Cu-Catalyzed 1,2-Dihydroisoquinolines Synthesis from *o*-Ethynyl Benzacetals and Sulfonyl Azides

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An efficient synthesis of 1,3-/1,1-dialkoxy 1,2-dihydroisoquinolines from *o*-ethynylbenzacetals and sulfonyl azides *via* a cascade process combining copper-catalyzed alkyne—azide cycloaddition (CuAAC), Dimroth rearrangement, 1,5-OR shift/1,5-H shift, and 6π -electrocyclic ring closure (6π -ERC) is described. Extension of the produced 1,3-dialkoxy-1,2-dihydroisoquinolines to isoquinolium salts is also disclosed.

Preparations of various heterocycles containing an isoquinoline skeleton have attracted great attention because of their utilities in pharmaceutical¹ and material sciences.² Traditional methods include Bischler–Napieralski cyclization,³ Pictet–Spengler synthesis,⁴ and Pomeranz–Fritsch isoquinoline synthesis⁵ (Scheme 1). There are some obvious drawbacks in these reactions. Strong Bronsted acids were used and could not be avoided. As a unique example of base promoted domino approaches, a reaction between phthalaldehyde and 2-aminomalonate can prepare isoquinolines.⁶ With the rapid development of the transition metal catalyzed reactions, which makes reactions more efficient under mild reaction conditions, isoquinolines could be approached by Pd-catalyzed reactions between *o*-iodobenzaldimines and alkynes through a sequence of Sonogashira coupling and cyclization.⁷ As an alternative strategy, Lewis acid catalyzed addition of nucleophiles to *o*-alkynylbenzaldimines could aslo furnish isoquinolines.⁸ Further studies revealed that isoquinolines could be directly constructed from benzaldimines and alkynes via Rhcatalyzed oxidative cross-coupling cyclization.⁹ Here, we would like to report an alternative way leading to an isoquinoline skeleton (Scheme 1).

Attracted by the vivid chemistry of the ketenimine and our previous contributions to this field, ¹⁰ we designed the substrate (**1a**) functionalized with an adjacent acetal and triple bond. The terminal triple bond was set for the formation of ketenimine *via* a CuAAC and a subsequent Dimorth rearrangement, while it was possible for acetal to intramolecularly trap the ketenimine. Based on this

^{(1) (}a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (b) Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 780. (c) Mahmoud, S.; Aboul-Fadl, T.; Sheha, M.; Farag, H.; Mouhamed, A. I. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 573.

⁽²⁾ Su, Y. J.; Huang, H. L.; Li, C. L.; Chien, C. H.; Tao, Y. T.; Chou, P. T.; Datta, S.; Liu, R. S. *Adv. Matter.* **2003**, *15*, 884.

⁽³⁾ Kurti, L.; Czako, B. Strategic Applications of Named Reactions in Organic Synthesis; Elsevier Academic Press: 2005; p 62.

⁽⁴⁾ Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: 2005; p 348.

⁽⁵⁾ Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: 2005; p 358.

⁽⁶⁾ Meziane, M. A. A. A.; Bazureau, J. P. Molecules 2002, 7, 252.

^{(7) (}a) Roesch, K. R.; Larock, R. C. Org. Lett. **1999**, 1, 553. (b) Roesch, K. R.; Larock, R. C. J. Org. Chem. **1998**, 63, 5306.

^{(8) (}a) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339. (b) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (c) Asao, N.; Iso, K.; Yudha, S. S. *Org. Lett.* **2006**, *8*, 4149. (d) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822. (e) Chen, Z. Y.; Yang, X. D.; Wu, J. *Chem. Commun.* **2009**, 3469. (f) Sun, W.; Ding, Q. P.; Sun, X. Y.; Fan, R. H.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 690. (g) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. J. Org. Chem. **2007**, *72*, 4462. (h) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611.

⁽⁹⁾ Guimond, N.; Fagnou, K. J. Am. Chem. Soc. 2009, 131, 12050.

^{(10) (}a) Lu, P.; Wang, Y. G. Chem. Soc. Rev. 2012, 41, 5687. (b) Kim,
S. H.; Park, S. H.; Choi, J. H.; Chang, S. Chem. Asian J. 2011, 6, 2618.
(c) Lu, P.; Wang, Y. G. Synlett 2010, 2, 165.

Scheme 1. Approaches to Isoquinoline Skeleton



consideration, we refluxed the reaction of 1a and 2a in the presence of CuI and *i*-Pr₂NEt in dichloroethane (DCE) for 2 h. To our surprise, 3a was obtained in 94% yield. 3a contained a dihydroisoquinoline substructure, the structure of which was confirmed by the comparative analysis of the single crystal of 3k.¹¹

Due to the significance of dihydroisoquinolines in nature, we optimized the reaction conditions (see Table S1 in Supporting Information). By decreasing the reaction temperature to 50 °C, **3a** was isolated in 81% yield after reaction was carried out for 3 h (Table S1, entry 2). Altering CuI to CuBr or CuCl, decreased yields were observed (Table S1, entries 3 and 4). By screening the base and the solvent, *i*-Pr₂NEt was found to be the optimal among Et₃N, K₂CO₃, and pyridine (Table S1, entries 5–7), while DCE was determined to be the optimal solvent among CH₃CN, THF, CH₂Cl₂, and toluene (Table S1, entries 8–11). Increasing the amount of either CuI or diisopropylethylamine did not give better yields of **3a** (Table S1, entries 12 and 13). The optimal reaction conditions were established (Table S1, entry 1).

With the optimized reaction conditions in hand, we tested the substrate scope. First, we tested the various azides (2a-2g) (Table 1, entries 1–7). It was obvious that aryl azides, with the electron-withdrawing group, afforded corresponding dihydroisoquinolines (3a, 3e, and 3f) in moderate to excellent yields. Upside-down, aryl azide, with the electron-donating group, afforded 3d in 33% only. When methanesulfonyl azide was used, the desired dihydroisoquinoline was not isolable although both 1a and methanesulfonyl azide were completely consumed after reacting for 2 h. Although a substitute effect on the benzalacetals (1b–1f) (Table 1, entries 8–12) was not apparent, a slight difference between electron withdrawing and electron donating was seen. When 1d, 1e, and 1f reacted

R ² R ¹ + R ⁴ S	$ \begin{array}{c} $	reflux R ² R ² R ² R ² R ² R ² R ² R ³	R ³ N-SO ₂ R ⁴
entry	${\bf 1}(R^1,R^2,R^3)$	$2\left(\mathrm{R}^{4} ight)$	3 /Y (%) ^b
1	1a (H, H, Me)	$2a (p-ClC_6H_4)$	3a /94
2	1a	2b (Tol)	3b /73
3	1a	2c (Ph)	3c /80
4	1a	$2d (p-MeOC_6H_4)$	3d /33
5	1a	$2e (p-NO_2C_6H_4)$	3e /81
6	1a	$2f(p-CF_3C_6H_4)$	3f /82
7	1a	2g (2-naphthyl)	3g/74
8	1b (H, F, Me)	2a	3h /92
9	1c (F, H, Me)	2a	3i /94
10	1d (H, OMe, Me)	2a	3j /89
11	1e (Cl, H, Me)	2a	3k /94
12	1f (Me, H, Me)	2a	31 /88
13	1d	2e	3m /79
14	1e	2e	3n /86
15	1 f	2e	30 /68
16	$\mathbf{1g}(\mathrm{H},\mathrm{H},\mathrm{Et})$	2a	3p/77
17	1g	2b	3q /76
18	1g	2g	3r /62

Table 1. Synthesis of 3^a

^{*a*} Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), CuI (0.025 mmol), *i*-Pr₂NEt (0.5 mmol), DCE (4 mL), N₂. ^{*b*} Isolated yields refer to **1**.

with 4-nitrobenzenesulfonyl azide (NsN₃) (2e), 3m, 3n, and 3o were obtained in 79%, 86%, and 68% yield, respectively (Table 1, entries 13–15). When benzalacetals were derived from ethanol, the reaction worked and afforded 3p, 3q, and 3r in relatively lower yields (Table 1, entries 16–18). It is noticeable that this transformation is reproducible and scalable. When 4 mmol of 1a was reacted with 2a, 1.03 g of 3a was isolated.

When benzalacetal was changed into 2-(2-ethynylphenyl)-1,3-dioxolane (**4a**), spiroisquinoline (**5a**) was isolated as a major product. The structure of **5a** was confirmed by its single crystal analysis.¹² In order to have a better transformation, the reaction conditions were screened (Table S2). DCE was found to be optimal in comparison with others, such as CH₂Cl₂, CH₃CN, THF, and toluene (Table S2, entries 1–5). Decreasing the reaction temperature would decrease the yields (Table S2, entries 5–7). CuBr and CuCl did not give better yields than CuI did (Table S2, entries 8 and 9). Much lower yields were observed when other cuprous sources were tested, such as CuOTf and CuCN. *i*-Pr₂NEt was found to be optimal in comparison with others, such as Et₃N, pyridine, K₂CO₃, and Cs₂CO₃. DBU did not work for this reaction

⁽¹¹⁾ CCDC 965973 contains the supplementary crystallographic data for 3k. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(Table S2, entries 10-14). The optimal amount of CuI was set to be 0.05 equiv, while the optimal amount of *i*-Pr₂NEt was found to be 1.0 equiv (Table S2, entries 5, 15–17).

By using the optimized reaction conditions, a series of 5 were prepared (Table 2). Yields of **5a** to **5l** were moderate, varying from 28% to 61%. It is interesting that **4c** afforded **5i** in the highest yield, while **4e** gave the lowest yield although both of them have fluorine on the phenyl ring of benzacetal. It is also noticeable that 2-(2-ethynylphenyl)-1,3-dioxane reacted with 4-chlorobenzenesulfonyl azide (**2a**) under the same reaction conditions, but no major product was isolable.

Based on the screening of the reaction conditions and the investigation of the substrate scope, we postulated a working mechanism for the formation of **3** and **5** (Scheme 2). *o*-Ethynylbenzalacetal **1** or **4** reacts with sulfonyl azide **2** in the presence of Cu(I) to generate the ketenimine intermediate **A**. Then, **A** undergoes a 1,5-OR shift to form dienimine **B**. A subsequent 6π -electrocyclic ring closure (6π -ERC) efficiently affords dihydroisoquinoline **3** with 1,3-dialkoxy substitution. However, if the benzacetals were in the form of 1,3-dioxolanes, the 1,5-OR shift is inhibited. Instead of a 1,5-OR shift, a 1,5-H shift occurs to form dienimine **C**. This step is promoted by hydricity.¹³ Finally, **5** is obtained *via* 6π -ERC. The 1,3-dioxolane ring remained after reaction. Migration depends upon the substrate structure.



entry	$4 (R^1, R^2)$	$2(R^3)$	$(\%)^{b}$
1	4a (H, H)	2b (Tol)	5a /51
2	4a	2c (Ph)	5b /51
3	4a	$2a (p-ClC_6H_4)$	5c /58
4	4a	$2d(p-MeOC_6H_4)$	5d /37
5	4a	$2e(p-NO_2C_6H_4)$	5e /43
6	4a	$2f(p-CF_3C_6H_4)$	5f /48
7	4a	2g (2-naphthyl)	5g /55
8	4b (Cl, H)	2a	5h /56
9	4c (F, H)	2a	5i /61
10	4d (Me, H)	2a	5j /60
11	4e (H, F)	2a	5k /28
12	$4f(H, CF_3)$	2a	5l /47

 $[^]a$ Reaction conditions: **4** (0.5 mmol), **2** (0.6 mmol), CuI (0.025 mmol), *i*-Pr₂NEt (0.5 mmol), DCE (4 mL), N₂. b Isolated yields refer to **4** .

Scheme 2. Proposed Mechanism for the Formation of 3 and 5



When **3e** was stored in CDCl₃ at room temperature for several days, a white crystal was obtained. By analyzing its single crystal, it was shown that *N*-methyl isoquinolinium 4-nitrobenzenesulfonate **6a** was formed (Scheme 3).¹⁴ Similar phenomena was discovered for compound **3m**, which gave an isoquinolinium salt **7a**. Formation of **6a** and **7a** was postulated in Scheme 3. The process involves an E1 elimination, a nucleophilic addition–elimination, and an S_N^2 nucleophilic substitution (for **6a**) or a proton transfer (for **7a**) in a single step. Two competitive transformations were observed for the cleavage of the N–S bond of intermediate **D**. For compound **3m**, the electron-donating group (OMe) might increase the basicity of isoquinoline **F** prior to abstraction of a proton to form **7a**.

Due to the importance of an isoquinolium salt in the preparation of isoquinoline alkaloids,¹⁵ some transition metal catalyzed C–H activations were applied in the preparation of isoquinolium salts directly from benzaldimines and alkynes, for instance, Pd,¹⁶ Ni,¹⁷ Rh,¹⁸ Ru,¹⁹ and Ir.²⁰

⁽¹³⁾ For examples of a 1,5-H shift and 1,5-OR shift of ketenimines, see: (a) Alajarín, M.; Bonillo, B.; Ortín, M. M.; Sánchez-Andrada, P.; Vidal, A. Org. Lett. 2006, 8, 5645. (b) Alajarin, M.; Bonillo, B.; Ortin, M. M.; Sanchez-Andrada, P.; Vidal, A.; Orenes, R. A. Org. Biomol. Chem. 2010, 8, 4690. (c) Alajarin, M.; Bonillo, B.; Ortin, M. M.; Sanchez-Andrada, P.; Vidal, A. Eur. J. Org. Chem. 2011, 1896.

⁽¹⁴⁾ CCDC 965975 contains the supplementary crystallographic data for **6a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

⁽¹⁵⁾ Akiba, K.; Nakatani, M.; Wada, M.; Yamamoto, Y. J. Org. Chem. 1985, 50, 63.

⁽¹⁶⁾ Wu, G. Z.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. J. Org. Chem. 1988, 53, 3238.

⁽¹⁷⁾ Korivi, R. P.; Wu, Y. C.; Cheng, C. H. Chem.—Eur. J. 2009, 15, 10727.

⁽¹⁸⁾ Jayakumar, J.; Parthasarathy, K.; Cheng, C. H. Angew. Chem., Int. Ed. 2012, 51, 197.

⁽¹⁹⁾ Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C. H. Org. Lett. **2012**, *14*, 3478.

⁽²⁰⁾ Li, L.; Brennessel, W. W.; Jones, W. D. J. Am. Chem. Soc. 2008, 130, 12414.

Scheme 3. Formation of Isoquinolium Salts 6a and 7a



Consequently, we investigated the generality of conversion from 3 to 6 and isolated the precipitation from solutions of 3e, 3m, 3n, and 3o in $CH_2Cl_2\hexane\CH_3OH$ (Scheme 4). When these solutions were allowed to sit under room temperature and ambient conditions for 3 days, 6a, 6b, 7a, and 7b were isolated in 62%, 45%, 58%, and 50% yields, respectively.

As an extesion of this method, the resulted **6a** was treated with phenylacetylene in the presence of $AgOTf^{8e}$ and base and 3-alkoxy-1-(alkynyl)-1,4-dihydroisoquinoline **8** was isolated in 75% yield (Scheme 4).

In conclusion, we developed a feasible method to prepare 1,3/1,1-dialkoxy 1,2-dihydroisoquinolines *via* a tandem process, including CuAAC, Dimroth rearrangement, 1,5-OR shift/1,5-H shift, and 6π -ERC from *o*-ethynyl Scheme 4. Synthesis of Isoquinolium Salts 6-8



benzalacetals and sulfonyl azides. Reactions were carried out smoothly under mild reaction conditions. 1,3-Dialkoxy 1,2-dihydroisoquinolines could be further converted into isoquinolium salts by sitting for 3 days without any treatment. Further studies into the application of this method in the preparation of isoquinoline alkaloids are underway.

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Supporting Information Available. Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for all products, and crystallographic information files (CIF) for compounds **3k**, **5a**, **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.