Published in final edited form as:

Tetrahedron Lett. 2013 June 19; 54(25): 3245–3247. doi:10.1016/j.tetlet.2013.04.011.

Preparation of Aryl-Substituted 2-Oxyindoles by Superelectrophilic Chemistry

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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.

Keywords

Heterocycle; oxyindole; superacid; Friedel-Crafts; superelectrophile

1. Introduction

Substituted oxyindoles are known to have a variety of biological activities. The aryl-substituted oxyindole substructure is present natural products¹ 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-Crafts-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.

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Supplementary data

Supplementary data associated with this article – analytical data and copies of ¹H and ¹³C NMR spectra – can be found in the online versions, at <http://dx.doi.org/>

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2. 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-bromoindolin-3-one is reacted with 2-picoline in dioxane with catalytic $\text{CF}_3\text{SO}_3\text{H}$ 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-Crafts-type reactions.

(1)

Thus, reaction of compound **4** in a mixture of $\text{CF}_3\text{SO}_3\text{H}$ 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 ($\text{CF}_3\text{CO}_2\text{H}$) does not promote the reaction. In the $\text{CF}_3\text{SO}_3\text{H}$ promoted conversion, 10 equivalents of acid are necessary to obtain high yields of product within several hours.¹¹ With substituted arenes, alcohol **4** reacts regioselectively in $\text{CF}_3\text{SO}_3\text{H}$ 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 regioselectivity, an observation previously made with the condensation of isatins and arenes in superacid.⁶ Likewise, reaction of nitro- and chloro-substituted 2-oxyindoles give 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 $\text{CF}_3\text{SO}_3\text{H}$.

As Friedel-Crafts-type reactions, the conversions involve 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 pyridinium ring and adjacent carbonyl group. Further protonation or hydrogen bonding at the carbonyl oxygen (by the superacid) 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

3. Conclusions

In summary, we have found that pyridyl-aryl disubstituted 2-oxyindoles may be prepared in good yields from Friedel-Crafts-type reactions with involving 3-hydroxyl-2-oxyindoles.^{13,14} The reactions may be accomplished with H₂SO₄ or CF₃SO₃H and a mechanism is proposed involving dicationic electrophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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13. General synthetic method: The 3-hydroxy-2-oxindoles (1 mmol) is dissolved in 2 ml C₆H₆ and triflic acid (CF₃SO₃H, 0.9 mL, 10 mmol) is then added. The mixture stirred for 2 hours at 60°C and then poured over several grams of ice. To the resulting solution, CHCl₃ (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 H₂O and twice with brine. The solution is dried with MgSO₄ 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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Scheme 1.

Table 1

Products (**5-20**) and isolated yields from the reactions of arenes and 3-hydroxy-2-oxyindoles in $\text{CF}_3\text{SO}_3\text{H}$.

Product	Yield
5	74%
6	80%
7	81%
8	78%
9	70%

General reaction scheme showing the synthesis of indole-3-carboxamide derivatives (10-15) from a substituted indole-3-carboxamide and a substituted phenol (ArH) using $\text{CF}_3\text{SO}_3\text{H}$ as a catalyst, with loss of H_2O .

Product	Yield
10	69%
11	60%
12	96%
13	94%
14	71%
15	58%

Product	Yield
<p>16</p>	70%
<p>17</p>	77%
<p>18</p>	81%
<p>19</p>	75%
<p>20</p>	74%