



Use of ligand-assisted click reactions for the rapid synthesis of novel 1,2,3-triazole pharmacophore-based 1,2,4-triazines and their benzo-fused analogues



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ABSTRACT

The click reaction was successfully employed for the synthesis of a series of new 1,2,3-triazole-based 1,2,4-triazinones and benzo[e][1,2,4]triazines from the reaction of 6-methyl-3-(prop-2-yn-1-ylthio)-1,2,4-triazin-5(4*H*)-one and 1,4-dihydro-3-(prop-2-ynylthio)benzo[e][1,2,4]triazine with aromatic azides or sodium azide and aliphatic halides in one-pot two- or three-component reactions. The Schiff base ligands accelerated the reactions and decreased the amount of the toxic copper catalyst required. Simplicity, short reaction times, high reaction yields, mild reaction conditions, and easy work-up are the main advantages of this method. All the new 1,2,3-triazole-based 1,2,4-triazines and their benzo-fused ring system formed were screened for their *in vitro* anti-bacterial activity against the Gram-positive and Gram-negative bacteria using a well-diffusion method.

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1. Introduction

After the introduction of “click chemistry” by Sharpless in 1999, it immediately became a very popular topic. This concept was developed in parallel with the interests within the pharmaceutical, materials, and other industries in capabilities for generating large libraries of compounds for screening in discovery research works. The click reaction can be defined by a set of stringent criteria. It is modular and wide in scope, affords high reaction yields, generates inoffensive by-products that can be removed by non-chromatographic methods, and is stereospecific. The other characteristics of this reaction include simple reaction conditions, readily available starting materials and reagents, absence of a solvent or presence of a solvent that is safe or easily removed, and simple product isolation.¹ One major category of the click reaction is the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction that satisfies all the stringent criteria of Sharpless, and has found applications in medicinal chemistry,² biological and

biomedical research works,³ combinatorial chemistry,⁴ and materials and surface science.⁵ In addition, the azide and alkyne functionalities can be easily introduced into the organic moieties and remain considerably tolerable with other functional groups and common chemical reagents, which enhance the significance of the reaction.

It has been previously reported that the usage of ligands accelerates the copper-catalyzed azide-alkyne cycloaddition reaction.^{6,7} The acceleratory effect of the ligands has been attributed to a) their basicity, which helps deprotonating the alkyne to facilitate the formation of copper(I) acetylide; b) their coordination lability that allows fast ligand exchange, which is beneficial to catalytic turnover; c) their chelation, which facilitates the rapid reduction of Cu(II) species to highly catalytic Cu(I) species; and d) their multidenticity, by which the ligands encapsulate and thus protect copper(I) species from oxidation by molecular oxygen.⁸ The ligands can also be used to prevent the formation of inactive polynuclear copper(I) aggregates and increase the solubility of the copper complex to deliver higher solution concentrations of the necessary Cu(I) species.^{6c,9} In the past few years, several polydentate azaligand frameworks have also been found to aid CuAAC reactions (Fig. 1).^{7,6c,10} The polytriazole and polybenzimidazole ligands such as tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) and

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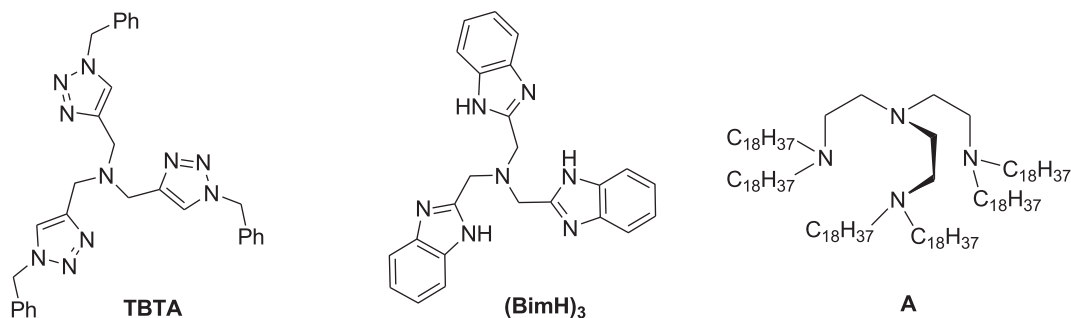


Fig. 1. Polydentate aza-ligands accelerating copper catalyzed click reactions.

tris(2-benzimidazolylmethyl)amine ((**BimH**)₃) have been found to be powerful stabilizing ligands, assisting the copper-catalyzed azide-alkyne click reactions. Furthermore, the copper(I) complex of the ligand tris(2-dioctadecylaminoethyl)amine (**A**) is a highly reactive catalyst for the click reaction of azides with terminal or internal alkynes, and it is a useful catalyst for the preparation of “click” dendrimers.

Triazoles represent a class of five-membered heterocyclic compounds of great importance for the preparation of new drugs with diverse biological activities because they may present several structural variations with the same number of carbon and nitrogen atoms. 1,2,3-Triazoles have attracted interest since their moieties have been widely used in pharmaceuticals, agrochemicals, dyes, photographic materials, and corrosion inhibitors.¹¹ These compounds display a wide range of biological properties such as antiviral, anti-epileptic, anti-allergic,¹² anti-cancer,¹³ anti-HIV,¹⁴ and anti-microbial activities against the Gram positive bacteria.¹⁵ 1,2,4-Triazines and their analogs occupy a pivotal position in modern medicinal chemistry due to their high potential for pharmacological activities.¹⁶ These compounds have been reported to possess a broad spectrum of biological properties including anti-fungal,¹⁷ anti-HIV,¹⁸ anti-tumour,¹⁹ neuroprotective,²⁰ anti-malarial,²¹ antibacterial,²² anti-proliferative,²³ and CRF1 receptor antagonistic²⁴ activities. Considering the above subjects, we decided to synthesize the 1,2,3-triazole pharmacophore-based 1,2,4-triazine moiety via copper-catalyzed click reactions.

2. Results and discussion

The synthesis of 1,2,3-triazole pharmacophore-linked heterocyclic moieties via copper-catalyzed click reactions has recently been reported.^{25–28} However, to the best of our knowledge, no example involving the synthesis of 1,2,3-triazole-linked 1,2,4-triazine and its fused ring system through an S-bridge atom has yet been reported. In continuation of our efforts for the efficient synthesis of new heterocyclic compounds,²⁹ herein we wish to report the efficient synthesis of new 1,2,3-triazole-linked 1,2,4-triazine and benzo[e][1,2,4]triazine rings from the reaction of 6-methyl-3-(prop-2-yn-1-ylsulfanyl)-1,2,4-triazin-5(2H)-one (**1**) and 1,4-dihydro-3-(prop-2-ynylthio)benzo[e][1,2,4]triazine (**2**) with an aromatic azide or sodium azide and an aliphatic halide via click chemistry in the presence of salophen Schiff base ligand (**L2**) (Schemes 1 and 2).

The starting materials 6-methyl-3-(prop-2-yn-1-ylsulfanyl)-1,2,4-triazin-5(2H)-one (**1**) and 1,4-dihydro-3-(prop-2-ynylthio)benzo[e][1,2,4]triazine (**2**) were prepared, respectively, from the reaction of 6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one or 1,2-dihydrobenzo[e][1,2,4]triazine-3(4H)-thione with 3-bromoprop-1-yne in methanol in the presence of sodium methoxide.³⁰

Compound **1** was reacted with 1-azido-3-nitrobenzene (**3g**) in the presence of 10 mol% of Cu(OAc)₂ and 20 mol% of sodium ascorbate in ethanol at room temperature to obtain 6-methyl-3-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methylthio)-1,2,4-triazin-5(4H)-one (**4g**) in 60% yield (Table 1, entry 10). When the solvent was replaced with DMF, the yield increased to 96% (Table 1, entries 6 and 7). In these reactions, a large amount of the copper catalyst (10 mol%) was used, whereas the Cu salts are toxic, polluting the biologically relevant compounds, and their complete removal from the reaction mixture is difficult. The nitrogen-containing ligands allow the use of copper catalysts in reduced amounts compared to the original classic catalysts (CuSO₄ and sodium ascorbate), which are still the most commonly utilized catalysts but in much larger quantities that are often even stoichiometric or superior to stoichiometry.³¹ A number of researchers have efficiently decreased the required amount of the copper catalyst for the click reactions by the usage of ligands.³² In order to decrease the amount of the copper catalyst used, we decided to use the Schiff base ligands **L1**, **L2**, **L3**, and **L4** as additives in the reaction (Fig. 2). Surprisingly, in the presence of **L2** (salophen) and with 2 mol% of Cu(OAc)₂, the reaction proceeded effectively, and was completed in less than 20 min to afford the desired product in a 96% yield (Table 1, entry 21). Therefore, the optimal reaction conditions were 2 mol% of Cu(OAc)₂, 4 mol% of sodium ascorbate, and 2 mol% of salophen (**L2**) at room temperature in DMF (Table 1, entry 15).

A similar approach was applied for modifying the reaction conditions in the synthesis of 1,2,3-triazole-linked benzo[e][1,2,4]triazine system. The results obtained are tabulated in Table 2.

In order to explore the scope and generality of these procedures, various aromatic azides were used as the substrates for the synthesis of the substituted target products 6-methyl-3-((1-aryl-1H-1,2,3-triazol-4-yl)methylthio)-1,2,4-triazin-5(4H)-ones (**4a-g**) and 3-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methylthio)-1,4-dihydrobenzo[e][1,2,4]triazine (**5a-f**) under the optimized reaction conditions. The results obtained are tabulated in Tables 3 and 4.

In order to investigate the synthesis of a variety of 1,2,3-triazole-linked 1,2,4-triazines and their fused ring system, we decided to carry out the reactions in a multi-component manner. The three-component reaction of 6-methyl-3-(prop-2-yn-1-ylsulfanyl)-1,2,4-triazin-5(2H)-one (**1**) and 1,4-dihydro-3-(prop-2-ynylthio)benzo[e][1,2,4]triazine (**2**) with sodium azide and aliphatic halides (**6a-b**) in the presence of a copper catalyst gave the desired products (**7a-c**) and (**8a,b** and **8d,e**) in good-to-high yields (Scheme 2). In order to optimize the reaction conditions for this three-component synthesis, the reaction of 6-methyl-3-(prop-2-yn-1-ylsulfanyl)-1,2,4-triazin-5(2H)-one (**1**) with 4-nitrobenzyl chloride (**6a**) and sodium azide was used as a model reaction. The reactions carried out in different solvents, temperatures, and various amounts of catalysts and Schiff base ligands revealed that the

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