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Relay Catalysis by a Multifunctional Cu Catalyst in a Tandem Dehydro-/Dehalogenation Sequence along with N-Arylation

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ABSTRACT



A Cu-catalyzed tandem dehydrogenation/dehalogenation sequential reaction along with N-arylation has been developed for the synthesis of pyridazinone derivatives in an aerobic and aqueous environment. To achieve the transformation of three chemical bonds in a one-pot reaction, a multifunctional copper catalyst was used which afforded excellent activity, high selectivity, and recyclability. The catalytic system consists of a water-soluble Cusalen complex and Na₂CO₃ in neat water and an air atmosphere.

Presently, an increasing interest in developing 'green' processes has emerged, as the green initiative and sustainability have become major trends in the pharmaceutical industry.¹ According to the 12 principles of Green Chemistry, water is the premier solvent recommended since it is abundant, nontoxic, noncorrosive, and nonflammable, and the use of water as the sole reaction medium is one of the latest challenges for modern chemists.² Recently, tremendous effort has been focused toward using water as the solvent, and several reactions have been proven successful such as Cu-catalyzed Ullmann reactions, Cu-catalyzed alkyne–azide cycloadditions.³

On the other hand, pyridazinone, as a useful heterocyclic scaffold, was used as a pharmacophore with versatile functions [Figure 1a]. Recently, N-arylated pyridazinones

have been developed as G-Protein-Coupled Receptor (GPCR) histamine 3 receptor (H₃R) antagonists associated with central nervous system (CNS) diseases.⁴ However, neither the synthetic route nor the individual steps for the synthesis of pyridazinone derivatives have been fully developed [Figure 1b].⁵ For instance, although numerous attempts have been made to facilitate the aqueous Cucatalyzed reaction, it has not been applied in the Narylation of pyridazinones since most of the substrates are insoluble in water, resulting in poor reactivity.⁶

Besides the N-arylation, two key steps in the synthetic route of pyridazinones have been less developed

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[Figure 1b]. The dehydrogenation of a C(4)—C(5) single bond to a C=C double bond is one of them. In previous reports, several oxidants were used such as MnO₂, SeO₂, $Br_2/HOAc$, etc.⁷ However, neither the efficiency nor the economy meets the green chemistry standards. Recently, transition-metal catalyzed oxidation in aerobic condition emerged as a powerful tool for dehydrogenation of C-C single bond to C=C double bond.⁸ However, most of the reactions were carried out in organic solvents and the catalysts are expensive and unrecyclable. Another essential is the dehalogenation which represents critical significance in improvement of the medicinal properties of pyridazinones.⁹ However, the high stability of the aryl C—Cl bond renders it less reactive. Furthermore, only a few methods using transition-metal catalysts are reported.¹⁰ The traditional catalytic systems can still be improved, as most suffer from expensive transition-metal systems, poor selectivity, extreme conditions, or narrow functional group tolerance. So far, few Cu-catalyzed dehydrogenations of C-C bond to C=C bond and Cu-catalyzed dechlorination in an aerobic and aqueous environment have been reported.11



Figure 1. (a) Bioactive compounds containing a pyridazinone scaffold. (b) Improved procedure of 6-phenyl-4,5-dihydropyridazin-3(2H)-one reaction to N(2) substituted 6-phenyl-pyridazin-3(2H)-one.

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Initially, we chose 2',3'-dichloro-6-phenyl-4,5-dihydropyridazin-3(2H)-one and bromobenzene as the substrates, and the results of the screening of the reaction conditions are summarized in Table 1. First, Na₂CO₃ was used as the base, and a series of copper salts were used to study the efficiency of the catalyst (Table 1, entries 1-4). Although the use of $Cu(OAc)_2$ gave a detectable yield (21%, Table 1, entry 1), other copper salts barely gave the desired product. We attribute the poor reactivity to the reaction of the copper ion with the inorganic base in water. To solve this problem, we synthesized several water-soluble copper-salen complexes and introduced them to this reaction. To our delight, the results improved dramatically (for detailed information of the copper salen complexes, see Supporting Information (SI) Table S1). After catalyst screening, inorganic and organic bases including Cs₂CO₃, K₂CO₃, K₃PO₄, NaOH, KOH, and triethylamine were investigated and Na₂CO₃ was found to be the best choice (Table 1, entries 6-11). Moreover, the catalytic system showed low reactivity in organic solvents such as DMF (26%, Table 1, entry 12). A low temperature decelerated the reaction rate and resulted in a lower yield with a prolonged reaction time (48 h, 62%, Table 1, entry 13). A decreased yield was also observed when 1% catalyst was loaded, while 10% loading of the catalyst gave a negligible increase in yield (Table 1, entries 14 and 15). In addition, a series of experiments were carried out to identify the relationship of this reaction. In an oxygen atmosphere, dechlorinated pyridazinone was obtained without N-arylation occurring (Table 1, entry 16). However, the desired product was not observed in a nitrogen atmosphere (Table 1, entry 17). Therefore, we hypothesize that N-arylation is independent of the dehydrogenation/dechlorination sequence; the detailed mechanism of

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this reaction is now under our investigation. In the absence of Cu4 or Na_2CO_3 , the reaction could not proceed (Table 1, entries 18 and 19). As a result, Cu4 was chosen and Na_2CO_3 was confirmed as the base for our following study.

Table 1. Selected Screening of the Cu-Catalyzed Reaction^a

	$= 0 + Br - 4$ $H_20, 100$		
		_	Cu4
entry	catalyst	base	yield (%) ^b
1	Cu(OAc) ₂	Na ₂ CO ₃	21
2	CuCl ₂	Na ₂ CO ₃	7
3	CuCl	Na ₂ CO ₃	trace
4	CuI	Na ₂ CO ₃	15
5	Cu4	Na ₂ CO ₃	93
6	Cu4	K_2CO_3	60
7	Cu4	Cs_2CO_3	74
8	Cu4	K_3PO_4	53
9	Cu4	NaOH	34
10	Cu4	KOH	20
11	Cu4	Et ₃ N	0
12	Cu4	Na ₂ CO ₃	26 ^c
13	Cu4	Na ₂ CO ₃	62 ^d
14	Cu4	Na ₂ CO ₃	55 ^e
15	Cu4	Na ₂ CO ₃	94 ^f
16	Cu4	Na ₂ CO ₃	
17	Cu4	Na ₂ CO ₃	0^{h}
18	-	Na ₂ CO ₃	0
19	Cu4	-	0

^{*a*} Reactions were carried out with dihydropyridazinone (1.0 mmol), bromobenzene (1.1 mmol), catalyst (5 mol %), and base (2.0 mmol), in H₂O (2 mL) at 100 °C for 12 h in the air. ^{*b*} Isolated yields. ^{*c*} DMF as solvent. ^{*d*} 80 °C. ^{*e*} 1% catalyst loading. ^{*f*} 10% catalyst loading. ^{*g*} O₂ atmosphere. ^{*h*} N₂ atmosphere.

With the optimized conditions obtained, we further investigated the generality of the reactions between aryl/ alkyl halides and 2',3'-dichloro-6-phenyl-4,5-dihydropyridazin-3(2H)-one, and the results are listed in Table 2. For example, 4-bromonitrobenzene, 4-bromobenzotrifluoride, 4-bromobenzonitrile, 1-bromo-4-chlorobenzene, and 1-bromo-4-fluorobenzene afforded excellent yields. The parasubstituted aryl bromides bearing an electron-donating group such as methoxy, tert-butyl, and methyl showed lower yields (78%, 82%, 84%). The meta-substituted aryl bromides bearing an electron-withdrawing group also showed higher reactivity than those bearing electrondonating groups. 3-Bromonitrobenzene, 3-bromobenzonitrile, 1-bromo-3-chlorobenzene, and 1-bromo-3-fluorobenzene afforded high yields respectively (87%, 92%, 85%, 84%). 3-Bromoanisole and 3-bromotoluene afforded modest yields (76%, 82%). The ortho-substituted aryl bromides showed remarkably lower yields probably due to the steric effect. For instance, 2-bromonitrobenzene, 1-bromo-2chlorobenzene, 1-bromo-2-fluorobenzene, and 2-bromotoluene afforded modest yields respectively (70%, 79%,

70%, 68%). Disubstituted aryl bromides such as 3,5bis(trifluoromethyl)bromobenzene, 3,5-dichlorobromobenzene, and 3,5-dimethylbromobenzene also gave good yields (86%, 85%, 80%). In addition, other aryl halides such as 2-bromonaphthalene, 6-bromo-1,4-benzodioxane, 3bromoquinoline, 4-bromoisoquinoline, 2-iodothiophene, 1-bromopentafluorobenzene, and 5-bromo-3'-propoxy-1,1'-biphenyl-3-carbonitrile gave good to modest yields. Alkyl bromides including cyclopentyl bromide and cyclohexyl bromide were also examined, and considerable yields were obtained (69%, 78%).





^{*a*} Reactions were carried out with dihydropyridazinone (1.0 mmol), halide (1.1 mmol), **Cu4** (5 mol %), and Na₂CO₃ (2.0 mmol), in H₂O (2 mL) at 100 °C for 12 h in the air; yields were calculated as isolated results.

Figure 2 shows the crystal structure of **2ca**. The dihydropyridazinone converted to the aromatic pyridazinone scaffold, and the 2'-Cl of the 6-phenyl group has been removed. A different view reveals that the N(2) and C(6) substituted phenyl rings show certain dihedral angles with the pyridazinone ring.



Figure 2. X-ray structure of compound 2ca.

In order to expand the substrate scope, we applied this catalytic system to a variety of dihydropyridazinones. To our delight, most of the substrates afforded the desired products with good yields. As shown in Table 3, a monochloride substrate, 2'-chloro-6-phenyl-4,5-dihydropyridazin-3(2H)-one, converted to arylated pyridazin-3(2H)-one in high yields (Table 3, entries 1 and 5). Highly selective dehalogenations of dichloride substrates were also observed. For example, both 2',3'-dichloro and 2',4'-dichloro substrates converted to the products with dechlorination of the ortho-Cl and retention of the meta-Cl or para-Cl (Table 3, entries 2, 3, 6, 7). Moreover, the dehalogenation also proceeded smoothly with 2'-bromo-6-phenyl-4,5-dihydropyridazin-3(2H)-one (90% and 83%, Table 3, entries 4 and 8). Furthermore, a nonhalogenated substrate was also investigated. In the absence of ortho-Cl on the 6-phenyl group, a dehydrogenated product along with N-arylation was obtained in high yield (86%, Table 3, entry 9).

We further investigated the reusability of this catalytic system. After the first cycle, the product could be separated from the reaction mixture by filtration. Subsequently the second portion of substrates and Na_2CO_3 were added to the remaining aqueous solution for the next round. Three parallel sets of experiments were carried out, and **Cu4** could be reused at least 5 times in relatively high yields above 80% (see SI Figure S1).

In conclusion, a simple and efficient one-pot reaction has been developed for the synthesis of N-functionalized pyridazinone derivatives with transformation of multiple chemical bonds. The multifunctional copper catalyst affords excellent activity, high selectivity, and recyclability. The catalytic system consists of a water-soluble Cusalen complex and Na_2CO_3 in neat water and an air atmosphere. Further work to explore the detailed mechanism and the application of this approach to other substrates is currently underway in our laboratory.

Table 3. Reaction	of Halogenated	Dihydropyri	dazinone v	with
Bromobenzene or	1,4-Dibromobe	nzene ^a		



^{*a*} Reactions were carried out with dihydropyridazinone (1.0 mmol), bromobenzene or 1,4-dibromobenzene (1.1 mmol), **Cu4** (5 mol %), and Na₂CO₃ (2.0 mmol), in H₂O at 100 °C for 12 h in the air. ^{*b*} Isolated yields.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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