



Copper-catalyzed click synthesis of functionalized 1,2,3-triazoles with 3,4-dihydropyrimidinone or amide group via a one-pot four-component reaction



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ABSTRACT

A Cu (I) generated in situ from Cu(OAc)₂·H₂O/sodium ascorbate catalyzed one-pot multicomponent reaction for the synthesis of a series of *N*-functionalized 1,2,3-triazoles with 3,4-dihydropyrimidinone from 3,4-dihydropyrimidinones, paraformaldehyde, sodium azide and alkynes is described. Remarkably *N*-functionalized 1,2,3-triazoles with amide were prepared by this method. This procedure eliminates the need to handle organic halides or organic azides, as they are generated in situ, making this already powerful click process even more user-friendly and safe.

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1. Introduction

Multicomponent reactions (MCRs) were increasingly important in organic and medicinal chemistry, because they offered significant advantages over conventional linear-type syntheses.¹ For example, MCRs themselves were chemo- and regioselective, convergent step-efficient procedures and took place with high atom economy.² Another important feature implied the diminution of waste production due to the decrease of synthetic or isolation steps along with saving time.³

Since copper (I)-catalyzed azide–alkyne cycloaddition (CuAAC) was reported independently by the groups of Sharpless and Meldal in 2002.⁴ It proceeded highly regioselectively when using terminal alkynes, thereby lead to exclusively 1,4-disubstituted 1,2,3-triazoles as the sole products. The *N*-heterocyclic compound of 1,2,3-triazoles has rapidly become one of the most popular structures owing to their diverse uses, ranging from medicinal,⁵ material,⁶ to biological⁷ research. Recent efforts have been aimed at the investigation of the chemical and biological properties of this unique heterocycle.⁸ A few methods were designed to circumvent the handling of azides, whose synthesis and isolation can be

problematic due to their potential explosive or unstable nature. For example, three-component copper catalyzed reactions in which azides were generated in situ from corresponding alkyl or aryl halides and sodium azide in the presence of terminal alkynes gave access to diversely substituted 1,2,3-triazoles.⁹

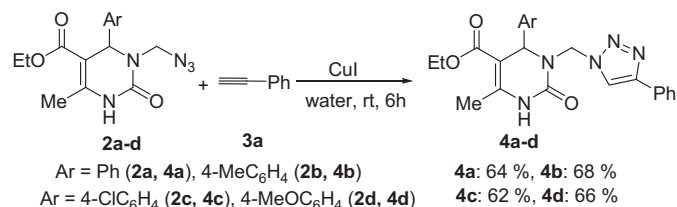
3,4-Dihydropyrimidinones (DHPMs) have attracted considerable interest due to their interesting pharmacological properties, such as calcium channel modulator, antihypertensive, α_{1a} -adren-ergic agonists mitotic kinesin inhibitor and hepatitis B virus replication suppressor.¹⁰ Among DHPM derivatives, most of the pharmacologically attractive forms are *N*3-substituted analogues.¹¹ For example, *N*3-functionalized 4-aryl-3,4-dihydropyrimidinone-2 (1*H*)-ones exhibited a broad range of biological effects^{11b} and have recently appeared as, e.g., antihypertensive agents SQ32547, SQ32926 and α_{1a} -adrenergic receptor antagonists.¹²

We recently reported a regioselective synthesis of the *N*3-functionalized DHPMs by reaction of DHPMs with paraformaldehyde and various reagents in the presence of trimethyl chlorosilane (TMSCl).¹³ In the context, we became interested in combining click chemistry (azide–acetylene cycloadditions) with MCR strategies. Herein, we reported an efficient approach for the one-pot synthesis of libraries including both 3,4-dihydropyrimidinones/amides and 1,2,3-triazole rings in their structures.

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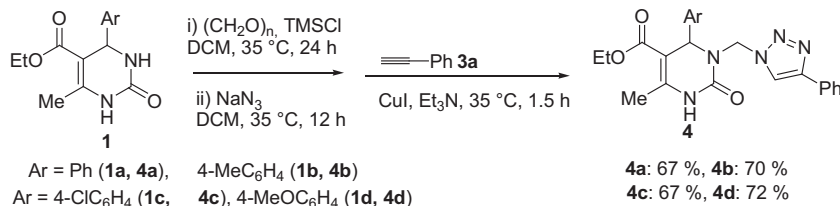
2. Results and discussion

Initially, the desired products **4a–d** were synthesized via the 1,3-dipolar cycloaddition between *N*3-azide functionalized DHPMs **2a–d**, which can be conveniently prepared according to our reported process,¹³ with phenylacetylene **3a** using water as the reaction medium in the presence of 10 mol % of CuI (Scheme 1).



Scheme 1. Fractional-step synthesis of triazoles using *N*3-azide functionalized DHPMs.

Then, we moved to the development of the one-pot three-step version of this transformation. By heating the mixture of DHPM **1** with paraformaldehyde in the presence of TMSCl in dichloromethane (DCM) at 35 °C for 24 h and subsequently adding NaN₃ for another 12 h gave the intermediate **2**. Without isolation of the compound **2**, then phenylacetylene **3a**, triethylamine (Et₃N) and 10 mol % CuI were added to the reaction mixture and the mixture was stirred at refluxing for another 1.5 h giving the cycloaddition products **4a–d** in a total yields of 67–72% (Scheme 2).



Scheme 2. One-pot three-step synthesis of triazoles from DHPMs.

Subsequently, we probed a modular synthesis of triazoles **4** through a click chemistry of four components by a one-pot two-step method. Treatment the DHMP **1a** with paraformaldehyde and TMSCl in DCM at 35 °C for 12 h and subsequently adding NaN₃ and phenylacetylene **3a** for another 8 h gave the product **4a**. Various copper salts were tested, Cu (I) salts, for example, CuCl, CuBr and CuI all gave good yields (Table 1, entries 1–3). Cu(OAc)₂·H₂O was

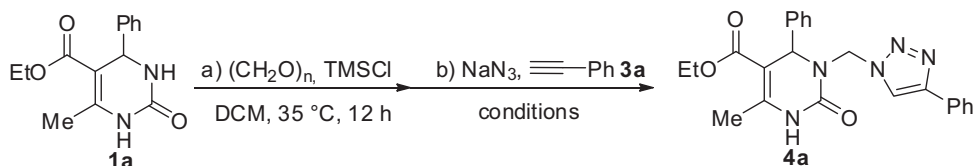
ineffective and most starting materials (**2**) were recovered (entry 4). Improved yields were obtained when Cu(OAc)₂·H₂O/NaAsc and CuSO₄·5H₂O/NaAsc were screened (entries 5 and 6). The reaction was obviously enhanced by addition of Et₃N (entries 7–8). Thus we used Cu(OAc)₂·H₂O/NaAsc as the optimal catalyst system.

With the optimized conditions in hand, we used DHPMs and diverse set of alkynes to test the reaction scope. In general, good to excellent yields were obtained under the standard reaction conditions. Therefore, a variety of triazoles **4** were obtained (Table 2), displaying both electron-rich (entries 1–4) as well as functionalized electron-deficient (entries 5 and 6) aryl-substituents of DHPMs, while *o*-chloro group on the phenyl ring give a slightly lower yield (entry 5). Sulfur-containing analogues of DHPMs **1** exhibited a slightly lower reactivity, the yields of the desired products decreased about 20% (entries 9 and 10). The structures of the final product **4d** were characterized by X-ray crystallographic analysis (Fig. 1).¹⁴ Good to moderate yields of desired 1,2,3-triazole derivatives were obtained employing terminal alkynes with different groups, including alkyl and aryl alkynes (entries 11–15).

Quinazolinones **5** were also exposed to the standard reaction conditions, resulting in the formation of *N*-functionalized quinazolinones with 1,2,3-triazole derivatives **6a–c** (Scheme 3). It is noteworthy that this four-component one-pot synthesis involved the formation of three C–N bonds in a highly selective fashion. It was obvious that the one-pot method didn't need the separation of organic azides and had greater advantages due to simplifying the experimental procedure.

To explore the scope of differentiated substrates in the one-pot two-step reaction, extensive amides **7** were exposed to the standard reaction conditions at rt, resulting in the formation of 1,2,3-triazole products **8a–e** (Table 3). As depicted in Table 3, all the two-step reactions can be carried out at room temperature (rt) within shorter reaction times (total 12 h) and good yields of azide–alkyne cycloaddition products were obtained.

Table 1
 Optimization of the sequential azide–alkyne cycloaddition^a



Entry	Catalysts (mol %)	Base	Time (h)	Yield ^b (%)
1	CuI (10)	Et ₃ N	8	73
2	CuBr (10)	Et ₃ N	8	72
3	CuCl (10)	Et ₃ N	8	70
4	Cu(OAc) ₂ ·H ₂ O (20)	Et ₃ N	8	48
5	Cu(OAc) ₂ ·H ₂ O (20)/NaAsc (40)	Et ₃ N	8	76
6	CuSO ₄ ·5H ₂ O (20)/NaAsc (40)	Et ₃ N	8	73
7	Cu(OAc) ₂ ·H ₂ O (20)/NaAsc (40)	—	12	10
8	Cu(OAc) ₂ ·H ₂ O (20)	—	12	5

^a Reaction conditions: the compound **2a** was prepared to our previous procedure and not isolated. DHPM (**1a**, 0.5 mmol), phenylacetylene (**3a**, 0.6 mmol), triethylamine (1 mmol), catalyst, 35 °C.

^b Isolated yields.

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