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Articles

Facile Access to a Variety of 2,5-Biaryl-1,2,4-triazol-3-ones *via* Regioselective *N*-Arylation of Triazolones

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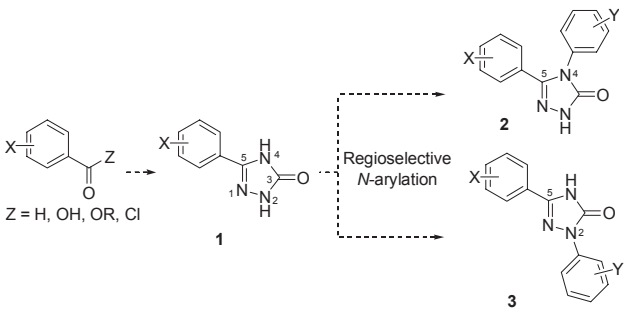
A selective synthetic method of the 2,5-biaryltriazolones has been developed *via* copper-catalyzed *N*-arylation reaction. Aryltriazolones, which were readily prepared from commercially available compounds, were *N*-arylated to 2,5-biaryl-triazolones with high regioselectivity. This approach allows for access to a variety of 2,5-biaryl-1,2,4-trizol-3-ones in a simple and practical manner.

Key Words: *N*-Arylation, Copper-catalyzed cross-coupling, *N*-Heterocycles, Regioselectivity, Triazolones

Introduction

Triazolone ring structure is often found in a number of biologically active compounds.[1] Depending on the substituents at N-2, N-4, and C-5 positions of the triazolone ring, triazolones show various pharmaceutical activities such as antitumor, anti-inflammatory, antifungal, PPARs agonistic, NK_1-antagonistic activities. In particular, biaryltriazolones having different patterns of aryl substituents (2,5-biaryl-1,2,4-triazol-3-ones and 4,5-biaryl-1,2,4-triazol-3-ones) are currently being developed as Maxi-K channel opener[2] and Hsp90 inhibitors.[3] So far, a majority of biaryltriazolones have been prepared by late-stage ring cyclization.[2,4] In this route, the installation of desired substituents at specific nitrogens is first carried out, and subsequent ring cyclization results in the substituted biaryltriazolones. However, tedious protection and deprotection steps are often unavoidable[5] because of little reactivity differences of nitrogens in the linear intermediates, and harsh cyclization conditions for biaryl intermediates are also problematic especially when they are functionalized. In our efforts to synthesize the derivatives of 2,5-biaryl-1,2,4-triazol-3-ones for SAR study, we realized that the traditional stepwise synthetic methods hamper efficient production of a series of compounds in a short time. Therefore, we proposed an efficient synthetic route to 2,5-biaryl-1,2,4-triazol-3-ones as shown in Scheme 1. This scheme involves the synthesis of a common intermediate (**1**), in which two reactive nitrogen sites (N-2 *vs*. N-4) are available. In order to obtain **2** and/or **3** in a selective manner, highly regioselective *N*-arylation must be developed. Herein, we report a highly selective route to a variety of 2,5-biaryl-1,2,4-triazol-3-ones *via* copper-catalyzed *N*-arylation.

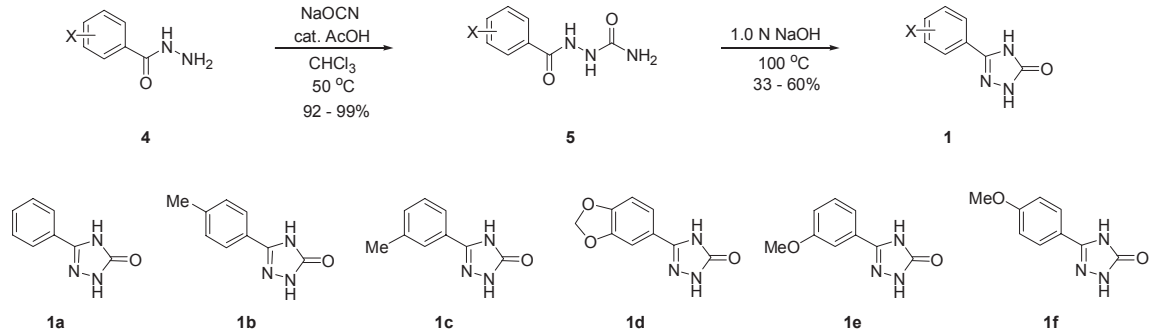


Scheme 1. Synthetic strategy for biaryltriazolones

Results and Discussion

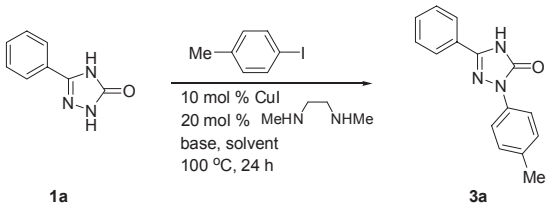
Aryltriazolones (**1**), the common intermediates for various biaryltriazolones, can be synthesized in a straightforward way from commercially available starting compounds following the literature procedures (Scheme 2).[6] Aryl hydrazides (**4**), which were either purchased or prepared from aryl ester by substitution with hydrazine, were converted to aryl hydrazine carboxamides (**5**). Then, they were subsequently cyclized to a series of 5-aryl-triazolones (**1**) in 1.0 N aq. NaOH solution. Aryl hydrazine carboxamides (**5**) were precipitated from the reaction mixture as the reaction proceeded and aryltriazolones (**1**) were also precipitated when neutralized with acid after the reaction was completed. Isolation of the product in each step by simple filtration greatly streamlined the whole process and made possible a large scale synthesis (*ca*. 10 g) of a series of aryltriazolones (**1a-1f**) in a short period of time.

With aryltriazolones (**1**) in hand, we explored the regioselective *N*-arylation. We envisioned that subtle stereoelectronic and steric differences between the two reactive nitrogens (N-2 and N-4) in the triazolones[7] can be used as a handle for the regioselective arylation by proper choice of reaction conditions. Although both palladium and copper are well-known transition metals for C-N cross-coupling reactions,[8,9] copper was found to be more effective in the triazolone systems after our preliminary screening. The initial attempts utilizing catalytic CuI, *N*,*N*′-dimethylethylenediamine and K_2CO_3 in dioxane revealed that



Scheme 2. Synthesis of aryltriazolones

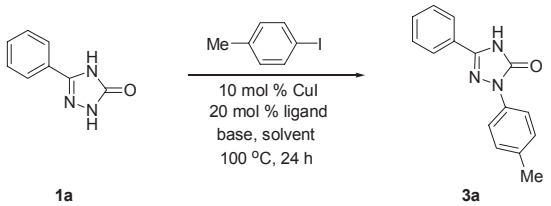
Table 1. *N*-Arylation of aryltriazolone **1a** with *p*-toluic iodide[a]

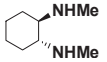
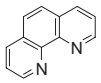


Entry	Base	Solvent	Yield[b]
1	K_2CO_3	Dioxane	5%
2	*t*-BuOK	Dioxane	3%
3	K_3PO_4	Dioxane	20%
4	Cs_2CO_3	Dioxane	14%
5	K_2CO_3	*t*-BuOH	1%
6	K_2CO_3	Toluene	19%
7	K_2CO_3	NMP	37%
8	K_2CO_3	DMSO	55%
9	K_2CO_3	DMF	63%

[a]Reaction conditions: *p*-toluic iodide (2.0 equiv), CuI (10 mol % equiv), *N*,*N*-dimethylethylenediamine (20 mol % equiv), base (3.0 equiv), solvent 1.0 mL. [b]Yield determined by HPLC.

Table 2. Optimization of *N*-arylation of aryltriazolone **1a**[a]



Entry	Ligand	Base	Solvent	Yield[b]
1		**K_2CO_3**	**DMF**	**97%**
2		**K_2CO_3**	**DMSO**	**97%**
3		K_2CO_3	Toluene	25%
4		K_3PO_4	Dioxane	38%
5		K_2CO_3	DMSO	45%
6		K_2CO_3	DMF	45%
7		K_2CO_3	DMSO	43%
8		K_2CO_3	DMF	16%
9		K_2CO_3	DMSO	55%
10		K_2CO_3	DMF	69%

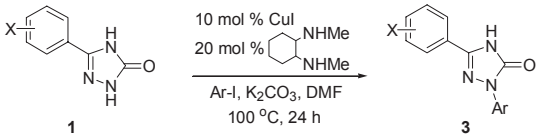
[a]Reaction conditions: *p*-toluic iodide (2.0 equiv), CuI (10 mol % equiv), ligand (20 mol % equiv), base (3.0 equiv), solvent 1.0 mL. [b]Yield determined by HPLC.

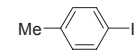
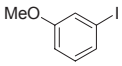
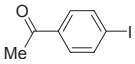
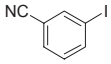
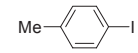
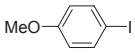
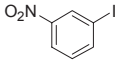
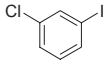
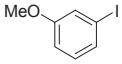
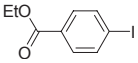
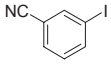
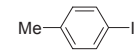
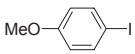
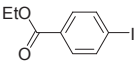
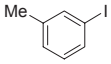
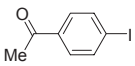
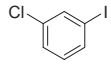
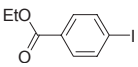
the coupling reaction of arytriazolone **1a** and *p*-toluic iodide gave *N*-2-arylated product with less than 10% conversion. Similar results were observed when various bases and solvents were tested (Table 1); *N*-2-arylated product **3a** was exclusively formed while *N*-4-arylated product **2a** was rarely found.[10]

However, the unsatisfactory yields suggested that the initial reaction conditions suffer from low catalytic activity. In order to search for more reactive catalytic systems which still need to be regioselective, we screened various Cu-catalyzed C-N cross-coupling systems including several ligands, bases, and solvents, and their combinations (Table 2). Then, we found that use of *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as the ligand was the key to success. Switching the ligand to *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine greatly improved the reaction yields. This is also consistent with the fact that *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine is a more reactive ligand than *N*,*N*′-dimethylethylenediamine.[11] While the choice of bases among K_2CO_3, K_3PO_4, and Cs_2CO_3 was not critical, employing polar solvents such as DMF and DMSO was crucial; the use of toluene or dioxane led to a slower reaction rate even at an elevated temperature. The poor yield seems to be partially due to low solubility of the reactants in these solvents. Either lesser amount of catalyst loading or lower reaction temperature resulted in an incomplete reaction. Thus, after screening with aryltriazolone **1a**, we established the optimal reaction conditions, which use CuI as the catalyst, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as the ligand, and DMF as the polar aprotic solvent.

The optimized conditions were applied to the aryltriazolones (**1a-1f**) to afford corresponding 2,5-biaryltriazolones (Table 3). A range of aryl iodides, including electron-neutral (Table 3, entries 12, 16, and 20), electron-rich (entries 1, 2, 5, 6, 9, 13, 14, and 17), and electron-poor (entries 3, 4, 7, 8, 10, 11, 15, 18, 19, and 21) aryl iodides, were reacted with aryltriazolones under the conditions to afford 2,5-biaryltriazolones regioselectively in good to excellent yields. Functional groups such as carboxylic ester and nitrile were compatible under the reaction conditions, which would not survive under traditional cyclization condi-

Table 3. Synthesis of a variety of 2,5-biaryltriazolones *via* regioselective *N*-arylation of aryltriazolones[a]



Entry	1	Ar-I	Product	Yield[b]
1	**1a**		**3a**	94%
2			**3b**	91%
3			**3c**	99%
4			**3d**	99%
5	**1b**		**3e**	99%
6			**3f**	81%
7			**3g**	99%
8			**3h**	97%
9	**1c**		**3i**	77%
10			**3j**	92%
11			**3k**	99%
12	**1d**		**3l**	99%
13			**3m**	92%
14			**3n**	68%
15			**3o**	89%
16	**1e**		**3p**	93%
17			**3q**	89%
18			**3r**	99%
19			**3s**	99%
20	**1f**		**3t**	93%
21			**3u**	79%

[a]Reaction conditions: aryl iodide (2.0 equiv), CuI (10 mol % equiv), *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (20 mol % equiv), K_2CO_3 (3.0 equiv), DMF 1.0 mL. [b]Isolated yields of > 95% purity as determined by HPLC and ^{1}H-NMR.

tions.[2,4] In most cases, very little amount of 4,5-biaryl-triazolones were formed, which was determined by LC-MS analysis. As the isolation yields in Table 3 suggested, even in the case of contamination with *N*-4-arylated product up to 5%, it was easily removed by recrystallization from the reaction mixture. Incidentally, we found that methoxyaryl iodides such as 3- and 4-iodoanisole are less effective reactants than other aryl iodides, showing the lower reaction yields (Table 3, entries 2, 6, 9, and 14). The lower yields are due to the formation of unknown side-products which are not the *N*-4-arylated regioisomers. *Ortho*-substituted aryl ioides gave less than 10% of the desired products under these conditions; attempts to couple them by extending the reaction time or elevating reaction temperature caused the decomposition of aryltriazolones (**1**). Although NH-site having more acidic proton can be preferably arylated,[7,12] the selectivity of the *N*-arylation process appears to be largely controlled by steric factors under these conditions. Thus, all the aryl iodides, which are believed to be readily added to the copper-substrate complex, undergo the reaction at the kinetically favored *N*-2 position. We are currently testing various aryl iodides under the reaction conditions to see how they affect the selectivity so that we can gain an insight on the mechanism of the cross-coupling reaction.

In summary, we have developed a novel approach to the selective synthesis of 2,5-biaryltriazolones, which are important structures present in biologically active compounds. Aryltriazolones, which are the precursors for biaryltrizolones, were prepared in a straightforward manner from commercially available compounds at large scales. Then, a range of aryl groups were introduced regioselectively to the aryltriazolones *via* copper-catalyzed C-N cross-coupling reactions. This new method provides an efficient means to access a variety of 2,5-biaryl-1,2,4-triazol-3-ones that are not trivial to prepare *via* other methods.

Experimental Section

Representative procedure for *N*-arylation. To a suspension of aryltriazolone (0.5 mmol), CuI (9.5 mg, 0.05 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in anhydrous DMF (1.0 mL) under N_2 was added aryl iodide (1.0 mmol) followed by *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (13 μL, 0.1 mmol) and the reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to room temperature, quenched with water (10 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with water, brine, dried over $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was recrystallized from ethyl acetate or purified by flash column chromatography (*n*-hexane:ethyl acetate).

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C. R.; Schrier, D. J.; Dyer, D. D. *J. Med. Chem.* **1993**, *36*, 1090. (c) Neslihan, D.; Reyhan, U.; Ahmet, D. *Bioorg. Med. Chem.* **2002**, *10*, 3717. (d) Xu, Y.; Mayhugh, D.; Saeed, A.; Wang, X.; Thompson, R. C.; Dominianni, S. J.; Kauffman, R. F.; Sing, J.; Bean, J. S.; Bensch, W. R.; Barr, R. J.; Osborne, J.; Montrose-Rafizadeh, C.; Zink, R. W.; Yumibe, N. P.; Huang, N.; Luffer-Atllas, D.; Rungta, D.; Maise, D. E.; Mantlo, N. B. *J. Med. Chem.* **2003**, *46*, 5121. (e) Cowden, C. J.; Wison, R. D.; Bishop, B. C.; Cottrell, I. F.; Davies, A. J.; Dollong, U. *Tetrahedron Lett.* **2000**, *41*, 8661.

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7. N-4 position is more sterically hindered than N-2 position. pK_a's of protons at N-2 and N-4 of aryltriazolone **1a** were calculated as 17.1 and 7.5, respectively, using the software ACD (Advanced Chemistry Development)
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