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An efficient copper-catalyzed N-arylation of pyridazinones with a structurally well-defined copper complex

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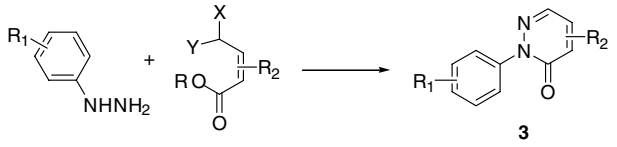
Abstract—N-Arylation of pridazinone derivatives **1** with an aryl or heteroaryl bromide or iodide **2** has been achieved in 70–94% isolated yield using catalytic amounts of the stable and structurally well defined copper catalyst **4b** under standard Ullmann–Goldberg reaction conditions. The structure of copper catalyst **4b** was characterized by ESI-MS, DSC and the single crystal X-ray.

The pyridazine and its derivatives, although known for almost a century, received little attention until the recent discovery of medicinally useful natural products.[1] Today, the pyridazine nucleus and its 3-oxo derivative (2*H*-pyridazin-3-one) moieties have been recognized as versatile pharmacophores. This key subunit is constituted in many biologically active substances with a broad range of biological and pharmaceutical activities including inhibitors of PED III and IV,[2] α_1- and α_2-adrenoceptors,[3] anti-bacterial and anti-fungal activities,[4] 5-lipoxygenase inhibitors,[5] and inhibitors of interleukin-1β production.[6]

Recently, during the course of our investigation into the synthesis of potent and selective COX II inhibitors,[7] it was necessary to prepare a series of 2-aryl or heteroaryl substituted pyridazin-3-one derivatives **3** for SAR studies. A survey of the literature revealed the lack of a general, and efficient method for their preparation. Thus, we became interested in developing an efficient procedure for their synthesis. Traditionally, these compounds were obtained by base-catalyzed cyclocondensation reaction of *N*-arylhydrazine with various 1,4-difunctionalized compounds (Scheme 1). However, only a limited number of arylhydrazines are commercially available, and their preparation often involved either a diazotization-reduction protocol starting from more readily available anilines or a cross-coupling reaction of an aryl halide and a protected hydrazine.[8] On the other hand, the transition-metal catalyzed N-arylation of pyridazin-3-one with an aryl halide could offer a greater potential for access to a wide range of 2-aryl or 2-heteroaryl substituted pyridazin-3-ones **3** (Scheme 2).



Scheme 1. Synthesis of **3** via classic cyclocondensation of arylhydrazine with 1,4-difunctionalized compound.

Palladium-catalyzed N-arylation of a variety of nitrogen-base nucleophiles has recently emerged as an important synthetic tool in the preparation of arylamine derivatives.[9] However, N-arylation of pyridazin-3-one **1a** with aryl bromides did not succeed under the typical palladium-catalyzed amination or amidation conditions, presumably due to the poor nucleophilicity of this substrate. This prompted us to consider a copper-mediated cross-coupling reaction as an alternative method. Copper-catalyzed N-arylation reactions typically call for the use of a stoichiometric amount of copper catalyst at high reaction temperatures in polar solvents.[10] However, significant progress has been made in the past few years to address these concerns with the judicious choice of efficient ligands, suitable copper sources, appropriate bases and solvents.[11] As results, a number of novel applications have been reported.[12–15] Herein,

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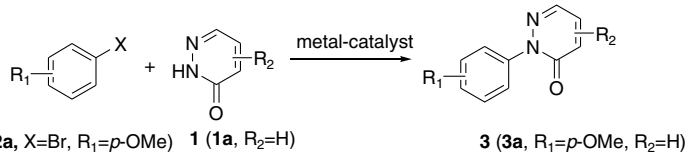
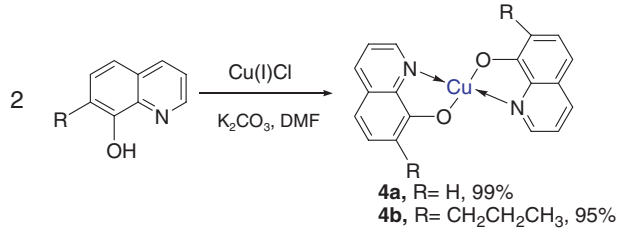


Scheme 2. Synthesis of **3** via transition-metal catalyzed cross-coupling reaction.

we describe our results in developing an efficient N-arylation protocol for pyridazinones and its derivatives.

Our initial investigation for the suitable reaction conditions started by studying cross-coupling of 2*H*-pyridazin-3-one (**1a**) with 4-bromoanisole (**2a**) as a model reaction. In the first stage, the source of copper catalyst in a ligandless system was investigated. A number of copper catalysts using DMF as the solvent, and K_2CO_3 as the base were examined. Preliminary results showed that Cu(I) salts such as CuCl, CuI, and CuBr were more effective catalysts than Cu(II) salts such as $Cu(OAc)_2$, $CuBr_2$, and $CuSO_4$. CuCl was found to be the most efficient among the Cu(I) salts investigated. For this reason, CuCl was used to further study the catalytic system (Table 1). As shown in Table 1, dramatic differences in yield were observed in reactions using chelating ligands such as TMEDA, *cis*-1,2-diaminocyclohexane, 1,10-phenanthroline, 8-hydroxyquinoline and 2,2′-dipyridyl. 8-Hydroxyquinoline appears to be the most effective (Table 1, entry 6); presumably acting as *O*- and *N*-donor ligands forming a copper complex (vide infra). Our attention then turned to the effect of base and solvent, using the CuCl and 8-hydroxyquinoline as the catalyst system in the reaction. Among the inorganic bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, KOH, K_3PO_4) and *t*-butoxides (KO*t*Bu, NaO*t*Bu) examined, K_2CO_3 and KO*t*Bu proved very effective in DMF, and much less effective in DMA, NMP, toluene, and dioxane.

To better understand the nature of copper catalyst, complex **4a** was prepared from the reaction of CuCl with 8-hydroxyquinoline in the presence of K_2CO_3 in DMF

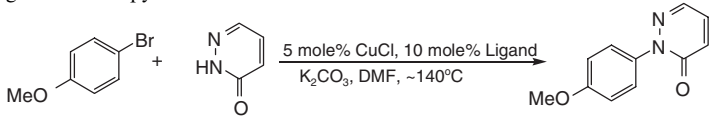


Scheme 3. Preparation of copper complex **4a** and **4b**.

(Scheme 3). When catalyst **4a** was used in the subsequent cross-coupling reaction, there was no erosion in catalytic activity for the reaction. However, attempts to elucidate the structure of this precatalyst either by NMR or X-ray were not successful, as it is very insoluble in most organic solvents at ambient temperature. To circumvent this difficulty, we envisioned that the solubility of a copper-catalyst should be increased if an alkyl substituted 8-hydroxyquinoline ligand was employed. In fact, when commercially available 7-*n*-propyl-8-hydroxyquinoline was used, copper catalyst **4b** was obtained in 95% yield. Having sufficient solubility and stability, the structure of **4b** was readily characterized by ESI-MS, and later confirmed unambiguously by the single crystal X-ray (Fig. 1).[20,21]

The X-ray of **4b** clearly indicated that one copper ion is bound to two 7-*n*-propyl-8-hydroxyquinolinate anions through the ring nitrogen atoms and the O^- groups in a transplanar configuration. The bond lengths for two Cu–O bonds are identical (1.920(4) Å) and comparable

Table 1. Copper-catalyzed coupling reaction of pyridazin-3-one with 4-bromoanisole[a]



Entry	Ligand	Yield[b] (%)
1	—	30
2	DMAP	31
3	TMEDA	28
4	*cis*-1,2-Diaminocyclohexane	30
5	1,10-Phenanthroline	46
6	8-Hydroxyquinoline	94
7	2,2′-Dipyridyl	31

[a] Reaction conditions: 1.0 mmol of 4-bromoanisole, 1.5 mmol of pyridazin-3-one, 0.05 mmol copper(I) chloride, 1.5 mmol of K_2CO_3 in DMF (3.0 mL) under nitrogen for 20 h.

[b] The yields are the average of two runs, and are assayed by HPLC against a pure and characterized standard.

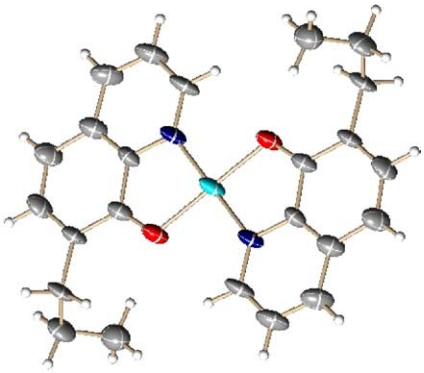
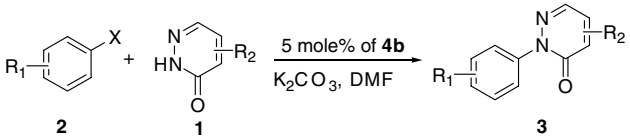


Figure 1. ORTEP plot of copper catalyst **4b**.

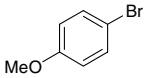
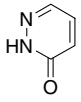
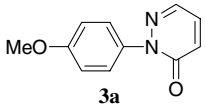
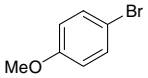
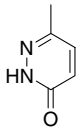
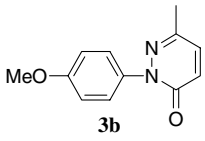
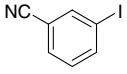
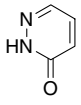
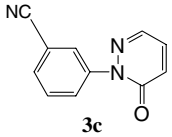
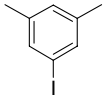
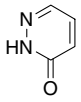
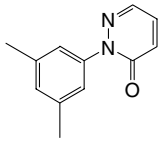
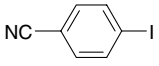
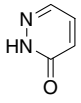
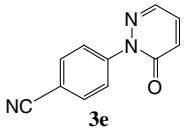
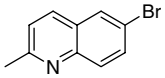
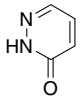
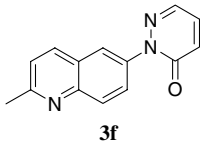
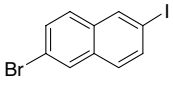
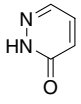
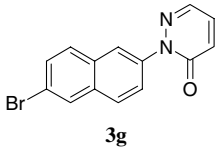
with average Cu–O of 1.95(3) seen in other copper(II)hydroxyquinolinate complexes. These data suggested that copper(II) ion is in the complex, similar to those of **4a**.[16]

The complex is flat with the *n*-propyl groups curled out of the plane. Although a copper(I) species was initially used in the preparation of **4b**, it is likely that the copper(I) species is oxidized to copper(II) species prior to, or during complex formation. Moreover, this explanation was supported by the fact when either a Cu(I) or Cu(II) salt was used, **4b** was always obtained. Although **4a** has been utilized as the anti-fungal, anti-bacterial and anti-microbial agents,[17] its application as precatalyst in

Table 2. Cu-catalyzed N-arylation of pyridazinone core



2 **1** **3**

Entry	Aryl halide	Pyridazinones	Product	Isolated yield[a] (assayed[b])
1			 **3a**	85 (93)
1′				75 (82)[c]
2			 **3b**	80 (90)
3			 **3c**	80 (89)
4			 **3d**	80 (90)
5			 **3e**	94 (98)
6			 **3f**	90 (98)
7			 **3g**	70 (80)

[a] Not optimized.
[b] The yields are the average of two runs, and are assayed by HPLC against a pure and characterized standard.
[c] Performed under air.

organic reactions is rare.[18] Given consideration with the better solubilities of **4b** in many organic solvents than **4a**, **4b** was the catalyst of choice for our purposes. When **4b** was subjected to the model reaction, we were pleased to find that **3a** was produced in excellent yield (Table 2, entry 1).

With the optimal reaction conditions and the catalyst in hand, we began to examine C–N bond forming reactions involving functionalized aryl bromides or iodides and pyridazinone derivatives (Table 2).[19] There was no significant difference in yield in all reactions surveyed under the reaction conditions. A variety of functional groups including cyano, methoxy, bromo, and hydroxyl on the aryl halide component are well tolerated. Also, no significant electronic or steric effects were observed for *para*- and *meta*-substituted aryl halides. It should be noted that this Cu-catalyzed reaction is sensitive to the presence of exogenous oxygen to some extent. The yield was found to be ~10% lower when the reaction was performed under air rather than under nitrogen (Table 2, entry 1′).

In conclusion, we have developed an effective cross-coupling protocol using the structurally well-defined copper (II) catalyst **4b** for the N-arylation of pyridazinones, complimentary to Pd-catalyzed C–N bond forming reactions. The reaction proceeds at ~100 °C for aryl iodides and ~140 °C for aryl bromides. Many functional groups in aryl halide are well tolerated. Extension of this protocol to include other nitrogen nucleophiles is in progress.

Acknowledgement

We are grateful to Dr. Zhe Wang, safety evaluation lab. for DSC data of **4a** and **4b**.

Supplementary data

Electronic supplementary data: a complete description of experimental details and product characterization. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.164.

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19. A typical experimental procedure: To a resealable pressure tube were charged copper catalyst **4b** (87.1 mg, 0.20 mmol), K_2CO_3 powder (828 mg, 6.0 mmol), aryl halide (4.0 mmol), pyridazinone derivative (6.0 mmol), and DMF (5.0 mL). The tube was evacuated, and backfilled with nitrogen. The reaction mixture was heated to 100 °C (aryl iodide) or 140 °C (aryl bromide), and stirred for 20 h. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2, washed with concd NH_4OH solution, and 25% brine. The organic was filtered through a pad of Celite, and the filtrate concentrated to dryness. Purification of the crude product by flash chromatography on silica gel gave the desired

product (see Supplementary data for MS, NMR spectral data).

20. Crystal data for **4b**: MW = 436.006, $C_{24}H_{24}CuN_2O_2$, crystal dimensions $1.0 \times 0.2 \times 0.02$ mm, monoclinic, $P2_1/c$, $a = 5.112(2)$ Å, $b = 18.974(8)$ Å, $c = 10.324(4)$ Å, $\beta = 98.532(8)°$, $V = 990.3(7)$ Å^3, $Z = 2$, $D_{calcd} = 1.462$ g/cm^3, $2\theta max = 56.62°$, crystallographic data were collected with a Bruker SMART system using MoKα radiation ($\lambda = 0.71073$ Å). Refinement of the structure using full matrix least squares refinement of 135 parameters on 1456 observed reflections with $I > 2.0\sigma(I)$ gave $R = 0.0937$, $Rw = 0.2072$ and GOF = 1.063.
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