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Synthesis of *N*-aryl-D-glucosamines through copper-catalyzed C–N coupling

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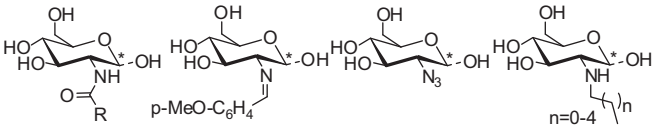
ABSTRACT

A catalytic protocol was developed to synthesize *N*-aryl-D-glucosamines from the corresponding aryl halides. Cross-coupling of 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine with aryl iodides or bromides was catalyzed with copper. Subsequent deprotection of the benzyl group gave the arylation product *N*-aryl-D-glucosamines.

D-Glucosamine, produced commercially by the hydrolysis of crustacean exoskeletons, is one of the most abundant monosaccharides. D-Glucosamine and its N-substituted derivatives are found in numerous biologically active molecules[1] such as cell surface *N*-glycoproteins, proteoglycans, glycosylphosphatidylinositol (GPI) anchors, glycosphingolipids, lipopolysaccharides, and chitin/chitosan. Furthermore, these molecules have been used as ligands or organocatalysts to introduce chirality in catalytic asymmetric reactions.[2] Chemical modifications of D-glucosamine at the *N*-position mainly rely on acylation,[3] Schiff-base formation[4], azidation,[5] and alkylation[6] (Scheme 1). However, N-arylation of D-glucosamine has rarely been studied due to synthetic difficulty in the past. Only in a few examples N-arylation of D-glucosamine was accomplished by the S_NAr reaction between D-glucosamine and aryl halides containing a strong electron-withdrawing group.[7]

Recently we have been interested in the copper-catalyzed arylation of nucleophiles.[8] Herein we report the synthesis of *N*-aryl-D-glucosamines by the copper-catalyzed cross-coupling between aryl halides and D-glucosamine (Scheme 2) in the hope to develop more general and practical catalytic protocols for the synthesis of D-glucosamine derivatives.

Initially, D-glucosamine (**1**) and iodobenzene (**2a**) were selected as model substrates for the coupling reaction. Chemoselective copper-catalyzed N- or O-arylation of amino alcohols has been achieved with [O,O] ligands (Scheme 3).[9,10] However, we could not obtain the N-arylation product **3a** from D-glucosamine with the reported ligands (Table 1, entries 1–3). We speculated that the hydroxyl groups, especially the 1-hydroxyl, have influence on the cross-coupling reaction. Then we turned to the protected D-glucosamine. 1,3,4,6-Tetra-*O*-benzyl-β-D-glucosamine (**4**)[11] was selected as a model substrate because the benzyl protecting group is stable in the catalytic system and can be readily removed under mild conditions (Scheme 2).[12]



Scheme 1. Chemical modification of D-glucosamine.

The key step for the *N*-aryl-D-glucosamine (**3**) synthesis is the Cu-catalyzed cross-coupling between 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine (**4**) and aryl halides (**2**). Although a number of catalytic systems[9,10,13] have been shown to promote the Cu-catalyzed arylation of amines, it remains unclear how the glycosyl and benzyl groups would affect the efficiency. Thus we evaluate the ligands in the cross-coupling of iodobenzene with 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine (Table 1).

As shown in Table 1, when 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine (**4**) was used as a surrogate for D-glucosamine (**1**), the cross-coupling could be achieved in 25 °C with CuI as catalyst and glycol, BINOL, and 2-acetylcyclohexanone as ligands, although the designed product is obtained in only 5–11% yield (entries 4–6). Then we elevated the temperature to 110 °C and a satisfactory

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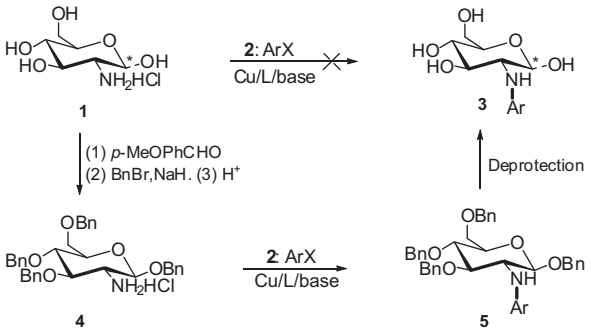
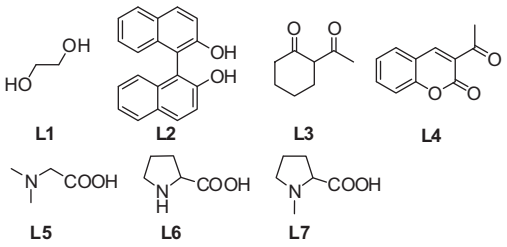
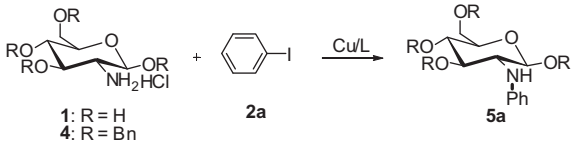


Scheme 2. Synthesis of *N*-aryl-D-glucosamines.



Scheme 3. Ligands used in this study.

Table 1
Copper-catalyzed cross-coupling of *D*-glucosamine with iodobenzene (**2a**)[a]

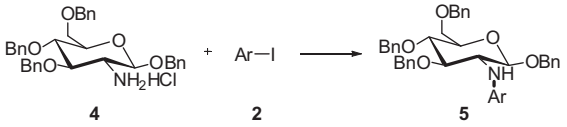


Entry	R	Cat.	Ligand	Base	Sol.	Temp.	Yield[b] (%)
1	H	CuI	L1	Cs_2CO_3	DMF	25	0
2	H	CuI	L2	Cs_2CO_3	DMF	25	0
3	H	CuI	L3	Cs_2CO_3	DMF	25	0
4	Bn	CuI	L1	Cs_2CO_3	DMF	25	5
5	Bn	CuI	L2	Cs_2CO_3	DMF	25	10
6	Bn	CuI	L3	Cs_2CO_3	DMF	25	11
7	Bn	CuI	L1	Cs_2CO_3	DMF	110	36
8	Bn	CuI	L2	Cs_2CO_3	DMF	110	40
9	Bn	CuI	L3	Cs_2CO_3	DMF	110	69 (81)[c]
10	Bn	CuI	L4	Cs_2CO_3	DMF	110	42
11	Bn	CuI	L5	Cs_2CO_3	DMF	110	45
12	Bn	CuI	L6	Cs_2CO_3	DMF	110	32
13	Bn	CuI	L7	Cs_2CO_3	DMF	110	44
14	Bn	CuI	L3	K_2CO_3	DMF	110	33
15	Bn	CuI	L3	K_3PO_4	DMF	110	46
16	Bn	CuI	L3	Cs_2CO_3	DMSO	110	61
17	Bn	CuI	L3	Cs_2CO_3	Toluene	110	34

[a] Reaction conditions: 0.5 mmol **1** or **4**, 1.5 mmol **2a**, 20 mol % CuI, 40 mol % Ligand, 1.5 mmol base, 0.25 mL solvent, 20 h.
[b] Isolated yields.
[c] Reaction temperature = 130 °C.

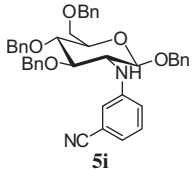
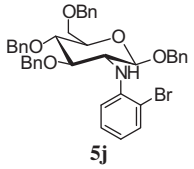
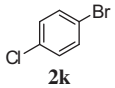
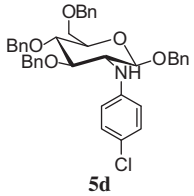
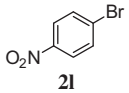
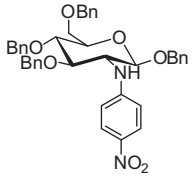
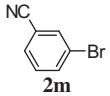
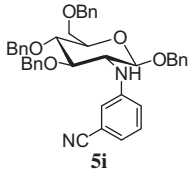
yield (36–69%) was obtained (entries 7–9). 3-Acetylcoumarin, a ligand developed by our group previously,[8c] was also investigated. However, a lower yield was obtained even when the temperature was increased to 110 °C (entry 10). Ligands from the amino acid (Scheme 3), which are known in the copper-catalyzed arylation of amines,[13] were also evaluated. However, the yields were unsatisfactory and the coupling yields from *N*,*N*-dimethylglycosine, L-proline, and *N*-methyl-L-proline were 32–45% (entries 11–13).

Table 2
CuI/**L3**-catalyzed N-arylation of 1,3,4,6-tetra-O-benzyl-β-D-glucosamine (**4**) with aryl iodides and aryl bromides (**2**)[a]

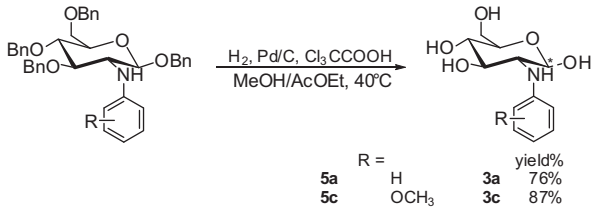


Entry	Aryl halide	Product	Yield[b] (%)
1	**2a**	**5a**	81
2	**2b**	**5b**	72
3	**2c**	**5c**	65
4	**2d**	**5d**	83
5	**2e**	**5e**	74
6	**2f**	**5f**	63
7	**2g**	**5g**	65
8	**2h**	**5h**	54

Table 2 (*continued*)

Entry	Aryl halide	Product	Yield[b] (%)
9	 **2i**	 **5i**	66
10	 **2j**	 **5j**	0
11	 **2k**	 **5d**	40[c]
12	 **2l**	 **5g**	57[c]
13	 **2m**	 **5i**	36[c]

[a] Reaction conditions: 0.5 mmol **4**, 1.5 mmol **2**, 20 mol % CuI, 40 mol % 2-acetylcyclohexanone, 1.5 mmol Cs_2CO_3, 0.25 mL DMF, 130 °C.
[b] Isolated yields.
[c] At 145 °C.



Scheme 4. Deprotection of *N*-aryl-1,3,4,6-tetra-*O*-benzyl-β-D-glucosamines.

Subsequently, with the use of **L3** as the ligand, a range of combinations of bases and solvents were examined (entries 14–17), and the optimal condition was as follows: 20 mol % CuI as the catalyst, 40 mol % 2-acetylcyclohexanone as the ligand relative to 1,3,4,6-tetra-*O*-benzyl-*β*-D-glucosamine, DMF as the solvent, and Cs_2CO_3 as the base at 130 °C.

Having identified the optimal catalytic system of CuI/2-acetylcyclohexanone, we next examined the scope of the coupling of 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine with various aryl halides (Table 2).[14] It was found that aryl iodides carrying electron-donating groups could be smoothly converted into the desired products with good isolated yields (65–81%, entries 1–3). The coupling of aryl iodides containing electron-withdrawing groups also afforded *N*-aryl-1,3,4,6-tetra-*O*-benzyl-β-D-glucosamines in moderate to good isolated yields (54–83%, entries 4–9). However, aryl iodides carrying an *ortho*-substituent failed to participate in the reaction (entry 10). Functional groups including ether, halo, ester, nitro, and cyano moieties were tolerated under the current conditions. Satisfactory yields (36–57%) of arylation products were obtained when the electron deficient aryl bromides (entries 11–13) were utilized.

The above arylation products can easily be converted into the target *N*-aryl-D-glucosamines. Many classic methods[12] are known to deprotect the benzyl group from alcohol, and hydrogenolysis catalyzed by Pd/C was employed to release the hydroxyl of *N*-aryl-1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine. As shown in Scheme 4, under the standard conditions,[12] *N*-phenyl-D-glucosamine (**3a**) and *N*-(4-methoxyl phenyl)- D-glucosamine (**3c**) were obtained with high yields (76%, 87%).[15]

To conclude, we have developed a general, cheap, and practical catalytic protocol for the synthesis of *N*-aryl-D-glucosamines. 1,3,4,6-Tetra-*O*-benzyl-β-D-glucosamine is used as a D-glucosamine surrogate and CuI is used as the catalyst to achieve the C–N coupling. The efficiency and functional-group tolerance of this procedure have been demonstrated by the synthesis of a number of functionalized *N*-aryl-1,3,4,6-tetra-*O*-benzyl-β-D-glucosamines. The final *N*-aryl-D-glucosamines were easily obtained by deprotection of the benzyl protecting group. Given the fact that D-glucosamine derivatives play an important role in biomedical research and chiral molecule design, we anticipate that the method described in the present report will find applications in a number of fields such as pharmaceutical research and organic material synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.069.

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14. General procedure for coupling aryl iodides (**2**) with 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine (**4**): An oven-dried Schlenk tube was charged with 1,3,4,6-tetra-O-benzyl-β-D-glucosamine 4 (288 mg, 0.5 mmol), CuI (20 mg, 20 mol %), and Cs_2CO_3 (490 mg, 1.5 mmol). The tube was evacuated and backfilled with nitrogen (this procedure was repeated three times). Then aryl halide 2 (1.5 mmol), 2-acetylcyclohexanone (26 μL, 40 mol %), and DMF (0.25 mL) were added under nitrogen. The tube was sealed and the reaction mixture was stirred at 130 °C for 16–20 h. The resulting suspension was cooled to room temperature and filtered through a pad of silica gel with the help of CH_2Cl_2 (50 mL). The filtrate was concentrated and the residue was purified by column chromatography (silica gel, EtOAc-PE) to afford the product **5**.
15. General procedure for the deprotection of N-Aryl-1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine(**5**): Under hydrogen atmosphere, a solution of 5 (0.5 mmol) in CH_3OH and EtOAc (4 mL + 2 mL) were stirred in the presence of Pd/C (10%, 100 mg) and trichloroacetic acid (80 mg, 0.5 mmol) at 40 °C. After 40 h the reaction mixture was cooled to room temperature and filtered through a pad of silica gel with the help of CH_3OH. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, $CHCl_3$–CH_3OH) to afford the product **3**.