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Efficient synthesis of 1,4-disubstituted triazolyl *N*-carboxamides *via* a simple and convenient MCR using basic alumina as solid support

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Abstract: A microwave assisted green protocol for the synthesis of 1,4-disubstituted triazolyl *N*-carboxamides was explored using basic alumina as solid support. The method allows domino Ullmann-type reaction, Click reaction and formation of ester or amide linkages in a single reaction vessel using Cu(phen)(PPh_3)Br and CMPA as catalyst and basic alumina as solid support in high yield. The protocol did not require addition of any external ligands or base. The method was also found to be equally good for the synthesis of *bis* triazole adducts.

Key words: Triazolyl *N*-carboxamide; Domino reaction, Ullmann-type reaction; Click reaction; ester and amide linkages; Cu(phen)(PPh_3)Br; CMPA

Organic reactions executed under non-traditional experimental conditions using less expensive and recyclable mineral supports (*e.g.*, silica gel, alumina) have attracted great attention in recent years, primarily to circumvent growing environmental concerns.[1] The use of solid support in microwave-assisted reactions eliminates the need for solvents and also the requirement of sealed vessels. It also enables microwave-accelerated reactions to occur at atmospheric pressure and is suitable for preparative scale synthesis.[2] Moreover, the homogenous dispersion of active sites, improved selectivity, enhanced reaction rates, easy work-up procedure make the solid-supported reactions more attractive than the conventional solution phase reactions.[3]

Glycoconjugates, namely glycoproteins, glycolipides or peptidoglycans, have been found to play crucial roles in varied life processes.[4] There are numerous methodologies[5] for the preparation of such glycoconjugates. However, these compounds are often not suitable for biological studies as the glycosidic bonds are venerable towards chemical and enzymatic hydrolysis. Synthesis of unnatural glycoconjugates, for example triazolyl glycosides, where triazole is connected to the sugar unit *via* an isosteric linkage, may lead to metabolically more stable analogues and provide a way for the elucidation of biochemical pathways.[6] These

unnatural glycosides may also be useful for targeting drugs to specific binding sites.[7]

Glucose-based inhibitors with NHCO as linker between the sugar and the aromatics showed potent activity against glycogen phosphorylase which is a validated target against type 2 diabetes mellitus (Fig. 1a and 1b).[8] Successful bioisosteric modification of the amide with different heteroaromatic compounds leading to compounds having better inhibition properties are also known[8]. These motivated us to synthesize a library of compounds where sugar moieties were linked to 1,2,3-triazoles by NHCO bonds and long hydrophobic chain in an environmentally benign chemical process (Fig. 1c). The long linking arm is likely to make the sugar moiety available for better binding with the appropriate receptor.[9] Beside this, the triazole-linked glycoconjugates are also known to display wide range of biological activities such as anti-HIV,[10] anti-allergic,[11] antibacterial,[12] herbicidal,[13] and fungicidal activity;[13] act against the cognate and non-cognate GH1[14] and also as FimH antagonists.[15] Syntheses of triazole-linked glycoconjugates with varied spacer arms thus may be significant for the evaluation of such biological activities. These new class of compounds may also influence the pharmacokinetics and may be used for drug targeting.

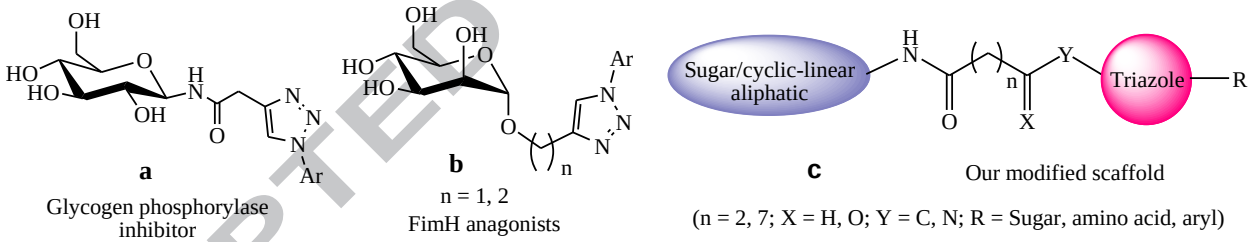


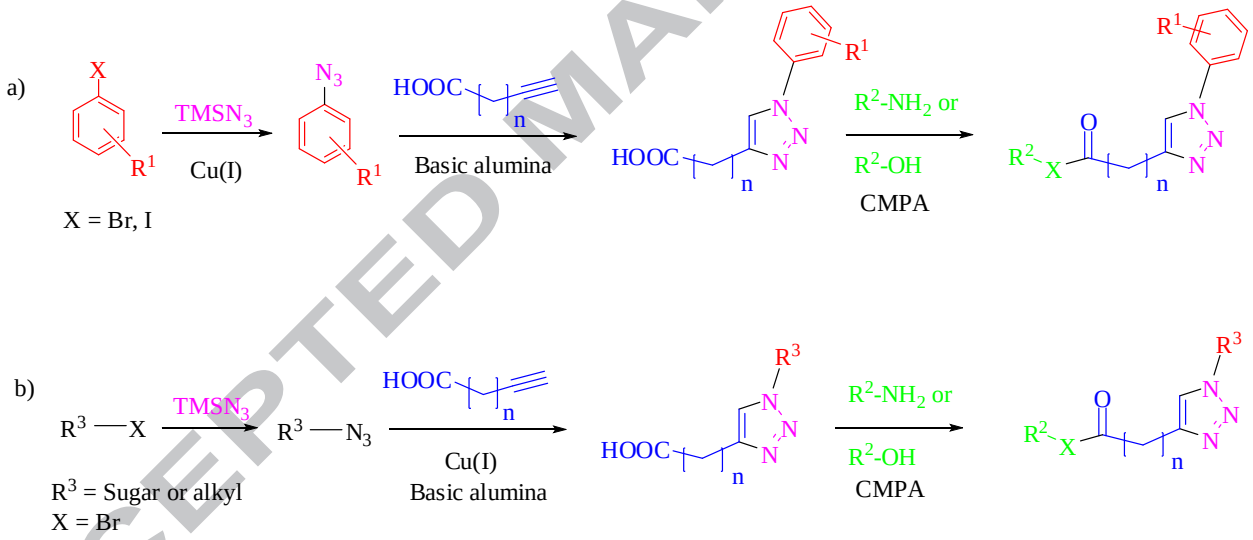
Figure 1. Carbohydrate linked triazole and triazolyl *N*-carboxamides.

The synthesis of triazolyl *N*-carboxamides using traditional methods is a three-step process. Firstly, the aliphatic or aromatic azides are synthesized followed by copper-mediated azide–alkyne cyclization. Finally the amide or ester linkages are formed. The traditional chemical synthesis requires extensive chromatographic purification of intermediates, which is tedious and time consuming.

Aryl azides are normally prepared by the replacement of diazonium salts or activated aryl halides with azides.[16] Coupling of inactivated aryl halides with sodium azide in presence of Cu(I)-ligands are also reported.[17] However, like other Ullmann-type reaction[18] the methods suffer from the use of high temperature and slow reaction rate. Several other factors such as nature of the ligand or solvent system are crucial in these processes. But, the main drawback

of this method is the handling of triflic azide.

Therefore, our aim was to develop an environmentally benign chemical process, where these limitations could be avoided by using recyclable solid support without utilization of any solvent, additional base or ligands. The one-pot reaction was designed in such a way that consecutive cyclization and ester/amide bond formation could be achieved in a single pot without purification of the intermediates (Scheme 1a and 1b). The new protocol allows domino Ullmann-type reaction, Click reaction and formation of ester or amide linkages in a single reaction vessel using Cu(phen)(PPh_3)Br as catalyst and chloro-phenyl-thio-methylene-dimethylammonium chloride (CMPA) as coupling agent using basic alumina as solid support. The use of basic alumina eliminates requirement of any additional solvent and it also act as base. Moreover, the microwave heating at controlled temperature and pressure reduces the reaction time drastically.



Scheme 1. Four-component one-pot synthesis of triazolyl-*N*-carboxamides under microwave irradiation.

At the outset, we opted iodobenzene and $TMSN_3$ as model reactants and investigated the feasibility of a ligand-free Ullmann-type reaction to form phenyl azide, under microwave irradiation (Table 1) at 70 °C (100 W). Systematic studies of the reaction conditions in presence of different solid supports (*viz*. basic alumina, TiO_2, MgO and etc.), and various copper catalysts[19] demonstrated that the use of basic alumina as solid support gave better yield (Table 1) even in the absence of additional base (triethyl amine, DBU) or without the requirement of any extra ligand. The effect of different copper catalysts (Fig. 2) were also

investigated (Table 1, entry 1-12). Copper catalysts **1a-b**, yielded azido benzene in 52% and 40% (found in repetitive experiments) respectively. Use of catalysts **1c** and **1d** gave yield of 47% and 53% respectively. Similar observations were noted for thio-copper complex **1e-g**. Use of catalyst **1h** was found to be very effective for the particular reaction with an excellent yield of 88% (Table 1, entry 12).

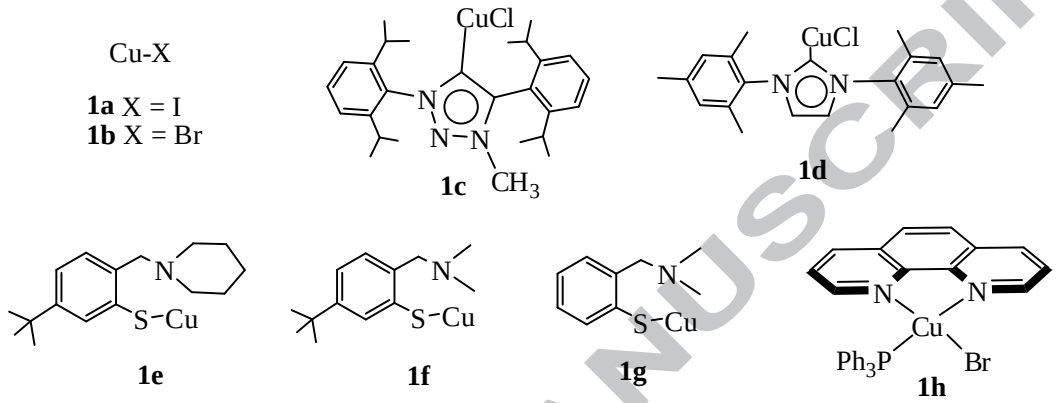


Figure 2. Copper catalysts used in the study.

Table 1: Optimization of catalyst towards the synthesis of azido benzene from iodobenzene and $TMSN_3$ using various solid-supports

Entry[a]	Solid support	Catalyst used	Catalyst (mol %)	Time (min)	Yield[b] (%)
A. *Without additional base*					
1	TiO_2	**1a**	10	8	20
2	TiO_2	**1a**	15	10	24
3	TiO_2	**1a**	20	10	24
4	MgO	**1a**	15	10	32
5	Basic alumina	**1a**	15	10	52
6	Basic alumina	**1b**	15	10	40
7	Basic alumina	**1c**	15	10	47
8	Basic alumina	**1d**	15	10	53
9	Basic alumina	**1e**	15	10	64
10	Basic alumina	**1f**	15	10	68
11	Basic alumina	**1g**	15	10	72
12	Basic alumina	**1h**	15	10	88
B. *With Et_3N as additional base*					

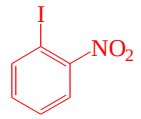
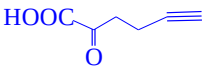
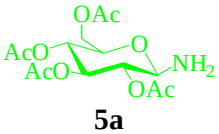
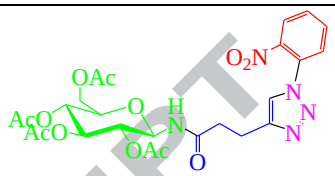
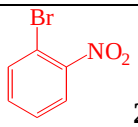
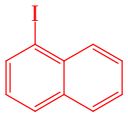
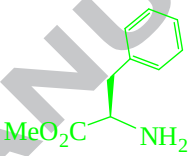
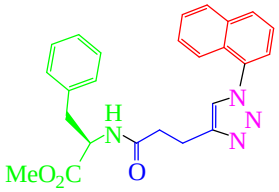
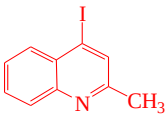
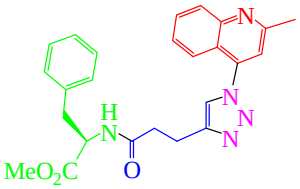
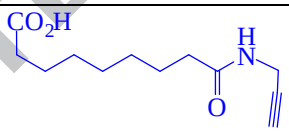
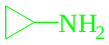
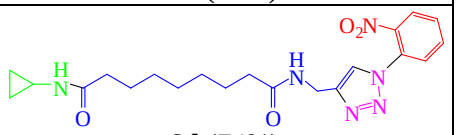
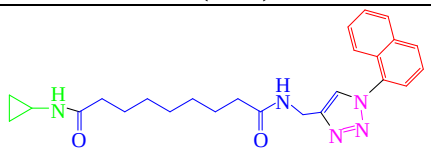
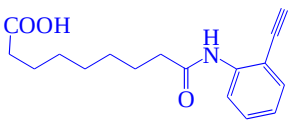
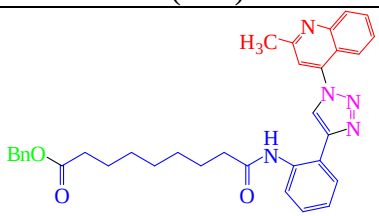
13	Basic alumina	**1h**	15	10	88
C. *With DBU as additional base*					
14	Basic alumina	**1h**	15	10	86

[a]All reactions were performed using iodobenzene (1.0 equiv.) and $TMSN_3$ (1.1 equiv.) under microwave irradiation (100 W, 70 °C). Solid support (500 mg-1 gm) was used in each case.
[b]Isolated yield

Formation of triazoles by Huisgen 1,3-dipolar cycloaddition reaction between terminal alkynes and organic azides is quite efficient and had proved to be an easy route to 1,4-disubstituted 1,2,3-triazoles.[20] So, organic azides generated *in situ*, were reacted further with terminal alkyne (Scheme 1a) for additional 2-3 min (100 °C, 60W). The complete conversion to corresponding triazole was confirmed by TLC. Our next challenge was the consecutive formation of ester or amide linkages in the same reaction vessel. Usually the ester/amide bond is formed by the nucleophilic substitution of activated esters generated *in situ* from the corresponding acids. Several reagents such as Palomo's reagent, Castro's or Taddei's reagent, chloro-phenyl-thio-methylene-dimethylammonium chloride, carbodiimide derivatives or Mukayama's reagent are used for this purpose.[21] Although these reagents are very useful and efficient, some of these exhibit drawbacks like formation of side products, slow reaction rate, difficulty during removal, use of organic solvents and low solubility or chemo-selectivity. In our one-pot protocol, CMPA was used which was added to the reaction mixture and further irradiated under microwave for an additional period of 5 min. Basic alumina here plays dual role. It acts as solid support (absorb the organic compounds on their surface) and transmits microwave irradiation without absorbing or restricting it. It also acts as base by trapping HCl, generated during the reaction and hence the equilibrium was shifted towards the forward direction. No additional base was required.

Once we standardized our one-pot domino protocol, the scope of the methodology was tested with with varied functionalities (Table 2). All the reactions proceeded well and products were formed in good yield. Both aromatic iodides and bromides (Table 2, entry 1 & 2) participated well in the tandem reaction with $TMSN_3$. However, with NaN_3 the yield was found to be low (Table 2, entry 3).

Table 2: Synthesis of versatile 1,4-disubstituted triazolyl-*N*-carboxamides[a]

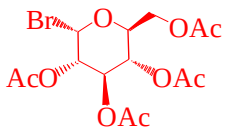
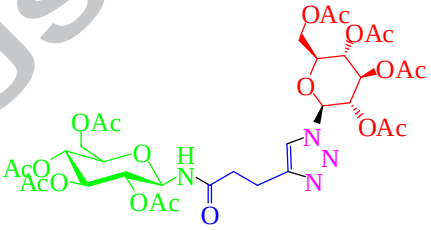
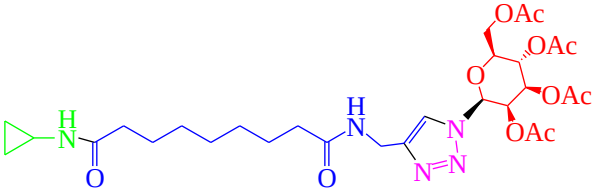
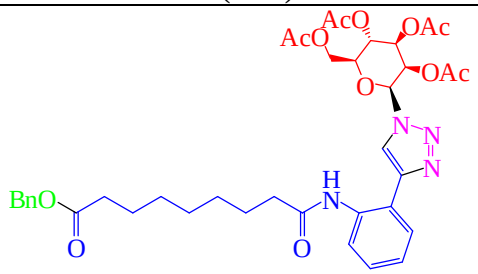
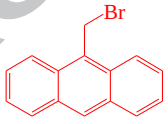
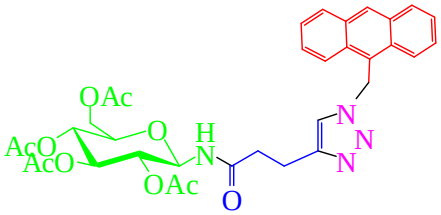
Entry	Halide	Azide	Alkyne	Amine/Alcohol	Product (% Yield)[b]
1	 **2a**	$TMSN_3$ **3a**	 **4a**	 **5a**	 **6a** (81%)
2	 **2b**	**3a**	**4a**	**5a**	**6a** (66%)
3	**2a**	NaN_3 **3b**	**4a**	**5a**	**6a** (31%)
4	 **2c**	**3a**	**4a**	 **5b**	 **6b** (77%)
5	 **2d**	**3a**	**4a**	**5b**	 **6c** (86%)
6	**2a**	**3a**	 **4b**	 **5c**	 **6d** (74%)
7	**2c**	**3a**	**4b**	**5c**	 **6e** (79%)
8	**2d**		 **4c**	$PhCH_2OH$ **5d**	 **6f** (73%)

[a]Reactions were performed using organic halide (1.0 equiv.), $TMSN_3$ (1.1 equiv.), **1h** (15 mol%), terminal alkynes (1.1 equiv.), organic amines or alcohols (1.0 equiv.), CPMA (1.3 equiv.) and basic alumina (500 mg-1 gm), under microwave irradiation. Products were characterized by spectroscopic and analytical techniques.

[b]Yield of the isolated pure product; some losses during purification is unavoidable in certain cases.

The scope of the method was further extended by using different non-aromatic halides (Table 3). The reactions were found to be equally good for glycosyl bromides (Table 3, entry 1-3) as well as activated alkyl bromides (Table 3, entry 4). Maximum yield of 72% was obtained with glycosyl bromides (Table 3, entry 2). All compounds could be deacetylated easily in high yield using sodium methoxide in methanol to obtain the modified scaffold.

Table 3. Synthesis of versatile 1,4-disubstituted triazolyl-*N*-carboxamides[a]

Entry	Halide	Azide	Alkyne	Amine/Alcohol	Product (% Yield)[b]
1	 **2e**	**3a**	**4a**	**5a**	 **6g** (70%)
2	**2e**	**3a**	**4b**	**5c**	 **6h** (72%)
3	**2e**	**3a**	**4c**	**5d**	 **6i** (65%)
4	 **2f**	**3a**	**4a**	**5a**	 **6j** (67%)

[a]Reactions were performed using organic halide (1.0 equiv.), $TMSN_3$ (1.1 equiv.), **1h** (15 mol%), terminal alkynes (1.1 equiv.), organic amines or alcohols (1.0 equiv.), CMPA (1.3 equiv.) and basic alumina (500 mg - 1 gm), under microwave irradiation. Products were characterized by spectroscopic and analytical techniques.

[b]Yield of the isolated pure product; some losses during purification is unavoidable in certain cases.

Different life processes *viz.* immunological process, inflammation, cell differentiation and many signal transductions are governed by multivalent carbohydrate-protein interactions in human body.[22-23] But the molecular basis of such processes are not well known. The syntheses of multidentate carbohydrate-triazole ligands had been achieved recently.[24] For complex oligosaccharides, the binding efficiency to a specific receptor depends on its cluster effect and topological arrangement.[25] Here we have extended the aforementioned protocol for the syntheses of bis-triazole derivatives (Fig. 3). It was observed that the protocol described herein is also well applicable for the synthesis of the bidentate compound **7** and **8**, with a satisfactorily yield (70% and 68% respectively).

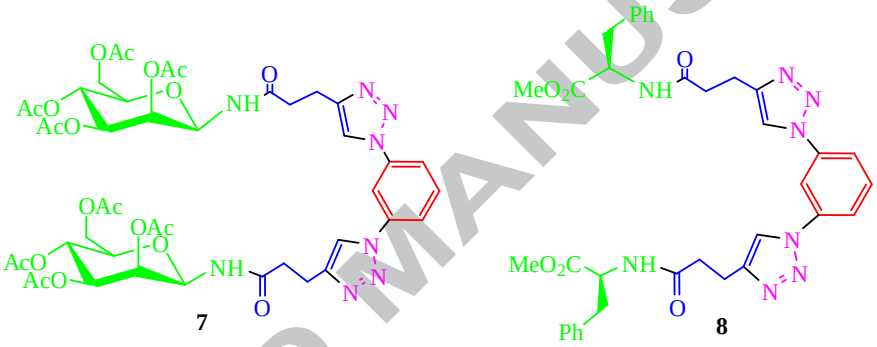


Figure 3. Synthesis of bidentate1,4-disubstituted triazolyl *N*-carboxamides.

In conclusion, we have developed a novel one-pot protocol for the synthesis of triazolyl *N*-carboxamides.[26-27] Unlike previously known processes, the present method excludes the necessity of using additional ligands for the one-pot domino reaction. Use of basic alumina eliminates the necessity of solvents and additional bases. Moreover, application of microwave significantly reduces reaction time. The method was also found to be useful for the synthesis of complex bidentate molecules.

Acknowledgment

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all new compounds) associated with this

article can be found in the online version, at doi…..

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26. *General reaction procedure for the synthesis of triazolyl-N-carboxamides (**6a-j**):* $CHCl_3$ (10-15 mL) was added to a mixture of the aryl halide (1 equiv.), $TMSN_3$ (1.1 equiv.), **1h** (15 mol%.) and basic alumina (500 mg-1 gm) in a round bottomed flask. It was evaporated to dryness and the mixture was stirred at r.t. for an additional 10–15 min to ensure efficient mixing. The flask was then fitted with a septum, and was irradiated in the microwave reactor (70 °C, 100 W) for 6-10 min. The mixture was then cooled and corresponding alkyne (1.1 equiv.) in $CHCl_3$ (1 mL) was added in it and the slurry was stirred at r.t. for 10 min followed by further irradiation of 2-3 min (100 °C, 60 W). Amines or alcohol (1.0 equiv.) and CMPA (1.3 equiv.) was then added in it and irradiated further under microwave (5 min, 60 °C, 100 W). The mixture was then cooled and extracted with EtOAc (25 mL x 3). Column chromatography afforded pure compound.
27. *Representative physical data of the synthesized compounds: Compound 6c***:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (t, 2H, *J* = 7.2 Hz), 2.82 (s, 3H), 3.07-3.13 (m, 2H), 3.20 (t, 2H, *J* = 7.2 Hz), 3.70 (s, 3H), 4.87-4.90 (m, 1H), 6.10 (d, 1H, *J* = 7.5 Hz), 7.06(d, 2H, *J* = 6.9 Hz), 7.12-7.25 (m, 3H), 7.42 (s, 1H), 7.56 (t, 1H, *J* = 7.2 Hz), 7.76-7.83(m, 2H), 7.90 (d, 1H, *J* = 8.4 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.12, 25.32, 35.22, 37.75, 53.12, 117.03, 120.51, 122.65, 123.61, 127.14, 127.33, 128.60, 129.10, 130.58, 135.65, 141.08, 146.86, 149.31, 159.24, 171.32, 171.90 ppm; HRMS (ESI): m/z calcd. for $C_{25}H_{25}N_5O_3$ [M + Na]+: 466.1855; found: 466.1862.

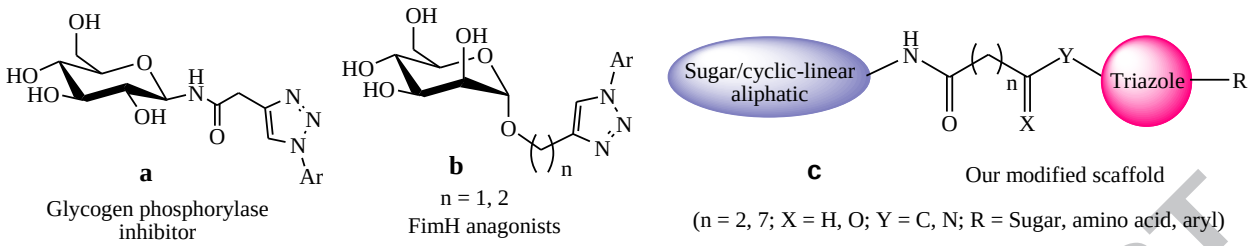
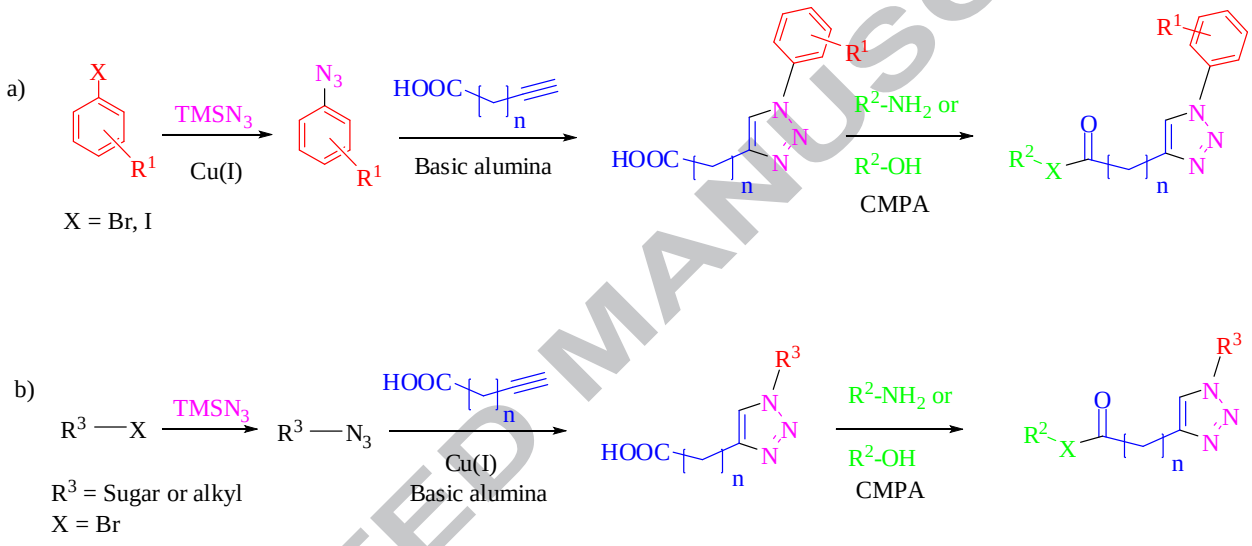


Figure 1. Carbohydrate linked triazole and triazolyl *N*-carboxamides.



Scheme 1. Four-component one-pot synthesis of triazolyl-*N*-carboxamides under microwave irradiation.

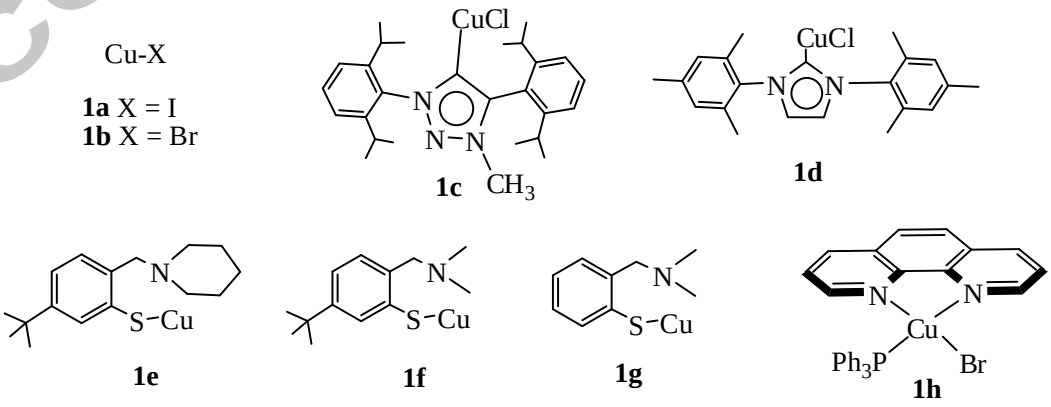


Figure 2. Copper catalysts used in the study.

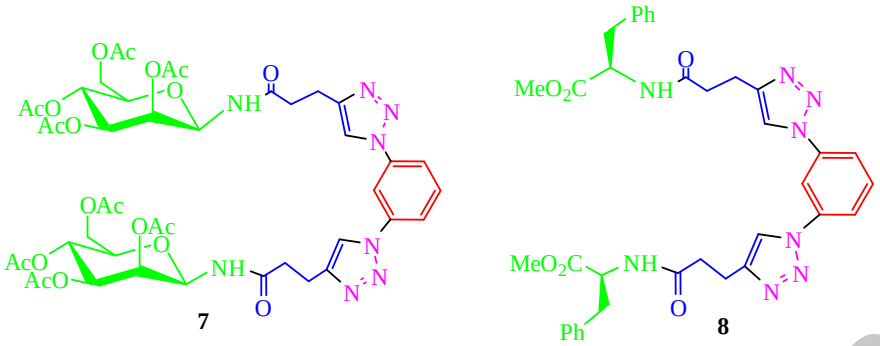


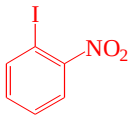
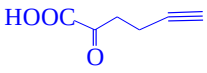
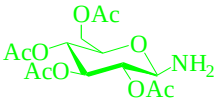
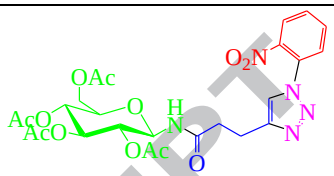
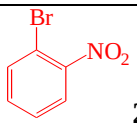
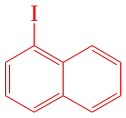
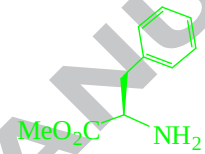
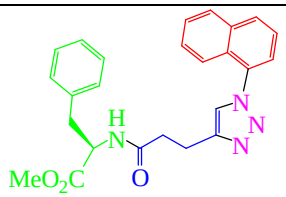
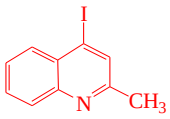
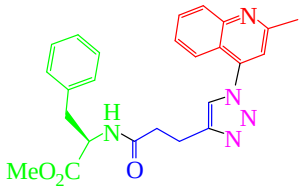
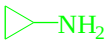
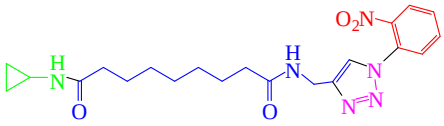
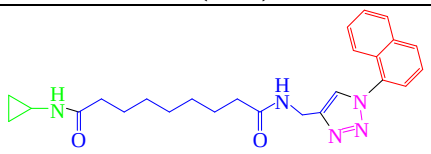
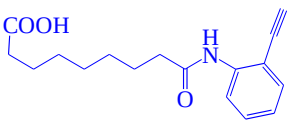
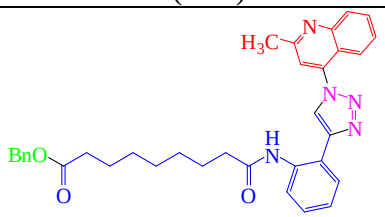
Figure 3. Synthesis of bidentate1,4-disubstituted triazolyl *N*-carboxamides.

Table 1: Optimization of catalyst towards the synthesis of azido benzene from iodobenzene and $TMSN_3$ using various solid-supports

Entry[a]	Solid support	Catalyst used	Catalyst (mol %)	Time (min)	Yield[b] (%)
A. *Without additional base*					
1	TiO_2	**1a**	10	8	20
2	TiO_2	**1a**	15	10	24
3	TiO_2	**1a**	20	10	24
4	MgO	**1a**	15	10	32
5	Basic alumina	**1a**	15	10	52
6	Basic alumina	**1b**	15	10	40
7	Basic alumina	**1c**	15	10	47
8	Basic alumina	**1d**	15	10	53
9	Basic alumina	**1e**	15	10	64
10	Basic alumina	**1f**	15	10	68
11	Basic alumina	**1g**	15	10	72
12	Basic alumina	**1h**	15	10	88
B. *With Et_3N as additional base*					
13	Basic alumina	**1h**	15	10	88
C. *With DBU as additional base*					
14	Basic alumina	**1h**	15	10	86

[a]All reactions were performed using iodobenzene (1.0 equiv.) and $TMSN_3$ (1.1 equiv.) under microwave irradiation (100 W, 70 °C). Solid support (500 mg-1 gm) was used in each case.
[b]Isolated yield

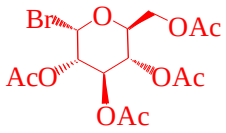
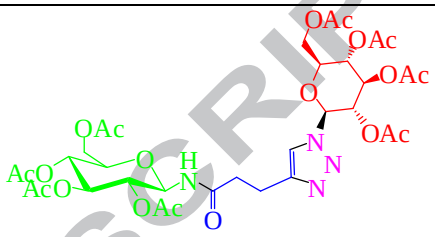
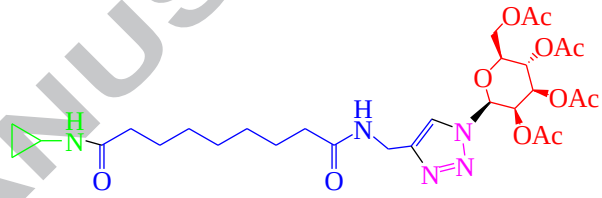
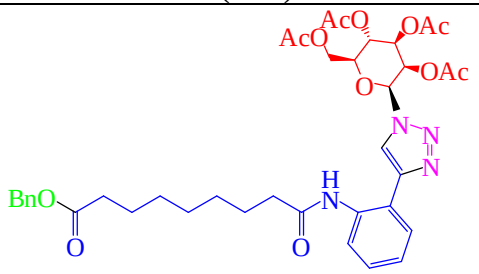
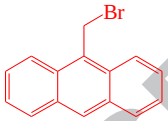
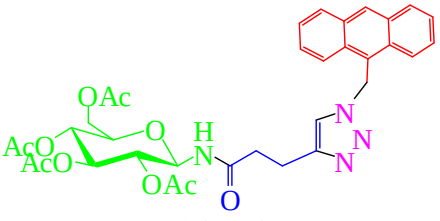
Table 2: Synthesis of versatile 1,4-disubstituted triazolyl-*N*-carboxamides[a]

Entry	Halide	Azide	Alkyne	Amine/Alcohol	Product (% Yield)[b]
1	 **2a**	$TMSN_3$ **3a**	 **4a**	 **5a**	 **6a** (81%)
2	 **2b**	**3a**	**4a**	**5a**	**6a** (66%)
3	**2a**	NaN_3 **3b**	**4a**	**5a**	**6a** (31%)
4	 **2c**	**3a**	**4a**	 **5b**	 **6b** (77%)
5	 **2d**	**3a**	**4a**	**5b**	 **6c** (86%)
6	**2a**	**3a**	 **4b**	 **5c**	 **6d** (74%)
7	**2c**	**3a**	**4b**	**5c**	 **6e** (79%)
8	**2d**		 **4c**	 **5d**	 **6f** (73%)

[a]Reactions were performed using organic halide (1.0 equiv.), $TMSN_3$ (1.1 equiv.), **1h** (15 mol%), terminal alkynes (1.1 equiv.), organic amines or alcohols (1.0 equiv.), CPMA (1.3 equiv.) and basic alumina (500 mg-1 gm), under microwave irradiation. Products were characterized by spectroscopic and analytical techniques.

[b]Yield of the isolated pure product; some losses during purification is unavoidable in certain cases.

Table 3. Synthesis of versatile 1,4-disubstituted triazolyl-*N*-carboxamides[a]

Entry	Halide	Azide	Alkyne	Amine/Alcohol	Product (% Yield)[b]
1	 **2e**	**3a**	**4a**	**5a**	 **6g** (70%)
2	**2e**	**3a**	**4b**	**5c**	 **6h** (72%)
3	**2e**	**3a**	**4c**	**5d**	 **6i** (65%)
4	 **2f**	**3a**	**4a**	**5a**	 **6j** (67%)

[a]Reactions were performed using organic halide (1.0 equiv.), $TMSN_3$ (1.1 equiv.), **1h** (15 mol%), terminal alkynes (1.1 equiv.), organic amines or alcohols (1.0 equiv.), CMPA (1.3 equiv.) and basic alumina (500 mg - 1 gm), under microwave irradiation. Products were characterized by spectroscopic and analytical techniques.

[b]Yield of the isolated pure product; some losses during purification is unavoidable in certain cases.

Graphical Abstract

Efficient synthesis of 1,4-disubstituted triazolyl *N*-carboxamides *via* a simple and convenient MCR using basic alumina as solid support

Rammyani Pal, Swarbhanu Sarkar, Nivedita Chatterjee, Asish Kumar Sen*