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A Novel Method for the Preparation of 4-Arylimidazolones

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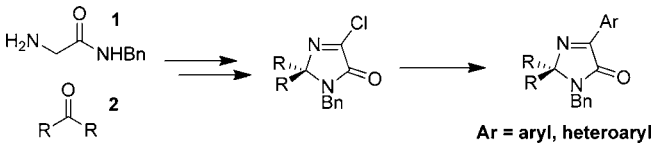
ABSTRACT



A series of 4-arylimidazolones have been accessed *via* late-stage, palladium-mediated arylation of acetone- and cyclohexanone-derived 4-chloroimidazolones. The 4-chloroimidazolones were prepared *via* a novel rearrangement of the corresponding imidazolone *N*-oxides. This communication serves as an expansion of chemistry originally developed for our glucagon receptor antagonist program.

The imidazolone moiety is a structural motif found in the Kottamide family of natural products and glycine transporter type 1 inhibitors such as GSK 2137305.[1,2] In our laboratories, we have utilized the imidazolone heterocycle in the preparation of a series of orally available glucagon receptor antagonists for the potential treatment of type II diabetes mellitus (T2DM).[3]

Our initial approach to the synthesis of 4-aryl-substituted spiroimidazolones (Scheme 1) involved starting with an *N*-Boc-arylglycine (**1**), coupling with a primary amine to afford amide **2**, and deprotection resulting in amine **3**. Condensation of **3** with a ketone afforded **4**, which upon oxidation with NBS or *t*-BuOCl afforded the desired 4-arylimidazolone **5**.

For our glucagon receptor antagonist program, it was desired to develop an effective means to install 4-aryl and 4-heteroaryl groups at a late stage in the synthetic sequence, rather than at the first step, as was the case with the *N*-Boc-arylglycine approach.

Previous reports had described the synthesis of imidazolone *N*-oxides for use as a chiral synthon in the case of compounds **6** and **7a**–**c** (Figure 1) and as an example of unique chemical matter (**8a**).[4–8] More recently, imidazolone *N*-oxides **8b** and **9** were used to prepare a series of structurally unique 4-alkenylimidazolones and 6-acyl-3-benzyl-2,2-dialkyl-1,3-diazabicyclo[3.1.0]hexan-4-ones.[9]

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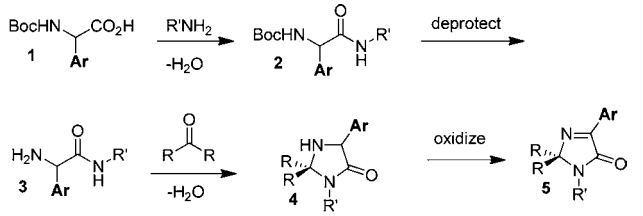
Direct arylation of the 4-position of imidazolone *N*-oxides has also been demonstrated.[10]

Scheme 1. Initial Synthetic Approach to 4-Arylimidazolones



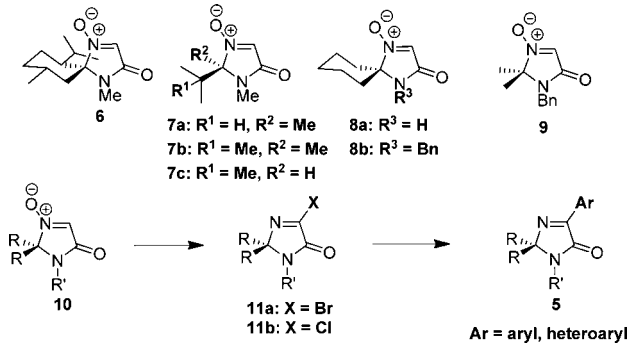


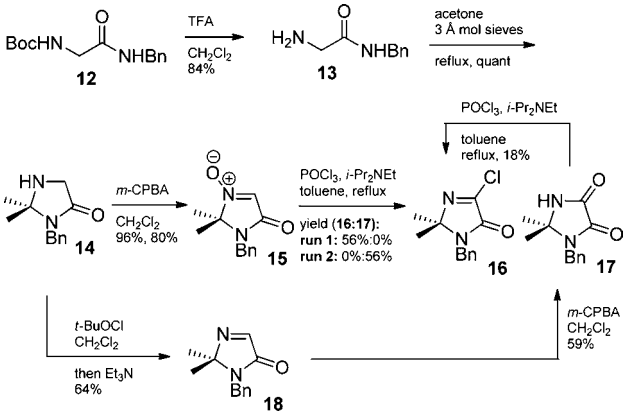
Figure 1. Proposed synthetic approach to 4-arylimidazolones.

For our purposes, we hypothesized that an imidazolone *N*-oxide such as **10** could be transformed into the corresponding 4-haloimidazolones **11a** and **11b** in a manner analogous to the conversion of pyridine *N*-oxides to 2-halopyridines. Palladium catalyzed cross-coupling of **11a** or **11b** with the requisite boronic acid or ester would afford the desired 4-arylimidazolone **5**. This approach was originally validated in our previously described glucagon receptor antagonist efforts.[3]

With this initial success, we decided to further probe the generality of this chemistry. The results of our efforts are described herein.

Glycinamide **12** was deprotected with TFA to afford amine **13** (Scheme 2). Heating of **13** in refluxing acetone in

Scheme 2. Preparation of 4-Chloroimidazolone **16**



the presence of 3 Å molecular sieves afforded the dihydroimidazolone **14**. Oxidation of **14** with 2.2 equiv of *m*-CPBA afforded the nitrone **15**.[11,12] Treatment of **15** with $POCl_3$ in the presence of Hunig's base in refluxing toluene, followed by quenching of the reaction with brine and silica gel chromatography (run 1), afforded the chloroimidazolone **16** in 56% yield. Conversely, quenching of the reaction with saturated aqueous sodium bicarbonate followed by silica gel chromatography (run 2) afforded none of **16**, but rather a 56% yield of the hydrolysis product, hydroxyimidazolone **17**.

Additionally, dihydroimidazolone **14** can be converted to chloroimidazolone **16** *via* a second route. Treatment of **14** with *tert*-butyl hypochlorite resulted in *N*-chlorination of the dihydroimidazolone. Subsequent treatment with triethylamine resulted in elimination to the imidazolone **18**. Interestingly, treatment of **18** with *m*-CPBA did not provide the nitrone **15**, but rather the 4-hydroxyimidazolone **17**.[13]

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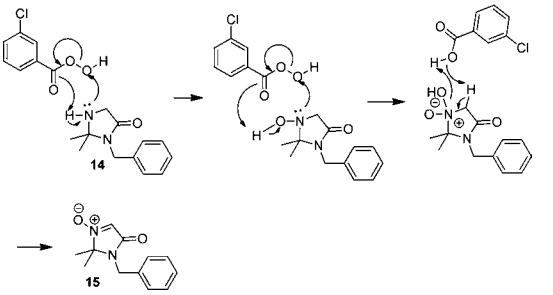
(10) Zhao, H.; Wang, R.; Chen, P.; Gregg, B. T.; Hsia, M. M.; Zhang, W. *Org. Lett.* **2012**, *14*, 1872.

(11) Proposed mechanism:



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(13) Proposed mechanism:

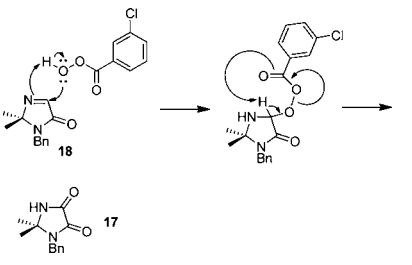
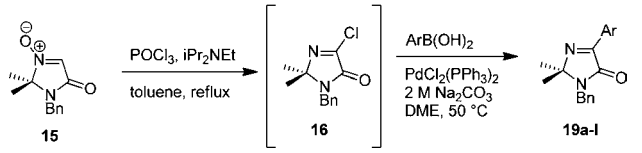
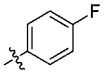
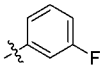
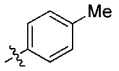
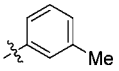
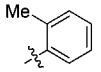
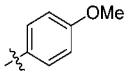
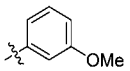
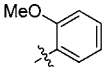


Table 1. Arylation of Chloroimidazolone **7**[a]



entry	Ar	yield
19a		42%
19b		45%
19c		57%
19d		47%
19e		44%
19f		60%
19g		61%
19h		47%
19i		24%
19j		7%
19k		49%
19l		45%

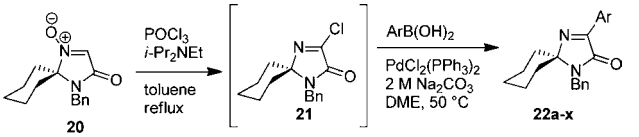
[a] Isolated yields.

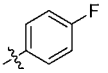
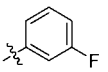
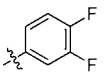
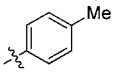
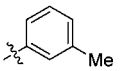
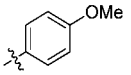
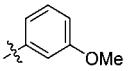
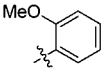
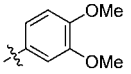
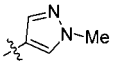
As was seen with the treatment of nitrone **15**, treatment of **17** with $POCl_3$ and Hunig's base in toluene at reflux also afforded the chloroimidazolone **16**.

To avoid hydrolysis of the chloroimidazolone on work-up, the conversion of **15** to **16** was immediately followed by removal of the volatile reactants *in vacuo* and Suzuki coupling with the requisite boronic acid or boronic ester to afford 4-arylimidazolones **19a**–**l** (Table 1). In general, the Suzuki coupling products were isolated in modest yields with a variety of substituted aromatics. Suzuki products arising from coupling with methoxy-substituted phenyl boronic acids were isolated in the lowest yields, with only a minimal amount of the *ortho*-methoxyphenyl imidazolone **19j** being isolated. Pyridinylimidazolones **19k** and **19l** were isolated in yields similar to those observed with phenylimidazolones.

At this point, we explored the palladium-mediated arylation of cyclohexanone-derived 4-chlorospiroimidazolones (Table 2). The preparation of imidazolone *N*-oxide **20** and 4-chloroimidazolone **21** proceeded in a manner similar to that observed with the preparation of the analogous

Table 2. Preparation of 4-Aryl Spirocyclohexylimidazolones[a]



entry	$ArB(OH)_2$	yield
22a		53%
22b		77%
22c		63%
22d		64%
22e		74%
22f		64%
22g		44%
22h		58%
22i		66%
22j		69%
22k		65%
22l		41%
22m		45%
22n		43%
22o		17%

[a] Isolated yields.

acetone-derived intermediates **15** and **16**. With the exception of the *N*-methylpyrazole compound **22o**, moderate isolated yields were observed across the board, including the *o*-methoxyphenyl compound **22k**.

The imidazolone motif has seen a significant increase in utility in recent years. A wide variety of unique synthetic transformations have emerged from imidazolone *N*-oxides in particular. In our laboratories, we have demonstrated a novel method for the synthesis of 4-chloroimidazolones, and their subsequent palladium-catalyzed cross-coupling with arylboronic acids. This approach allows for the rapid, late-stage incorporation of a wide variety of aryl and heteroaryl groups that would not be readily available *via* the original arylglycine-based approach.

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

The authors declare no competing financial interest.