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# Copper (I) 3-Methylsalicylate, an efficient catalyst for *N*-arylation of heterocycles under moderate reaction conditions

Abdelbasset A. Farahat[a,b] and David W. Boykin[a]*.

[a]Department of Chemistry, Georgia State University, Atlanta, GA, 30303.

[b]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt.

Tel: +1404 413 5498, E-mail: dboykin@gsu.edu

**Abstract**

Copper (I) 3- methylsalicylate mediates *N*-arylation reactions of both aliphatic and aromatic heterocycles under moderate reaction conditions. Both electron rich and electron poor aryl bromides and a diverse set of *N*-heterocycles were allowed to react and gave *N*-arylation products in high yields which demonstrated the efficiency and utility of this catalyst.

**Keywords.**

Ullmann type coupling, Copper (I) 3-methylsalicylate, *N*-arylation, C-N bond formation.

The direct formation of aryl C-N bonds between aryl halides and *N*-heterocycles, amides and related compounds represents an important approach for synthesis of more complex molecules. In the past two decades, the use of metal mediated reactions to achieve aryl C-N bond formation has

been the focus of extensive research efforts due to the importance of such structures in medicinal chemistry and natural products research. The work has centered in large part on Pd (Buchwald-Hartwig coupling[1,2]) and Cu (Ullmann type coupling[3,4]) based catalysis. Approaches employing both metals have limitations, although those using copper are generally less expensive and the reagents are less toxic. The importance of copper mediated arylation is attested to by the extensive number of publications describing the search for improvements in copper reagents and reaction conditions.[5] This rapidly expanding field has led to the regular appearance of comprehensive reviews.[6] We note that a great deal of attention has been given to searching for effective ligands to use with copper salts to provide efficient copper catalyst systems in situ, including assessment of libraries of ligands[7], whereas relatively less attention has been given to the use of defined copper complexes.[5,6] Copper complexes containing aryl amines have been reported to react with aryl iodides to form further arylated amines.[8] Copper (I) thiophene-2-carboxylate (CuTC), which has been successfully used as a cofactor in Liebeskind-Srogl protocols for Suzuki type coupling reactions[9], has seen moderate results when used for *N*-arylation of 2-imidazolines[10] and very good results when used at high loading (25 mol%) to mediate the reaction between aryl bromides and imidazole and other

similar *N*-heterocycles.[11] To our knowledge the use of the related complex copper(I) 3-methylsalicylate (CuMeSal) has not been reported for *N*-arylation reactions using aryl halides. This report describes, for the first time, the efficient arylation of various *N*-heterocycles mediated by CuMeSal.

To initiate these studies we used similar conditions to those optimized for the CuTC meditated *N*-arylation of imidazole[11]; DMSO as solvent, open to air, potassium carbonate as base, relatively high loading of CuMeSal ( 25 mol%) and heating at 110$^{o}$C for 24 h (CuTC methodology was under nitrogen atmosphere at 135 $^{o}$C [11]). Using both 4-nitrobromobenzene and 4-methoxybromobenzene we were pleased to find complete conversion to the respective *N*-arylimidazoles.

Having determined that CuMeSal effectively mediates *N*-arylation of imidazole we then set out to explore the scope of the reaction. First, we examined the effect of catalyst load using 4-nitrobromobenzene as the arylating agent as outlined in Table 1 and Scheme 1, where isolated yields serve as the indicator of conversion to product. As can be seen 10 mol % of CuMeSal seems to be the lowest amount of catalyst that should be used to form high yields of product in a relatively short time period. Consequently, in the subsequent optimization studies we employed 10 mol % of CuMeSal.

Insert scheme 1 and Table 1 here

Next we explored the use of a range of different type of solvents at or near their boiling points as shown in Table 2 and Scheme 2, which shows reaction temperature, reaction time and isolated yield. In those cases in which TLC analysis indicated little conversion to product after 3h the reaction times were extended up to 24 h. It is clear from Table 2 that heating in DMSO for 3 h at 110$^{o}$C is the condition of choice. NMP and DMF are acceptable solvents to use however the reaction times must be extended beyond that required of DMSO to obtain reasonable yields. The remaining six solvents studied are ineffective for this reaction.

Insert scheme 2 and Table 2 here

We then examined the effect of base on the course of the reaction as can be found in Table 3 and Scheme 3. These results indicate that cesium and potassium carbonate are essentially equally effective, consequently for economic reasons we used potassium carbonate in subsequent studies. We examined the effect of base concentration by using one equivalent of potassium carbonate which, gave a significantly lower yield (42%). Potassium phosphate is moderately effective, however sodium carbonate is essentially ineffective for this reaction.

Insert scheme 3 and Table 3 here

We next turned our attention to the effect of structure of both the aryl bromide and the *N*-heterocycle on the course of the CuMeSal mediated *N*-arylation using our optimized conditions.[12] These results can be found in Table 4 and Scheme 4. First, we compared the reactivity of bromobenzene and both *o*- and *p*- nitro and methoxybromobenzene with imidazole under the optimized conditions.[12] There appears essentially no electronic effect of substituents on the aryl bromide on the reaction under these conditions as both *p*-nitro and *p*-methoxybromobenzene give nearly equivalent isolated yields of the *N*-arylimidazoles. The results using the *o*-isomers show a modest steric effect; the yields of the *N*-arylimidazoles using *o*-nitro and *o*–methoxybromobenzene are reduced to 90 and 87%, respectively. As an initial probe of the effect of changing the aryl halide from bromo to chloro we allowed 4-nitrochlorobenzene to react with imidazole under the optimized conditions[12] and observed a 76% yield of 1-(4-nitrophenyl)-1*H*-imidazole after 6h reaction time (not shown in Table 1). This suggests that conditions may be found for optimization of *N*-arylation with aryl chlorides using CuMeSal, however such studies are beyond the scope of the present investigation. In addition to coupling reactions with imidazole, Table 4 contains the results for coupling three aryl bromides with pyrazole, 1,2,4-triazole, pyrrolidine, indole and benzimidazole. All of the five ring

heterocycles gave isolated coupling yields of 90% or higher. The results with pyrrolidine show that CuMeSal mediated coupling reactions are not limited to *N*-heteroaromatics and likely can be used for other aliphatic amines. In general, the isolated yields for the benzimidazole and indole coupling reactions were somewhat lower (mostly high 80s %) than noted for the simple 5-ring analogues. The lower yields may be a result of steric interactions arising from the peri-like 7-proton of both benzimidazole and indole which is consistent with the modest steric effect noted above for the *o*-substituted aryl bromides.

Insert scheme 4 and Table 4 here

In summary we have shown, for the first time, that CuMeSal mediates *N*-arylation of *N*-heterocycles, including aliphatic ones, in high yields under moderate conditions. The protocol developed provides efficient and economical methodology for performing Ullmann type *N*-arylations.

**Acknowledgment**

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**Supplementary data**

Supplementary data associated with this article, which includes compound characterization results, can be found, in the online version, at http:

**References and notes**


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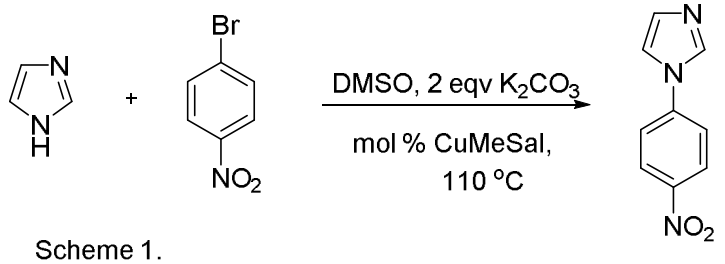
12. **General method of *N*-arylation.** A dry flask was charged with a nitrogen containing heterocycle (1.5 mmol), aryl halide (1 mmol), potassium carbonate (2 mmol) and CuMeSal (0.01 mmol) then anhydrous DMSO (5 ml) was added. The reaction mixture was stirred at 110 $^{o}$C, open to air, for 3 h , cooled to rt, filtered, and the precipitate was washed with DMSO (2 ml) then stirred with ice water

(30 ml) and extracted with ethyl acetate (3 x 50 ml), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by chromatography or recrystallization as indicated with each compound (see supplementary information).

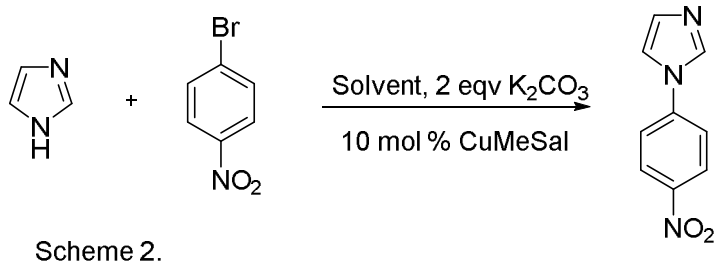
**Table 1. Effect of Mol % of catalyst.**




Scheme 1.

| Mol % Catalyst | Time (h) | % Isolated yield |
|---|---|---|
| 5 | 6 | 72 |
| 10 | 3 | 97 |
| 15 | 3 | 97 |
| 20 | 3 | 97 |
| 25 | 3 | 97 |

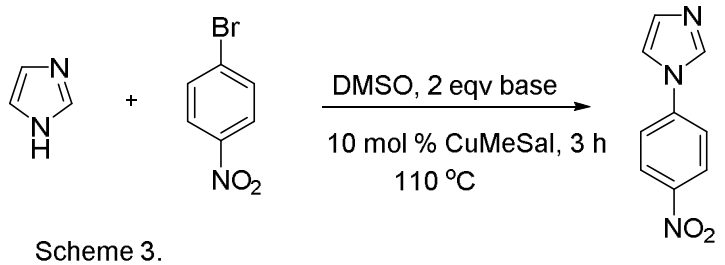
**Table 2. Effect of solvent, temperature and reaction time.**




Scheme 2.

| Solvent | Temp. (°C) | Time (h) | % Isolated yield |
|---|---|---|---|
| DMSO | 110 | 3 | 97 |
| NMP | 110 | 6 | 89 |
| DMF | 110 | 6 | 93 |
| DMA | 110 | 24 | No reaction |
| Toluene | 110 | 24 | No reaction |
| Dioxane | 101 | 24 | 10 |
| Isopropanol | 82 | 24 | No reaction |
| Acetonitrile | 81 | 24 | 5 |
| THF | 66 | 24 | No reaction |

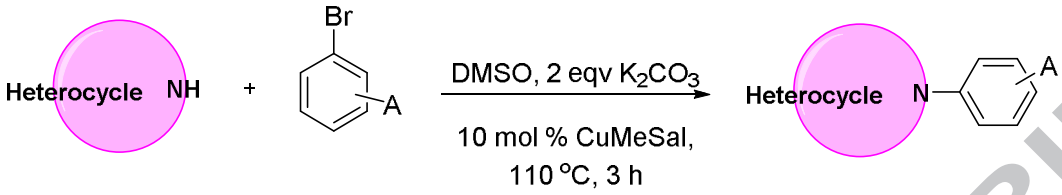
**Table 3. Effect of base.**



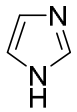
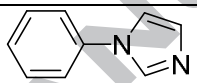
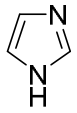
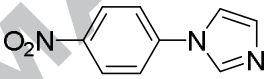
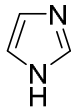
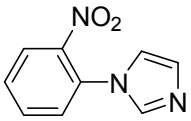
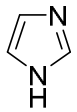
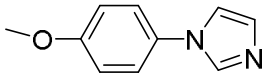
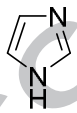
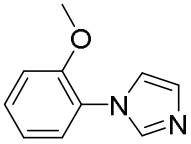
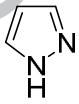
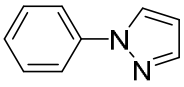
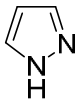
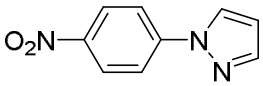
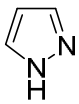
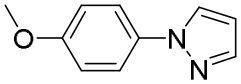

Scheme 3.

| Base | Time (h) | % Isolated yield |
|---|---|---|
| $CsCO_3$ | 3 | 98 |
| $K_2CO_3$ | 3 | 97 |
| $K_3PO_4$ | 12 | 86 |
| $Na_2CO_3$ | 24 | 15 |

**Table 4. Reaction of different *N*-containing heterocycles with different aryl bromides under the optimized reaction conditions[12].**




Scheme 4.

| N-heterocycle | A | Product | %Isolated yield |
|---|---|---|---|
|  | H |  | **95** |
|  | p-$NO_2$ |  | **98** |
|  | o-$NO_2$ |  | **90** |
|  | p-OMe |  | **94** |
|  | o-OMe |  | **87** |
|  | H |  | **90** |
|  | p-$NO_2$ |  | **97** |
|  | p-OMe |  | **96** |

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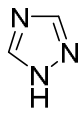
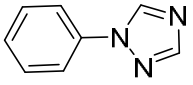
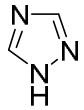
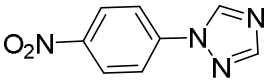
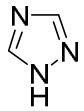
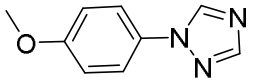
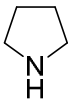
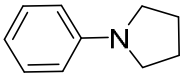
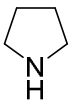
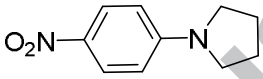
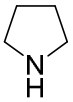
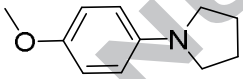
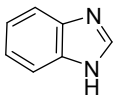
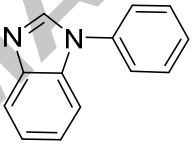
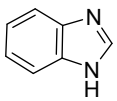
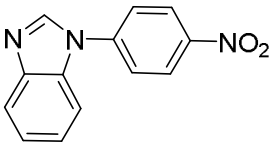
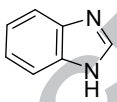
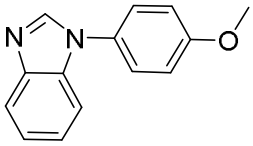
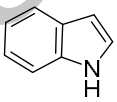
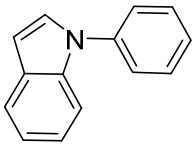
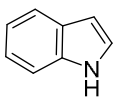
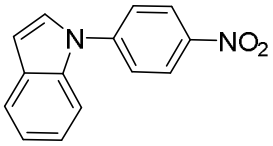
|  | H |  | **93** |
|  | p-$NO_2$ |  | **98** |
|  | p-OMe |  | **92** |
|  | H |  | **90** |
|  | p-$NO_2$ |  | **96** |
|  | p-OMe |  | **93** |
|  | H |  | **89** |
|  | p-$NO_2$ |  | **99** |
|  | p-OMe |  | **88** |
|  | H |  | **85** |
|  | p-$NO_2$ |  | **92** |

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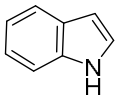
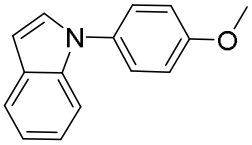
|  | p-OMe |  | **89** |