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Highly Efficient CuI-Catalyzed Coupling of Aryl Bromides with Oxazolidinones Using Buchwald's Protocol: A Short Route to Linezolid and Toloxatone†

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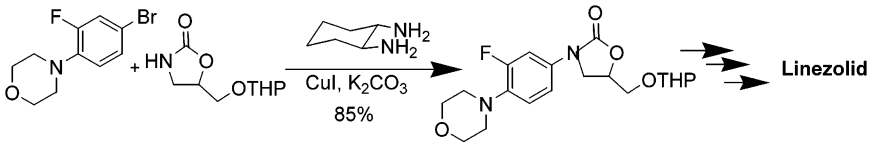
ABSTRACT



Coupling of a variety of substituted aryl bromides with oxazolidinones has been achieved using the Buchwald protocol for the amidation of aryl halides. This procedure is exemplified by the synthesis of two medicinally important molecules, linezolid and toloxatone.

N-Aryloxazolidinones constitute an important class of pharmacologically active compounds. They exhibit selective and reversible inhibition of monoamine oxidase A, an important enzyme responsible for the degradation of various amine neurotransmitters.[1] Over the past decade, a new class of antibacterial compounds have emerged with the same template, and in general, they are referred to as oxazolidinone antibiotics.[2] They have potent activity against a variety of Gram-positive bacterial pathogens including methicillin-resistant *Staphylococcus aureas* (MRSA) and vancomycin-resistant *Enterococci* (VRE). For these reasons, much attention has been given to the synthesis of these classes of compounds. Any general method developed for the synthesis of these compounds must ensure compatibility with the substitution on the aryl and oxazolidinone moieties (Figure 1).

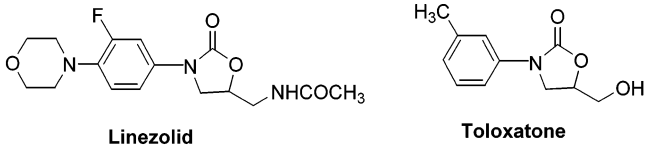


Figure 1.

Most of the methods reported involve construction of the oxazolidinone as the key step in the synthesis of 5-substituted 3-aryloxazolidinones.[2,3] Recently, Pd-catalyzed coupling of oxazolidinones with aryl bromides has been developed that could be used for the synthesis of this class of compounds.[4]

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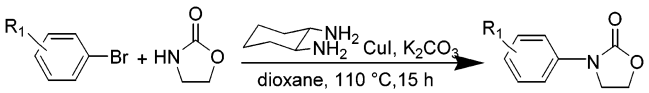
This work had the precedence in the pioneering work of Buchwald and Hartwig.[5] Recently, Buchwald reported a landmark development in the Goldberg coupling reaction using CuI (1−10 mol %) for the amidation of aryl halides.[6] In the reaction, (±)-*trans*-1,2-diaminocyclohexane was used to solubilize CuI, and K_3PO_4 or K_2CO_3 was used as base. The procedure, in addition to being cost-effective, could also tolerate some functional groups that are otherwise problematic in palladium-catalyzed coupling reactions.[6] In this procedure oxazolidinones were not evaluated for amidation of aryl halides. Subsequently, it was shown that ethylenediamine could be used instead of cyclohexanediamine.[6b,7] Two examples were reported in which oxazolidinones were coupled with aryl iodides using 10 mol % of CuI in only modest yields.[7] These results indicated the potential of CuI catalyzed reaction for the synthesis of 3-aryl-2-oxazolidinones.

In a program intended toward developing a cost-effective and direct method to this group of compounds in our laboratory, we have worked on CuI-mediated coupling reactions, and herein we disclose our efforts in this area. Initial attempts were carried out for the coupling of bromobenzene and oxazolidinone following Buchwald conditions using commercially available CuI (10 mol %) and (±)-*trans*-cyclohexanediamine (10 mol %) with various bases such as K_3PO_4, K_2CO_3, and Cs_2CO_3. Potassium carbonate gave product in 45% yield, and with the other two bases only a trace amount of product was formed. After having failed to improve the yield even after using CuI from three different commercial sources, we have achieved a dramatic increase in the yield (78%) by using recrystallized CuI.[8] Subsequently, performing the reaction using freshly distilled (±)-*trans*-cyclohexanediamine along with recrystallized CuI resulted in the product in excellent isolated yield. After some experimentation, the reaction conditions were optimized and it was found that 3 mol % CuI along with 10 mol % (±)-*trans*-cyclohexanediamine and 2 equiv of potassium carbonate in dioxane at 110 °C for 15 h gave product consistently in over 90% yield. To generalize this procedure, various aryl bromides and oxazolidinones were coupled, and the results are summarized in Table 1.

The coupled product was obtained in high yield in most of the cases except for the case where a strong electron-donating group was present on the aromatic ring. In this case, the yield was improved by using more CuI (5 mol %) (Compare entries 6 and 7). The yield with the formyl group on the aromatic ring resulted in product only in modest yield (entry 8). It is important to note that the thiomethyl group in the aromatic group was well tolerated in the reaction, which can be troublesome in Pd catalyzed reactions (entry 5).

Table 1. Coupling of Oxazolidinone with Various Aryl Bromides[a]

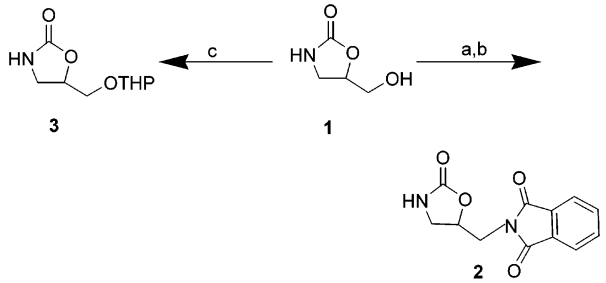


entry	aryl bromide	CuI (mol %)	% isolated yield
1	C_6H_5-Br	3	90
2	*p*-NO_2-C_6H_4Br	3	50
3	*p*-CN-C_6H_4Br	3	81
4	*p*-COMe-C_6H_4Br	3	98
5	*p*-MeS-C_6H_4Br	3	86
6	*p*-MeO-C_6H_4Br	3	45
7	*p*-MeO-C_6H_4Br	5	82
8	*p*-CHO-C_6H_4Br	3	30
9	*m*-Me-C_6H_4Br	3	80
10	*o*-MeO-C_6H_4Br	3	83

[a] All reactions were carried out in dioxane at 110−120 °C (bath temperature) under argon atmosphere.

To generalize the coupling reaction further, some substituted oxazolidinones were prepared from leucinol and phenyl glycinol by treatment with diethyl carbonate. Additionally, more relevant substituted oxazolidinones for the synthesis of targeted molecules were prepared from racemic 5-(hydroxymethyl)-2-oxazolidinone (Scheme 1).[2e,9] The alcohol

Scheme 1[a]



[a] Reagents: (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0−25 °C, 1 h; (b) potassium phthalimide, DMF, 70 °C, 4 h; (c) PPTS, dihydropyran, CH_2Cl_2, 25 °C, 12 h.

1 was protected with dihydropyran to give the compound **3**.[10] The alcohol **1** was also converted to compound **2** by a two-step procedure involving mesylation followed by treatment with potassium pthalimide. These substituted oxazolidinones were also coupled with aryl halides and the results are compiled in Table 2.

Substituted oxazolidinones also gave the coupled products in excellent yields. Oxazolidinone with free hydroxyl group could also be coupled with bromobenzene albeit in poor yield (Table 2, entry 5). Even though oxazolidinone **2** was partially

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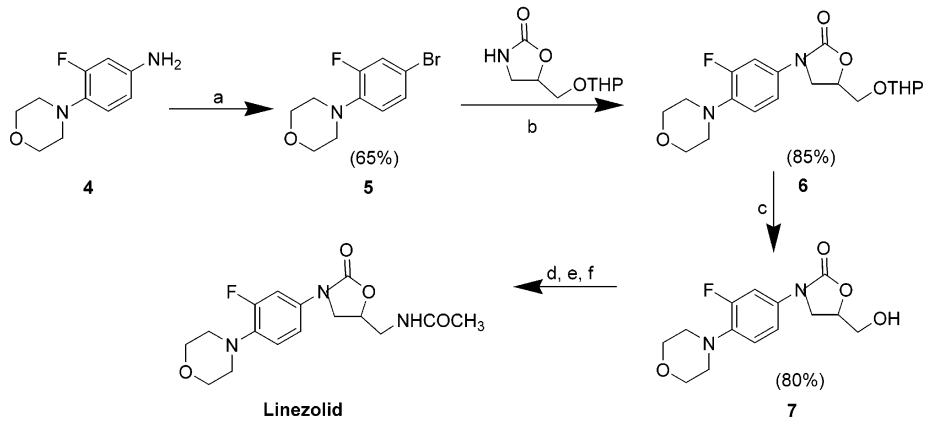
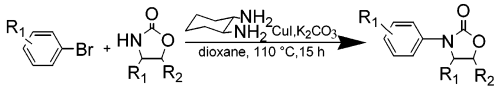
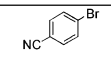
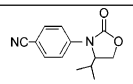
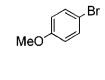
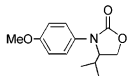
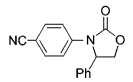
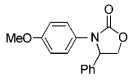
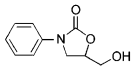
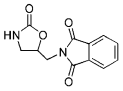
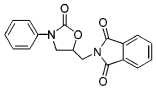
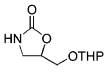
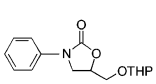
Scheme 2[a]



[a] Reagents: (a) HONO, CuBr, 47% HBr; (b) CuI (5 mol %), (±)-*trans*-1,2-diaminocyclohexane (10 mol %), dioxane, K_2CO_3, 110 °C, 15 h; (c) PPTS, EtOH, reflux,1 h; (d) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0−25 °C, 1 h; (e) NaN_3, DMF, 70 °C, 2 h; (f) CH_3COSH, 25 °C, 15 h.

Table 2. Coupling of Various Substituted Oxazolidinones with Aryl Bromides

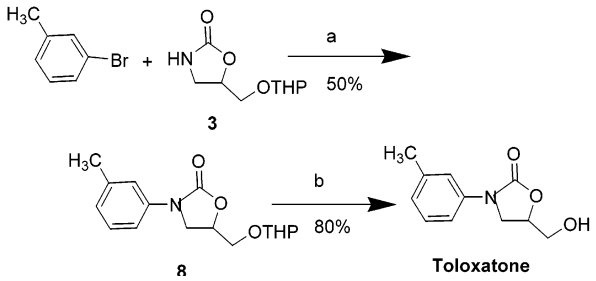


Entry	Aryl bromide	Oxazolidinone	Product	CuI (mol%)	% Isolated yield
1				3	99
2				3	50
3				3	96
4				3	98
5				3	20
6				5	65
7				5	85

soluble under these reaction conditions, the coupled product was still obtained in decent yield (Table 2, entry 6).

The utility of this protocol has been exemplified by the synthesis of linezolid and toloxatone (Figure 1) as shown in Schemes 2 and 3. The key step in the synthesis of linezolid is the coupling of the aryl bromide **5**, which was prepared from known aniline[2b] **4** via a Sandmeyer reaction, with the oxazolidinone **3**. Deprotection of compound **6** using PPTS in boiling ethanol gave alcohol **7**,[10] which was converted to

Scheme 3[a]



[a] Reagents: (a) CuI (5 mol %), (±)-*trans*-1,2-diaminocyclohexane (10 mol %), K_2CO_3, dioxane, 110 °C, 15 h; (b) PPTS, EtOH, reflux, 1 h.

linezolid using known procedures.[2c] Similarly, toloxatone[2d] was prepared in two steps from **3** and 3-bromotoluene (Scheme 3).

In conclusion, we have developed an efficient and high-yielding CuI-mediated N arylation of oxazolidinones using the Buchwald protocol. Various aryl bromides and substituted oxazolidinones were used to evaluate the utility of this procedure. The synthesis of linezolid and toloxatone has been achieved using the method developed.

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Note Added after ASAP Posting. In the version posted ASAP March 4, 2003, bonds were missing from the product structures in entries 1, 6, and 7 of Table 2. The corrected version was posted March 6, 2003.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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