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Stereoselective synthesis of isoindolinones and *tert*-butyl sulfoxides

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ABSTRACT

A reaction of Grignard reagents with an optically pure *N*-sulfinylimine derived from methyl 2-formylbenzoate yields enantioenriched isoindolinones and *tert*-butyl sulfoxides. The products are formed by the addition of the nucleophile to *N*-sulfinylimine followed by cyclization to form *N*-*tert*-butylsulfinylisoindolinone, which readily undergoes substitution with a second equivalent of Grignard reagent. The reaction can be carried out in dichloromethane at room temperature or at elevated temperatures without any loss of stereoselectivity. The use of nucleophiles other than Grignard reagents has also been investigated.

1. Introduction

3-Substituted isoindolinones possess diverse biological properties, such as anxiolytic,[1] sedative-hypnotic,[2] anticancer,[3] antileukemic,[4] antihyper-glycemic,[5] antiviral[6] and antihypertensive[7] properties. They are also potent neurokinin-,[8] serotonin-,[9] and dopamine-receptor[10] inhibitors or antagonists. For many years, they have become the target of medicinal chemists, particularly in enantiomeric form. Most methods for the synthesis of optically active isoindolinones are based on the use of chiral auxiliaries. Some good examples are addition of Grignard reagents to chiral *N*-substituted phthalimides,[11] reaction of chiral Schiff bases of glycine with 2-cyanobenzaldehyde,[12] cyclization of chiral α-substituted benzylamines,[13] and alkylation of chiral *N*-acylisoindolinones.[14] Catalytic methods include Rh(I)-catalyzed arylation of 2-bromobenzaldimines followed by aminocarbonylation,[15] enantioselective addition of isoindolinones to imines,[16] aminoacid-catalyzed Mannich reaction followed by lactamization,[17] and cinchoninium-catalyzed intramolecular aza-Michael reactions.[18] A thorough review of asymmetric syntheses of 3-substituted isoindolinones was published by Massa et al.[19]

In this paper, we propose a straightforward method for the preparation of enantioenriched isoindolinones using Ellman's *tert*-butylsulfinamide methodology.[20] The same reaction may be used for obtaining optically pure *tert*-butyl sulfoxides.

2. Results and discussion

We tried to obtain isoindolinones by using the following-three step procedure: addition of Grignard reagent to *N*-sulfinylimine **1** derived from 2-carboxybenzaldehyde, removal of the sulfinyl group from the nitrogen atom, and cyclization. A similar stepwise procedure was described earlier by Xu and coworkers[21] by using a stereoselective addition of allylindium to *N*-sulfinylimine **1** followed by desulfinylation and cyclization to give 3-allylisoindolinones with excellent stereoselectivity. The free radical approach of this reaction was described by Rodríguez-Fernández et al.[22] by using tributyltin-mediated isopropyl iodide addition at −78 °C to *N*-sulfinylimine **1**. Our procedure allows preparation of numerous derivatives of 3-substituted isoindolinones, not only limited to 3-allyl or 3-isopropyl.

The starting methyl 2-[(*tert*-butyl-*N*-sulfinylimine)-methyl] benzoate **1** can be conveniently prepared by the condensation of commercially available optically pure *tert*-butylsulfinamide with methyl 2-formylbenzoate in the presence of $KHSO_4$ (Scheme 1).[23] The enantiomeric excess of *N*-sulfinylimine **1** was 98%.

Unexpectedly, we found that the desired isoindolinones could be formed directly in one step by using Grignard reagents. The second product of this reaction was found to be *tert*-butyl sulfoxide (Scheme 2). Apparently, Grignard reagent after the addition to the C=N bond further reacted, yielding a substitution product at the sulfur atom.

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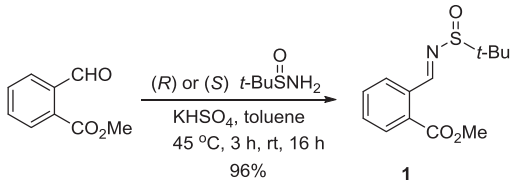
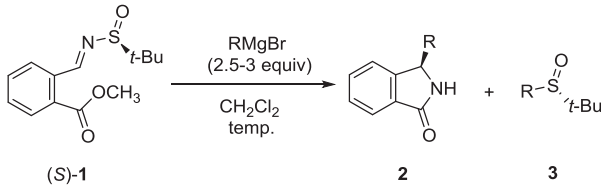


Scheme 1. Substrate preparation.



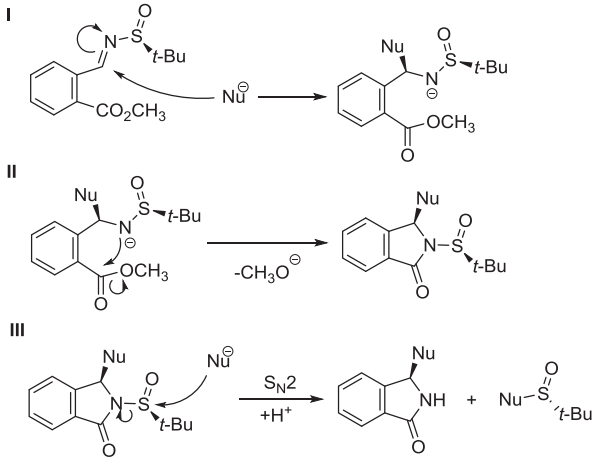
Scheme 2. Addition of Grignard reagents to *N*-sulfinylimine **1**.

The proposed mechanism is shown in Scheme 3. We assume that nucleophile addition to the *N*-sulfinylimine is followed by cyclization to form the corresponding *N*-*tert*-butylsulfinylisoindolinone, which finally undergoes a S_N2-type substitution with the second equivalent of Grignard reagent to form the products.

When we used more than two equivalents of an organomagnesium compound, the yield was excellent and the only products were isoindolinone and *tert*-butyl sulfoxide. The results are presented in Table 1. The enantioselectivity of isoindolinones strongly depends on the reaction conditions. The effects of different solvents, temperature, and additives are presented in Tables 2 and 3.

The best results were obtained when using dichloromethane as solvent (Table 2, entry 3). Additives, such as $AlMe_3$, CuI, or TMEDA, did not improve the ee. The presence of THF was also unfavorable. Solutions of organomagnesium reagents in THF provided low ee of isoindolinone (Table 2, entry 5). Therefore, we used solutions of Grignard reagents in diethyl ether. However, the ee remained medium. Decreasing the reaction temperature did not improve the results. The highest stereoselectivity was observed at 40 °C. The ee did not change significantly after 15 min and after several hours (Table 3, entry 3–5). Similar temperature dependence was observed for the BuLi addition to *O*-protected *N*-trimethylsilyl imines of (2*S*)-lactal.[24]

We could isolate the transition product **4** (major diastereomer)



Scheme 3. Reaction mechanism.

by using substoichiometric amounts of isopropylmagnesium chloride (Fig. 1). Usually, at 40 °C the reaction was complete in minutes; however, at 0 °C and at room temperature, we used longer reaction times to obtain a better yield. The configuration at C-3 was established based on the optical rotation discussed in earlier literature. It was in agreement with the chelated transition state mechanism of the addition of Grignard reagents to *N*-sulfinylimines as proposed by Ellman[25] and Davis.[26] The yield of isoindolinones is usually very high, but the chromatographic isolation of the product might be difficult in some cases (e.g., 3-hexylisoindolinone **2d**). Isoindolinones with an aromatic substituent at C-3 may be purified by simple trituration with a hexane-diethyl ether mixture. *tert*-Butyl sulfoxides are easily soluble in such a solution. Poor results were obtained with ethynyl and allylmagnesium bromides. Chelating substituents, such as 2-methoxyphenyl, significantly lowered the ee. The use of *n*-butyllithium instead of *n*-butylmagnesium bromide also results in low ee for the isoindolinone.

Moreover, the present reaction was particularly useful for the synthesis of enantiomerically pure *tert*-butyl sulfoxides **3** (Table 4). They were formed by a nucleophilic substitution of *N*-sulfinylisoindolinone (Scheme 2). The isoindolinone moiety seemed to be an excellent leaving group. Usually, the yields and the ee of sulfoxides were high when the reaction was carried out at room temperature or 0 °C. Considering that the ee of the *N*-sulfinylimine was 98%, there was no loss of optical purity. At 40 °C, the ee decreased to 93–95% (Table 4, entries 3 and 8). The presented approach might be useful because *tert*-butyl sulfoxides are valuable substrates in many reactions.[27] To the best of our knowledge, our synthesis of *tert*-butylsulfoxides can compete with existing methods in the literature.

The reaction of *N*-sulfinylimine **1** with strong nucleophiles was found very general. For example, the reaction with sodium methanolate yields 3-methoxy isoindolinone **5** (Scheme 4). The crude reaction mixture can be purified by simple trituration with hexane, which dissolves methyl *tert*-butylsulfinate.

The reaction of dimsyl lithium with *N*-sulfinylimine **1** yields 3-methyleneisoindolinone **6** (Scheme 5). In this example, the addition of a sulfoxide anion is followed by the elimination of sulfenic acid. An analogous reaction with a carbanion obtained from dimethyl sulfone failed. The reaction of *N*-sulfinylimine **1** and a phosphonate anion generated by deprotonation with LiHMDS or *n*-BuLi unexpectedly yielded phthalimide as the main product (Scheme 6). We assumed that the addition of phosphonate to *N*-sulfinylimine was followed by the elimination of sulfenic acid and a reaction at the phosphorus atom to yield phthalimide **7** and *O*,*O*-dibutyl-*S*-*tert*-butyl phosphorothioate **8**.

The use of K_2CO_3 as a base resulted in the addition of a phosphonate anion to the C=N bond without subsequent cyclization. Routine removal of the *tert*-butylsulfinyl group with ethanolic HCl and alkalization yielded isoindolinone-3-phosphonate **9** in the racemic form.

3. Conclusions

An efficient one-step method for the synthesis of enantioenriched 3-substituted isoindolinones and *tert*-butyl sulfoxides from methyl 2-[(*N*-*tert*-butylsulfinylimine)methyl] benzoate and Grignard reagents was developed. The procedure is robust, reliable, and straightforward. High stereoselectivity was observed at room temperature and at 40 °C. In the case of poorly soluble 3-aryl substituted isoindolinones, the purification did not require chromatography. *N*-*tert*-Butylsulfinyl-isoindolinone is a very good sulfinylating agent, so the reaction with Grignard reagents produced enantiopure *tert*-butyl sulfoxides in good yields. The use of sodium methanolate as a nucleophile yielded 3-methoxyisoindolinone. The