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One-pot synthesis of 1,2,3-triazole linked dihydropyrimidinones via Huisgen 1,3-dipolar/Biginelli cycloaddition

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Abstract The combination of the Biginelli reaction with click chemistry has been used for the one-pot synthesis of 1,2,3-triazole linked dihydropyrimidinones from azides, aromatic aldehydes containing a propargyl ether group, urea, and 1,3-dicarbonyl compounds using $\text{Cu}(\text{OAc})_2$ /sodium ascorbate as catalyst in acetic acid under mild reaction conditions.

Keywords Click chemistry · 1,2,3-Triazole · Multicomponent reaction · One-pot reaction · Dihydropyrimidinone · Biginelli

Introduction

The $[3 + 2]$ cycloaddition reaction of azides with numerous dipolarophiles is a standard Huisgen type cycloaddition reaction [1,2]. The Cu(I) catalyzed cycloaddition reaction of azides with terminal alkynes achieves the formation of 1,4-disubstituted 1,2,3-triazoles. This reaction is currently referred to as “click chemistry” which was introduced by Kolb and Sharpless in 2001 [3,4].

The turning point for the above-mentioned 1,3-dipolar cycloaddition occurred with the independent discovery that

copper(I) not only promotes the reaction, but also improves regioselectivity. The most prominent application of click reactions in recent years has been in drug research [5,6], bio-conjugate chemistry [7–10], and material science [11–15].

One of the potential of click reactions can be further fortified by combining them with multicomponent reactions. The idea of using MCRs followed by a Huisgen $[3 + 2]$ copper-catalyzed reaction was first presented by Barbas and co-workers [16]. Recently, a number of medicinally relevant heterocycles were synthesized via classical multicomponent reactions combined with click chemistry in separate steps such as: sequential Ugi/intermolecular alkyne-azide cycloaddition (IAAC) [17], sequential van-Leusen/alkyne-azide cycloaddition reactions [18], Baylis-Hillmann adducts [19,20], and synthesis of triazolyl-dihydropyrimidinone derivatives under microwave irradiation combining a Biginelli reaction with CuAAC [21].

Dihydropyrimidinones (DHPMs) are privileged structures associated with a plethora of biological activities. Their derivatives were found to exhibit antibacterial and antifungal [22], antiviral activity [23], as well as anti-inflammatory [24], and antioxidative properties [25]. In addition, being potent calcium channel modulators, they display coronary dilation and antihypertensive effects [25–27]. Noteworthy is that DHPMs and well-known 1,4-dihydropyridine calcium channel modulators of the nifedipine-type reveal high structural similarity and similar biological profiles [25]. The application of the click reaction allowed the straightforward generation of analogues which might preserve or improve their biological activities. In continuation of our program to find new and efficient methods for the synthesis of heterocyclic frameworks [28–30] we wish to report a novel domino Huisgen 1,3-dipolar cycloaddition/Biginelli condensation reaction for the synthesis of the desired skeletons **5a–t** via a one-pot reaction in the presence of copper catalyst.

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Results and discussion

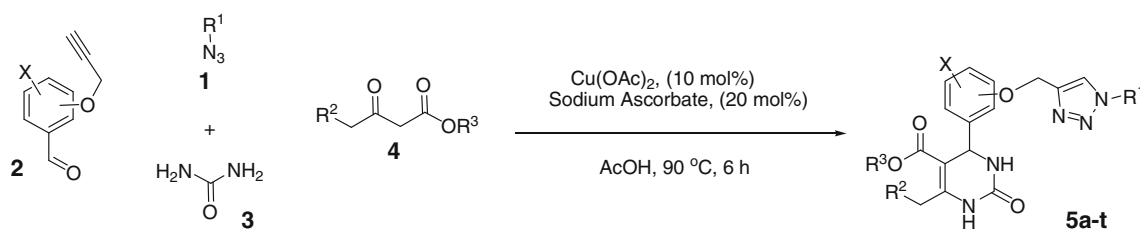
We report herein an efficient one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles linked dihydropyrimidinones **5a–t** using azides **1**, propargylated aromatic aldehydes **2**, urea **3**, and 1,3-dicarbonyl derivatives **4** in the presence of 10 mol% of copper salts, and 20 mol% sodium ascorbate in AcOH as a solvent at 90 °C (Scheme 1).

First, the reaction of 1-azido-4-chlorobenzene **1**, 5-bromo-2-(prop-2-ynoxy) benzaldehyde **2**, urea **3**, and ethylacetoacetate **4** was chosen to find the suitable reaction condition (Table 1). After preliminary screening of copper salts as the catalyst (Table 1, entries 1–3), Cu(OAc)₂ was found to be the most effective (Table 1, entry 1). In addition, the reaction was executed with various solvents, AcOH, DMF, EtOH, CH₂Cl₂, and CH₃CN, the best yield for **5b** being obtained with AcOH (Table 1, entries 1, 4–7).

We were pleased that under the optimized conditions of **1** (1 mmol), **2** (1 mmol), **3** (1.2 mmol), and **4** (1 mmol), Cu(OAc)₂ (0.1 mmol), and sodium ascorbate (0.2 mmol) in

1 ml AcOH at 90 °C for 6 h, the desired product **5b** was obtained in 93% yield. Next, under the optimized reaction conditions, the scope of this new multicomponent reaction has been examined. Gratifyingly, we found that this transformation is very general for a wide range of different propargylated benzaldehydes, 1,3-dicarbonyl compounds, and azides providing an easy access to densely substituted 1,2,3-triazole linked DHPMs **5a–t** in good to high yields (64–90%). The results are summarized in Table 2.

A plausible mechanism for this reaction is shown in Scheme 2. This reaction sequence could precede in two steps, namely, Huisgen 1,3-dipolar cycloaddition reaction between azide **1** and propargylated benzaldehyde **2**, leading to triazole derivative **I** as an intermediate (the production of **I** was confirmed by comparing with an authentic sample on TLC). This step was followed by the Biginelli condensation reaction of urea **3** and 1,3-dicarbonyl derivatives **4** to afford the 1,2,3-triazole linked dihydropyrimidinones **5** (second step). A notable point in this process is the efficient role of Cu(OAc)₂ in both steps.

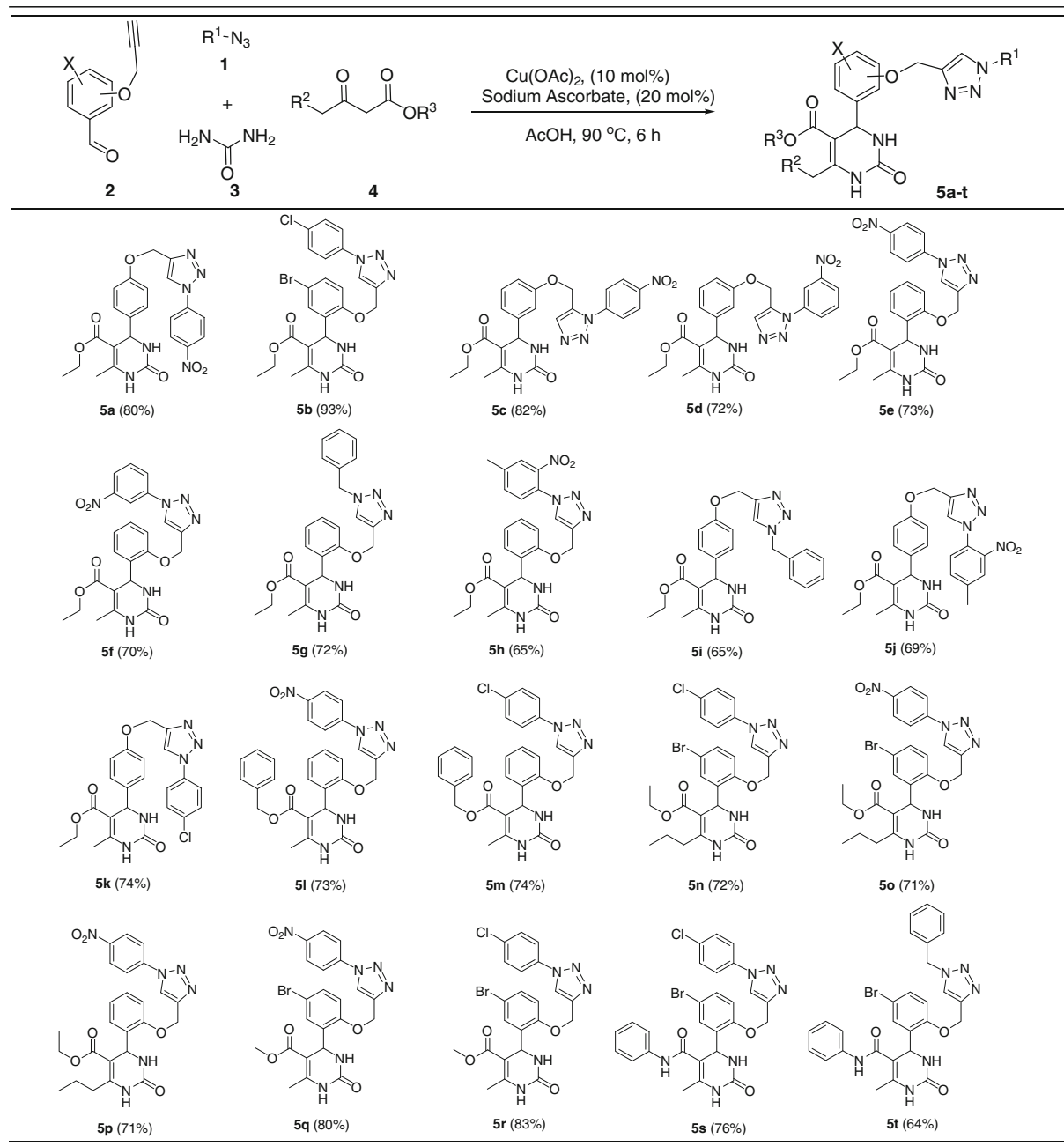


Scheme 1

Table 1 Optimization of reaction conditions^a

Entry	Solvent	Catalyst	Yield (%)
1	Acetic acid	Cu(OAc) ₂ /sodium ascorbate	93
2	Acetic acid	CuI ^b	68
3	Acetic acid	CuSO ₄ /sodium ascorbate	77
4	DMF	Cu(OAc) ₂ /sodium ascorbate	82
5	Ethanol ^c	Cu(OAc) ₂ /sodium ascorbate	67
6	CH ₂ Cl ₂ ^c	Cu(OAc) ₂ /sodium ascorbate	13
7	CH ₃ CN ^c	Cu(OAc) ₂ /sodium ascorbate	36

^a The reaction was carried out using 1-azido-4-chlorobenzene (1 mmol), 5-bromo-2-(prop-2-ynoxy)benzaldehyde (1 mmol), urea (1.2 mmol) and ethyl acetoacetate (1 mmol) in the presence of 10 mol% copper salts, and 20 mol% sodium ascorbate in 1 ml solvents at 90 °C for 6 h. ^b Without sodium ascorbate. ^c Under reflux condition

Table 2 Products obtained from Huisgen 1,3-dipolar cycloaddition/Biginelli condensation reaction

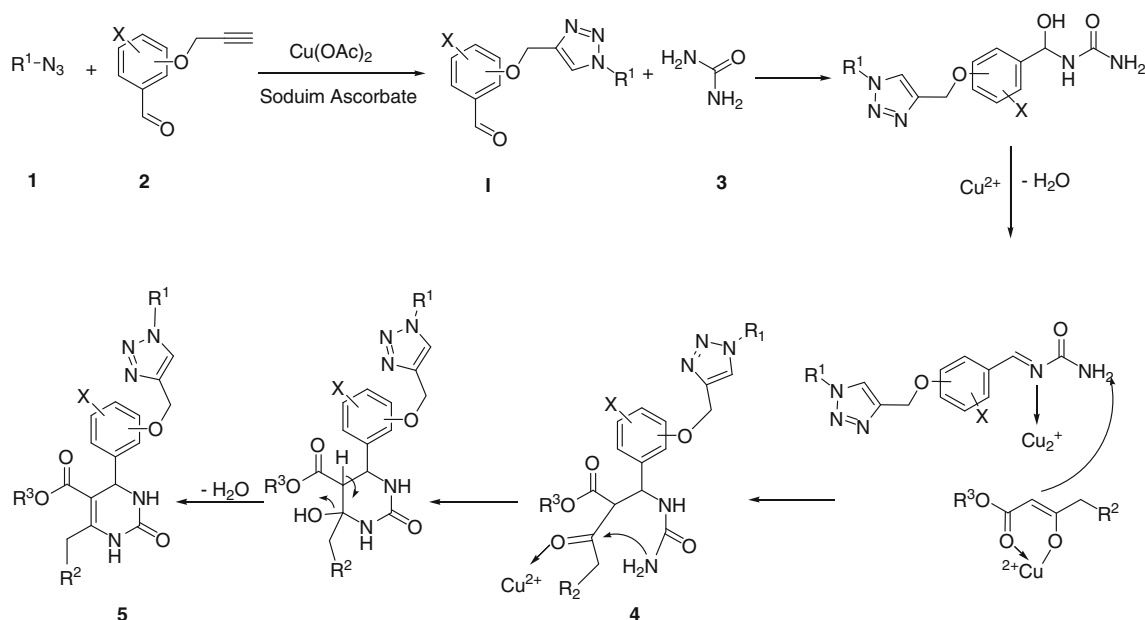
Conclusion

In summary, the aforementioned strategy presents a direct route to biologically relevant heterocyclic scaffolds by one-pot reaction via sequential Huisgen 1,3-dipolar cycloaddition/Biginelli condensation reaction. The high bond forming efficiency (BFE), good to high yields, and simple work up procedure and mild condition are advantages of this process. The method is applicable to a wide range of substituents tolerated in the starting materials.

Experimental section

General

All starting materials were obtained from Merck or Fluka, and were used without further purification. Azides **1** and propargylated benzaldehydes **2** were prepared according to known procedures [31–35]. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass



Scheme 2 A plausible mechanism for the synthesis of 1,2,3-triazole linked DHPM

spectrometer operating at an ionization potential of 70 eV and an Agilent Technology (HP) 5973 Network Mass Selective Detector operating at an ionization potential of 70 eV. on a Shimadzu IR-470 spectrometer. ¹H and ¹³C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. ¹H and ¹³C NMR spectra were obtained in DMSO-*d*₆ using TMS as internal standard. Elemental analyses were performed using a Heraeus CHN-O Rapid analyzer.

General procedure for the 1,2,3-triazol linked dihydropyrimidinones compounds

A mixture of propargylated benzaldehyde (1 mmol), urea (1.2 mmol), 1,3 dicarbonyl compound (1 mmol), and azide compound (1 mmol) in the presence of Cu(OAc)₂ (0.02 g, 10 mol%), sodium ascorbate (0.04 g, 20% mol) in the acetic acid (1 mL) as a solvent was stirred at 90 °C for 6 h. After reaction completion (monitored by TLC, ethyl acetate/*n*-hexane 1:3), ammonia and water were added and stirred for 30 min. Then the solid was filtered and washed with hot ethanol to afford pure desired products **5a–t**.

Ethyl 6-methyl-4-(4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5a)

M.p. 190–192 °C; IR (KBr) (ν_{\max} /cm⁻¹): 3220, 3085, 1698; ¹H NMR (300 MHz, DMSO-*d*₆): δ _H (ppm) 1.09 (t, 3H, ³*J*_{HH} = 6.8 Hz), 2.24 (s, 3H), 3.98 (q, 2H, ³*J*_{HH} = 6.8 Hz), 5.10 (s, 1H), 5.24 (s, 2H), 7.02 (d, 2H, ³*J*_{HH} = 7.9 Hz), 7.18 (d, 2H,

³*J*_{HH} = 7.9 Hz), 7.63 (s, 1H), 8.23 (d, 2H, ³*J*_{HH} = 8.4 Hz), 8.45 (d, 2H, ³*J*_{HH} = 8.3 Hz), 9.10 (br s, 1H), 9.13 (br s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ _C (ppm) 14.6, 18.2, 53.8, 59.6, 61.4, 99.9, 115.0, 121.1, 126.0, 127.9, 138.1, 141.2, 147.2, 148.6, 152.6, 157.5, 165.8; MS, *m/z* (%): 275 (M⁺-203, 50), 185 (25), 91 (45), 43 (100); Anal. Calcd for C₂₃H₂₂N₆O₆: C, 57.74; H, 4.63; N, 17.56. Found: C, 57.70; H, 4.59; N, 17.39.

Supporting information

Experimental procedures, complete analytical data and copies of ¹H and ¹³C NMR spectra for all compounds.

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