

Cascade Reactions

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Copper-Catalyzed Domino Cycloaddition/C—N Coupling/Cyclization/(C—H Arylation): An Efficient Three-Component Synthesis of Nitrogen Polyheterocycles**

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Transition-metal-mediated cascade reactions constitute one of the most vibrant areas of modern-day organic chemistry. The efficiency of a catalytic system in these step-economical processes should be evaluated by the number and diversity of individual transformations involved and the number of new bonds that can be formed by the catalyst, as these factors are usually proportional to the complexity of the final products. From this point of view, it is not surprising that a significant portion of the existing catalytic cascade reactions have been based on palladium, which has highly versatile reactivity and well-understood mechanisms. [2,3]

Copper-mediated Ullmann-type coupling reactions (Ullmann, Goldberg, and Hurtley reactions) have provided some of the most useful methods for the formation of aryl C-N, C-O, and C-C bonds for more than a century. However, it was not until the beginning of the 21st century, with the discovery of much more efficient copper/ligand catalytic systems that operate under much milder conditions, that the full potential of these classical transformations began to be unveiled. [4,5] Another significant breakthrough was made by the Daugulis research group in a novel copper-mediated direct C-H arylation of a variety of (hetero)aromatic compounds. [6]

As a result of vastly improved procedures, Ullmann-type coupling reactions have become increasingly popular for the synthesis of aromatic heterocycles. Some examples in this area involve cascade reactions in which two individual catalytic transformations are directly mediated by copper (mostly on the basis of the sequential coupling of dihalosubstituted substrates). In general, the area of copper-promoted cascade reactions is still underdeveloped as compared to the remarkable versatility of domino events mediated by palladium. Amoreover, copper has not been widely used for the catalysis of multiple-component condensations.

Interestingly, almost simultaneous with the renaissance of copper-mediated coupling reactions was the discovery of the copper-catalyzed azide-alkyne cycloaddition reaction

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(CuAAC), which quickly attracted enormous attention owing to its excellent chemo- and regioselectivity, efficiency, and reliability under a wide range of reaction conditions. [11,12] To our surprise, these two general types of copper-catalyzed reactions have rarely overlapped despite their rapid development in parallel in the past decade. [13,14] We reasoned that a combination of these two orthogonal and complementary transformations should be compatible with at least the four different functional groups involved. Therefore, it would provide unique opportunities for the development of novel multiple-component cascade reactions, which would maximize the catalytic utility of copper.

Recently, we demonstrated that the electronic effect of switching from the azide to the moderately electron-with-drawing triazole in CuAAC reactions can have a significant impact on the reactivity of its neighboring groups for subsequent transformations. This general "click-and-activate" strategy has been applied in the multiple-component assembly of several polyheterocycles.

From these general considerations, we envisioned that 2-azidoacetamides would be unique building blocks with high bond-forming potential: both cycloaddition and C-N coupling reactions would be possible under the action of one copper catalyst (Scheme 1). Furthermore, upon triazole formation, the methylene group would become more acidic, thus enabling the formation of a stable anion for reactions with electrophiles. The triazole would also provide an opportunity for direct C-H functionalization mediated by the same copper species.

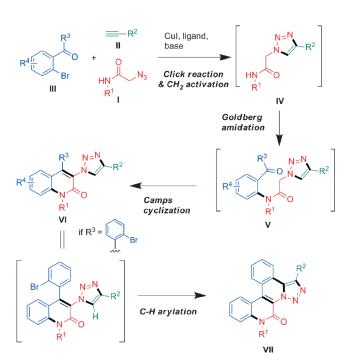
On the basis of this analysis, we communicate herein a one-pot, copper-catalyzed, three-component cascade condensation to construct novel polyheterocyclic systems from readily available starting materials (Scheme 2). First, a facile copper-catalyzed [3+2] cycloaddition between a 2-azidoacetamide I and an acetylene II should lead to a triazole IV, in which the adjacent methylene group is activated. Then, in the presence of an ortho-carbonyl-substituted aryl halide III, the same catalytic system should enable an intermolecular Goldberg amidation (to give V), followed by a Camps cyclization (intramolecular aldol-dehydration sequence) to form a 2quinolinone ring VI.[16,17] In the case of more reactive electrophiles, such as 2-bromobenzaldehyde, an alternative sequence involving a Knoevenagel condensation followed by intramolecular N-arylation is also possible and leads to the same product VI. When the R3 substituent in VI is a 2'bromoaryl group, the domino sequence should continue to evolve, as the triazolyl group is now perfectly positioned for

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Scheme 1. Merging of copper-mediated cross-coupling and cycloaddition reactions by a "click-and-activate" protocol.

under copper catalysis



Scheme 2. Proposed copper-mediated, three-component cascade seauence.

an intramolecular copper-mediated C-H arylation to afford a pentacycle VII.[14,18]

Although this plan was conceptually appealing, we realized that its practical execution could be challenging because the catalytic cycles and optimal conditions for each individual transformation are very different.^[5,6,11] In principle, this reaction sequence could be conducted in a modular, stepwise manner with a specific order of addition of components/reagents to avoid undesired by-products. However, our goal was to develop an "ideal" multiple-component reaction^[10a,e] by combining everything at once in one reaction vessel as an ultimate test of chemoselectivity in the presence of the multiple functional groups involved in this cascade.

N,N'-Dimethylethane-1,2-diamine (DMEDA), one of the most frequently employed ligands for C-N coupling, [4f,5] was reported to be a moderate promoter of the CuAAC reaction in tBuOH/water.^[19] In the first set of control experiments, we observed that it dramatically accelerated the click reaction in organic solvents at a relatively high catalyst loading. In all three solvents (toluene, dioxane, and N,N-dimethylformamide (DMF)) tested at a 0.5 m concentration, the cycloaddition between 2-azidoacetamide (1a, 1 equiv) and phenylacetylene (2a, 1.1 equiv) proceeded to completion within 10 min upon the addition of a catalytic amount of CuI (10 mol%) and DMEDA (20 mol%) to give triazole 3a in excellent yield (Scheme 3). In comparison, with the combi-

Scheme 3. CuAAC reaction accelerated by DMEDA

nation CuI/NEt3, a widely used catalytic system for click chemistry, the reaction required 2 h to reach completion in

Next, the six compatible functional groups of the three simple components 1, 2, and 4 were combined with remarkable selectivity in a one-pot condensation under the standard Buchwald conditions for copper-catalyzed amidation (Scheme 4).^[5] In a typical example, a mixture of the three components 2-azidoacetamide (1a, 1 equiv), phenylacetylene (2a, 1.2 equiv), and 2-bromobenzophenone (4a, 1.2 equiv), the CuI catalyst (10 mol%), and K₂CO₃ (3 equiv) in dioxane (at a $0.5 \,\mathrm{M}$ concentration with respect to $1 \,\mathrm{a}$) under a N_2 atmosphere was treated with a catalytic amount of DMEDA (20 mol %). The reaction vial was sealed, and the mixture was stirred at room temperature for 10 min and then heated at 120°C for 24 h to give the 3-triazolylquinolinone product 5a in 64% yield after purification. The activation effect of the triazole moiety is mild and suitable for this tandem transformation. The methylene group between the amide and the triazole groups in the intermediate 3a can be deprotonated for the intramolecular Camps cyclization under the mildly basic conditions. Importantly, at the same time, it is not acidic enough for an intermolecular α arylation to compete with the desired amidation.

Under similar conditions, a wide spectrum of molecular diversity around the quinolinone core was rapidly assembled

Scheme 4. Synthesis of 3-triazolylquinolinones 5 by the copper-catalyzed, three-component condensation of a 2-azidoacetamide 1, an acetylene 2, and an o-acyl aryl bromide 4. [a] Cs2CO3/toluene (120°C, 36 h) was used instead of K2CO3/dioxane.

5n (62 %)

from readily available starting materials (Scheme 4). 2-Bromobenzaldehyde was also a good coupling partner and gave a 4-unsubstituted analogue 5b. Owing to the activation effect of the triazole group and the weakly basic conditions, even enolizable ketones underwent the condensation selectively to afford 2-quinolinones 5c and 5d without the formation of an α-arylation product or the corresponding 4quinolinones (another possible regioisomer from the Camps cyclization^[16b]). Aryl bromides bearing either electron-donating or electron-withdrawing groups were incorporated effectively. Furthermore, both electron-rich and electron-deficient heteroaryl bromides were converted into the desired condensation products (51, 5m, and 5n) in reasonable yields. In terms of the alkyne component, this assembly process also enjoyed the same wide substrate generality as click chemistry. A variety of functional groups, such as acetal, ester, hydroxy, amino, chloro, and heteroaryl groups, were tolerated and installed.

One remaining issue in the Goldberg amidation has been its sensitivity to steric hindrance on the amide.^[5] This limitation was also observed in our three-component reactions of secondary-amide intermediates. Following smooth triazole formation between the secondary amide and phenylacetylene, only a trace amount of the final amidation/ cyclization product was detected under our standard reaction condition. When the system K₂CO₃/dioxane was replaced with Cs₂CO₃/ toluene, the desired products 50 and 5p were obtained in modest yields after a reaction time of 36 h at 120 °C.

Encouraged by the results of this threecomponent coupling (Scheme 4), we then explored the possibility of a subsequent direct intramolecular C-H arylation of the triazole moiety by employing the triple electrophile bis(2-bromophenyl)methanone (6) in the one-pot condensation (Scheme 5). This ring-closing event would further elongate the reaction cascade and increase the complexity of the final product. However, as compared to the preceding steps, this concluding transformation could be more problematic. Although some heteroarenes with more acidic C-H bonds (with p K_a < 27 in dimethyl sulfoxide (DMSO)) can be directly functionalized by the use of copper and a weak base, such as K₃PO₄,^[6] all previously described arylation reactions on 1,2,3-triazoles require much more reactive coupling partners, such as aryl iodides, a strong base, such as LiOtBu, and a polar solvent, such as DMF.[14] In a recent study it was found that even intra-

Scheme 5. One-pot construction of dibenzotriazolonaphthyridinones 8 by a copper-catalyzed cycloaddition/amidation/cyclization/C-H-arylation cascade.

5o,R = Me $(35\%)^{[a]}$

5p,R = Ph (22%)^[a]

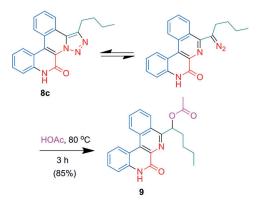
5m (62 %)

molecular arylation reactions on such substrates demand similarly harsh conditions. [20] In our one-pot procedure, the use of a strong base would not be compatible with the preceding steps. Several potential pitfalls associated with strong bases, such as side reactions at carbonyl groups, decreased efficiency of catalytic amidation, [5] and competing α -arylation reactions, can be expected. Although a strong base could be introduced separately in the final phase of the reaction, after the preceding three steps had been completed under mildly basic conditions, the cascade nature of this one-pot procedure would be interrupted. Moreover, to enable maximum experimental simplicity and functional-group tolerance, we still sought to identify effective, weakly basic conditions to accommodate all steps in one operation.

Initial attempts under our standard K₂CO₃/dioxane conditions resulted in the formation of only the bromide intermediate 7 after extended heating (120-140 °C for 60 h). We then screened combinations of three weak bases (K_2CO_3 , Cs₂CO₃, and K₃PO₄) with three common solvents (toluene, dioxane, and DMF) with fixed amounts of the CuI/DMEDA catalyst. Cs₂CO₃/toluene was identified as the most effective system for this full cascade, with the formation of 8a in 61 % yield after rigorous degassing followed by heating at 120°C for 60 h (Scheme 5). To the best of our knowledge, this transformation is the first copper-catalyzed direct C-H arylation of a triazole with an aryl bromide in the presence of a weak base in a nonpolar solvent. [6] An ester group, which is incompatible with strong bases, was tolerated under these conditions, and product 8b was obtained in moderate yield. When alkyl-substituted acetylenes were used, a mixture of 7 and 8 was obtained after heating of the reaction mixture at 120 °C for 60 h. This incomplete ring closure is most likely due to the slightly weaker C-H acidity in 7 as compared to that of the aryl-substituted triazoles. Nevertheless, the fully cyclized products 8c and 8d were obtained in very good yields by heating of the reaction mixture at 140°C for an additional 12 h after initial heating at 120 °C for 48 h.

Several factors might contribute to the success of the final step under the unprecedented mild conditions. First, the C–H acidity of the triazole moiety in 7 could be enhanced through conjugation with the quinolinone core. At the same time, the aryl bromide subunit is more reactive in the oxidative addition step owing to the dual activation by the triazole and amide groups through long-distance conjugation. Furthermore, the neighboring amide group might be able to provide some assistance in the metalation (deprotonation) and/or the transmetalation process in the catalytic cycle of C–H functionalization. More detailed model studies are ongoing to better understand and further optimize this transformation.

Having accomplished its "multiple missions" in the domino sequence, the triazole moiety in the final products $\bf 8$ became also readily cleavable under mild conditions in acetic acid. When applied to $\bf 8c$, this step led to a novel α -functionalized dibenzonaphthyridinone $\bf 9$, the relationship of which to the four original simple components is barely recognizable (Scheme 6). The formation of the aromatic quinoline subunit following the release of a nitrogen molecule by either a cationic or a carbene mechanism is believed to be the thermodynamic driving force of this transformation. $^{[21]}$



 $\textbf{\textit{Scheme 6.}} \ \ \text{Facile triazole cleavage of the condensation product } \textbf{\textit{8c}}.$

Furthermore, the ring-opening event could be further facilitated by repulsion between the electron lone pairs on the oxygen atom of the amide group and the adjacent N2 atom of the triazole group in **8**. This reactivity provides interesting opportunities for a variety of postcondensation functionalization steps (such as transannulation to other fused heterocycles through a carbene pathway), which will be the subject of future studies.^[22]

In summary, we have demonstrated that the potential of copper catalysis in the construction of complex heterocycles can be greatly expanded by merging Ullmann-type coupling reactions with the highly compatible azide-acetylene cycloaddition reaction along with a "click-and-activate" approach. Facile triazole formation not only introduced additional diversity, but also facilitated the Camps cyclization by activating the adjacent methylene group as a nucleophile. [15c] After cyclization, the triazole subunit seemed to play a subsequent role in activating the 2'-bromoaryl group as an electrophile^[15a] in intermediate **7** to enable an intramolecular direct C-H functionalization of itself under much milder conditions than those previously reported. With just a single copper catalyst, up to five new bonds (three C-N and two C-C) and three new rings can be created through a cascade of four types of reactions involving three different copper catalytic cycles. It is rare in copper chemistry to have this number and diversity of individual transformations in a cascade that can be accurately controlled by one catalytic system in a simple one-pot operation. The application of this strategy to the synthesis of other complex heterocycles is under way.

Experimental Section

Synthesis of **5c**: 2-Azidoacetamide (25 mg, 0.25 mmol), copper(I) iodide (4.8 mg, 0.025 mmol), and potassium carbonate (104 mg, 0.75 mmol) were placed in a microwave vial with a magnetic stirring bar. The reaction vial was evacuated and backfilled with nitrogen three times. Dry dioxane (0.5 mL) followed by 1-(2-bromophenyl)-ethanone (60 mg, 0.3 mmol), phenylacetylene (31 mg, 0.30 mmol), and N_iN' -dimethylethylenediamine (4.4 mg, 0.05 mmol) were added to this mixture under nitrogen with syringes. The vial was then sealed, and the mixture was stirred at room temperature for 10 min and then heated to 120 °C for 24 h. After cooling, the solvent was removed, and the residue was loaded directly onto a column for flash chromatography (SiO₂, CH₂Cl₂ \rightarrow CH₂Cl₂/MeOH (100:4)). The tan solid

obtained by chromatography was triturated with MeOH, filtered, and dried in air to afford 4-methyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one (57 mg, 0.19 mmol, 76 % yield) as a tan solid. 1H NMR (400 MHz, [D₆]DMSO): δ = 12.41 (s, 1 H), 8.82 (s, 1 H), 7.97 (d, J = 7.8 Hz, 3 H), 7.73–7.67 (m, 1 H), 7.55–7.45 (m, 3 H), 7.43–7.34 (m, 2 H), 2.31 ppm (s, 3 H); 13 C NMR (100 MHz, [D₆]DMSO): δ = 157.5, 146.1, 145.6, 138.0, 132.0, 130.5, 129.0, 128.0, 126.5, 126.3, 125.2, 124.4, 122.7, 118.5, 115.8, 14.1 ppm; HRMS (ESI): m/z calcd for $C_{18}H_{14}N_4O$: 303.1246 [M+H] $^+$; found: 303.1245.

Compounds **5a-p** were prepared by similar procedures.

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Communications



Cascade Reactions

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Copper-Catalyzed Domino Cycloaddition/ C-N Coupling/Cyclization/(C-H Arylation): An Efficient Three-Component Synthesis of Nitrogen Polyheterocycles

A cat of all trades: A single copper catalyst promoted up to three reaction steps with separate catalytic cycles in a domino sequence (azide-alkyne cycloaddition/Goldberg amidation/Camps cyclization/(C-H arylation)) for the rapid

construction of complex heterocycles from three simple components under mild conditions (see scheme). Facile cleavage of the triazole ring enables further elaboration of the condensation products.