Synthesis of Diheterocyclic Compounds Based on Triazolyl Methoxy Phenylquinazolines via a One-Pot Four-Component-Click Reaction

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A facile and highly efficient method for one-pot four-component synthesis of triazolyl methoxy phenylquinazolines is described. A mixture of aromatic propargylated aldehydes, different azides, 2-aminobenzophenone derivatives, and ammonium acetate were condensed in the presence of catalytic amounts of acidic ionic liquid, 1-methylimidazolium trifluoroacetate, ([Hmim]TFA), and $Cu(OAc)_2$/sodium ascorbate to afford the corresponding products in excellent yields. This methodology is highly efficient for structurally diverse azides.

Introduction

Click chemistry is a rather new approach to the synthesis of chemical scaffolds that was introduced by Sharpless in 2001 and describes chemistry tailored to generate substances quickly and reliably by joining small units together. This is inspired by the fact that nature also generates substances by joining small modular units.[1] Click chemistry has been defined as reactions that are modular, wide in scope, high yielding, free from offensive byproduct, stereospecific, and simple to perform that require benign or no solvent.[2] Such chemistry has found wide applications not only in synthetic organic chemistry[3] but also in dendrimer and polymer chemistry,[4] material sciences,[5] bioconjugation chemistry,[6] and pharmaceutical sciences.[7]

From the list of click reactions, we were especially interested in the Cu (I)-catalyzed variant of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes for the synthesis of 1,4-disubstituted 1,2,3-triazoles, which are important targets for drug discovery.[8] 1,2,3-Triazoles possess diverse biological properties including antibacterial, antiallergic, anti-HIV, herbicidal, fungicidal, and anticonvulsant activity.[9] Additionally, they are used as optical brighteners, light stabilizers, fluorescent whiteners, and corrosion retarding agents.[10]

Several multicomponent reactions with a subsequent click step have already been reported.[11−14] In the context of our studies in the area of multicomponent reactions (MCRs),[15,16] we also became interested in combining click chemistry with MCR strategies. Here, we report an efficient approach for the one-pot synthesis of libraries including both quinazoline and triazole rings in their structures. Quinazolines are an important class of biologically active N-heterocycles. They have been introduced with diverse activities, such as fungicide, anticancer, antiinflammatory, antimicrobial, and antihypertensive.[17,18]

Results and Discussion

As a part of our ongoing project devoted toward the development of a practical synthesis of biologically interesting heterocyclic molecules,[19−21] herein, we have explored the possibility of one-pot synthesis of triazolyl methoxy phenylquinazolines from suitable precursors. Therefore, we designed a one-pot four-component reaction of aromatic propargylated aldehydes **1a**−**d**, azides[22] **2a**−**f**, 2-aminobenzophenones **3a**, **b**, and ammonium acetate **4** for the synthesis of compounds **5a**−**v** (Scheme 1).

Encouraged by gaining satisfactory results in this stage, the synthesis of **5a** was selected for optimization of the reaction conditions. As listed in Table 1, the optimal reaction conditions for the reaction of propargylated aldehyde **1a**, benzyl azide **2a**, 2-amino-5-chlorobenzophenone **3a**, and ammonium acetate **4** were screened. After preliminary screening of copper salts as catalyst (entries 1−4), $Cu(OAc)_2$ was be found the most effective (entry 4). In addition, the use of H_2O as solvent resulted in higher yield than CH_2Cl_2 and CH_3CN (Table 1, entries 4, 6, 8). The use of *p*-TsOH as a Brönsted acid did not led to an improved yield (Table 1, entries 9 and 10), while an excellent yield was obtained when 1-methylimidazolium

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Scheme 1. Synthesis of Triazolyl Methoxphenyl Quinazolines **5a−v**

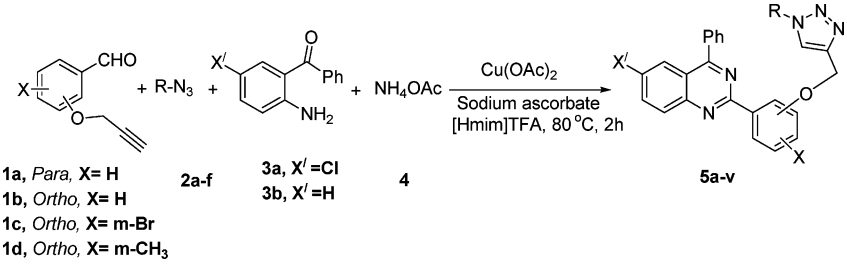
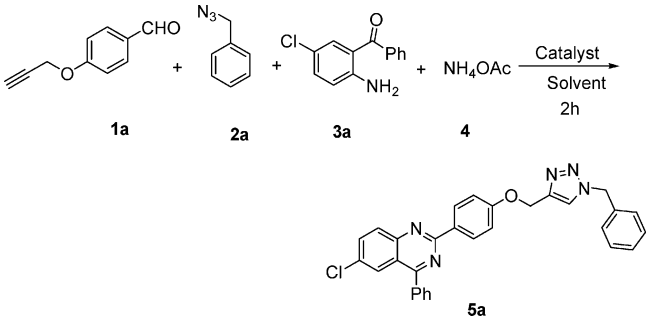


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	yield of **5a** (%)
1	CuCl	H_2O	reflux	trace
2	CuI	H_2O	reflux	35
3[b]	$CuSO_4$/sodium ascorbate	H_2O	reflux	40
4[b]	$Cu(OAc)_2$/sodium ascorbate	H_2O	reflux	55
5	CuI	CH_3CN	reflux	20
6[b]	$Cu(OAc)_2$/sodium ascorbate	CH_3CN	reflux	43
7	CuI	CH_2Cl_2	reflux	23
8[b]	$Cu(OAc)_2$/sodium ascorbate	CH_2Cl_2	reflux	47
9[c]	CuI/*p*-TsOH	H_2O	reflux	45
10[d]	$Cu(OAc)_2$/sodium ascorbate/ *p*-TsOH	H_2O	reflux	53
11[e]	CuI/IL	solvent-free	80	62
12[f]	$Cu(OAc)_2$/sodium ascorbate/IL	solvent-free	80	87

[a] Reaction conditions: propargylated aldehyde **1a** (1 mmol), benzyl azide **2a** (1 mmol), 2-amino-5-chlorobenzophenone **3a** (1 mmol), ammonium acetate **4** (1 mmol), catalyst (10 mol %), solvent (10 mL), 2 h, reflux. [b] Sodium ascorbate (20 mol %). [c] *p*-TsOH (10 mol %). [d] Sodium ascorbate (20 mol %), *p*-TsOH (10 mol %). [e] IL ([Hmim]TFA), (10 mol %), under solvent-free condition at 80 °C. [f] Sodium ascorbate (20 mol %) and [Hmim]TFA, (10 mol %), under solvent-free condition at 80 °C.

trifluoroacetate, ([Hmim]TFA), as an IL was used (Table 1, entry 12).

To probe the scope and generality of this new four-component reaction, different aromatic propargylated aldehydes **1**, various azides **2**, and two types of 2-aminobenzophenones **3** were selected to undergo one-pot reaction in the presence of catalytic amounts of $Cu(OAc)_2$ (10 mol %), sodium ascorbate (20 mol %) as a reducing agent for Cu(II) and [Hmim]TFA as an IL at 80 °C under solvent-free condition (Scheme 1). The results of this study are summarized in Table 2 and the structure of target compounds 5a−v is represented in Figure 1.

To investigate the scope of this method, a variety of functional groups such as nitro, chloro, methyl, and methoxy were tolerated on aromatic azides that could be successfully converted to the desired product in high yields. (Table 2, entries 3−6, 8−18 and 21). Benzyl azide also reacted satisfactorily in all reactions (Tables 2, entries 1, 2, 7, 19, and 20). Moreover, the effect of the character of substituent in the benzene ring of aromatic propargylated aldehydes were examined. Results revealed that both an electron-releasing group, such as methyl, and an electron-withdrowing group, such as bromo, substitution led to the corresponding adducts (Table 2, entries 19−22).

Conclusions

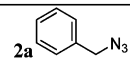
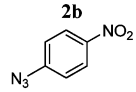
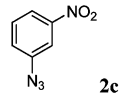
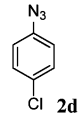
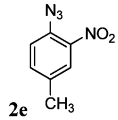
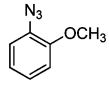
In summary, we have developed the combination of the four-component reaction with the intermolecular azide−alkyne cyclization provides access to unique fused triazole ring systems in high yields and simple procedure. This protocol may have interesting implications on the construction of structurally diverse heterocyclic molecules and will find applications in combinatorial chemistry, diversity-oriented synthesis and drug discovery.

Experimental Section

General. Melting points were measured on an Electrothermal 9100 apparatus and were not corrected. IR spectra were recorded on a FT-IR 10MB BOMEM spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 AVANCE spectrometer (300.13 and 75.47 MHz, respectively). Mass spectra were determined on a FINNIGAN-MAT8430 mass spectrometer operating at an ionization-potential of 70 eV. Elemental analyses were performed on an Elementar Analysensysteme GmbH VarioEL CHNS mode. All reagents were purchased from Merck or Fluka and used without purification.

Typical Procedure for the Synthesis of 2-(4-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-6-chloro-4-phenylquinazoline (5a). Propargylated aldehyde **1a** (0.16 g, 1.0 mmol), benzyl azide (0.13 g, 1.0 mmol), 5-chloro-2-aminobenzophenone **3a** (0.23 g, 1.0 mmol), and ammonium acetate **4** (0.07 g, 1.0 mmol) in the presence of $Cu(OAc)_2$ (0.02 g, 10 mol %), sodium ascorbate (0.04 g, 20 mol %), and [Hmim]TFA (0.02 g, 10 mol %) were mixed thoroughly. The mixture was stirred for 2 h at 80 °C. Water was added, and the solid was filtered. Finally, the pure product **5a** was obtained after recrystallization from ethanol as yellow solid (0.44 g, 87%). mp: 160−162 °C. IR (KBr) (υ_{max}, cm^{-1}): 1601, 1533, 1510, 1245. ^1H NMR (300.13 MHz, $CDCl_3$) δ: 5.28 (2H, s, CH_2), 5.54 (2H, s, CH_2), 7.09−8.61 (18H−Ar, m). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 54.30, 62.13, 114.72, 121.88, 122.83,

Table 2. One-Pot Four-Component Synthesis of Triazolyl Methoxphenyl Quinazolines **5a**−**v**

Entry	Propargylated aldehyde **1**	Azide **2**	2-Aminobenzophenone **3**	Product **5**	Mp (°C)	Yield (%)[a]
1	**1a**	 **2a**	**3a**	**5a**	160-162	87
2	**1a**	**2a**	**3b**	**5b**	165-168	90
3	**1a**	**2b** 	**3a**	**5c**	227-230	85
4	**1a**	**2b**	**3b**	**5d**	180-182	88
5	**1a**	 **2c**	**3b**	**5e**	211-212	82
6	**1a**	**2c**	**3a**	**5f**	236-238	86
7	**1b**	**2a**	**3a**	**5g**	217-219	95
8	**1b**	**2c**	**3a**	**5h**	196-198	75
9	**1b**	**2b**	**3a**	**5i**	190-191	90
10	**1b**	**2b**	**3b**	**5j**	169-170	88
11	**1a**	 **2d**	**3a**	**5k**	215-216	92
12	**1a**	 **2e**	**3a**	**5l**	204-205	77
13	**1a**	**2e**	**3b**	**5m**	129-130	80
14	**1a**	**2d**	**3b**	**5n**	175-176	91
15	**1b**	**2d**	**3b**	**5o**	119-120	85
16	**1b**	**2e**	**3a**	**5p**	218-220	78
17	**1b**	**2e**	**3b**	**5q**	190-192	80
18	**1a**	 **2f**	**3a**	**5r**	100-102	76
19	**1d**	**2a**	**3a**	**5s**	143-145	78
20	**1c**	**2a**	**3a**	**5t**	160-163	81
21	**1c**	**2e**	**3a**	**5u**	193-195	75
22	**1c**	**2b**	**3a**	**5v**	186-188	78

[a] Isolated yield based on the 2-aminobenzophenones **3**.

122.91, 125.79, 128.15, 128.73, 128.84, 129.17, 130.02, 130.21, 130.42, 130.58, 130.93, 132.18, 134.12, 134.48, 137.12, 150.44, 160.08, 160.54, 167.48. MS, *m*/*z* (%): 503 (M^+, 20), 332 (40), 144 (58), 91 (100). Anal. Calcd for $C_{30}H_{22}ClN_5O$: C, 71.49; H, 4.40; N, 13.90. Found: C, 71.38; H, 4.51; N, 14.03.

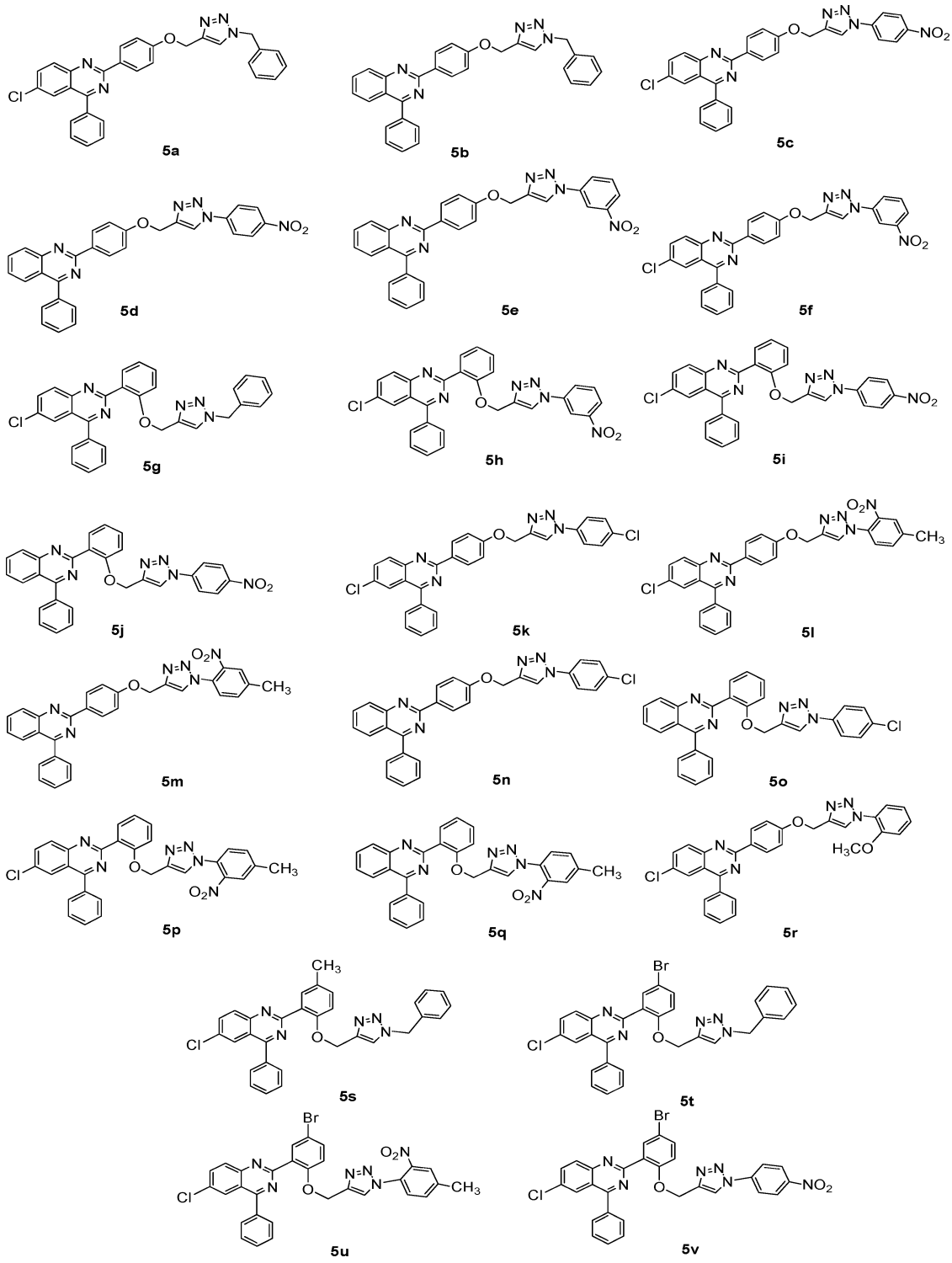


Figure 1. Structure of products **5a**−**v**.

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Supporting Information Available. Experimental procedures and mass, IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **5a**−**v**. This information is available free of charge via the Internet at http://pubs.acs.org/.

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(22) ***Caution!*** Azides are highly explosive under pressure or shock. Therefore, a protective blast shield is needed during purification and handling.

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