Graphical Abstract

Synthesis of Functionalized 2-Oxindoles by Friedel-Crafts Reactions.

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ABSTRACT

A series of acetyl-substituted 3-hydroxy-2-oxindoles have been prepared and reacted with arenes in superacid promoted Friedel-Crafts reactions. The product aryl-substituted 2-oxindoles are formed in generally good yields. With substituted arenes such as toluene, bromobenzene, or anisole, the Friedel-Crafts reactions occur with excellent regioselectivity. A mechanism is proposed involving carbocationic electrophiles leading to the aromatic substitution chemistry.

Keywords: heterocycles, 2-oxindoles, superacid, electrophiles, carbocation

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1. Introduction

The 2-oxindoles are an important class of heterocyclic compounds. This substructure is present in several potent therapeutic agents, such as the anti-cancer drug (**1**) and cardiovascular drug (**2**).² It is also present in many natural products, including spirotryprostatine A (**3**) and alstonisine (**4**).³ Moreover, 2-oxindoles are useful synthetic intermediates, for

example in their use as precursors to the furoindoline and pyrroloindoline cores.⁴ The 2-oxindoles 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-oxindoles to provide aryl-substituted 2-oxindoles.⁷ Nevertheless, new synthetic routes to 2-oxindoles are highly sought after, especially those producing novel structures. In the following letter, we describe a convenient method for preparing 3,3-disubstituted 2-oxindoles from 3-acetonyl-3-hydroxy-2-oxindoles.

2. Results and Discussion

Our studies began with the preparation of a 3-hydroxy-2-oxindole series. Using a published procedure, isatin reacts with acetone in the presence of potassium carbonate to give good yields of the adduct **5** (eq 1).⁸ The procedure also works well with acetophenone, providing the

[eq 1]

respective 3-hydroxy-2-oxindole. Acid-promoted ionization 3-hydroxy-2-oxindoles is known to be useful procedure for generating reactive cationic electrophiles.⁷ When compound **5** is subjected to the superacid-promoted reaction with benzene, two types of products are observed depending on the reaction conditions (Scheme 1). At 25°C, the condensation product **6** is formed in good yield as a mixture of stereoisomers. The two diastereomers of **6** were inseparable by column chromatography. Using more mild reaction conditions, compound **7** is the major product. The low temperature and short reaction time leads to selective product formation from a single equivalent of benzene.⁹ Other arenes likewise provide the substitution products (**8-11**) in good yields. Product formation is characterized by very high regioselectivity. Moreover, the mild reaction conditions lead to no transalkylation or isomerization of the alkyl-substituted aryl groups.

Scheme 1.

[Scheme 1]

Other 3-hydroxy-2-oxindoles were prepared and provided good conversions with bromobenzene (Table 1). Functionalized isatins are readily available – providing substrates with substituents on the ring carbons (**12**) and the ring nitrogen (**13-15**). Likewise, aryl ketones such as the acetophenone may provide the corresponding 3-hydroxy-2-oxindole (**16**). In each of these cases, the respective Friedel-Crafts products (**17-21**) are formed with good regioselectivities and fair to excellent yields.

Regarding a mechanism for the conversion, the 2-oxindole carbocation is likely the key intermediate (eq 2). Thus, cleavage of the oxonium ion **22** leads to the carbocation **23**. While **23** may be the electrophile in the Friedel-Crafts reactions, and α -carbonyl carbocations are known to be reactive electrophiles,¹⁰ a more highly ionized species (i.e., **24**) cannot be ruled out. Some degree of interaction is likely between the carbonyl group(s) and excess superacid. Any protonation – partial or complete – will lead to enhanced electrophilic reactivity compared to the monocation **22**. This superelectrophilic reactivity has been demonstrated in numerous carbonyl electrophiles.¹¹

[eq 2]

Table 1. Products and yields from the reactions of 3-hydroxy-2-oxindoles (**12-16**) with bromobenzene in $\text{CF}_3\text{SO}_3\text{H}$.

[Table 1]

We also attempted to carryout the Friedel-Crafts reaction with the 3-hydroxy-2-oxindole (**25**), assuming the olefinic group would undergo a secondary cyclization reaction. When compound **25** is reacts with $\text{CF}_3\text{SO}_3\text{H}$ in C_6H_6 , the major product is 3,3-diphenyl-2-oxindole (**26**) rather than the expected indane derivative **26**. Clearly, this conversion involves the loss of the isobutene fragment. This may be understood by the formation of carbocation **28** ($\text{R} = -\text{Ph}$ or $-\text{OH}$) and cleavage of the C-C bond to give the electrophile **28**. Either the benzylic carbocation (**29**, $\text{R} = -\text{Ph}$) or the carboxonium ion (**29**, $\text{R} = -\text{OH}$) is expected to provide 3,3-diphenyl-2-oxindole (**26**) under the reaction conditions.

Scheme 2.

[Scheme 2]

Derivatives with *N*-heteroaromatic substituents have also been prepared. Pyridine and pyrazine derivatives (**31-35**) have been synthesized by direct addition of the corresponding heterocyclic ketones to isatin in DMF with 4 Å molecular sieves.¹² When the heterocyclic derivatives were subjected to a reaction with benzene in $\text{CF}_3\text{SO}_3\text{H}$, the respective substitution products (**36-40**) were formed in good yields. Given the *N*-heteroaromatic substituents are fully protonated in excess superacid, ionization of the hydroxyl group likely involves formation of dicationic and possibly tricationic electrophiles as precursors to the substitution products (**36-40**). In the case of the pyrazine derivative **34**, two equivalents of benzene react with the substrate and the major product has been identified as compound **39**. A similar phenylation of acetylpyrazine has been previously reported.¹³

Table 2. Products and yields from the reactions of 3-hydroxy-2-oxindoles (**12-16**) with benzene in $\text{CF}_3\text{SO}_3\text{H}$.

[Table 2]

3. Conclusions

In summary, we have found that disubstituted 2-oxindoles may be prepared in good yields from Friedel-Crafts-type reactions with involving 3-acetonyl-3-hydroxyl-2-oxindoles. The reactions may be accomplished with $\text{CF}_3\text{SO}_3\text{H}$ and a mechanism is proposed involving heterocyclic, carbocation electrophiles.

Acknowledgments

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- Typical procedure: the 3-acetonyl-3-hydroxyl-2-oxindole (1 mmol) is dissolved in CH₂Cl₂ (2 mL), the arene nucleophile (10 mmol) is added, and the solution is cooled to 0 °C. To this mixture, triflic acid (2 mL, 22 mmol) is slowly added and the resulting solution is stirred for 1 hr at 0 °C. The product mixture is then poured over ice and extracted (3x) directly into CHCl₃. The combined organic extracts are then washed successively with water, saturated NaHCO₃, and then saturated brine (2x). The solution is then dried over anhydrous Na₂CO₃ and the solvent removed. The resulting crude product may be further purified by silica gel chromatography with hexane:ethyl acetate. The waste triflic acid may be quantitatively recycled, see: Booth, B. L.; El-Fekky, T. A. *J. Chem. Soc. Perkin I* **1979**, 2441-2443.
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Scheme 1

Scheme 2

Table 1

Starting Material	Product	Yield
		67%
		85%
		90%
		52%
		67%

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Table 2

Starting Material	Product	Yield
31	36	81%
32	37	61%
33	38	75%
34	39	49%
35	40	88%