yields of the corresponding triazoles. Data for **maj-8a**: Yellow oil; IR absorption (neat) ν 1606, 1497, 1416, 1248 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.35 (s, 9H), 2.22 (s, 3H), 5.51 (s, 2H), 7.15–7.20 (m, 2H), 7.27–7.39 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ -0.9, 9.3, 51.2, 127.2, 128.1, 128.9, 135.1, 138.1, 143.8; HRMS (ESI^+): m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{20}\text{N}_3\text{Si}$ 246.1412, found 246.1421. Elemental analysis calcd (%) for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{Si}$: C 63.63, H 7.80, N 17.11; found: C 63.22, H 7.88, N 16.94. Data for **10a**: Yellow oil; IR absorption (neat) ν 1606, 1497, 1456, 1249 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.05 (s, 6H), 0.90 (s, 9H), 5.35 (s, 2H), 6.94–7.00 (m, 2H), 7.05–7.10 (m, 2H), 7.21–7.28 (m, 3H), 7.35–7.40 (m, 2H), 7.43–7.48 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ -5.3, 26.6, 51.4, 127.6, 127.9, 128.2, 128.5, 128.8, 129.3, 130.4, 135.6, 142.8, 144.1, 173.4; HRMS (ESI^+): m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{21}\text{H}_{28}\text{N}_3\text{Si}$ 350.2050, found 350.2047. Elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{Si}$: C 72.16, H 7.79, N 12.02; found: C 72.24, H 8.27, N 11.87. Data for **5c**: Yellow oil; IR absorption (neat) ν 1611, 1570, 1544, 1247 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 0.89 (t, $J=7.0$ Hz, 3H), 0.98 (t, $J=7.4$ Hz, 3H), 0.98 (t, $J=7.4$ Hz, 3H), 1.20–1.40 (m, 10H), 1.53–1.62 (m, 2H), 1.68–1.77 (m, 2H), 1.83–1.96 (m, 2H), 2.55–2.61 (m, 4H), 4.16–4.20 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): 13.85, 13.98, 14.05, 22.58, 22.60, 22.94, 22.94, 24.49, 26.69, 27.23, 29.06, 29.70, 30.35, 31.71, 47.89, 132.44, 144.71. HRMS (ESI^+): m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{32}\text{N}_3$ 266.2591, found 266.2594. Elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{31}\text{N}_3$: C 72.40, H 11.77, N 15.83; found: C 72.13, H 12.28, N 15.53.

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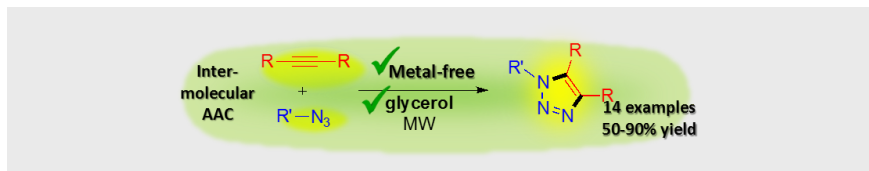
Keywords: glycerol • azide-alkyne cycloaddition • metal-free • microwave activation • DFT modelling

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- [20] For **8a**, the assignment of both regioisomers was carried out by NOESY NMR correlations (see Figure S2 in the Supporting Information). For **9a** and **10a**, desilylation reactions with TBAF were carried out to unambiguously determine the major isomer (see Figure S3 in the Supporting Information).
- [21] Reaction conditions: 0.4 mmol of azide and 0.6 mmol of the corresponding alkyne in 1 mL of solvent under microwaves activation (250 W) at 100 °C for 1h (**1c**), 2h (**5c**) and 30 min (**9c**). For **1b**, similar conditions were used but applying a power of 150 W for 1h. Reactions involving PhN₃ were protected from light.
- [22] 70% and 56% of PhN₃ was recovered from a glycerol solution of PhN₃ after 30 min under MW activation at 150 and 250 W respectively. Under classical heating, 95% of PhN₃ was recovered after 20h at 100 °C.
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FULL PAPER



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**Metal-free intermolecular azide-
alkyne cycloaddition promoted by
glycerol**

Neat glycerol promotes the Huisgen reaction under eco-friendly conditions, to give fully substituted 1,2,3-triazoles, including those with alkyl groups. Glycerol presumably activates the azide partner, favoring the cycloaddition kinetics in the absence of any metal.