

## Accepted Manuscript

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PII: S0040-4039(16)30021-1  
DOI: <http://dx.doi.org/10.1016/j.tetlet.2016.01.021>  
Reference: TETL 47185

To appear in: *Tetrahedron Letters*

Received Date: 12 December 2015  
Revised Date: 5 January 2016  
Accepted Date: 6 January 2016



Please cite this article as: Al-Jaroudi, Z., Mohapatra, P.P., Jha, A., Facile synthesis of 3-substituted isoindolinones, *Tetrahedron Letters* (2016), doi: <http://dx.doi.org/10.1016/j.tetlet.2016.01.021>

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## Facile synthesis of 3-substituted isoindolinones

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### ARTICLE INFO

#### Article history:

Received

Received in revised form

Accepted

Available online

Dedicated to the memory of Professor Sharon Roscoe, a colleague and mentor instrumental in shaping the careers of many chemists.

#### Keywords:

*N*-aryl-3-hydroxyisoindolinones

alkyl aryl ketones

Lewis acid

isoindolinones

*N*-acyliminium ion

Mannich reaction

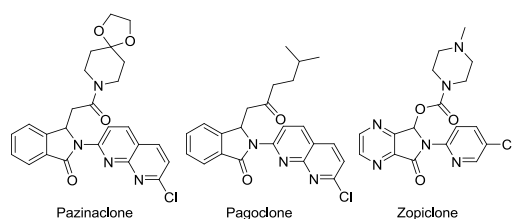
### ABSTRACT

The reactions of *N*-aryl-3-hydroxyisoindolinones and alkyl aryl ketones under Lewis acid-catalyzed anhydrous conditions afforded the corresponding substituted isoindolinones in good to excellent yields.

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### Introduction

Substituted isoindolinones possess anxiolytic activity and are of interest as sedatives, hypnotics, and muscle relaxants.<sup>1</sup> Typical examples are pazinaclone,<sup>2</sup> pagoclone,<sup>3,4</sup> and zopiclone<sup>5,6</sup> (Figure 1). Several procedures are known in the literature<sup>7-9</sup> for the synthesis of these types of substituted isoindolinones.

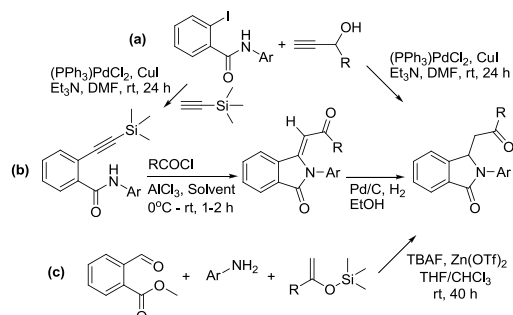


**Figure 1.** Structures of bioactive substituted isoindolinones.

In 1999, Kundu *et al.* reported that the Pd-catalyzed reactions of 2-iodobenzamides with acetylenic carbinols bearing a terminal acetylenic group and carbinol functionality next to the acetylenic moiety afforded 3-acyl methyl isoindolin-1-ones in one step (Scheme 1a). The reactions involved Sonogashira coupling, followed by ring closure and redox reactions to afford the products in one step.<sup>7</sup>

In the same year, the same research group reported that the Pd-catalyzed reactions of 2-iodobenzamides with trimethylsilyl acetylene afforded 2-(2-trimethylsilyl)ethynyl benzamides in excellent yields. Then, Friedel-Crafts reactions with acid

chlorides or anhydrides under mild conditions smoothly afforded the corresponding 3-alkylidene isoindolin-1-ones. Finally, the double bond was reduced with Pd/C and H<sub>2</sub> to afford isoindolinones (Scheme 1b).<sup>8</sup>



**Scheme 1.** Previous syntheses of substituted isoindolinones

Very recently, Dhanasekaran *et al.* reported the synthesis of diverse isoindolinones in moderate-to-high yields via a Lewis-acid-catalyzed domino Mukaiyama–Mannich lactamization/alkylation using *o*-formyl methylbenzoate, aryl amines, and silyl enol ethers.<sup>9</sup>

However, the reported methods suffer from the use of expensive reagents and catalysts, and multistep procedures. In continuation with our efforts on the development of green synthetic methodologies,<sup>10-19</sup> we herein report an alternate novel approach for the synthesis of substituted isoindolinones starting

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