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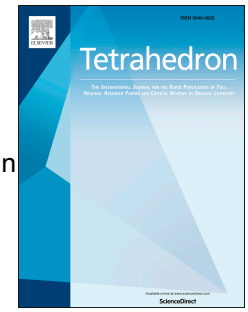

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A One-Pot, Copper-Catalyzed Azidation/Click Reaction of Aryl and Heteroaryl Bromides in an Environmentally Friendly Deep Eutectic Solvent

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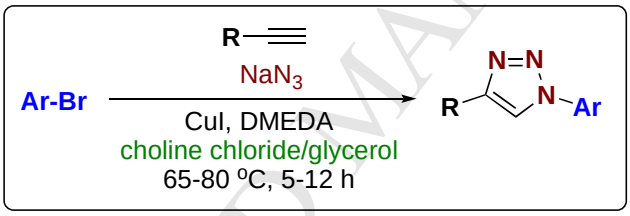

ABSTRACT

In an effort to avoid the hazards of isolating and handling azides in click chemistry, many groups have turned to *in situ* generation of azides from halide precursors. This option is readily accomplished for alkyl azides, but is more challenging for aryl azides. In this paper, we discuss our success in transforming aryl bromides into 1,4-disubstituted triazoles employing DMEDA as a ligand with a copper catalyst in a deep eutectic solvent. Further, we are able to recycle the solvent, catalyst, and ligand several times, thereby increasing the attractiveness of this method.

1. Introduction

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The copper-catalyzed Huisgen reaction of an azide and an alkyne (CuAAC) has very rapidly become one of the preeminent reactions in organic chemistry.[1] It generally affords very good yields of the triazole product as a single regioisomer and tolerates a wide range of functionality, enabling its utilization in areas ranging from biological to materials research.[2] As broad as this application has been, the azide component remains a limitation. Organic azides are well known to be unstable and explosive compounds and thus their isolation is not desirable, particularly on larger scale.[3] As a result, it is not surprising that many groups have explored ways to generate azides *in situ*.

For alkyl azides, this is usually simple as the azide anion is a good nucleophile. Thus, the combination of an alkyl halide with sodium azide in the presence of an alkyne and a copper catalyst accomplishes both the synthesis of the azide and the click reaction in one pot.[4] The first reported example of this approach was in 2004 from the Fokin group.[4c] They reported a microwave-assisted, three-component, one-pot procedure in which the Cu(I) catalyst was prepared *in situ* by comproportionation of a Cu(0)/Cu(II) couple for the synthesis of 1,4-disubstituted 1,2,3-triazoles with 100% regioselectivity at 125 °C. The reaction times were quite short, and the products were easy to isolate in very high yield, although the reaction temperature was relatively high.

For aryl azides, the problem is more difficult, as direct nucleophilic displacement is not generally an option. In substrates which can undergo facile S_NAr reactions, Ramana has reported successful one-pot azidation/click tandems, but this scope is quite narrow.[5] Substitution of other types of leaving groups have been reported, including iodoniums[6] and diazonium salts,[7] but in all of these cases hazardous reagents and/or poorly accessible starting materials still limit their general application.

The most ideal situation would be the direct conversion of an aryl halide to an aryl azide. Using the more reactive aryl iodides, the Fokin group in 2004 demonstrated *in situ* generation of aryl azides.[8] Thus, treatment of an aryl iodide with sodium azide and a copper catalyst formed from copper sulfate, sodium ascorbate, and L-proline with sodium carbonate in DMSO/water at 60 °C formed the azide, which then underwent a CuAAC reaction with an alkyne. Again, yields were good, although reaction times were longer (overnight). Further, reaction was limited to aryl iodides, with aryl bromides failing to afford any triazole product.

The following year, Liang and co-workers employed very similar reaction conditions which a change in ligand from proline to *trans-N,N'*-dimethyl-1,2-diaminocyclohexane to overcome this limitation and reported the first successful one-pot azidation/click reactions of aryl bromides.[9] Since this report, these basic conditions (copper catalyst, ligand, and sodium ascorbate) have been used by several groups with little modification to perform these reactions, most frequently on simple benzenoid aromatics.[10]

With one recent exception, to the best of our knowledge, there has been no attempt to develop a system in which the catalyst could be recycled or used at a lower loading than 10 mol% for the one-pot conversion of aryl bromides to aryl triazoles and in this one case, only one example was reported with an unusual alkyne, making its generality uncertain.[11] With this in mind and our ongoing interest in the combination of unusual solvents and catalyst recycling, we elected to study the application of a recyclable deep eutectic solvent (DES) based upon choline chloride and glycerol for the one-pot azidation/click reaction of aryl bromides.[12]

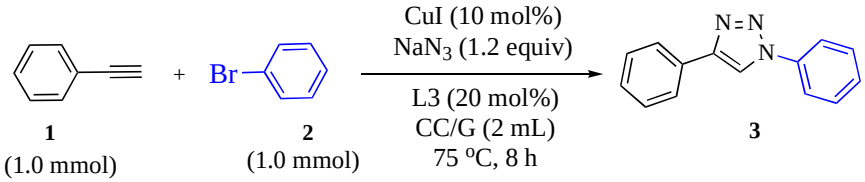
DES are a rapidly growing variation on the idea of ionic liquids.[13] In general, they are comprised of a mixture of two or more components that exhibit a very dramatic depression in

melting point compared to the pure components in the mixture, most typically via a combination of a salt with a hydrogen-bond donor or a salt with another metal salt capable of forming complex anions. Although many such solvents have been reported, choline chloride (CC – 2-hydroxyethyltrimethylammonium chloride) is the most widespread salt component as it is inexpensive, biodegradable, and available on large scale due to its use as a dietary additive in animal feed.[13c, 13f] While the CC/urea combination is the most frequently used,[14] the combination with glycerol in a 1:2 molar ratio is another very easily formed DES and was the focus of this work.[15] It is worth noting that the CuAAC reaction has been reported before by Ilgen and Koenig using an unusual DES comprised of a 7 : 2 : 1 mixture of D- sorbitol, urea and NH_4Cl respectively, as a solvent and 5 mol% CuI as a catalyst yielding 91% of 1,4-disubstituted 1,2,3-triazole in 5 hrs.[16] This reaction gave a 55% yield under the similar conditions with another deep eutectic solvent – L-carnitine/urea which was attributed to the higher reactivity of the melt. (Scheme 5) In both cases, no attempt was made at catalyst and solvent recycling and the reaction was only studied for alkyl azides.

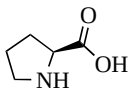
2. Results and discussions

In light of Köenig's success, we elected to pursue a one-pot azidation/click reaction in the easily available, inexpensive, and non-toxic DES choline chloride/glycerol (CC/G). We hoped to achieve conditions that would enable the conversion of aryl bromides to aryl azides and also be able to recycle the solvent and catalyst.

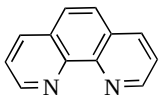
Table 1. Survey of Click Reactions Using Deep Eutectic Mixtures



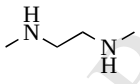
1 (1.0 mmol) + **2** (1.0 mmol) → **3**



L- Proline
L1



1, 10- Phenanthroline
L2



N,N' - Dimethyl-
ethylenediamine (L3)

entry	modified conditions	yield[a] (%)
1	ligand L1 instead of L3	0
2	ligand L2 instead of L3	0
3	standard conditions	88
4	without ligand	trace
5	5 mol% CuI	60
6	without CuI	0
7	CC/Urea instead of CC/Glycerol	11

[a] Isolated yields

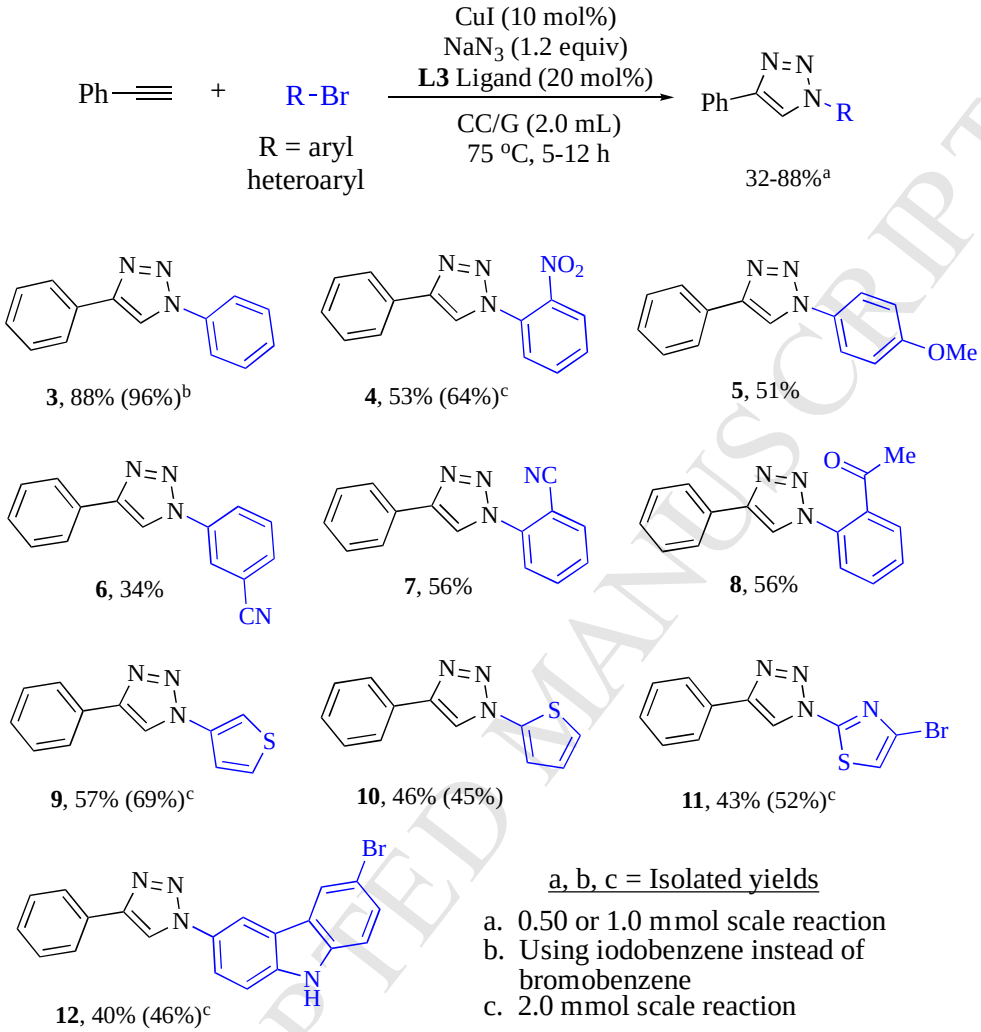
Initial screening was done using bromobenzene as the aryl halide and phenyl acetylene as the alkyne. Several different ligands commonly used in copper-catalyzed chemistry were explored, including proline, *N*,*N*'-dimethylethylenediamine (DMEDA), and phenanthroline. Of these, only DMEDA afforded the desired triazole product, fortunately in good yield (88%). (Table 1) While proline is a very common ligand for copper catalyzed chemistry, it has not been reported by any group to be effective for the one-pot azidation/click reaction of aryl bromides – only aryl iodides. It seems likely that DMEDA, a stronger electronic rich sigma donor, is likely better able

to both stabilize and activate the copper catalyst, compared to proline.[17] As such, it is likely that other 1,2- *N*,*N'*-dimethylamines would also work under the present conditions.

Not surprisingly, both ligand and copper were important for reaction, but the catalyst loading could be lowered to 5 mol% with a modest decrease in yield, (Table 1, entry 5) indicating that some further optimization of this parameter may be possible. It is also worth noting that use of the more common choline chloride/urea DES afforded a very low yield (Table 1, entry 7) of the triazole product, presumably due to the urea interfering in the catalytic cycle of the reaction.[18]

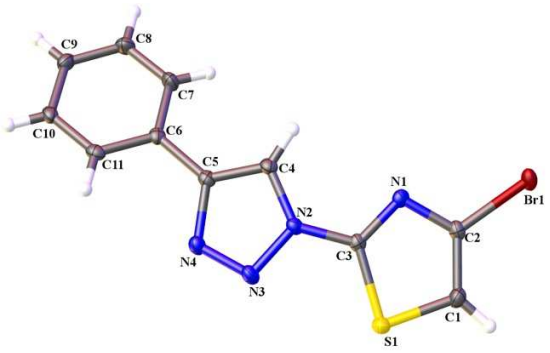
Armed with this success, a wider range of aryl bromide were explored including electron rich and deficient, ortho-substituted, heteroaromatic, and even dibromo arenes. (Figure 1) Yields ranged from excellent to modest. Not surprisingly, iodobenzene afforded a better yield when compared to the less reactive bromide (Figure 1, compound **3**). Interestingly, electron-deficient aryl bromides did not afford better yields when compared to the reaction with electron-rich para-bromoanisole (Figure 1, compound **5**) and ortho substitution did not appear to affect the reaction negatively based upon the examples studied. In the case of 3,6-dibromocarbazole, only a 40 % yield of the monotriazole product (**12**), was observed, which can likely be attributed to its poor solubility in the DES.

Figure 1. Reactions with Phenylacetylene



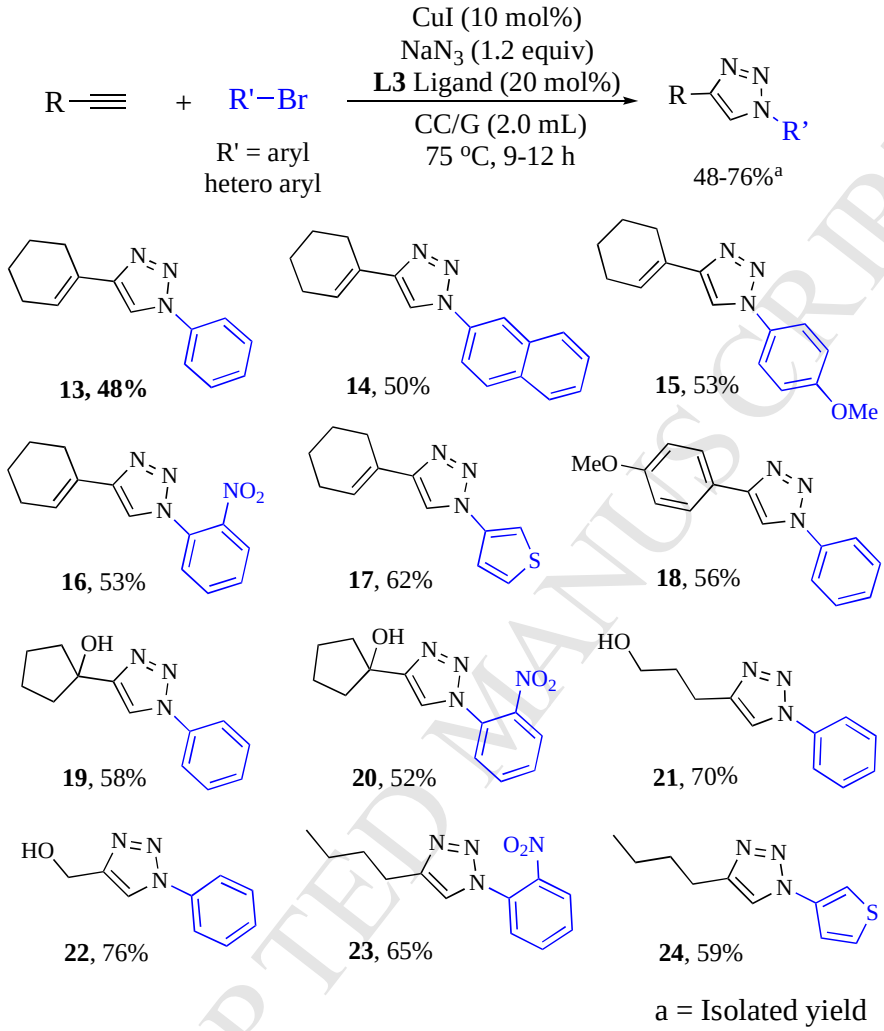
The reaction between phenylacetylene and 2,4-dibromothiazole resulted in 4-bromo-2-(4-phenyl-*1H*-1,2,3-triazol-1-yl)thiazole (**11**) as a major product. For unequivocal determination of the regioselectivity of this reaction, compound **11** (the only isomer formed) was crystallized from an ether solution layered with pentane at 4 °C and the resulting crystal subjected to x-ray crystallography (Figure 2).

Figure 2. X-ray Structure of Compound **11**



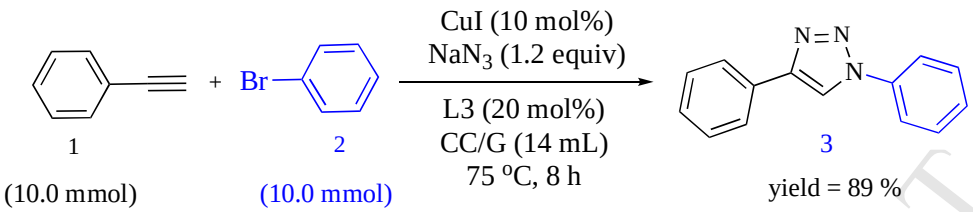
To further probe the utility of these reaction conditions, the reaction of various alkynes with different aryl bromides were performed. (Figure 3) Various functionalized alkynes afforded reasonable yields of the anticipated triazoles. 1-Ethynylcyclohexene and 1-hexyne were found to react successfully with heteroaryl 3-bromothiophene (**17** and **24**) resulting in yields of the predicted products comparable to those observed with the generally more reactive phenylacetylene, thus supporting the generality of these reaction conditions.

Figure 3. Alkyne Studies



a = Isolated yield

Next, the scalability of the reaction protocol was evaluated by performing the gram-scale synthesis of 1,4-diphenyl-1*H*-1,2,3-triazole (**3**) employing 10.0 mmol each of **1** and **2** in the presence of DMEDA and CuI in a deep eutectic solvent. The desired product (**3**) was isolated in 89% yield (Scheme 1) demonstrating the utility of the protocol in large scale synthesis of 1,4-disubstituted triazoles.

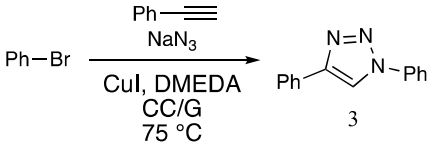


Scheme 1. Scale-up Experiment

More modest scale-up (2 mmol) was performed on four other combinations. (Figure 1) Interestingly, an overall increase of 6-12% in yield was observed for these reactions, affording improved yields of compounds **4**, **9**, **11**, and **12** respectively. These observations strongly support the scalability of this reaction protocol accompanied by a modest increase in the reaction yield in comparison to small scale reactions.

One other key feature of the DES was also explored – its recyclability. This feature was demonstrated using two reactions (Tables 2 and 3). All reactions were carried out using 1.0 mmol aryl halides, 1.0 mmol alkyne, 1.2 mmol sodium azide, 0.1 mmol CuI, 0.2 mmol DMEDA, and 2 mL solvent kept in a reaction vessel and stirred at 75 °C for the specified time. Product separation was accomplished by extraction with ethyl acetate. Each cycle represents a subsequent use of the recycled reaction medium which includes catalyst and ligand.

Table 2. Recycling Study Using Bromobenzene

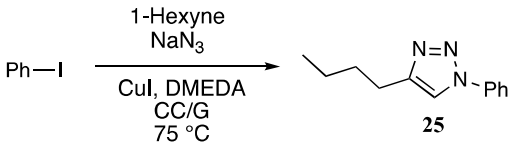


Entry	Time (h)	Yield (%)
0	9	86%
1	9	83%
2	10	56%
3	12	18%
4[a]	9	83%

a. 0.20 mmol of DMEDA was added

For Table 2, during the extraction process, the addition of ethyl acetate resulted in a suspension which made layer separation more difficult and raised the possibility of catalyst leaching. In the presence of copper catalyst, the addition of ligand gives a bluish green color to the mixture. But, after the second cycle, the reaction mixture turned reddish. This may be presumed to be the result of a significant decrease in the ligand concentration during the previous extraction processes. In the fourth cycle, the addition of 0.2 mmol of DMEDA restored activity, giving an 83% yield. This suggests that a small amount of catalyst is also sufficient to drive the reaction if there is a certain minimum amount of ligand present in the reaction medium.

Table 3. Recycling Study Using Iodobenzene and 1-Hexyne



25

Entry	Time (h)	Yield [a](%)
0	9	97%
1	9	88%
2	10	81%

a. Isolated yield

In case of Table 3, a different reaction using iodobenzene was explored for recycling. Not surprisingly, yields were good for the initial reaction and two subsequent recyclings, with less reduction in yield than had been observed in the case of bromobenzene. While part of this observation can be attributed to the higher reactivity of iodobenzene, it is also likely a feature of the easy and complete extraction of the product because of its high solubility in EtOAc and the fact that no suspension was formed. As a result, leaching of both the catalyst and ligand presumably decreased allowing more efficient recycling of reaction medium and catalyst, although the observed decrease in yield suggests some loss (most likely of ligand) even in this case.

3. Conclusions

In conclusion, we have developed a convenient, versatile, and scalable one-pot method for the synthesis of N-aryl 1,2,3-triazoles starting from aryl and heteroaryl bromides in which both the

solvent (an environmentally friendly DES) and the catalyst are recyclable. Key features include the use of simple and relatively inexpensive reaction conditions, the ability to use a wide range of aryl and heteroaryl bromides as well as alkynes with moderate to good efficiency, and the ability to recycle the catalyst and solvent (with ligand leaching being the current limiting feature). This method serves to considerably expand the range of triazoles that are readily available for further study and application.

4. Experimental section

General Information. All the reactions were done under an air atmosphere. ^{1}H and ^{13}C NMR of all the compounds were recorded on JEOL AS (500 and 125 MHz, respectively) NMR instrument and chemical shifts were recorded in ppm. All the chemical shifts were recorded taking $CDCl_3$ or DMSO as a standard reference.[19] The following conventions are used for multiplicities: s, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; *dd*, doublet of doublet; *tt*, triplet of triplet; *dt*, double of triplet; *ddd*, doublet of double doublet; *br*, broad. Varian 8000 FT-IR was used to collect IR spectra. All the extracts were concentrated under reduced pressure using a Buchi Rotary Evaporator. During purification and identification of compounds, Thin Layer Chromatography (TLC) was performed on silica coated TLC plates and it was monitored by short wavelength (254 nm) UV light. The product was purified by silica gel column chromatography. ACS grade reagents were employed during the experiments.

4.1. General Procedure (1.0 mmol scale reaction)

To a reaction vessel (3-dram scintillation glass vial), terminal alkyne (1.0 mmol), aryl bromide (1.0 mmol), 0.079 g (1.20 mmol) sodium azide, 0.019 g (0.10 mmol) CuI, 0.018 mg (0.2 mmol)

ligand (*N,N'*-dimethylethylenediamine, L3), and 2.0 mL solvent (1:2 molar mixture of choline chloride and glycerol) was added and placed in a sand bath heated at 75 °C (unless otherwise specified) over a magnetic hot plate. The reaction mixture was stirred for the specified time (5-12 hr). The resulting mixture was extracted by EtOAc and concentrated in vacuo. The residue obtained was purified by flash column chromatography.

4.2. General Procedure (0.5 mmol scale reaction)

To a reaction vessel (3-dram scintillation glass vial), terminal alkyne (0.50 mmol), aryl bromide (0.50 mmol), 0.040 g (0.60 mmol) sodium azide, 9.5 mg (0.05 mmol) CuI, 8.8 mg (0.10 mmol) ligand (*N,N'*-dimethylethylenediamine, L3), and 1.5 mL solvent (1:2 molar mixture of choline chloride and glycerol) was added and placed in a sand bath heated at 75 °C (unless otherwise specified) over a magnetic hot plate. The reaction mixture was stirred for the specified time (5-12 hr). The resulting mixture was extracted by EtOAc and concentrated in vacuo. The residue obtained was purified by flash column chromatography.

4.3. Characterization Data for Isolated Compounds

Characterization data for the compounds 3, 4, 5, 8, 9, 10, 13, 15, 18, 21, 22, and 25 can be found in the supplementary information.

3-(4-phenyl-1H-1,2,3-triazol-1-yl)benzonitrile ***(6)***

Reaction (0.5 mmol scale) was stirred for 12 hours under standard condition. Yield: 41%; white solid, mp 208 ^{o}C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 9.42 (s, 1H), 8.48 (m, 1H), 8.34 (dd, *J* = 7.5, 2.5 Hz,1H), 8.0 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 6.0 Hz, 2H), 7.85 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5, Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 147.6, 137.0,

132.3, 131.4, 129.9, 129.2, 128.5, 125.4, 124.6, 123.4, 119.9, 177.9, 112.8. IR (neat) 3123, 3100, 2925, 2233, 1588, 1477, 1402, 1235, 1045, 1019, 907, 810, 773, 686 cm-1. HRMS (EI): [M+H]+, calcd for $C_{15}H_{11}N_4$, 247.0983, found 247.0985.

*2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzonitrile (**7**)*

Reaction (1 mmol scale) was stirred for 12 hours under standard condition. Yield: 56%; white solid, mp 148-150 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.47 (s, 1H), 7.99 – 7.96 (m, 1H), 7.95 – 7.91 (m, 2H), 7.89 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.62 (td, *J* = 7.5, 1.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 148.7, 138.6, 134.6, 134.5, 129.7, 129.6, 129.1, 128.8, 126.2, 125.4, 119.9, 115.9, 105.4. IR (neat) 3131, 2922, 2232, 1601, 1579, 1509, 1484, 1449, 1414, 1230, 1162, 1026, 993, 763, 688 cm^{-1}. HRMS: M^+, calcd for $C_{15}H_{10}N_4$, 246.09054, found 246.09052.

*4-bromo-2-(4-phenyl-1H-1,2,3-triazol-1-yl)thiazole **(11)***

Reaction (1 mmol scale) was stirred for 12 hours under standard condition. Yield: 43%; off-white solid, mp 118-120 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.62 (s, 1H), 7.91-7.89 (m, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.18 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 157.4, 148.9, 129.2, 129.1, 126.1, 123.2, 116.9, 115.5. IR(neat) 3166, 3108, 2920, 1521, 1451, 1417, 1227, 1022, 985, 877, 769, 695 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{11}H_8BrN_4S$, 306.9653 and 308.9632, found 306.9650 and 308.9631.

*3-bromo-6-(4-phenyl-1H-1,2,3-triazol-1-yl)-9H-carbazole **(12)***

Reaction (1 mmol scale) was stirred for 9 hours under standard condition. Yield: 40%; off-white solid, mp > 250 ^{o}C). ^{1}H NMR (500 MHz, DMSO-D_6) δ = 11.82 (s, 1H), 9.31 (s, 1H), 8.82 (d, *J* = 2.0 Hz, 1H), 8.53 (d, *J* = 1.5 Hz, 1H), 7.05-7.98 (m, 3H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.63 (dd, *J* =

8.5, 2.0 Hz, 1H), 7.57 (dd, *J* = 15.0, 8.0 Hz, 3H), 7.43 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-D_6) δ = 148.0, 140.6, 140.2, 131.4, 130.2, 129.9, 129.8, 129.0, 126.2, 125.1, 124.3, 122.7, 121.0, 120.3, 114.4, 114.1, 113.1, 112.1. IR (neat) 3290, 2925, 2854, 1510, 1458, 1279, 1242, 950, 795, 762, 695 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{20}H_{14}BrN_4$, 389.0401 and 391.0381, found 389.0404 and 391.0399.

4-(cyclohex-1-en-1-yl)-1-(naphthalen-2-yl)-1H-1,2,3-triazole ***(14)***

Reaction (0.5 mmol scale) was stirred for 9 hours under standard condition. Yield: 50%; white solid, mp 141-142 ^oC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.11 (s, 1H), 7.95-7.92 (m, 2H), 7.88-7.85 (m, 3H), 7.55-7.50 (m, 2H), 6.66-6.65 (m, 1H), 2.47-2.44 (m, 2H), 2.26-2.22 (m, 2H), 1.82-1.78 (m, 2H), 1.72-1.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 150.2, 134.6, 133.3, 132.8, 129.9, 128.3, 127.9, 127.4, 127.0, 126.9, 125.9, 118.9, 118.1, 116.4, 26.5, 25.4, 22.5, 22.3. IR (neat) 3134, 2929, 1607, 1514, 1484, 1424, 1366, 1235, 1216, 1037, 814, 754 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{18}H_{18}N_3$, 276.1500, found 276.1498.

4-(cyclohex-1-en-1-yl)-1-(2-nitrophenyl)-1H-1,2,3-triazole ***(16)***

Reaction (0.5 mmol scale) was stirred for 9 hours under standard condition. Yield: 53%; yellow solid, mp 130-131 ^oC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.04 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.77 (td, *J* = 8.0, 1.5 Hz, 1H), 7.68-7.65 (m, 2H), 7.62 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.66-6.64 (m, 1H), 2.44-2.41 (m, 2H), 2.26-2.22 (m, 2H), 1.82-1.77 (m, 2H), 1.72-1.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 150.0, 144.4, 133.8, 130.5, 130.3, 127.7, 126.6, 126.4, 125.5, 119.5, 26.4, 25.4, 22.4, 22.2. IR (neat) 3152, 2929, 2862, 1607, 1525, 1503, 1354, 1045, 1026, 858, 788, 747, 706 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{14}H_{15}N_4O_2$, 271.1195, found 271.1196.

4-(cyclohex-1-en-1-yl)-1-(thiophen-3-yl)-1H-1,2,3-triazole ***(17)***

Reaction (0.5 mmol scale) was stirred for 12 hours under standard condition. Yield: 62%; off-white solid, mp 128-130 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.74(s, 1H), 7.52 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.46-7.41 (m, 2H), 2.43-2.40 (m, 2H), 2.23-2.20 (m, 2H), 1.80-1.76 (m, 2H), 1.70-1.67 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 149.7, 136.2, 127.2, 126.9, 125.9, 120.8, 116.8, 113.6, 26.5, 25.4, 22.5, 22.2. IR (neat) 3141, 3048, 2926, 2858, 1559, 1436, 1231, 1052, 791, 706 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{12}H_{14}N_3S$, 232.0910, found 232.0908.

*4-(1-hydroxycyclopentyl)-1-phenyl-1H-1,2,3-triazole (**19**)*

Reaction (1 mmol scale) was stirred for 12 hours under standard condition. Yield: 58%; white solid, mp 120-123 °C. ^{1} H NMR ($CDCl_3$, 500 MHz) δ = 7.92 (s, 1H), 7.73 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 2.33 (s, 1H, -OH), 2.25-2.19 (m, 2H), 2.09-1.97 (m, 4H), 1.91-1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 155.1, 137.2, 129.7, 128.7, 120.6, 118.3, 79.1, 41.4, 23.7. IR (neat) 3332, 3144, 2944, 1599, 1502, 1441, 1217, 1179, 1063, 937, 751 cm^{-1}. HRMS: M^+, calcd for $C_{13}H_{15}N_3O$, 229.12151, found 229.12153.

*1-(1-(2-nitrophenyl)-1H-1,2,3-triazol-4-yl)cyclopentan-1-ol **(20)***

Reaction (0.5 mmol scale) was stirred for 12 hours under standard condition. Yield: 52%; yellow solid, mp 130-131 ^{o}C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.06 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.80-7.77 (m, 2H), 7.69 (td, *J* = 7.5, 1.0 Hz, 1H), 7.63 (dd, *J* = 7.5, 1.0 Hz, 1H), 2.39 (s, 1H, -OH), 2.25-2.19 (m, 2H), 2.08-1.96 (m, 4H), 1.90-1.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 155.0, 144.5, 133.9, 130.7, 130.4, 128.0, 125.6, 121.7, 79.0, 41.4, 23.7. IR (neat) 3353, 3141, 2955, 2873, 1532, 1510, 1365, 1231, 1067, 1015, 780, 747 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{13}H_{15}N_4O_3$, 275.1144, found 275.1148.

4-butyl-1-(2-nitrophenyl)-1H-1,2,3-triazole (**23**)

Reaction (0.5 mmol scale) was stirred for 12 hours under standard condition. Yield: 65%; yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.03 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.78 (tt, *J* = 7.8, 1.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.64-7.63 (m, 1H), 7.61 (s, 1H), 2.81 (t, *J* = 7.2 Hz, 2H), 1.77-1.67 (m, 2 H), 1.48-1.36 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 149.1, 144.4, 133.8, 130.5, 127.8, 125.5, 122.2, 31.4, 25.2, 22.3, 13.8. IR (neat) 3145, 3074, 2959, 2933, 2866, 1611, 1536, 1510, 1357, 1235, 1041, 855, 784, 736 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{12}H_{15}N_4O_2$, 247.1195, found 247.1191.

4-butyl-1-(thiophen-3-yl)-1H-1,2,3-triazole (**24**)

Reaction (0.5 mmol scale) was stirred for 12 hours under standard condition. Yield: 59%; colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.66 (s, 1H), 7.52 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.46-7.42 (m, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 1.73-1.67 (m, 2 H), 1.45-1.38 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 148.6, 136.1, 127.0, 120.7, 113.5, 118.6, 31.4, 25.2, 24.6, 22.2, 13.7. IR (neat) 3109, 2960, 2929, 2862, 1566, 1547, 1469, 1425, 1227, 1045, 862, 780 cm^{-1}. HRMS (EI): $[M+H]^+$, calcd for $C_{10}H_{14}N_3S$, 208.0908, found 208.0907.

4.4.Recyclability of the Reaction Medium

To study the recyclability of the reaction medium, two reactions were employed (Table 3 and 4). General method involved addition of phenylacetylene (1.00 mmol), bromobenzene (1.00 mmol), sodium azide (1.20 mmol), CuI (0.10 mmol), ligand (0.20 mmol) (*N*,*N*'-dimethylethylenediamine), and 2.0 mL of solvent (1:2 molar mixture of choline chloride and glycerol) into a reaction vessel and placed in a sand bath heated at 65 °C. The reaction mixture was stirred overnight. After the completion of reaction, the reaction mixture was extracted with EtOAc. Once the extraction process was completed, additional reactant species i.e. aryl bromide,

phenyl acetylene, and sodium azide were added to the same reaction vessel and reaction was conducted under the same conditions. In this way, after the complete extraction of the desired product in each cycle, a new cycle was carried out in the same vessel using the same reaction medium. Unless specified, no additional ligand (*N*,*N'*-dimethylethylenediamine) and catalyst were added.

4.5. Crystallographic data for compound 11

The structure was solved by SHELXT (Sheldrick 2015) program and refined by anisotropic (isotropic for H atoms) full-matrix least-squares method against F2 of all reflections also by SHEXL (Sheldrich, 2008). The positions of the hydrogen were geometrically calculated. Details are available in CIF file, attached as a supplementary information. Alongside some useful information is summarized in SI-7.

Supporting Information

The Supporting Information can be found at …….

Characterization data for isolated compounds

X-ray Crystallographic Data of compound **11** (CIF)

NMR Spectra of isolated products **3-25**

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