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A "Click and Activate" Approach in One-Pot Synthesis of a Triazolyl-Pyridazinone Library

Wenyuan Qian,* David Winternheimer, and Jennifer Allen

Chemistry Research and Discovery, Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, United States

wqian@amgen.com

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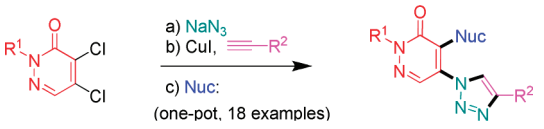
ABSTRACT



A "click and activate" strategy was designed and executed in a four-component, stepwise condensation that led to a trisubstituted triazolyl-pyridazinone library. This one-pot process included regioselective azide substitution at 2-substituted-4,5-dichloropyridazinones, followed by a Cu(I) catalyzed triazole formation which triggered subsequent nucleophilic substitution at the neighboring position to achieve three points of diversity.

The efficient and precise assembly of molecular diversity is one of the key aspects in library synthesis and medicinal chemistry. Multiple component reactions (MCRs), in which three or more reactants condense in a single reaction vessel to form a new product containing portions of all components, are well suited for this purpose.[1,2] Although all components are not necessarily condensed in a mechanistically concerted fashion, MCRs are a one-pot process and are attractive in terms of atom- and step-economy, operational simplicity, and environmental friendliness.

Recently, as the most significant example of click chemistry,[3] a Cu(I) catalyzed azide−alkyne cycloaddition (CuAAC) to form 1,2,3-triazoles, first reported by the Sharpless and Meldal groups, has attracted enormous attention in both academia and industry.[4−6] Compared to traditional triazole syntheses, this new approach offers not only high yields under mild conditions but also high regioselectivity for the 1,4-disubstituted triazoles. As an extension of this efficient reaction, some elegant examples involving *in situ* formation of an organic azide followed by click chemistry in one pot have also been disclosed.[7]

Efficient synthesis via CuAAC click chemistry and unique physicochemical properties of triazoles makes them attractive partners for participation in multiple component condensations to form more complex structures with potential biological activities. In the literature, triazole formation has been combined with other reactions, such as the Biginelli reaction,[8] domino Wittig−Knoevenagel/Diels−Alder reaction,[9] and Ugi reaction,[10] etc., either in multiple steps or in one pot. However, in most existing

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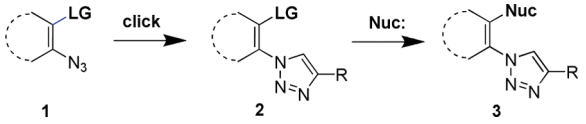
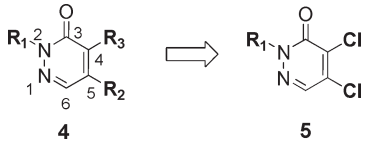
examples, the triazole formation is always introduced in the last step as the final decoration of the previous intermediates.[11]

Scheme 1. Proposed "Click and Activate" General Approach



An alternative and largely unexplored approach for incorporating click chemistry into multiple component condensations would place the CuAAC step in the *mid-stage* rather than the final step of the one-pot process. One obvious advantage of introducing CuAAC click chemistry earlier is that triazoles are usually chemically more stable than alkynes or azides, thus resulting in better compatibility with other reaction components. More importantly, in our recent medicinal chemistry program, we observed a subtle activation effect of the triazole moiety on its neighboring groups in subsequent transformations. Based on this observation, here we propose a broader "click and activate" strategy illustrated in Scheme 1: After CuAAC click chemistry on azide **1**, the resulting triazole group in **2** allows activation of the conjugated double bond with a leaving group toward nucleophilic substitution to give **3** in one pot. This double bond can be a part of an electron-deficient aromatic or heteroaromatic ring.

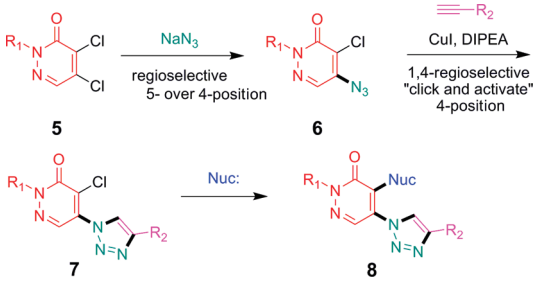
Scheme 2



2-Substituted-4,5-dichloropyridazinone (**5**) provides an ideal substrate to explore this approach (Scheme 2). 2,4,5-Trisubstituted-3(2*H*)-pyridazinones (**4**) are well-known compounds of agrochemical and pharmaceutical interest.[12] Several commercial products containing this scaffold, such as Chloridazon (herbicide),[13] Pyridaben (miticide/insecticide),[13] and Emorfazone (anti-inflammatory agent),[12c] are worth mentioning.

Efficient synthetic approaches that allow selective and convenient derivatization of this pharmacological privileged core structure would expand their assessment and value. Because a variety of 2-substituted-4,5-dihalo-pyridazinones (**5**) are commercially available or can be easily made, there has been an ever growing amount of work in the literature aimed at the selective functionalization of the 4- and 5-positions.[14,15] However, many existing approaches are either nonregioselective or require stepwise reactions (sometimes including protection and deprotection) and separation of intermediates.

Scheme 3



Here we report a one-pot synthesis of general structure **8** utilizing CuAAC as the key step that allows easy access to three points of diversity on the pyridazinone scaffold (Scheme 3). First, a regioselective azide substitution at the 5-position of **5** is required. With azide **6**, a click reaction with terminal acetylenes would be expected to give triazole **7** in a highly regioselective manner. As the final step in the sequence, we reasoned that the formation of the triazole **7** should switch the reactivity of the 4-(chloro) position from a "neutral" or "deactivated" (as in azide **6**) to an "activated" state toward nucleophilic attack due to the subtle electronic effect of triazole. We set out to identify the optimal conditions suitable for all elementary transformations to proceed in a highly organized manner in one pot.

The solvent effect of the nucleophilic substitution on the 4,5-dihalopyridazinones by amines, alkoxides, and alkylthiolates is well documented in terms of regioselectivity.[16,17] However, azide substitution on this core has been studied to a lesser extent in the literature.[17] In fact, all reported examples required heating for extended periods and favored substitution at the 5-position. To enable our

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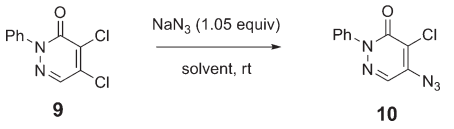
Table 1. Solvent Screening for Regioselective Azide Substitution at Room Temperature[a]



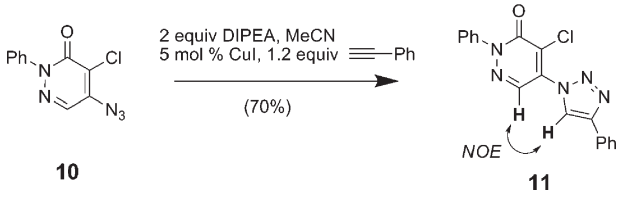
9 **10**

solvent	% conversion at 30 min	% conversion at 90 min
toluene	0	0
DCM	0	0
THF	0	0
dioxane	0	0
MeOH	0	0
MeCN	1	4
DMSO	85	95
DMF	96	98

[a] The solvent screening was conducted at a concentration of 1 M. The conversion was calculated based on HPLC peak area integrations of **9** and **10** at 254 nm. In DMF, the reaction gave similar conversion at 2.5 M. The isolated yield was 78%.

proposed one-pot reaction sequence, we sought to identify a solvent that provided high selectivity and acceptable reaction rates at room temperature. Among the various solvents we screened, polar aprotic solvents such as DMSO and DMF gave the best results (Table 1). This step with **9** is fast and highly regioselective to give **10**. In addition, this reaction only requires a minimal amount of DMF. When using 1 equiv of NaN_3, no bis-azido product was observed.

Scheme 4

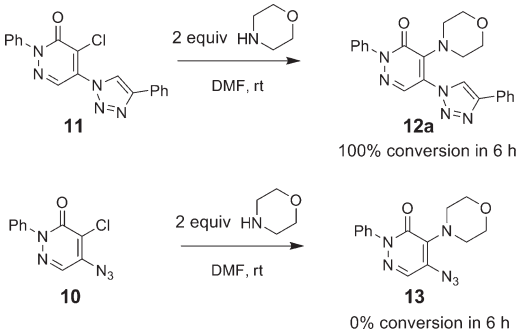


10 **11**

Although DMF was the best solvent for the azide substitution, it gave rise to a significant amount of side products in the CuAAC click reaction under standard conditions. Instead, acetonitrile as the solvent provided a much cleaner result for this step (Scheme 4). Because there was no precedence for using DMF as the solvent for the azide substitution on 4,5-dichloropyridazinone **5** in the first step, we studied the regioselectivity after triazole formation by 2-D HNMR. A clear NOE between the proton on the 6-position of the pyridazinone core in **11** and the proton on the triazole moiety was detected by NOESY experiments, supporting the desired regiochemistry of both transformations (Scheme 4).

The concept of the "click and activate" approach was clearly demonstrated in the following control experiments (Scheme 5). Treatment of triazole **11** with 2 equiv of morpholine in DMF led to 100% conversion to **12a** in

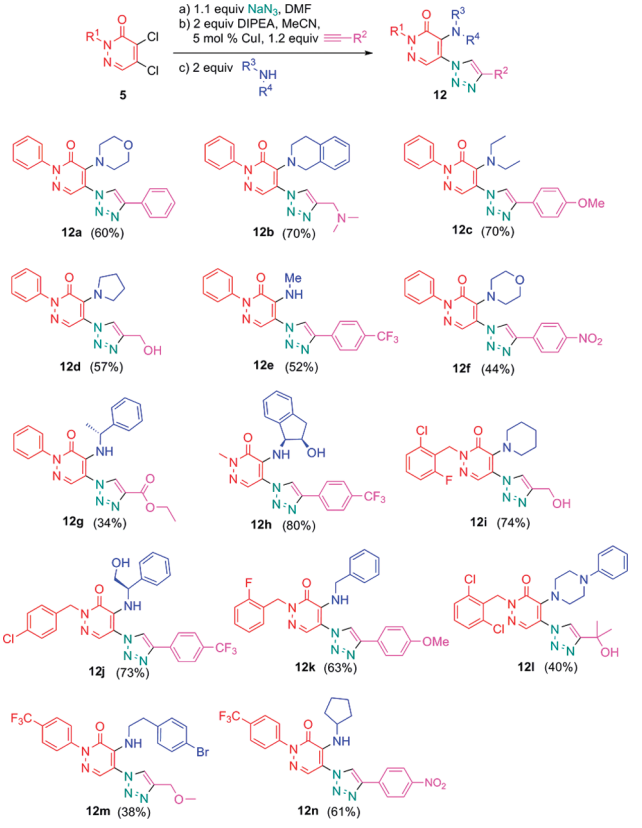
Scheme 5



6 h at room temperature. In parallel, azide **10** failed to afford any HPLC detectable amount of morpholine substitution product **13** under the same conditions, *pointing to the importance of activation by the triazole*.

Having established suitable conditions and secured the selectivity in each step separately, we conducted the entire synthesis in one pot: A 2.5 M solution of 4,5-dichloro-2-phenylpyridazin-3(2*H*)-one **9** was treated with 1.1 equiv of sodium azide, and the reaction was stirred at room temperature for 2 h until **9** was consumed as indicated by TLC. The reaction mixture was diluted with MeCN and was treated with 2 equiv of *N*-diisopropylethylamine (DIPEA), 1.2 equiv of phenylacetylene, and a catalytic amount of

Scheme 6. One-Pot Condensation with Amines

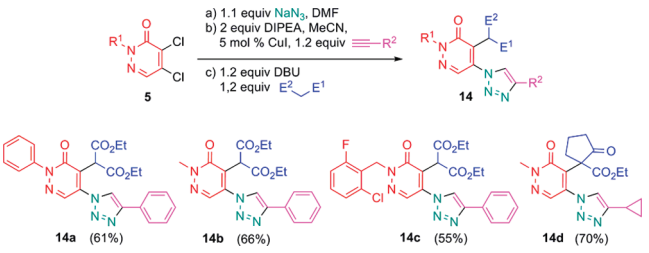


copper(I) iodide. After 30 min, 2 equiv of morpholine were added and the reaction was stirred overnight to afford product **12a** in 60% isolated yield. In a simpler procedure, 2 equiv of morpholine were added to the *in situ* formed azide in MeCN, together with phenylacetylene and copper(I) iodide, affording **12a** directly in a comparable yield (54%). The entire procedure was performed at room temperature without extra caution for air and moisture.

The simple operation and the mild conditions of this one-pot procedure provide an easy access to a wide diversity of the triazolyl-pyridazinone scaffold **12** by condensing a variety of 2-substituted-4,5-dichloro-pyridazinones **5**, sodium azide, terminal acetylenes, and amines as shown in Scheme 6. Substituted phenyl, alkyl, and substituted benzyl groups are all tolerated at the 2-position of the pyridazinone core. Similarly, a range of alkynes, such as phenylacetylenes bearing electron-donating (**12c**, **12k**) or -withdrawing groups (**12e**, **12f**, **12h**, **12j**, **12n**) and smaller acetylenes with other functional groups, can be easily incorporated with high regioselectivity. Likewise, a wide spectrum of different primary and cyclic or acyclic (**12c**) secondary amines were readily installed due to the activation effect after click reaction. These included bicyclic amines (**12b**) and amines with one (**12g, 12j**) or even two (**12h**) chiral centers. The overall yields are moderate to very good as a result of the combined efficiency of three individual transformations.

In order to extend the scope of this strategy, several carbon nucleophiles were briefly explored (Scheme 7). After *in situ* azide substitution followed by CuAAC click reaction, the reaction mixture was treated with 1.2 equiv of DBU and 1.2 equiv of diethyl malonate to give **14a**−**c** in good yields. Surprisingly, a cyclic ketoacetate led to **14d** bearing a quaternary center in very good yield under the same conditions. One-pot condensation with other types of nucleophiles will be the subject of future studies.

Scheme 7. One-Pot Condensation with Carbon Nucleophiles



In summary, the CuAAC "click and activate" strategy presented herein is a powerful approach in diversity-oriented, multiple component condensation sequences. As demonstrated in the first case study in this paper,[18] the regioselective triazole formation not only stitches together an alkyne and an azide but also switches the reactivity of the neighboring group, triggering the facile *in situ* nucleophile trapping to introduce additional diversity. The one-pot execution of this strategy is very simple and suitable for rapid assembly of molecular complexity, with four new bonds being formed in this case. Application of this general concept to the construction of other triazole-containing scaffolds with potential biological activity is underway.

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Supporting Information Available. Experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) To the best of our knowledge, this is the first example of one-pot, multiple component condensation sequence by a CuAAC "click and activate" approach. Early examples of 4-alkylamino-5-triazolyl-pyridazinone were synthesized in three separate steps. However, extended heating and the potential regiochemical control issue in the "nonclick" triazole formation step limits the scope of this old procedure and makes it unsuitable for one-pot operation. See: (a) Karklins, A.; Gudriniece, E. *Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija* **1969**, *5*, 579. (b) Gudriniece, E.; Urbans, V. *Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija* **1971**, *1*, 82. (c) Urbans, V.; Gudriniece, E.; Urbans, V. *Latvijas PSR Zinatnu Akademijas Vestis, Kimijas Serija* **1972**, *1*, 107.