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RESEARCH ARTICLE

Synthesis of 3–aryl 3–hydroxyisoindolinones by the Addition of Grignard and Organolithium Reagents to Phthalimides

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Abstract: ***Background*:** The 3-substituted 3-hydroxyisoindolinone motif is common to a variety of compounds with potent biological activities. In recent years, they have also been increasingly used as substrates in various asymmetric transformations. Current methods for their preparation either do not tolerate wide range of functional groups, or yield 3–hydroxyisoindolinones as *N*–substituted products, which makes them inapplicable as substrates for the asymmetric transformations.

***Objective*:** Aim of this study was a detailed examination of the synthesis of 3–substituted 3–hydroxyisoindolinones comprising various functional groups and unsubstituted phthalimide nitrogen.

***Method*:** Grignard and organolithium reagents were employed as nucleophiles for the synthesis of 3–substituted 3–hydroxyisoindolinones under various reaction conditions.

***Results*:** Phenyl substituents with electron donating groups are easily introduced by employing a Grignard reaction, while electron–poor arenes require a lithium exchange or direct lithiation strategy. The protocols are tolerant of various functional groups on the nucleophile, and a wide range of 3–hydroxyisoindolinones were afforded in good to excellent yields.

***Conclusion*:** Simple and inexpensive method for the synthesis of 3-substituted 3-hydroxyisoindolinone has been developed. By tweaking the reaction conditions, described protocols are tolerant of a wide range of functional groups, and yield 3–substituted isoindolinone alcohols with unsubstituted phthalimide nitrogen.

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1. INTRODUCTION

The 3-substituted 3-hydroxyisoindolinone motif is common to a variety of compounds with potent biological activities. They have been established as precursors to anti–ischemic stroke agents [1], MDM2–p53 protein–protein [2-6], HIV–1 integrase [7], and protein–tyrosine phosphatase inhibitors [8], as well as antimicrobial [9] and antitumor [10] agents. In addition, molecules containing the 3–substituted isoindolinone core are registered anxiolytic [11], anticonvulsant [12] and antihypertensive [13] drugs (Fig. **1**).

3–Substituted 3–hydroxyisoindolinones are usually prepared by reacting phthalimide with the corresponding organometallic reagents [14-17]. Apart from Grignard and organolithium reagents, nickel–catalyzed additions of diethylzinc to phthalimides have also been developed [18-20].

However, due to the availability of starting materials and functional group stability, the majority of these reactions employ highly reactive and commercially available nucleophiles, such as organometallic reagents derived from alkyl halides and electron–rich phenyl rings. Hence, in order to expand the number of functional groups that can be incorporated into the isoindolinone core, different protocols were required.

Cyclization of the parent benzamide compound is also a common synthetic strategy. Kim *et al.* prepared 3–substituted 3–hydroxyisoindolinones *via* tandem rhodium(III)–catalyzed oxidative acylation of secondary benzamides with aldehydes and cyclization [21], while the Huang and Zhao group performed the same reaction by employing palladium(II) acetate [22]. Recently, Li *et al.* used the same palladium catalyst for the cyclization with phenylglyoxylic acids [23]. Other methods for obtaining isoindolinone alcohols include fluoride–catalyzed nucleophilic additions [24, 25], reductive couplings with aldehydes, ketones and olefins [26-29], and photodecarboxylative additions of carboxylates to phthalimides [30, 31].

Although these cyclization procedures offer elegant and functional group tolerant methods for the preparation of substituted isoindolinones, they suffer from certain drawbacks. Apart from employment of expensive catalysts, oxidants, exotic reagents, and high reaction temperatures, probably the biggest limitation of these protocols is that the final isoindolinone alcohols are obtained as *N*–substituted products. Substituents on nitrogen atom play a significant role in the formation of products. They often serve as a catalyst coordination sites, but they also play a role in the solubility of precursors, as well as in preventing further reactivity of nitrogen.

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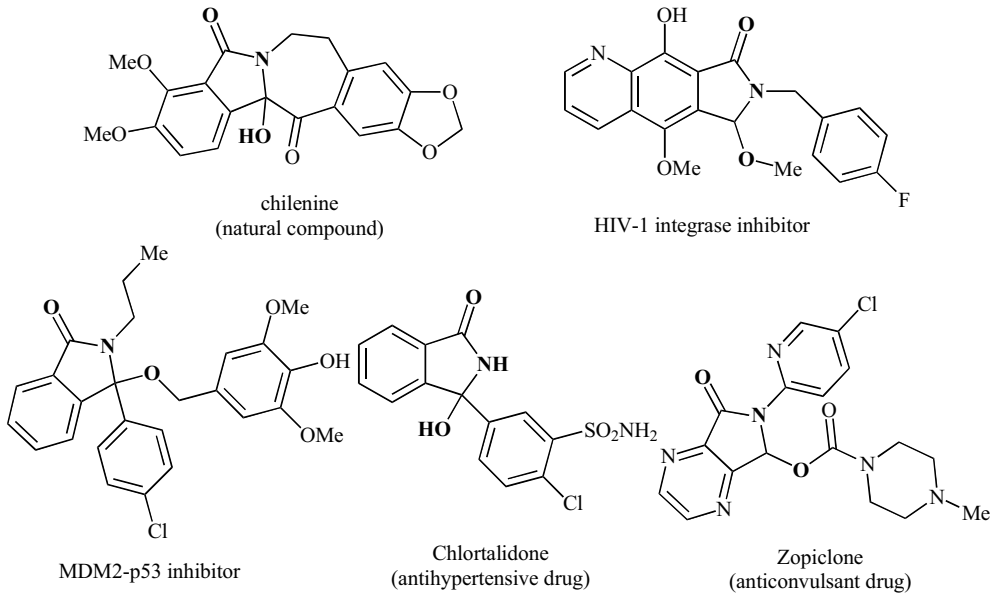


Fig. (1). 3–hydroxyisoindolinone motif in natural and pharmacologically active compounds.

In recent years, 3–hydroxyisoindolines have been increasingly used as substrates in asymmetric transformations. Their structure offers a possibility of generating reactive ketimine species. These ketimines react readily with nucleophiles, thus yielding products with quaternary carbon stereocentres. Therefore, isoindolinone alcohols have been successfully employed in a number of organocatalytic [32-35] and metallo–catalyzed [36, 37] asymmetric reactions, generating isoindolinone cores of natural compounds. Mechanistic investigations showed that hydrogen on the nitrogen atom of the isoindoline amide bond is required for the significant interaction with catalysts [32]. As a result, *N*–substituted 3–hydroxyisoindolinones yield products with substantially lower enantioselectivities.

As part of our ongoing research utilizing 3–substituted 3–hydroxyisoindolinones as substrates in asymmetric organocatalytic reactions [35], we were interested in preparing isoindolinone alcohols with various functional groups. However, literature protocols describing the synthesis of *N*–unsubstituted isoindolinone alcohols use only electron rich aryls, which substantially limits the substrate scope. Herein we report a synoptic study of the conditions for the preparation of a wide range of isoindolinone alcohols comprising unsubstituted nitrogen atoms, by employing various organometallic reagents.[1]

2. EXPERIMENTAL SECTION

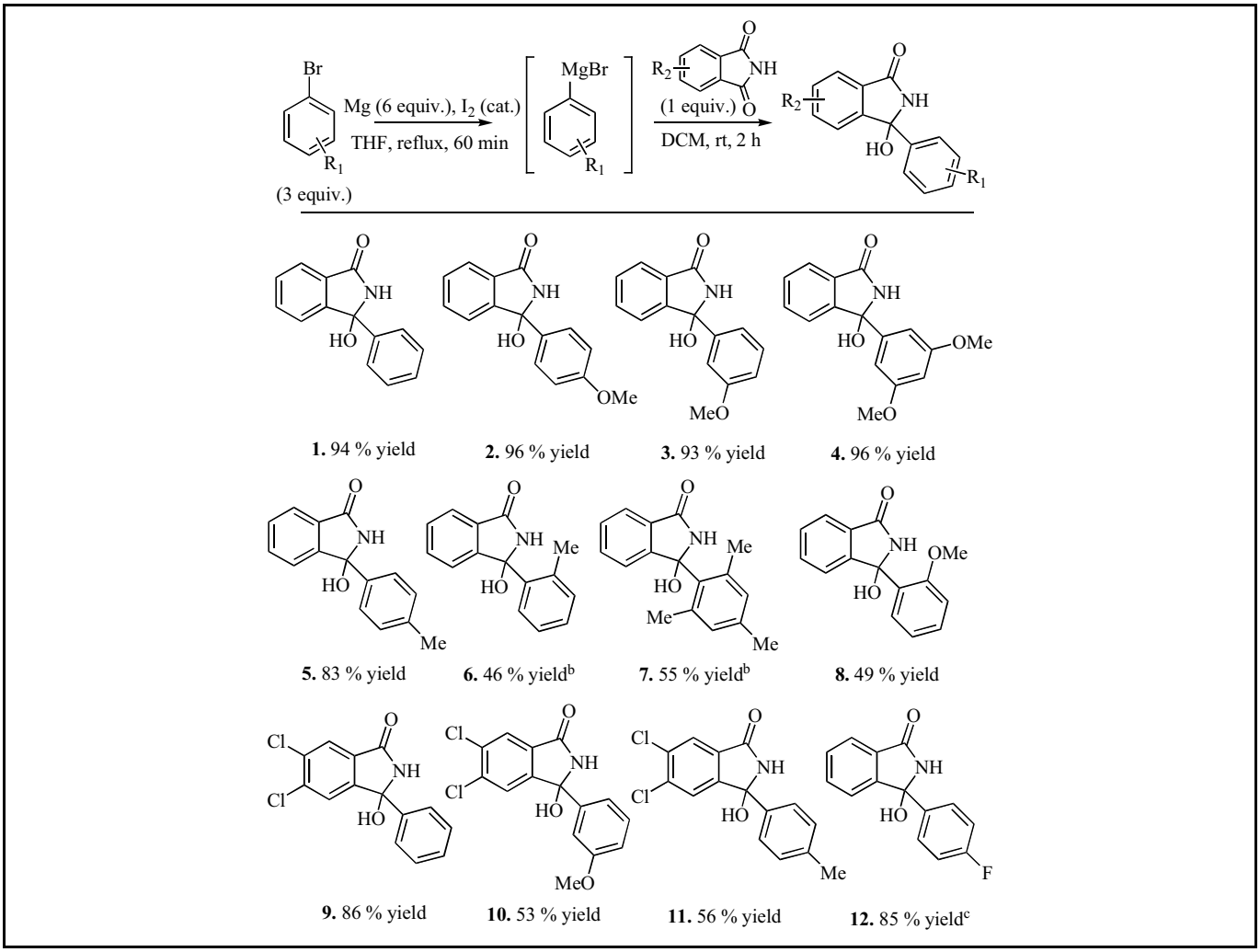
General procedure for the synthesis of 3–substituted 3–hydroxyisoindolinones *via* the Grignard reaction (1–12). A flame–dried Schlenk tube was charged with magnesium turnings (6 equiv.) and a crystal of iodine. The tube was evacuated, and charged with argon. Freshly distilled tetrahydrofuran was added, followed by ary bromide (3 equiv.). The resulting mixture was heated at reflux until all bromide was converted into a Grignard reagent (assessed by HPLC). The solution of Grignard reagent was added *via* cannula into a suspension of phthalimide (1 equiv.) in dichloromethane, and the reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched with sat. NH_4Cl solution and ethyl acetate was added. The aqueous layer was washed three times with ethyl acetate, the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The pure product was obtained by flash column chromatography in dichloromethane–methanol 40:1.

General Procedure for the Synthesis of 3–substituted 3–hydroxyisoindolinones *via* Bromine–lithium Exchange (13–19). Aryl bromide (4 equiv.) was dissolved in freshly distilled tetrahydrofuran in a flame–dried flask under argon, and cooled to -78 °C. *n*–Butyl lithium (1.6 M in hexanes, 4.4 equiv.) was added, and the resulting mixture was stirred until all bromide was converted into organolithium reagent (assessed by HPLC). Phthalimide (1 equiv.) was added in one portion, the reaction mixture was allowed to warm to room temperature, and stirred for 2 hours. The reaction was quenched with sat. NH_4Cl solution, and ethyl acetate was added. The aqueous layer was washed three times with ethyl acetate, organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The pure product was obtained by flash column chromatography in dichloromethane–methanol 40:1.

General Procedure for the Synthesis of 3–substituted 3–hydroxyisoindolinones *via* Direct Lithiation (20 and 21). *n*–Butyl lithium (1.6 M in hexanes, 4.4 equiv.) and TMEDA (4.8 equiv.) were dissolved in tetrahydrofuran in a flame–dried flask under argon at room temperature. The heteroarene (4 equiv.) was added, and the reaction mixture was stirred for 4 hours. The reaction was cooled to 0 °C, and phthalimide (1 equiv.) was added. The reaction mixture was allowed to warm to room temperature, and stirred for 2 hours. The reaction was quenched with sat. NH_4Cl solution, and ethyl acetate was added. The aqueous layer was washed three times with ethyl acetate, organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The pure product was obtained by flash column chromatography in petrol–ethyl acetate 1:1.

[1] Alkyl organometallic reagents are commercially available, and react readily with phthalimides in high yields. Since syntheses of 3–alkyl 3–hydroxyisoindolinones are well described [10], their preparation was not a part of this study.

Table 1. Addition of Grignard reagents to phthalimides.[a]



[a]Isolated yields. Conversion of aryl bromide to Grignard reagent monitored by HPLC. [b]Addition of Grignard reagent to phthalimide: 6 hours. [c]Generation of the Grignard reagent: 16 hours.

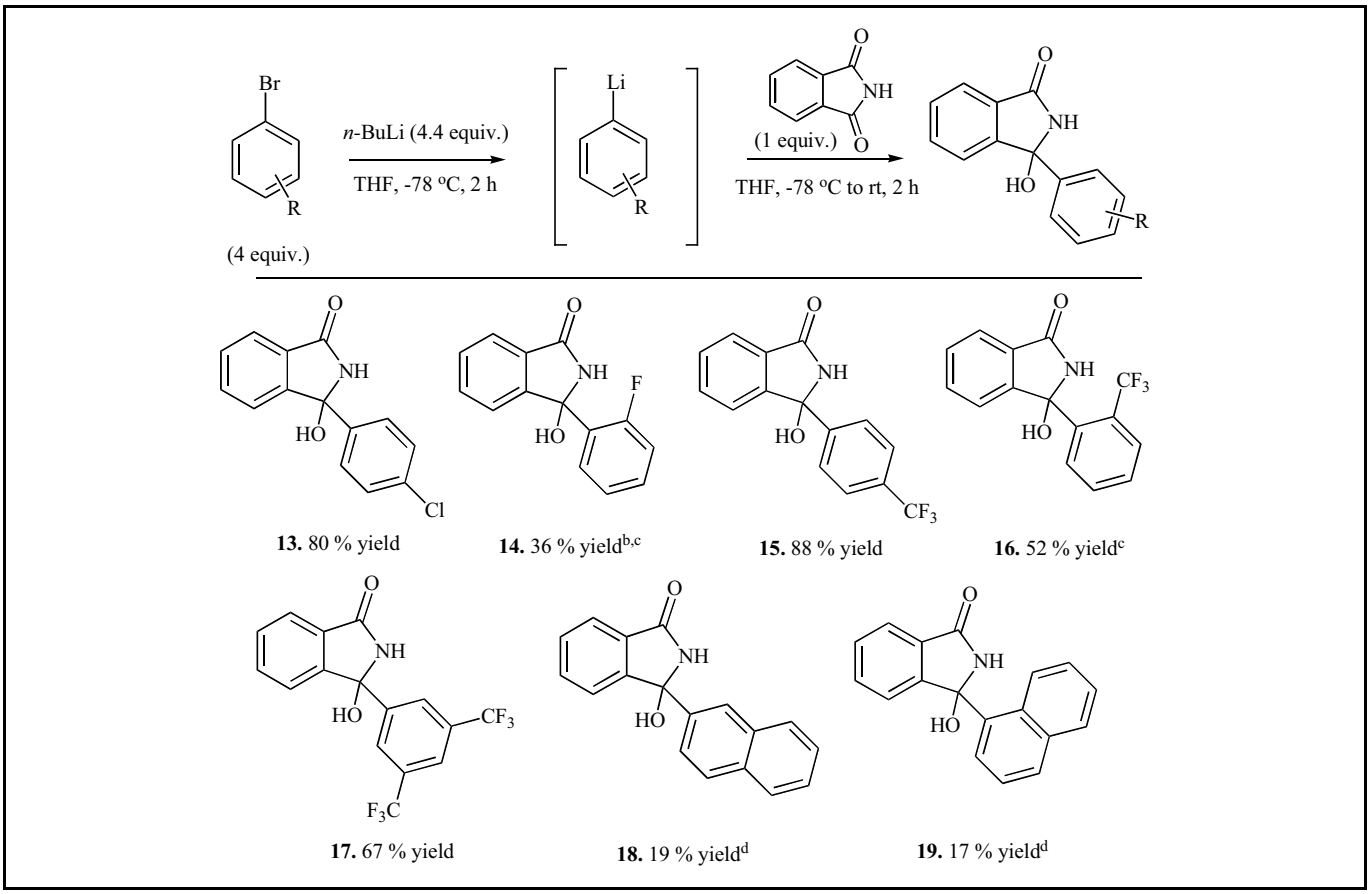
3. RESULTS AND DISCUSSION

We started our investigations by using the Grignard reaction (Table **1**). First, we tested the well-known addition of a phenylmagnesium bromide to phthalimide. As expected, the conversion of bromobenzene to its corresponding Grignard reagent was completed within one hour.[2] Upon addition of the organometallic reagent to phthalimide, 3–phenyl 3–hydroxyisoindolinone **1** was obtained after two hours in 94 % isolated yield. Next, we investigated the addition of aryl bromides possessing activating methoxy substituents. *p*–Methoxyphenylmagnesium bromide was formed within one hour, and the isoindolinone alcohol **2** was obtained in excellent yield (96 %). In order to test whether the conjugation effect is responsible for the reaction outcome, the reaction was performed with *m*–methoxyphenyl nucleophiles. After complete conversion to Grignard reagents within one hour, products **3** and **4** were obtained in excellent yields (93 % and 96 %, respectively), indicating that electron effects are not essential for the successful addition.

When weakly activating alkyl substitutents were employed, the formation of Grignard reagents was completed after one hour. However, isolated yields of final alcohols differed, depending on the position of substituents around the benzene ring. *p*–Methylphenyl Grignard reagent (sterically least hindered) reacted with phthalimide to yield isoindolinone alcohol **5** (83 %). On the other hand, *o*–methylphenyl Grignard reagent provided 3–hydroxyisoindolinone **6** only in moderate yield (46 %). Similar, but slightly better yield was obtained when methyl groups were placed in both *ortho* positions (**7**, 55 %). Monitoring the latter two additions to phthalimide by HPLC showed that most of the product was formed after two hours. In the following hours, the reaction substantially slowed down, until it completely stopped after six hours. Yields of the respective products did not improve even when reactions were performed at elevated temperatures, or when Grignard reagent was added dropwise. In both examples unreacted starting phthalimide was retrieved, which could indicate either decomposition and/or quenching of the nucleophile, or its much lower reactivity. In order to test whether electron conjugating effect of the *ortho* positioned methoxy group can overcome steric hindrance, we prepared iso-

[2] Apart from issues concerning the addition of organometallic reagents to phthalimide, the problem could also be their generation from electron–poor haloarenes. Hence, we monitored the formation of organometallic reagents by HPLC, as well as their addition to phthalimide. In that way we were not only able to determine when the haloarene was completely activated, but could also detect the progress of its addition to phthalimide.

Table 2. Addition of organolithium reagents to phthalimides.[a]



[a]Isolated yields. Conversion of aryl bromide to organolithium compound monitored by HPLC. [b]Bromine–lithium exchange: 6 hours. [c]Addition to phthalimide: 6 hours. [d]Bromine–lithium exchange: diethyl ether, 5 hours, room temperature.

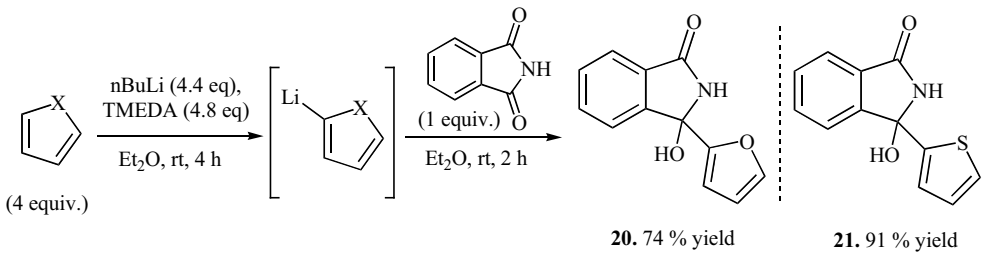
indolinone alcohol **8**. The formation of *o*–methoxyphenyl-magnesium bromide was completed after two hours, however, the addition reaction took place in the same fashion as with previous two compounds, affording isoindolinone alcohol **8** in 49 % isolated yield.

When a phthalimide bearing substitution on the aromatic ring was employed, isoindolinone **9** was obtained in slightly lower yield when compared to the same reaction with unsubstituted phthalimide (86 %). However, when substituted aryl bromides were used, isolated yields for their corresponding alcohols decreased significantly: **10** (53 %) in comparison to **3** (93 %), and **11** (56 %) in comparison to **5** (83 %). As in the case with *ortho* methyl substituents, the reaction rapidly slowed down after the initial two hours, before stopping completely after six hours. These results suggest that chlorine substituents lower the reactivity of phthalimide, though possible steric effects cannot be excluded.

With the study of electron–rich aryls completed, we turned our attention to electron poor arenes. Halogen substituents were tested as the most common functional groups. Unfortunately, only 3–(*p*–fluorophenyl) isoindolinone alcohol **12** could be prepared with this method (85 % yield). Moreover, *p*–fluorobromobenzene required overnight activation in order to be completely converted to the Grignard reagent. When *p*–chlorobromobenzene was used, conversion to its organometallic reagents was only 30% after 24 hours. On the other hand, the conversion of *o*–fluorobromobenzene was observed only in traces. Therefore, we switched to a halogen–lithium exchange strategy for these substrates. The results are summarized in Table **2**.

Bromochlorobenzene can be converted into chlorophenyl magnesiumbromide by employing lithium chloride with magnesium turnings [38]. However, preparation of lithium chloride for the reaction requires harsh conditions, and is difficult to handle. Hence, we opted for the halogen–lithium exchange rather than the Grignard reaction. *p*–Chlorobromobenzene was converted to its organolithium reagent after one hour. Upon the addition of phthalimide, the isoindolinone alcohol **13** was obtained in 80 % yield after two hours. In contrast, employing the Grignard strategy with this nucleophile afforded **13** in modest 22 % yield, due to the aforementioned incomplete activation of the bromide. On the other hand, *o*–fluorobromobenzene required six hours to completely generate the organometallic reagent. The reaction with phthalimide took place in a similar fashion as with other reagents with substituents in *ortho* positions, providing alcohol **14** in 36 % yield. Since other reagents with *ortho* substitution provided products in much higher yields, electronic effects in addition to steric hindrance cannot be excluded.

Trifluoromethylphenyl Grignard reagents are known to be highly reactive and potentially explosive [39]. Hence, trifluoromethylbenzenes were submitted to the activation by halogen–lithium exchange. All investigated trifluoromethyl aryl bromides were converted into their lithium derivatives within two hours. Addition of *p*–trifluoromethylphenyl lithium to phthalimide



20. 74 % yield **21.** 91 % yield

Scheme 1. Synthesis of 3–heteroaryl isoindolinone alcohols.

afforded isoindolinone alcohol **15** in 88 % yield. *o*–Trifluoromethyphenyl derivative **16** was obtained in moderate yield (52 %), while 3–(3,5–bis(trifluoromethyl)phenyl) 3–hydroxyisoindolinone **17** was afforded in 67 % yield.

Introduction of polycyclic aromatic hydrocarbons was also performed using this method. In order to achieve complete conversion, the activation of naphthyl bromides required stirring for 5 hours at room temperature in diethyl ether. However, the addition to phthalimide resulted in low yields (**18** 19 %, **19** 17 %), likely due to steric effects. Slightly lower yields of the products were obtained when the Grignard reaction was employed (**18** 17 %, **19** 13 %).

The halogen–lithium exchange strategy was successfully expanded to hydrogen–lithium exchange protocols (Scheme **1**). Activations of both furan and thiophene were completed after 4 hours at room temperature, though it is worth noting that the activation does not proceed without TMEDA. Both organolithium reagents reacted readily with phthalimide, providing 3–hydroxyisoindolinones **20** and **21** in 74 % and 91 % yield, respectively. This methodology offers a significant improvement in yields in comparison to previously reported procedure [36].

CONCLUSION

In conclusion, we conducted a study for the preparation of 3–substituted 3–hydroxyisoindolinones possessing an unsubstituted nitrogen atom with organometallic reagents. Electron rich phenyl substituents can be introduced *via* the Grignard reaction, while electron–poor aromatic rings require halogen–lithium exchange strategy for higher yields. In general, organometallic reagents with substitutions in *ortho* positions give lower yields. The methodology was successfully extended to direct lithiation protocols for the preparation of heterocyclic derivatives of isoindolinone alcohols. Utilization of prepared alcohols in asymmetric transformations generating isoindolinone cores of natural compounds is currently under way.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supporting information comprises full characterization data, and ^{1}H and ^{13}C NMR spectra. Supplementary material is available on the publishers Web site along with the published article.

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