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Synthesis of *N*-arylated oxazolidinones via a palladium catalyzed cross coupling reaction. Application to the synthesis of the antibacterial agent Dup-721

David J. Madar,* Hana Kopecka, Daisy Pireh, Jonathan Pease, Marina Pliushchev, Richard J. Sciotti, Paul E. Wiedeman and Stevan W. Djuric

Infectious Disease and Process Chemistry Research, Abbott Laboratories, D-47N, Bldg AP 52N, 200 Abbott Park Rd, Abbott Park, IL 60064-6217, USA

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Abstract—A method for the intermolecular coupling of aryl bromides and oxazolidinones is described. Application to intermediates useful for the preparation of a known class of antibacterial agent and the synthesis of the known antibacterial oxazolidinone Dup-721 are described.

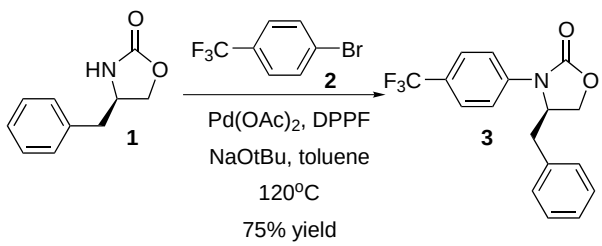
As part of a program directed at the identification of novel antibacterial agents of the oxazolidinone class,[1] we wanted to identify a highly convergent route with which to access the key oxazolidinone pharmacophore present in such key compounds as linezolid(ZYVOX) and eperezolid. This emerging class of antibacterials should prove useful for the treatment of resistant Gram-positive organisms.

We considered that the methods previously described by Buchwald and Hartwig for the coupling between aryl halides and amines via palladium(0) catalysis might well be translated to our case in hand.[2–4] Although this reaction had not been extended to cyclic carbamates, a report by Shakespeare described the coupling of aryl bromides with cyclic amides suggested that a similar approach could be successful.[5] Also, Hartwig has published the union between aryl halides and *tert*-butyl carbamate using sodium phenoxide as base.[6] More recently, Yin and Buchwald have described the coupling of aryl halides and amides as well as one example of an acyclic carbamate with an aryl bromide.[7]

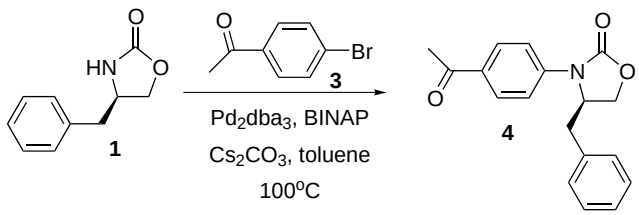
The first experiment was with (*S*)-(−)-4-benzyl-2-oxazolidinone and 4-bromobenzotrifluoride under the conditions described by Shakespeare (Scheme 1).[5] This reaction afforded the *N*-arylated product **3** in good yield (75%).

However, when these experimental conditions were utilized on more demanding substrates such as 4-bromoacetophenone, 2-fluoro-4-bromobenzaldehyde and 4-bromo-2-nitropyridine the reactions failed to give the desired product.

This prompted a screen of a number of palladium catalysts and phosphine ligands that were known to work well for the coupling between aryl halides and amines. After considerable experimentation, the use of



Scheme 1.



Scheme 2.

* Corresponding author.

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$Pd_2(dba)_3$ and BINAP with cesium carbonate as base was found to work with the widest variety of aromatic bromides. With 4-bromoacetophenone and (*S*)-(−)-4-benzyl-2-oxazolidinone, **1**, under our optimized conditions, a 61% isolated yield of coupled product **4** was obtained (Scheme 2).[8]

With a relatively optimized coupling protocol, attention was turned to the synthesis of oxazolidinones which are useful as antibacterial agents exemplified by Dup-721 (Fig. 1).

(*S*)-Hydroxymethyl-2-oxazolidinone, **5**, was prepared from D-malic acid in three steps by the method of Danielmeier and Steckhan.[9] This material was further elaborated to three useful intermediate oxazolidinones, **6**, **7**, and **8** (Fig. 2).

Silylated oxazolidinone **6** was prepared by treatment of alcohol **5** with TBDPS-Cl/imidazole in DMF (95% yield). *N*-Phthalamide derivative **7** was synthesized by the two step sequence of tosylation (TsCl, pyridine) and displacement with potassium phthalamide (71% overall yield). Protected amide **8** was prepared by the three step sequence of nosylation (2-nitrobenzenesulfonate, pyridine) displacement with 2,4-dimethoxybenzylamine in acetonitrile, and acetylation with acetic anhydride in pyridine (50% overall yield).

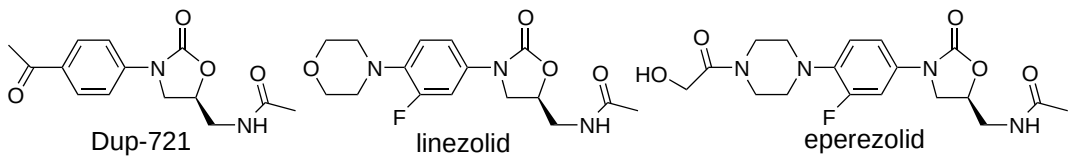


Figure 1.

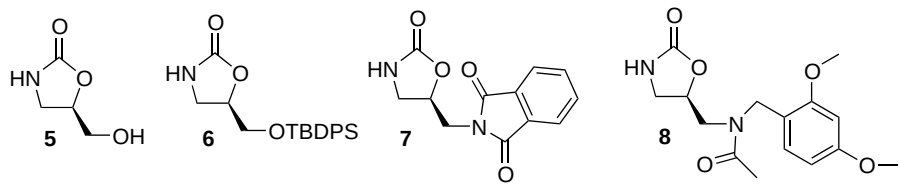


Figure 2.

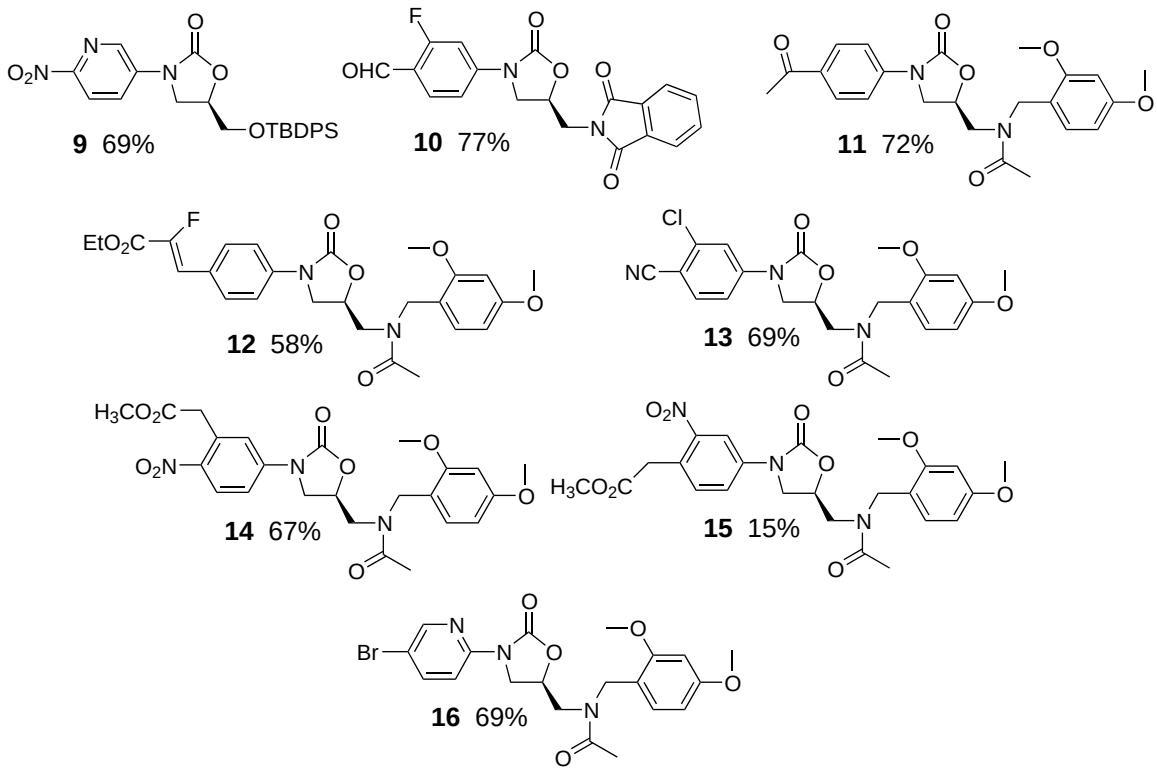
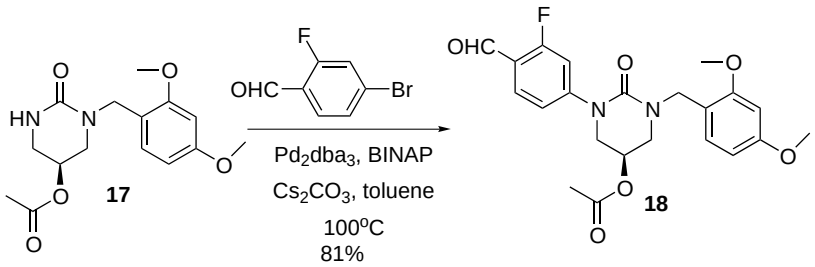
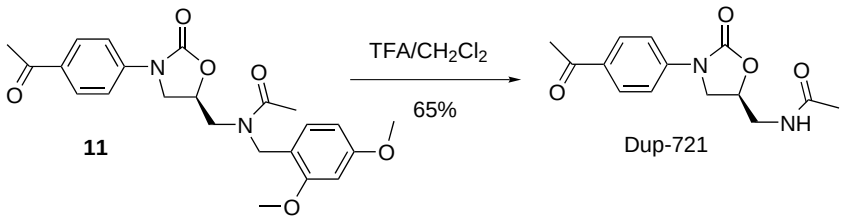


Figure 3.



Scheme 3.



Scheme 4.

These intermediates were then coupled with various aromatic bromides to provide useful intermediates for antibacterials. Shown below are representative examples prepared. Each *N*-arylated compounds in Fig. 3 was prepared from the corresponding oxazolidinone listed in Fig. 2 and the appropriate aryl bromide.[10] The coupling was found to be tolerant of a wide variety of functional groups including nitro, aldehyde, nitrile, esters and enolizable ketones and esters. The reaction with electron rich aryl bromides is exceedingly slow as to be impractical. Also, control experiments were conducted in the absence of the palladium catalyst to demonstrate the essential nature of Pd(0) catalysis for this reaction. No product was formed after heating for 36 hours (example **9** and **11**).

Ureas can also be arylated under the same type of conditions. Thus, when urea **17**[11] and 2-fluoro-4-bromobenzaldehyde were treated under our standard conditions, the unsymmetrical cyclic urea **18** was prepared in 81% isolated yield. To our knowledge, this is the first example of this type of bimolecular reaction with a urea (Scheme 3).

As a final note, we established the application of this chemistry to the known antibacterial compound Dup-721. The amide of arylated oxazolidinone **11** was deprotected with a 1:1 mixture of trifluoroacetic acid and methylene chloride to provide Dup-721 (which was identical in all respects with the literature values)[12] in 65% isolated yield (Scheme 4).

In summary, the Buchwald/Hartwig palladium coupling methodology has been extended to include the reaction of aryl bromides with cyclic carbamates and ureas. This chemistry provided very useful intermediates for the synthesis of potential antibacterials of the oxazolidinone class and the biological data on those derived compounds will be the subject of future publications.

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10. A representative procedure for compound **10** (Fig. 3): To a degassed suspension of oxazolidinone **7** (2.50 g, 10 mmol) in toluene (20 mL) in a resealable tube was added 2-fluoro-4-bromobenzaldehyde (2.03 g, 10.0 mmol), BINAP (498 mg, 0.80 mmol), cesium carbonate (4.56 g, 14.0 mmol) and finally $Pd_2(dba)_3$ (366 mg, 0.40 mmol). The reaction was resealed and heated at 100°C for 24 h. The reaction mixture was then cooled and partitioned between saturated ammonium chloride (200 mL) and ethyl acetate (200 mL). The aqueous layer was back extracted with ethyl acetate (2×200 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to a crude solid. Recrystallization from methylene chloride afforded **10** (2.85 g, 77%). ^{1}H NMR: σ 10.27 (s, 1H), 7.88 (m, 3H), 7.75 (m, 2H), 7.63 (dd,

$J=2.1$, 12.6 Hz, 1H), 7.27 (dd, $J=2.1$, 12.6 Hz, 1H), 5.04 (m, 1H), 4.16 (m, 2H), 4.00 (m, 2H). MS ESI (+) 369 $[M+1]^+$.

This procedure has been run on a 'process scale' with 145 g of **7** in 64% yield.

DMF was a more convenient solvent for the reaction.

11. Urea **17** was formed in high yield from the displacement of the tosylate derived from **5** with 2,4-dimethoxybenzylamine in DMSO at 40°C, followed by treatment with acetic anhydride/pyridine.
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