Cite this: Chem. Commun., 2011, 47, 5623–5625

www.rsc.org/chemcomm

## COMMUNICATION

## Diversity-oriented approach to 1,2-dihydroisoquinolin-3(4*H*)-imines *via* copper(1)-catalyzed reaction of (*E*)-2-ethynylphenylchalcone, sulfonyl azide and amine<sup>†‡</sup>

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*Received 28th February 2011, Accepted 25th March 2011* DOI: 10.1039/c1cc11176k

A three-component reaction of (E)-2-ethynylphenylchalcone, sulfonyl azide, and amine catalyzed by copper(1) chloride (5 mol%), in the presence of triethylamine, under mild conditions is described. This transformation proceeds efficiently to generate 1,2-dihydroisoquinolin-3(4*H*)-imines in good to excellent yields.

The tetrahydroisoquinoline skeleton is found in numerous structurally diverse natural products that display a wide range of antitumor activities, antimicrobial activities and other biological properties.<sup>1</sup> Moreover, the tetrahydroisoquinoline derivatives have found applications as chiral ligands in transition metal-catalyzed asymmetric synthesis.<sup>2,3</sup> Additionally, they have been demonstrated as organocatalysts in asymmetric Diels-Alder reactions,<sup>4</sup> and in borane-mediated hydrogenation reactions.<sup>5</sup> Consequently, continuous efforts have been made toward methodology development for the synthesis of tetrahydroisoquinoline derivatives. The well developed procedures for the construction of tetrahydroisoquinoline ring systems involve the Pictet-Spengler ring-closing reaction,6 the Pomeranz-Fritsch-Bobbitt reaction,<sup>1f,7</sup> and the Bischler-Napieralski cyclization/reduction reaction.<sup>8,10b</sup> Other methods, such as N-acyliminium ion cyclization reactions9 and transition-metal catalyzed reactions,<sup>10</sup> have also been recently described. These methods, however, usually suffer from multiple synthetic steps, harsh reaction conditions, and/or limited functional group tolerance. In the meantime, the multicomponent reactions

have been used as an efficient route for tetrahydroisoquinoline generation. For instance, Grigg<sup>11</sup> reported a palladiumcatalyzed three-component process for tetrahydroisoquinoline formation. Ferraccioli<sup>12</sup> described a straightforward path to 1,3-substituted tetrahydroisoquinolines *via* a palladium/ norbornene-catalyzed reaction of 2-iodotoluene, alkyl halides and an electron-poor olefin. Enders<sup>13</sup> presented one example of organocatalytic asymmetric synthesis of *trans*-1,3-disubstituted tetrahydroisoquinolines using a biphenyl-substituted benzothiazoline as a hydride source. Although these approaches have been used frequently for the synthesis of members of the tetrahydroisoquinoline family in the last decade, less attention has been focused on 1,2-dihydroisoquinolin-3(4*H*)-imines, which have found applications in material sciences and biological studies.<sup>14</sup>

During our efforts toward natural product-like compound generation for use in different biological assays, we became interested in exploring efficient methods for the construction of a small library of 1,2-dihydroisoquinolin-3(4H)-imines. Recently, we reported an efficient copper-catalyzed threecomponent reaction of 2-ethynylaniline, sulfonyl azide, and nitroolefin.<sup>15</sup> The reaction was assumed to proceed through the intramolecular addition of a nucleophile to a reactive ketenimine species,16-18 followed by an intermolecular Michael addition. Actually, this ketenimine chemistry has been well developed and involves a Cu-catalyzed azide-alkyne cycloaddition. In the last few years, Chang and Wang made a great contribution in this field. Encouraged by the ketenimine chemistry,<sup>16–18</sup> we envisioned that the 1.2-dihydroisoquinolin-3(4H)-imine scaffold could also be produced via a ketenimine intermediate. The proposed synthetic route is presented in Scheme 1. (E)-2-ethynylphenylchalcone 1 was utilized as the substrate for reaction development. We conceived that in the presence of a suitable copper catalyst, the reaction of (E)-2-ethynylphenylchalcone 1 with sulfonyl azide 2 would generate the key ketenimine species **b**. The double nucleophilic addition would occur if an amine 3 was involved in the reaction to afford the intermediate c. This, followed by protonation, would furnish the desired 1,2-dihydroisoquinolin-3(4H)-imine 4 (Scheme 1). With these considerations in mind, we started to explore the feasibility of this hypothesis.

Our studies commenced with the reaction of (*E*)-2-ethynylphenylchalcone 1a, tosyl azide 2a, and *p*-anisidine 3a (Scheme 2).

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<sup>†</sup> Electronic supplementary information (ESI) available: Experimental methods and characterization data.. CCDC 815165. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11176k

<sup>‡</sup> Crystal data and structure refinement for compound **4a**. Empirical formula:  $C_{32}H_{30}N_2O_5S$  (molecular weight: 554), Crystal system: Monoclinic, unit cell dimensions: a = 24.277(10) A,  $\alpha = 90$  deg., b = 10.347(4) A,  $\beta = 99.370(5)$  deg., c = 23.279(10) A,  $\gamma = 90$  deg. Volume: 5769(4) A<sup>3</sup>, refine\_1s\_shift/su\_max = 0.003 mean = 0.000, temperature: 293(2) K, space group: C2/c, Z, calculated density: 8, 1.314 mg m<sup>-3</sup>, Reflections collected/unique: 11615/5070 [*R*(int) = 0.0370], Final *R* indices [ $I > 2\sigma(I)$ ];  $R_1 = 0.0570$ ,  $wR_2 = 0.1711$ , *R* indices (all data):  $R_1 = 0.0859$ ,  $wR_2 = 0.1922$ . CCDC 815165.



Scheme 1 The proposed synthetic route for a three-component reaction of (E)-2-ethynylphenylchalcone, sulfonyl azide, and amine.



Scheme 2 Initial studies for the copper-catalyzed reaction of (E)-2-ethynylphenylchalcone 1a, tosyl azide 2a, and *p*-anisidine 3a.

Initially, the reaction occurred in the presence of CuI (10 mol%) and triethylamine (3.0 equiv.) in anhydrous CH<sub>3</sub>CN. To our delight, the desired product 4a was successfully isolated in 62% yield. The structure of 4a was confirmed by X-ray diffraction analysis (see ESI<sup>†</sup>). Other copper sources with the potential for use as the catalyst in the reaction were then screened. Copper(I) bromide (78% yield) and copper(I) chloride (81% yield) were proved to be more effective than copper(I) iodide, whereas copper(II) triflate (16% yield) or IPr/CuCl (7% yield) gave only low yield. The catalyst loading of copper(I) chloride could be reduced to 5 mol% without loss of efficiency (82% yield). A blank experiment, without the addition of a copper catalyst, indicated that the reaction was inert. We next examined the effect of base in the reaction. The reaction worked efficiently when triethylamine acted as the base (for details, please see ESI<sup>+</sup>). A similar yield was isolated when the reaction was carried out in the presence of 1.5 equiv. of triethylamine (81% yield), while no reaction took place in the absence of base. This result indicated that a combination of a copper catalyst and a base is indispensable to afford the target product. Additionally, we realized that THF was the most suitable solvent for the reaction, giving rise to the desired product in 92% yield. Inferior results were produced when the reaction proceeded in other solvents (DMSO, toluene, 1,4-dioxane, and dichloromethane).

With the conditions highlighted above (5 mol% of CuCl, 1.5 equiv. of triethylamine, THF, room temperature), the scope of the three-component reaction was studied. Table 1 and Table 2 show the summary of results for the evaluation of various substituted (*E*)-2-ethynylphenylchalcones 1, sulfonyl azides 2, and amines 3. In Table 1, (*E*)-2-ethynylphenylchalcone 1 reacted with sulfonyl azide 2 and *p*-anisidine 3a, leading to the corresponding 1,2-dihydroisoquinolin-3(4*H*)-imines 4 in good to excellent yields. Substrates bearing either electron-rich or electron-poor aryl substituents in the  $\mathbb{R}^2$  position were converted to the desired products with excellent reactivity. Noticeably, the reaction was also workable when an alkyl

Table 1Copper(1)-catalyzed three-component reactions of (E)-2-ethynyl-phenylchalcone 1, sulfonyl azide 2, and p-anisidine  $3a^a$ 



**Table 2** Copper(1)-catalyzed three-component reactions of (*E*)-2-ethynyl-phenylchalcone 1a, tosyl azide 2a, and amine  $3^{a}$ 



group was used as a replacement in the  $R^2$  position, affording product **4h** in 76% yield. The effect of the electronic variation in the  $R^1$  position was examined in the meantime. As expected, no influence was observed on the output. We next tested the reactions of (*E*)-2-ethynylphenylchalcone **1a**, sulfonyl azides **2**, and *p*-anisidine **3a** under the standard conditions. Several sulfonyl azides ( $R^3 = Ph$ , 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, and Me) were present in the reaction, which were proved to be excellent partners for the transformation.

We next investigated the three-component reactions of (E)-2-ethynylphenylchalcone 1a and tosyl azide 2a with various amines 3 under the optimized conditions (Table 2). As shown in Table 2, the desired products 4 were generated in high yields. A series of para-substituted anilines with electrondonating groups or electron-withdrawing groups attached to the aromatic ring worked well. It is noteworthy that an ester group and a nitro group were all tolerated in this transformation, which indicated that this diversity could easily be incorporated into the 1,2-dihydroisoquinolin-3(4H)-imine scaffold. Interestingly, little impact was observed on the reaction outcome when a sterically bulky aniline (2,6-diethylaniline) was employed in the reaction. Aliphatic amines (tert-butyl amine, benzyl amine, and 1-octyl amine) were also demonstrated as effective nucleophiles in the above reaction. Additionally, heterocyclic amines, such as piperidin-1-amine, showed good reactivity under the standard conditions, leading to 1,2-dihydroisoquinolin-3(4H)-imine 4v in 86% yield.

In summary, a novel and efficient reaction of (E)-2-ethynylphenylchalcone, sulfonyl azide, and amine catalyzed by copper(1) chloride has been successfully developed. Diverse 1,2-dihydroisoquinolin-3(4*H*)-imines are generated in good to excellent yields. This reaction proceeds with a wide substrate scope under extremely mild conditions. Library construction and subsequent biological assays are in progress in our laboratory.

Financial support from National Natural Science Foundation of China (No. 21032007) is gratefully acknowledged.

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