Tetrahedron Letters 54 (2013) 3245–3247

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Preparation of aryl-substituted 2-oxyindoles by superelectrophilic chemistry

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ARTICLE INFO

*Article history:*
Received 16 March 2013
Revised 2 April 2013
Accepted 3 April 2013
Available online 10 April 2013

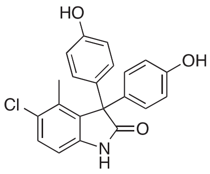
*Keywords:*
Heterocycle
Oxyindole
Superacid
Friedel–Crafts
Superelectrophile

ABSTRACT

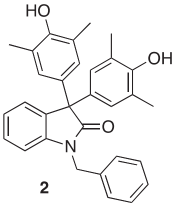
A series of pyridyl-substituted 3-hydroxy-2-oxyindoles have been prepared and reacted with arenes in superacid promoted Friedel–Crafts reactions. The product aryl-substituted 2-oxyindoles are formed in generally good yields. With substituted arenes such as toluene, bromobenzene, or ethyl salicylate, the Friedel–Crafts reactions occur with excellent regioselectivity. A mechanism is proposed involving dicationic, superelectrophilic species leading to the electrophilic aromatic substitution chemistry.

## Introduction

Substituted oxyindoles are known to have a variety of biological activities. The aryl-substituted oxyindole sub-structure is present in natural products[1] and in several biologically active compounds, such as the anti-cancer (**1**),[2] cardiovascular (**2**),[3] and laxative (**3**)[4] agents. The aryl-substituted oxyindoles may be prepared by a number of synthetic routes,[5] including the condensation of isatins with arenes in acid-promoted conversions.[6] Similarly, Friedel–Craft-type reactions have recently been done with 3-hydroxy-2-oxyindoles to provide aryl-substituted 2-oxyindoles.[7] Nevertheless, new synthetic routes to aryl-substituted 2-oxyindoles are highly sought after, especially those producing novel structures. In the following letter, we describe a synthetic methodology leading to highly functionalized 2-oxyindoles. A mechanism is proposed involving dicationic, superelectrophilic intermediates.



**1**



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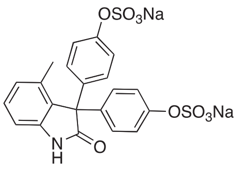
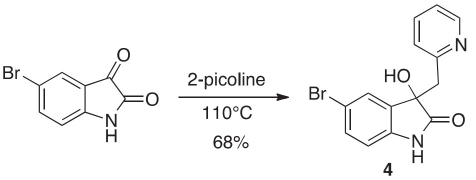


**3**

## Results and discussion

Our studies began with the reactions of 2-picoline with isatins to provide a series of (2-pyridyl)methyl-substituted 2-oxyindoles.[8] For example, 5-bromoisatin is reacted with 2-picoline in dioxane with catalytic $CF_3SO_3H$ to provide a good yield of the addition product (**4**, Eq. (1)). Previous work from our group and others has demonstrated the ability of pyridinium groups to strongly activate adjacent electrophiles.[9] This suggested to us that ionization of alcohol **4** would give a highly reactive dicationic – or superelectrophilic – species,[10] an intermediate likely to be useful in Friedel–Craft-type reactions.



**4**

(1)

Thus, reaction of compound **4** in a mixture of $CF_3SO_3H$ and $C_6H_6$ leads to product **5** in 74% yield (Table 1). The same conversion may be accomplished in 69% yield with $H_2SO_4$ as a catalyst. Trifluoroacetic acid ($CF_3CO_2H$) does not promote the reaction. In the $CF_3SO_3H$ promoted conversion, 10 equiv of acid is necessary to obtain high yields of product within several hours.[11] With substituted arenes, alcohol **4** reacts regioselectively in $CF_3SO_3H$ promoted reactions (Table 1). Toluene, bromobenzene, 2,6-dimethylphenol, 4-(3-phenylpropyl)pyridine, ethyl salicylate, and anisole provide the respective Friedel–Crafts products (**5–11**) in good yields. In all cases, the reaction shows excellent

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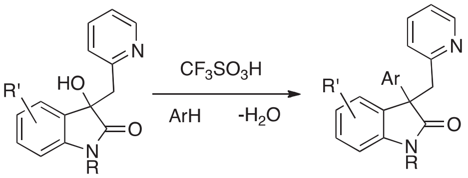
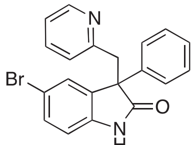
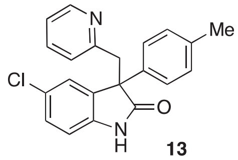
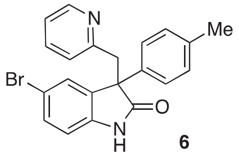
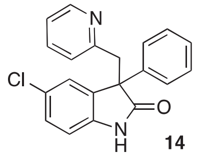
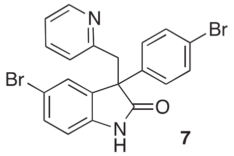
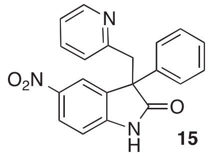
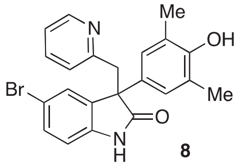
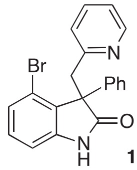
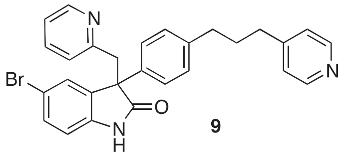
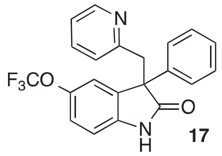
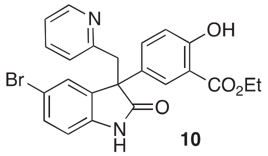
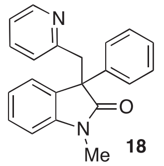
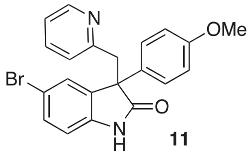
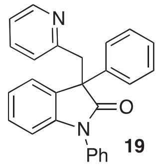
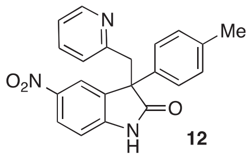
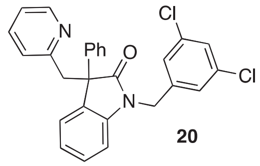
http://dx.doi.org/10.1016/j.tetlet.2013.04.011

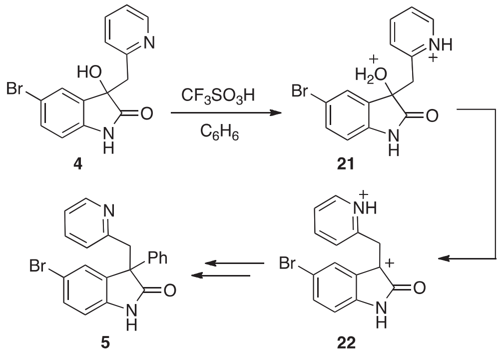
**Table 1**
Products (**5**–**20**) and isolated yields from the reactions of arenes and 3-hydroxy-2-oxyindoles in $CF_3SO_3H$



| Product | Yield (%) | Product | Yield (%) |
|---|---|---|---|
|  **5** | 74 |  **13** | 94 |
|  **6** | 80 |  **14** | 71 |
|  **7** | 81 |  **15** | 58 |
|  **8** | 78 |  **16** | 70 |
|  **9** | 70 |  **17** | 77 |
|  **10** | 69 |  **18** | 81 |
|  **11** | 60 |  **19** | 75 |
|  **12** | 96 |  **20** | 74 |

regioselectivity, an observation previously made with the condensation of isatins and arenes in superacid.[6] Likewise, reaction of nitro- and chloro-substituted 2-oxyindoles gives regioselective product formation (**12–13**) with toluene. Similar products (**14–20**) are prepared by reactions of C- or N-functionalized substrates with $C_6H_6$ and $CF_3SO_3H$.

As Friedel–Craft-type reactions, the conversions involve the formation of a carbocation intermediate (Scheme 1). Moreover, the tethered pyridyl ring should be fully protonated in the superacidic media, leading to a highly reactive dicationic electrophile. Thus, substrate **4** is initially ionized to the pyridyl-oxonium dication **21**, which undergoes dehydration to form the superelectrophilic carbocation **22**. Although the carbocation center is somewhat stabilized by the indolyl ring, it is also activated by both the pyridinum ring and the adjacent carbonyl group. Further protonation or hydrogen bonding at the carbonyl oxygen (by the superacid)



**Scheme 1.**

would provide increasing electrophilic activation at the carbocationic site. The need for strong or superacidic conditions is consistent with the formation of dicationic, superelectrophiles.[12]

## Conclusions

In summary, we have found that pyridyl-aryl disubstituted 2-oxyindoles may be prepared in good yields from Friedel–Craft-type reactions involving 3-hydroxyl-2-oxyindoles.[13,14] The reactions may be accomplished with $H_2SO_4$ or $CF_3SO_3H$ and a mechanism is proposed involving dicationic electrophiles.

## Acknowledgments

We gratefully acknowledge the support of the NIH-National Institute of General Medical Sciences (GM085736-01A1) and the Northern Illinois University for *Great Journeys Fellowship* (R.R.N.).

## Supplementary data

Supplementary data (analytical data and copies of $^{1}H$ and $^{13}C$ NMR spectra.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.011.

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13. General synthetic method: The 3-hydroxy-2-oxindoles (1 mmol) are dissolved in 2 ml of $C_6H_6$ and triflic acid ($CF_3SO_3H$, 0.9 mL, 10 mmol) is then added. The mixture is stirred for 2 h at 60 °C and then poured over several grams of ice. To the resulting solution, $CHCl_3$ (ca. 30 mL) is added and the aqueous phase is made basic (pH paper) with drop-wise addition of NaOH (10 M). Following product extraction, the organic phase is separated and washed successively with $H_2O$ and twice with brine. The solution is dried with $MgSO_4$ and the crude product is isolated by filtration and removal of solvent. Further purification is accomplished with column chromatography (silica gel; hexanes:ethyl acetate).
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