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General synthesis of (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines via a copper(I)-catalyzed three-component reaction in water

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Abstract—A copper(I)-catalyzed three-component reaction to form (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines based on the Huisgen cycloaddition using amine, propargyl halide and azide in water was proposed. The process showed considerable synthetic advantages in terms of high atom economy, low environmental impact, atmospheric oxygen, wide substrate scope, mild reaction condition and good yields.

1. Introduction

1,2,3-Triazole derivatives have received much attention because of their wide range of applications[1] and biological activities such as anti-HIV,[2] antimicrobial agents[3] and β_3-adrenergic receptor agonist.[4] The most popular method for the construction of 1,2,3-triazoles frameworks is the 1,3-dipolar Huisgen cycloaddition reaction of azides with alkynes.[1a,5] However, the early Huisgen cycloaddition process required a strong electron-withdrawing substituent either on azide or on alkyne, and were often conducted at high temperature for a prolonged period of time, and usually led to the isolation of a mixture of 1,4-disubstituted- and 1,5-disubstituted-1,2,3-triazoles.[1e,5] Therefore, it is desirable to develop a new, convenient and regiocontrolled synthetic approach for the formation of triazoles. Recently, some important concepts and transition-metal catalysts to overcome the above drawbacks have been proposed.[6] Furthermore, triazoles have been utilized as a backbone of a bidentate phosphine ligand, and some new compounds have been synthesized.[7] These potent usefulness exhibited that the use of triazoles for organic synthetic purposes has been growing in scope and importance.

After extensively reviewed, we found both *N*-substituted and 4- or 5-substituted 1,2,3-trizoles had more potential application than simple 1,2,3-triazole derivatives.[4] Due to the limited number of commercially available alkynes and azides, the complex triazoles are usually synthesized in multi-step sequences. Multi-component reactions have been proven to be a very elegant and rapid way to access complex structures from simple building blocks. As a one-pot reaction, multi-component reactions generally afford good yields and are fundamentally different from two-component reactions in several aspects.[8] Over the past decade, various advanced sequential multi-component reactions have been developed in three- and four-component reactions involving Passerini-,[9] Ugi-,[10] and Mannich-type[11] reactions. In the case of Huisgen cycloaddition reaction, some more recent examples were reported using a one-pot procedure to prepare 1,2,3-triazole derivatives based on the three-component coupling reaction.[1e,12]

The increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for chemical syntheses.[13] Although it would be best not to use any solvent, frequently a solvent is required for a reaction because of various reasons. In such cases, the use of some solvents such as water is desirable.[14] In the last decade, there has been increasing recognition that organic reactions in water may offer advantages over those occurring in organic solvents.[15] The use of water as a solvent offers practical convenience as it alleviates the need to handle flammable, and reduce or eliminate environment damage caused by organic solvents. Water is the cheapest and safest

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solvent available, and frequently better selectivity is obtained in water. It also simplifies the tedious protection–deprotection sequence for molecules containing acidic protons, and increases the overall synthetic efficiency.[15] Then, there is a general agreement about the future of the use of water as a solvent.[16]

On the other hand, 5-aminomethyl-substituted 1,2,3-triazol-4-yl-*N*,*N*-dimethylmethaneamine hydrochloride analogues was reported to be a human neurokinin-1 receptor antagonist with a solubility in water, and the preparation of these analogues generally involved the prior reaction of amine and alkyne to form propargylamine, followed by other two-step transformations to product 1,2,3-triazole.[17] The most attractive access of propargylamines is the classical mannich reaction. However, the efficient preparation of propargylamines was hindered by rather harsh conditions, moderate yields and complex workup and purification procedures.[18] Therefore, it is desirable to develop a new, convenient and regiocontrolled synthetic approach for the formation of triazoles-4-yl-methanamine. On the other hand, (1-benzyl-, and 1-phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-diethylamines were, respectively, prepared from various starting materials using the 'click' chemistry approach.[6d,12c] These promoted us to initiate a corresponding study of three-component reaction. Herein, we wish to report an efficient and facile one-pot reaction of amines, propargyl halide and azides to generate (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines in the presence of Cu(I) in water at room temperature (Scheme 1).

2. Results and discussion

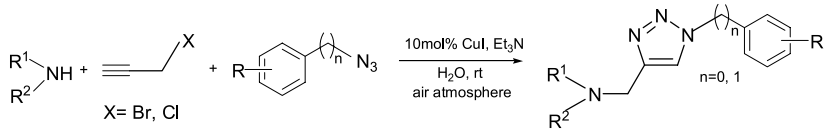
In preliminary experiments, we investigated the template reaction of diethylamine, propargyl bromide and benzyl azide using $CuSO_4 \cdot 5H_2O$–sodium ascorbate (Vc) system in a 2:1 mixture of water and *tert*-butyl alcohol (the 'click' chemistry condition),[6d] and the reaction only gave the corresponding compound **4b** in moderate yield (Table 1, entry 1). Encouraged by this positive result, an optimum reaction condition was explored using various solvents and catalysts. We were pleased to find Cu(I) could catalyze the three-component reaction in water in the presence of triethylamine without other co-solvent. Common Cu(I) salts, for example, CuCN, CuCl, CuBr, and CuI all gave good yields (entries 4–7). The reaction did not proceed in the presence of catalytic amount of copper powder. However, when the reaction was treated with stoichiometric copper powder (under 100 mol% amount of metal), a decent yield was obtained (entry 10). It was indicated that copper metal could also catalyze the three-component reaction, although it required a large amount of catalyst and extended reaction time, which was in good agreement with the previous results reported.[19] Furthermore, some Cu(II) salts, such as $CuSO_4$, $CuCl_2$, $Cu(OAc)_2$ in the absence of a reducing agent, were also evaluated, and negative results were observed. Other catalysts such as $ZnCl_2$, $InCl_3$, AgCl, AgI, and silver metal, were also investigated, which were not effective or non-active for the three-component reaction. However, a number of observations were worth highlighting, as they underscored the unusual reactivity aspects of the system. In other words, this was a very surprised process, which could effectively be catalyzed by either Cu(I) or copper metal. Finally, CuI was found to be the most effective in catalyzing the three-component reaction of amine, propargyl halide and azide (Table 1, entries 7–10).

Table 1. The effect of solvent and catalyst on three-component reaction[a]

Entry	Catalyst	Condition	Time (h)	Yield (%)
1	$CuSO_4$/Vc	H_2O–*t*-BuOH (1/1)	13	70
2	$CuSO_4$/Vc	H_2O	14	40
3	$CuSO_4$/Vc	H_2O–THF (1/1)	14	61
4	CuCl	H_2O	10	77
5	CuBr	H_2O	10	84
6	CuCN	H_2O	10	80
7	CuI	H_2O	10	88
8	CuI	H_2O–THF (1/1)	10	89
9	CuI	H_2O–DMF (1/1)	10	85
10	CuI	THF	10	86
11[b]	Cu	H_2O	24	54

[a] All reactions were performed with 2 mmol of Et_3N, 1.2 mmol of diethylamine, 2 mL of solvent, 1.2 mmol of propargyl bromide, 1.0 mmol of azide, and 10 mol% catalyst at room temperature, unless otherwise noted.
[b] Stoichiometric copper powder was used.

Under the optimized conditions, a number of substrates were investigated (Table 2). A variety of substituents, aromatic, benzyl, and aliphatic, were readily used in this transformation. Both electron-rich and -poor aromatic groups were tolerated in three-component reaction. Generally, the reaction was highly dependent on both electronic and steric effects. An evident steric effect was observed when we compared the yield of bulky diisopropylamine with that of dimethylamine (entries 1–3). On the whole, the better yields were obtained with cyclic amines in a short period of time (entries 4 and 6). Both aromatic azides bearing electron-withdrawing substituent Cl– and NO_2– group afforded the product in excellent yields (entries 12–15). Compared the propargyl bromide, the reaction of propargyl chloride, amines, and azide gave a slightly low yields (entries 5 and 11). Phenyl azide provided better results than electron-donating methylphenyl azide under the present reaction conditions (entries 16–18). The reaction was also tolerated with various functional groups. In addition to electron-rich and electron-poor C-aryl-substituted azides, benzyl azide, and even the less electrophilic phenoxyethyl azide could react to form the corresponding compounds in good yields, although the reaction time might be prolonged (entries 19–20). Moreover, this methodology could also be extended to the primary aliphatic amine (entry



Scheme 1.

Table 2. The reaction of amine, propargyl halide and azide catalyzed by Cu(I) in water[a]

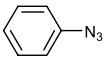
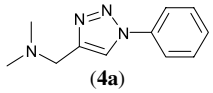
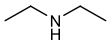
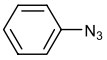
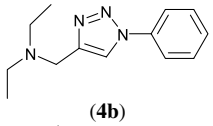
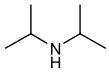
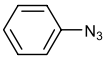
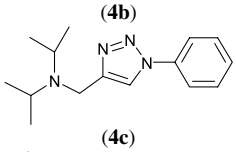
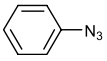
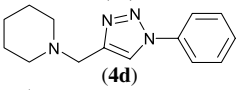
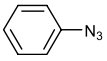
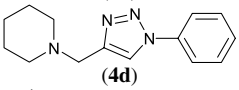
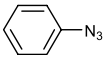
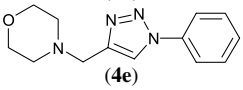
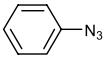
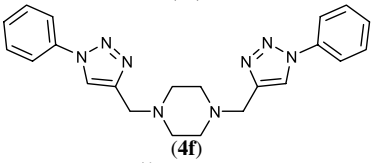
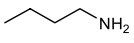
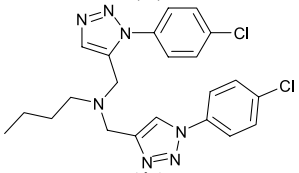
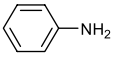
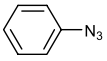
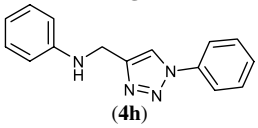
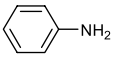
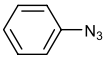
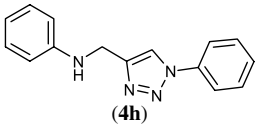
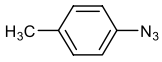
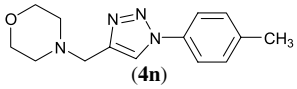
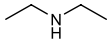
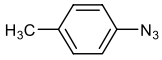
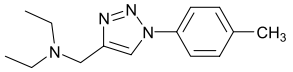
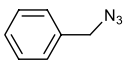
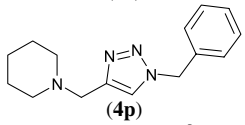
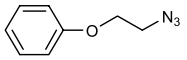
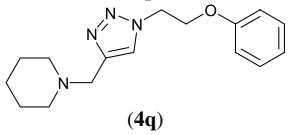
Entry	Propargyl halide	Amine	Azide	Time (h)/ medium	Product isolated	Yield (%)
1				8/water	 (**4a**)	92
2				10/water	 (**4b**)	88
3				14/water	 (**4c**)	75
4				7/water	 (**4d**)	95
5				12/water	 (**4d**)	89
6				7/water	 (**4e**)	93
7[b]				10/water	 (**4f**)	89
8[b]				14/water	 (**4g**)	86
9[c]				16/water	 (**4h**)	75
10[d]				16/water	 (**4h**)	78
11[c]				24/water	(**4h**)	70
12				7/water	(**4i**)	98
13				7/water	(**4j**)	95
14				10/water	(**4k**)	98
15				10/water	(**4l**)	96
16				9/water	(**4m**)	93

Table 2 (*continued*)

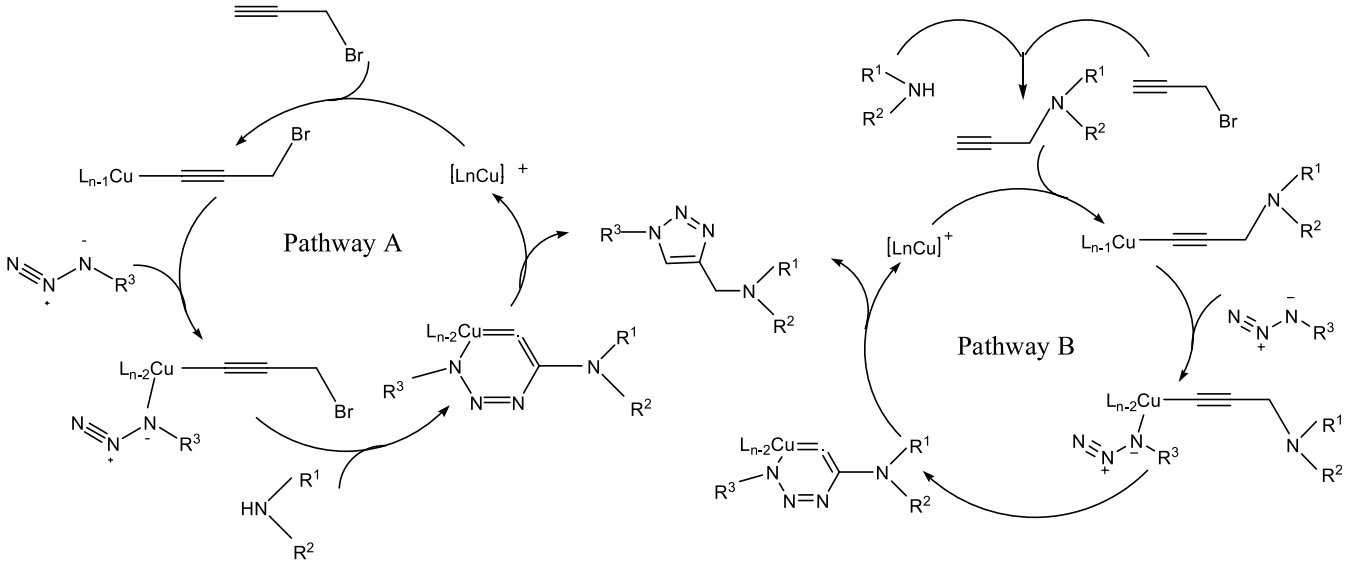
Entry	Propargyl halide	Amine	Azide	Time (h)/ medium	Product isolated	Yield (%)
17				10/water	 (**4n**)	90
18				13/water	 (**4o**)	83
19				16/water	 (**4p**)	94
20				16/water	 (**4q**)	91

[a] Typical procedure can be seen in 'Section 4', unless otherwise noted.
[b] Et_3N (3 mmol), 0.5 mmol of amine, 1.2 mmol of propargyl bromide and 1.2 mmol azide were used.
[c] Et_3N (2 mmol), 2 mmol of amine, 1 mmol of propargyl halide and 1 mmol azide were used.
[d] Et_3N (3 mmol), 0.5 mmol of amine, 2 mmol of propargyl bromide and 2 mmol azide were used; no disubstituted product was isolated.

8). Compared to secondary amines, the reaction of primary amines led to the disubstituted products in good yields when using an excess of Et_3N (3 equiv). For phenyl amine, only mono-substituted product was isolated even large excesses of propargyl bromide and phenyl azide were participated in the reaction (entries 9–11). It was presumed due to steric hindrance of bulk benzene ring. Diphenylamine, on the other hand, did not give the reaction even larger excess of base was used, presumably due to steric hindrance and/or weak nucleophilicity.

Herein, the effect of basicity was very vital in the three-component reaction. On the one hand, it could drive the rapid formation of propargyl amines and avoid self-coupling product of terminal alkynes. On the other hand, it was also known that copper(I) could readily inserts into terminal alkynes in the presence of base to promote the reaction.[20] Some inorganic and organic bases were investigated. Triethylamine showed better yields and no byproducts were observed. Moreover, it was known that, in the presence of a base and Cu(I) salts, terminal acetylenes could be converted to the corresponding alkynylides in water; if oxygen was not excluded, Cu(I)–acetylides could participate in oxidative Glaser coupling.[21] However, in our study, no coupling products were obtained, probably, six-membered copper(III) metallacycle was a preferable intermediate rather than alkynyl free radical one in Glaser coupling reaction (see below). We also observed that the three-component reaction in two-step gave higher yields in contrast to one-step procedure.[22] It was indicated that first the formation of propargylamines effectively suppressed the oxidative coupling reaction.

A tentative mechanism for the Cu(I)-catalyzed three-component reaction to form triazole derivatives was illustrated in Scheme 2, which may involve two possible



Scheme 2. Tentative mechanism for the three-component reaction of amine, propargyl bromide and azide.

pathway: A and B. For pathway B, in the first step, the reaction between propargyl bromide and a nucleophilic amine to form propargyl amine followed by the formation of copper(I) acetylide by displacing one of the H_2O ligands. The acetylide thus generated was reacted with azide to give the six-membered copper(III) metallacycle intermediate. After the ring contraction, a five-membered triazolyl-copper derivative was formed.[6d,19] Proteolysis of triazolyl-copper derivative released the triazole compound and regenerated the Cu(I) specie catalyst for further reactions. In further study, we prepared 1-phenyl-4-bromomethyl-1,2,3-triazole by a mixture of phenyl azide and propargyl bromide. Under the similar condition, the reactions of 1-phenyl-4-bromomethyl-1,2,3-triazole and several secondary amines were investigated, and expected products were obtained with lower yields. It was indicated that the early formation of 4-bromomethyl-1,2,3-triazole intermediates followed by the coupling of triazoles with amines to yield preferable compounds, was also an alternative mechanism (pathway A). Based on the above results, we proposed that pathway B was the preferable process. Herein, the formation of propargyl amine is a crucial factor for completion of the reaction in water because propargyl amine has a weak solubility in water, but the non-polar propargyl halide is not soluble in water.

3. Conclusions

In summary, we have demonstrated a new three-component protocol of amine, propargyl halide and azide in one-pot procedure for the synthesis of (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamine derivatives in the presence of copper(I) in water. The process showed the considerable synthetic advantages in terms of air, products diversity, mild reaction condition, simplicity of the reaction procedure, and good to excellent yields. The convenience with readily accessible starting materials (commercially available amines and propargyl halide) and simple experimental procedure as well as the simplicity of the reaction conditions (room temperature, water) can provide an access to a class of compounds that can serve as useful building blocks for synthesis. The rich array of functionality displayed by these products can provide opportunities for the creation of unique combinatorial libraries.

4. Experimental

4.1. General remarks

Column chromatography was carried out on silica gel. Melting points were measured using an electrothermal melting point apparatus, and uncorrected. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. The ^1H chemical shifts were reported in ppm relative to tetramethylsilane, using the residual solvent signal as an internal reference and ^{13}C with $CDCl_3$ as internal standard. IR spectra were obtained using an FT IR spectrometer and only major peaks were reported in cm^{-1}. Mass spectra were recorded by the EI method or FAB method. All reagents were used directly as unless otherwise noted.

4.2. General procedure

The reaction was carried out in micro scale: a mixture of 2 mL of water, 2 mmol of Et_3N, 1.2 mmol of amine and 1.2 mmol of propargyl halide was stirred vigorously for 60 min at room temperature.[21] Then, 1.0 mmol of azide and 10 mol% of CuI were added into the mixture until complete consumption of the starting materials monitored by TLC.[17] The reaction mixture was diluted with 25 mL of water, cooled in ice, and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified on silica gel with petroleum–ethyl acetate (8:1–1:10).

4.3. Data of spectra

4.3.1. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-dimethylamine (4a). Solid, mp 75–77 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.71 (d, $J=8.4$ Hz, 2H), 7.49 (t, $J=7.2$, 8.4 Hz, 2H), 7.39 (t, $J=7.2$ Hz, 1H), 3.68 (s, 2H), 2.31 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 137.0, 129.6, 128.5, 120.5, 120.3, 54.3, 45.1; IR (KBr, cm^{-1}) 2942, 2821, 2773, 1599, 1504, 1462, 1039; EI-MS *m*/*z* 202 (M^+), 202, 159, 130, 77; HRMS (EI) found $[M]^+=202.1208$, $C_{11}H_{14}N_4$ requires 202.1213.

4.3.2. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-diethylamine (4b). [12c]Sticky oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.75 (d, $J=8.4$ Hz, 2H), 7.52 (t, $J=6.9$, 8.4 Hz, 2H), 7.45–7.4 (m, 1H), 3.88 (s, 2H), 2.61 (q, $J=6.9$, 7.2, 7.5 Hz, 4H), 1.12 (t, $J=6.9$, 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 137.1, 129.6, 128.5, 120.5, 120.3, 47.6, 46.8, 11.8; IR (KBr, cm^{-1}) 2970, 1599, 1504, 1465, 1041; EI-MS *m*/*z* 230 (M^+), 215, 159, 130, 77.

4.3.3. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-diisopropylamine (4c). Solid, mp 45–47 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.73 (d, $J=7.8$ Hz, 2H), 7.49 (t, $J=7.2$, 7.8 Hz, 2H), 7.42–7.38 (m, 1H), 3.83 (s, 2H), 3.09 (m, 2H), 1.04 (d, $J=6.6$ Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 137.5, 129.9, 128.6, 120.6, 120.4, 49.1, 41.4, 21.0; IR (KBr, cm^{-1}) 2966, 1599, 1503, 1464, 1226, 1036; EI-MS *m*/*z* 258 (M^+), 243, 215, 159, 130, 100, 77; HRMS (EI) found $[M]^+=258.1840$, $C_{15}H_{22}N_4$ requires 202.1839.

4.3.4. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4d). Solid, mp 95–97 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.70 (d, $J=7.8$ Hz, 2H), 7.45 (t, $J=7.8$, 7.2 Hz, 2H), 7.41–7.38 (m, 1H), 3.70 (s, 2H), 2.47 (br s, 4H), 1.56 (m, 4H), 1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 137.0, 129.6, 128.5, 120.6, 120.3, 54.3, 54.0, 25.8, 24.0; IR (KBr, cm^{-1}) 2934, 1599, 1504, 1465, 1231, 1042; EI-MS *m*/*z* 242 (M^+), 159, 130, 84, 77; HRMS (EI) found $[M]^+=242.1528$, $C_{14}H_{18}N_4$ requires 242.1526.

4.3.5. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4e). Solid, mp 88–90 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.71 (d, $J=8.4$ Hz, 2H), 7.49 (t, $J=6.9$, 8.4 Hz, 2H), 7.42–7.37 (m, 1H), 3.72 (s, 2H), 3.70 (t, $J=7.8$, 6.9 Hz, 4H), 2.55 (t, $J=4.2$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 136.9, 129.6, 128.6, 120.7, 120.3, 66.8, 53.6, 53.4; IR (KBr, cm^{-1}) 2959, 2923, 2856,

2815, 1599, 1504, 1454, 1116; EI-MS *m/z* 244 (M^+), 226, 214, 201, 159, 130, 77; HRMS (EI) found $[M-N_2H]^+$ = 215.1179, $C_{13}H_{15}N_2O$ requires 215.1179.

4.3.6. 1,4-Bis-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperazine (4f). Solid, mp 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 2H), 7.71 (d, J=7.8 Hz, 4H), 7.50 (t, J=7.8, 7.2 Hz, 4H), 7.39 (t, J=7.2 Hz, 2H), 3.90 (s, 4H), 2.83 (br s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 130.0, 129.1, 122.1, 120.9, 120.7, 52.9, 52.1; IR (KBr, cm^{-1}) 1598, 1503, 1461, 1045; FAB-MS *m/z* 401.3 $[M+1]^+$; HRMS (EI) found $[M]^+$ = 400.2117, $C_{22}H_{24}N_8$ requires 400.2118.

4.3.7. Bis-(1-[4-chloro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-butylamine (4g). Solid, mp 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.61 (m, 4H), 7.37 (m, 4H), 3.79 (s, 4H), 2.50 (t, J=7.2 Hz, 2H), 1.54 (m, 2H), 1.24 (m, 2H), 0.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 135.2, 134.0, 129.6, 126.3, 121.2, 121.0, 53.3, 47.4, 29.2, 20.2, 13.8; IR (KBr, cm^{-1}) 2956, 2930, 1501, 1226, 1096, 1043; FAB-MS *m/z* 456.2 $[M]^+$; HRMS (EI) found $[M]^+$ = 455.1389, $C_{22}H_{23}N_7Cl_2$ requires 455.1387.

4.3.8. (1-Phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl)-phenylamine (4h). Solid, mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.69 (d, J=8.1 Hz, 2H), 7.53–7.40 (m, 3H), 7.26–7.18 (m, 2H), 6.78–6.70 (m, 3H), 4.55 (s, 2H); 4.32 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 147.0, 137.0, 129.7, 129.3, 128.7, 120.4, 119.8, 118.1, 113.1, 39.9; IR (KBr, cm^{-1}) 1598, 1462, 1320, 1105; EI-MS *m/z* 250 (M^+), 221, 130, 77; HRMS (EI) found $[M]^+$ = 250.1210, $C_{15}H_{14}N_4$ requires 250.1213.

4.3.9. (1-[4-Chloro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4i). Solid, mp 120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.70 (d, J=8.7 Hz, 2H), 7.41 (d, J=8.7 Hz, 2H), 3.72 (s, 2H), 2.50 (br s, 4H), 1.60 (m, 4H), 1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 135.5, 134.2, 129.8, 121.4, 120.7, 54.3, 53.9, 25.7, 23.9; IR (KBr, cm^{-1}) 2936, 1502, 1440, 1098, 1048; EI-MS *m/z* 276 (M^+), 247, 193, 84; HRMS (EI) found $[M]^+$ = 276.1136, $C_{14}H_{17}N_4Cl$ requires 276.1136.

4.3.10. (1-[4-Chloro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4j). Solid, mp 119–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.70 (d, J=8.7 Hz, 2H), 7.50 (d, J=8.7 Hz, 2H), 3.72–3.75 (m, 6H), 2.58 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 135.7, 134.7, 130.1, 121.8, 121.0, 67.0, 53.8, 53.7; IR (KBr, cm^{-1}) 2925, 1502, 1115; EI-MS *m/z* 278 (M^+), 235, 193, 164; HRMS (EI) found $[M-N_2H]^+$ = 249.0786, $C_{13}H_{14}N_2ClO$ requires 249.0789.

4.3.11. (1-[4-Nitro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4k). Solid, mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J=8.7 Hz, 2H), 8.09 (s, 1H), 8.00 (d, J=8.7 Hz, 2H), 3.75 (s, 2H), 2.51 (br s, 4H), 1.61 (m, 4H), 1.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 146.8, 141.2, 125.5, 120.5, 120.2, 54.4, 53.9, 25.8, 24.0; IR (KBr, cm^{-1}) 2938, 1600, 1528, 1507, 1447, 1343, 1111, 1042, 909; EI-MS *m/z* 287 (M^+), 204, 129, 84; HRMS (EI) found $[M]^+$ = 287.1380, $C_{14}H_{17}N_5O_2$ requires 287.1377.

4.3.12. (1-[4-Nitro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4l). Solid, mp 195–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J=8.7 Hz, 2H), 8.10 (s, 1H), 8.00 (d, J=8.7 Hz, 2H), 3.74–3.80 (m, 6H), 2.61 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 145.9, 141.1, 125.5, 120.7, 120.3, 66.7, 53.5 (2C); IR (KBr, cm^{-1}) 1523, 1343, 1113, 856; EI-MS *m/z* 289 (M^+), 246, 204, 129, 86; HRMS (EI) found $[M-N_2H]^+$ = 260.1028, $C_{13}H_{14}N_3O_3$ requires 260.1030.

4.3.13. (1-[4-Methyl-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4m). Solid, mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.58 (d, J=7.8 Hz, 2H), 7.27 (d, J=7.8 Hz, 1H), 3.68 (s, 2H), 2.46 (br s, 4H), 2.38 (s, 3H), 1.56 (br s, 4H), 1.41 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 138.5, 134.7, 130.1, 120.7, 120.2, 54.2, 54.0, 25.7, 24.0, 21.0; IR (KBr, cm^{-1}) 2938, 1528, 1113; EI-MS *m/z* 256 (M^+), 173, 91, 84; HRMS (EI) found $[M]^+$ = 256.1684, $C_{15}H_{20}N_4$ requires 256.1682.

4.3.14. (1-[4-Methyl-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4n). Solid, mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.59 (d, J=8.1 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 3.73 (s, 2H), 3.72 (t, J=4.5 Hz, 4H), 2.56 (br s, 4H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 139.0, 135.0, 130.5, 121.0, 120.6, 67.1, 53.9, 53.7, 21.3; IR (KBr, cm^{-1}) 1521, 1449, 1113; EI-MS *m/z* 258 (M^+), 240, 228, 215, 173, 144, 91; HRMS (EI) found $[M-N_2H]^+$ = 229.1378, $C_{14}H_{17}N_2O$ requires 229.1335.

4.3.15. (1-[4-Methyl-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-diethylamine (4o). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.57 (d, J=8.1 Hz, 2H), 7.26 (d, J=8.1 Hz, 2H), 3.85 (s, 2H), 2.59 (q, 4H), 2.37 (s, 3H), 1.09 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 138.9, 135.1, 130.4, 121.0, 120.5, 47.9, 47.0, 21.3, 11.9; IR (KBr, cm^{-1}) 2970, 1520, 1459, 1226, 1042; EI-MS *m/z* 244 (M^+), 229, 215, 201, 187, 173, 144, 91, 72; HRMS (EI) found $[M]^+$ = 244.1678, $C_{14}H_{20}N_4$ requires 244.1682.

4.3.16. (1-Benzyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4p). Solid, mp 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.38–7.34 (m, 2H), 7.28 (m, 3H), 5.51 (s, 2H), 3.62 (s, 2H), 2.43 (br s, 4H), 1.58–1.53 (m, 4H), 1.43–1.41 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 134.6, 129.0, 128.6, 128.0, 122.4, 54.2 (2C), 54.0, 25.7, 24.0; IR (KBr, cm^{-1}) 2931, 2771, 1445, 1306, 1050; EI-MS *m/z* 256 (M^+), 173, 91, 84; HRMS (EI) found $[M]^+$ = 256.1682, $C_{15}H_{20}N_4$ requires 256.1682.

4.3.17. (1-Phenoxyethyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4q). Solid, mp 103–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.28 (t, J=8.4, 7.5 Hz, 2H), 6.97 (t, J=8.4, 7.5 Hz, 1H), 6.86 (d, J=9.0 Hz, 2H), 4.74 (t, J=4.8 Hz, 2H), 4.35 (t, J=4.8 Hz, 2H), 3.66 (s, 2H), 2.45 (br s, 4H), 1.62–1.54 (m, 4H), 1.45–1.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 144.6, 129.5, 123.8, 121.5, 114.4, 66.2, 54.1, 53.9, 49.6, 25.7, 24.0; IR (KBr, cm^{-1}) 2930, 2770, 1596, 1497, 1460, 1252, 1118, 1047; EI-MS *m/z* 286 (M^+), 203, 84; HRMS (EI) found $[M]^+$ = 286.1785, $C_{16}H_{22}N_4O$ requires 286.1788.

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22. The following procedure also was investigated: a simultaneous mixture (one-step procedure) of water, Et_3N, amines, propargyl bromide, azides, and CuI was stirred vigorously until consumption of the starting material. However, lower yields were obtained.