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Tetrahedron Letters 48 (2007) 7618–7623

Tetrahedron Letters

A new organocatalyst for Friedel–Crafts alkylation of 2-naphthols with isatins: application of an organo-click strategy for the cascade synthesis of highly functionalized molecules

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Received 12 July 2007; revised 23 August 2007; accepted 30 August 2007
Available online 4 September 2007

Abstract—The three-component Friedel–Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions of 2-naphthols, substituted isatins and azides under dimethylamino-ethanol/Cu^I-catalysis furnished highly functionalized 1,4-disubstituted [1,2,3]-triazoles.

1. Introduction

Catalytic Friedel–Crafts alkylation is a powerful synthetic method for the preparation of highly functionalized aromatic compounds via C–C and C–N bond formation, which can generate important classes of building blocks for pharmaceutically relevant compounds.[1] Due to its atom-economy, the direct catalytic Friedel–Crafts alkylation has received increasing attention.[2] Recently, MacMillan and Jørgensen developed asymmetric Friedel–Crafts alkylation and amination reactions of aromatic molecules with active olefins and electron-deficient substrates using simple chiral amines (organocatalysts) as asymmetric catalysts.[3] Nevertheless, this interesting class of organocatalysts have been used so far only for the following two types of Friedel–Crafts alkylation reactions: (1) the direct Friedel–Crafts alkylation of pyrroles with enals via Michael addition;[3a] and (2) amination of 2-naphthols with diethyl azodicarboxylates to furnish asymmetric non-biaryl atropisomers.[3b]

Chiral dialkylamino-ethanol derivatives (e.g., cinchona alkaloids) have been catalysts of choice for the activation of CH-acids and alcohols, leading to a number of asymmetric additions of various nucleophiles to electron-deficient substrates.[4] However, the chiral dialkylamino-ethanol derivatives were only investigated for catalysis of Michael type reactions of CH-acids with electron-deficient substrates.[4] We have now utilized dialkylamino-ethanol derivatives **3f–i** as catalysts for the Friedel–Crafts alkylation of 2-naphthols **1** with substituted isatins **2** to furnish highly functionalized 3-aryl-3-hydroxyindolin-2-ones **5** in good yields as shown in Scheme 1. We have also developed organo-click,[5] three-component Friedel–Crafts alkylation/Huisgen cycloaddition (FCA/HC) reactions, which produce highly functionalized 1,2,3-triazoles **6** from 2-naphthol **1**, 1-prop-2-ynyl-1*H*-indole-2,3-dione **2l**, benzyl azide **4a** or bis-azido benzenes **4b–d**, catalyst **3i**, copper and copper sulfate as shown in Scheme 1.

3-Substituted-3-hydroxyindolin-2-ones **5** are important substrates for studying biological activity as well as useful synthetic intermediates for drug candidates and alkaloids. As a consequence, the development of practical methods for their preparation is of interest. The 3-substituted-3-hydroxyoxindole moiety is present in several pharmacologically active alkaloids such as celogentin K,[6] donaxaridine,[7] convolutamydines,[8] dioxibrassinine,[9] welwitindolinone C,[10] TMC-95s,[11] and 3′-hydroxyglucoisatisin,[12] in addition to several others.

The mechanistic proposal for the Lewis base-catalyzed Friedel–Crafts reaction of 2-naphthol **1** with isatins **2** in aprotic-nonpolar and protic-polar solvents indicates the involvement of **TS-1** and **TS-2**, respectively (Scheme 1). Interestingly, combination of a domino Lewis base and Brønsted acid-catalyzed Friedel–Crafts reaction of 2-naphthol **1** with isatins **2** in aprotic-nonpolar solvents indicates that **TS-3** is involved in the reaction. Thus, we

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Keywords: Azides; Dimethylamino-ethanol; Friedel–Crafts alkylation; Organo-Click; Organocatalysis.

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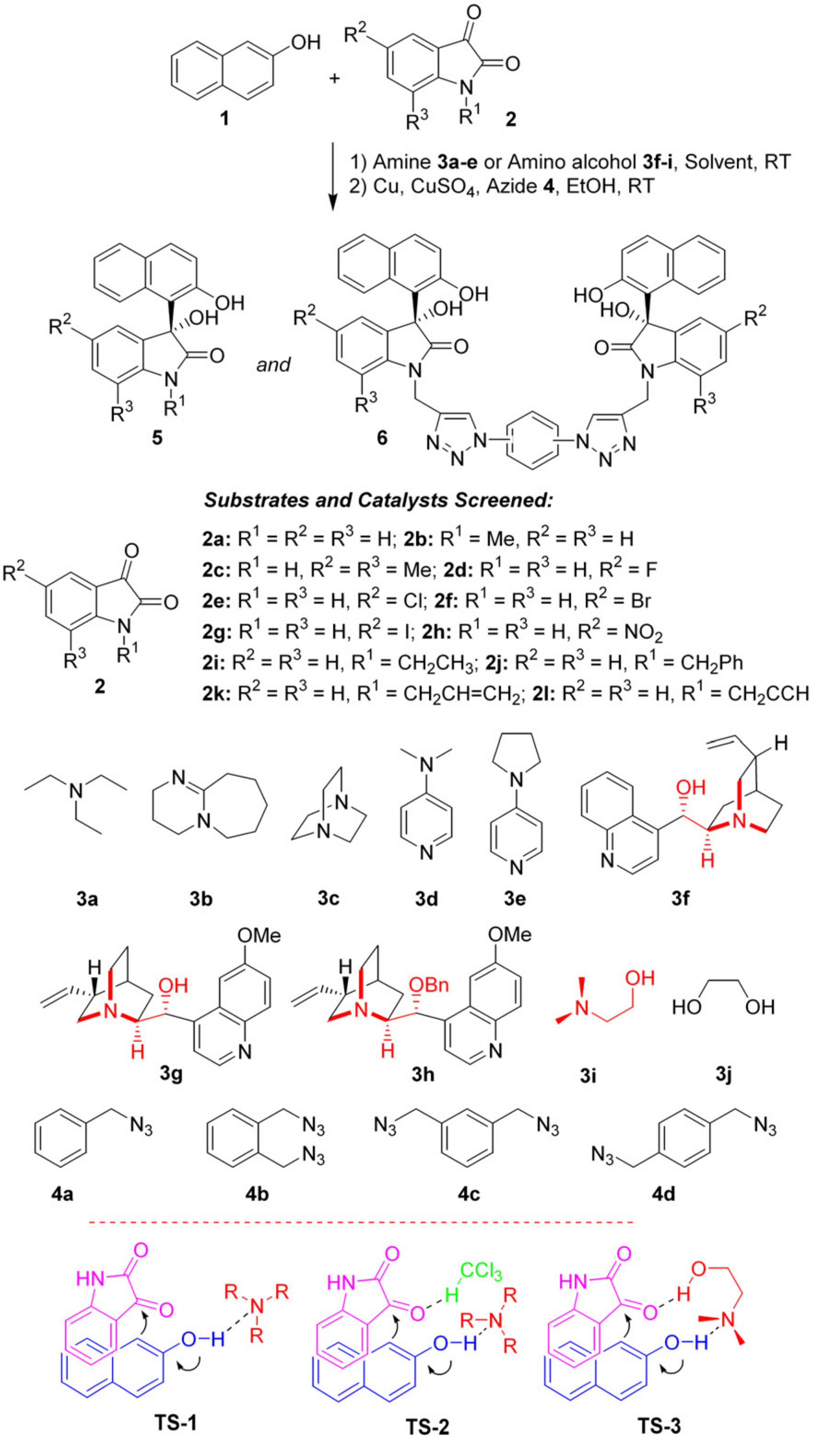
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.129



Scheme 1. Direct application of an organo-click strategy for the cascade synthesis of highly functionalized molecules.

speculated that simple dimethylamino-ethanol **3i** was capable potentially of promoting the direct Friedel–Crafts reaction via **TS-3**. Herein, we report our findings that a catalytic amount of dimethylamino-ethanol **3i** promoted the selective direct Friedel–Crafts alkylation of 2-naphthols **1** with substituted isatins **2** to furnish highly functionalized 3-aryl-3-hydroxyindolin-2-ones **5** in high yields (Scheme 1).

The preliminary Friedel–Crafts alkylation (FCA) reaction between 2-naphthol **1** and isatin **2a** was carried out with 10 mol % of TEA **3a** as catalyst in $PhCH_3$. As expected, the reaction afforded product **5a** in 99% conversion and 90% yield after 24 h (via **TS-1**, Table 1, entry 1), which was purified by simple filtration followed by column chromatography. The rate of the **3a**-catalyzed FCA reaction was increased in $CHCl_3$