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One-pot Synthesis of Highly Functionalizable 3-(Phenylsulfonyl)-2,3-dihydro-4(1*H*)-quinolinones via a Cu-catalyzed Aza-Michael Addition/Cyclization Reaction

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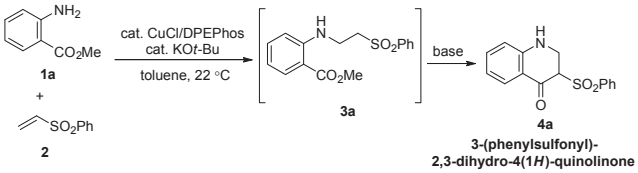
A straightforward and mild one-pot method used for the synthesis of 3-(phenylsulfonyl)-2,3-dihydro-4(1*H*)-quinolinones via a Cu-catalyzed aza-Michael addition/base-mediated cyclization reaction is described. Addition of a range of readily available 2-aminobenzoates to phenyl vinyl sulfone was catalyzed by 5 mol % of a Cu complex at ambient temperature, followed by cyclization with KO*t*-Bu at 0 °C to afford new versatile 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones in good yield (53–99%).

Keywords: Quinolinone | One-pot reaction | Copper catalyst

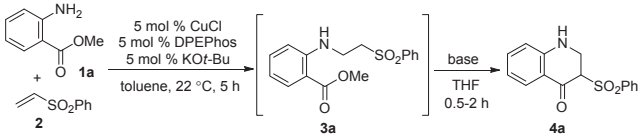
2,3-Dihydro-4(1*H*)-quinolinones serve as valuable building blocks in medicinal chemistry and useful intermediates in synthetic organic chemistry.[1] Due to the importance of 2,3-dihydro-4(1*H*)-quinolinones, various approaches towards their synthesis have been studied.[2] Commonly used methods are Brønsted acid- or Lewis acid-catalyzed annulations including the Friedel–Craft cyclization of *N*-aryl-substituted β-amino acid derivatives,[3] rearrangement of *N*-aryl-substituted β-lactams,[4] intramolecular Michael addition of aniline derivatives,[5] and S_NAr cyclization of fluoroaryl-substituted aminopropanones.[6] In addition, organocatalysis plays an important role in synthesizing 2,3-dihydro-4(1*H*)-quinolinones under mild reaction conditions; for example, the cyclization of 2-aminoacetophenone and aldehydes in the presence of chiral aminocyclodextrins or a proline catalyst[7] or intramolecular conjugate addition catalyzed by a chiral thiourea or thiazolium salt.[8] Another strategy uses palladium catalysts to promote the intramolecular cyclocarbonylation of 2-iodoanilines with α,β-unsaturated olefins and CO gas to afford highly functionalized 2,3-dihydro-4(1*H*)-quinolinones.[9] Despite the above-mentioned advances, only a few examples of the synthesis of functionalized 3-substituted-2,3-dihydro-4(1*H*)-quinolinones have been reported and new synthetic approaches are still required.

We have recently investigated a mild and efficient synthesis of *N*-aryl-substituted β-aminosulfones using a Cu-catalyzed aza-Michael addition of aromatic amines to vinyl sulfones.[10] Inspired by this recent discovery, we envisioned that β-aminosulfone **3a** derived from the addition of methyl anthranilate (**1a**) to phenyl vinyl sulfone (**2**) could be used as a precursor for the preparation of 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinone **4a** via the cyclization of the in situ generated **3a** with base in a single vessel (Scheme 1). Herein, we describe a facile and convenient approach to the synthesis of 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones via a one-pot sequential process that involves a Cu-catalyzed aza-Michael addition reaction followed by cyclization of the resulting β-aminosulfone under mild reaction conditions. A range of readily accessible 2-aminobenzoates and a vinyl sulfone can be used to obtain a variety of synthetically useful 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones in good to excellent yield.



Scheme 1. The synthesis of 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinone **4a**.

Table 1. Optimization of the one-pot reaction conditions[a]

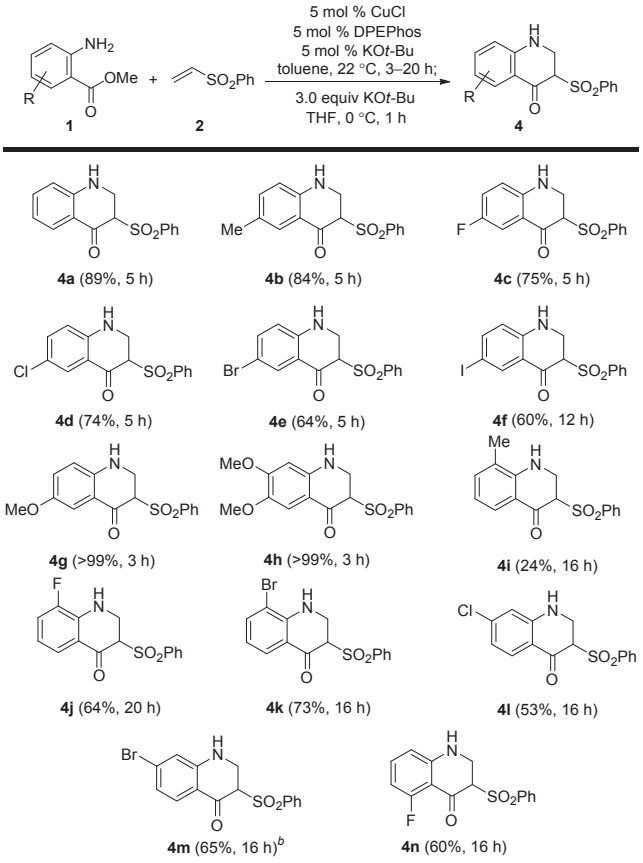


Entry	Base (equiv)	Temp /°C	Time /h	Toluene:THF	Yield /%[b]
1	KO*t*-Bu (3.0)	22	0.5	1:0	6
2	KO*t*-Bu (3.0)	22	0.5	1:2	71
3	LiO*t*-Bu (3.0)	22	0.5	1:2	<2
4	NaO*t*-Bu (3.0)	22	0.5	1:2	34
5	KO*t*-Bu (1.5)	22	0.5	1:2	52
6	KO*t*-Bu (3.0)	−78	2	1:2	48
7	KO*t*-Bu (3.0)	0	1	1:2	75
8	KO*t*-Bu (3.0)	0	1	1:3.3	93

[a]Reaction conditions: Anthranilate **1a** (0.36 mmol), vinyl sulfone **2** (0.30 mmol), CuCl (0.015 mmol), DPEPhos (bis[(2-diphenylphosphino)phenyl] ether, 0.015 mmol), KO*t*-Bu (0.015 mmol), toluene (1.5 mL) under N_2. [b]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Our study commenced with the optimization of a one-pot synthesis of 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinone **4a** as summarized in Table 1. Guided by the conditions previously optimized for the Cu-catalyzed aza-Michael addition,[10] anthranilate **1a** was treated with vinyl sulfone **2** in the presence of 5 mol % of CuCl, DPEPhos, and KO*t*-Bu in toluene at room temperature, generating β-aminosulfone **3a** with complete conversion. Then, it was directly reacted with KO*t*-Bu to perform the base-mediated intramolecular cyclization to afford a new type of 2,3-dihydro-4(1*H*)-quinolinone **4a**. As a result shown in Entry 1 of Table 1, the desired sequential process proceeded, but a low yield of product **4a** was obtained due to the poor cyclization reaction observed using toluene as the reaction solvent. When THF was added in the cyclization step, the desired product **4a** was obtained in 71% yield

Table 2. Substrate scope of 2-aminobenzoates **1**[a]



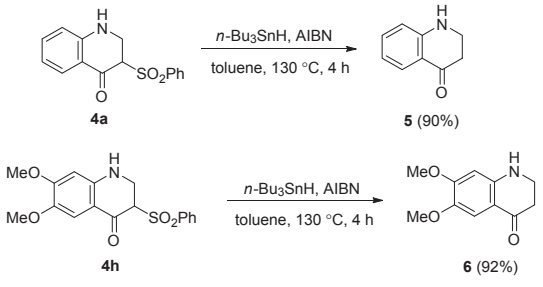
[a]Reaction conditions: 2-Aminobenzoate **1** (0.36 mmol), vinyl sulfone **2** (0.30 mmol), CuCl (0.015 mmol), DPEPhos (bis[(2-diphenylphosphino)phenyl] ether, 0.015 mmol), KO*t*-Bu (0.015 mmol), toluene (1.5 mL) under N_2. In the cyclization step, KO*t*-Bu (0.9 mmol) and THF (5 mL) were added. The values in parenthesis show the yields after purification and reaction times for the aza-Michael addition, respectively. [b]10 mol % CuCl was used.

(Entry 2). In order to improve the efficiency of the one-pot synthesis, different alkoxide bases, equivalents of base, and reaction temperatures for the cyclization were screened (Entries 3–8). It was found that a lower reaction temperature in the second step (0 °C vs. 22 °C) was more effective in decreasing the formation of unidentified by-products, and KO*t*-Bu was identified as the optimal base. Finally, when the cyclization was performed with 3 equiv of KO*t*-Bu in a 1:3.3 ratio of toluene and THF as solvent at 0 °C for 1 h, the one-pot sequential Cu-catalyzed conjugate addition–cyclization provided 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinone **4a** with high efficiency (93% yield, Entry 8).

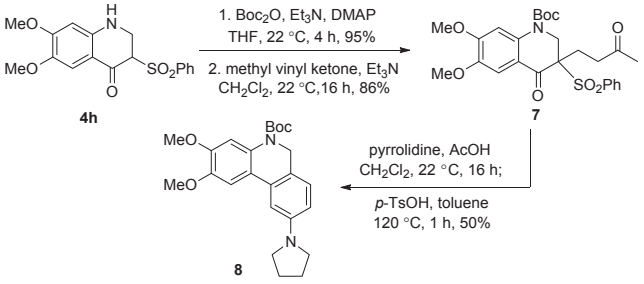
Under the optimized reaction conditions used for the one-pot process, the substrate scope of 2-aminobenzoates **1** was examined as shown in Table 2. A variety of readily available 2-aminobenzoates were reacted with vinyl sulfone **2** using the catalytic system of 5 mol % Cu complex in toluene at room temperature to generate the intermediate β-aminosulfones, which were cyclized using 3 equiv of KO*t*-Bu in THF. Although there are some exceptions, a new type of 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones **4** was obtained in good to excellent yield. When 2-aminobenzoates **1b**–**1e** including a methyl-, fluoro-, chloro-, and bromo-substituent in the *para*-position were used, the Cu-catalyzed conjugate addition reactions proceeded efficiently to give complete conversion within 5 h and the subsequent cyclization step afforded the desired dihydroquinolinones **4b**–**4e** in 64–84% yield. However, the reaction with *para*-iodo-substituted aminobenzoate **1f** was not efficient; a longer reaction time (5 h vs. 12 h) for the catalytic amination reaction was required and a moderate yield was obtained (60% yield of **4f**). The electron-donating methoxy group affected the high reactivity, affording the 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones **4g** and **4h** in >99% yield within 3 h. The use of the sterically demanding aminobenzoate **1i** bearing a methyl group in the *ortho*-position gave a poor yield of product **4i** (24% yield) due to the sluggish amination reaction (40% conversion). Methyl 2-aminobenzoates bearing a fluoro-, chloro-, and bromo-substituent in the *ortho*- or *meta*-position were also transformed to the corresponding dihydro-4(1*H*)-quinolinones **4j**–**4n** in 53–73% yields. It was noted that catalytic conjugate additions of *ortho*- or *meta*-halo-substituted starting materials to alkene **2** did not undergo full conversion, although the reaction time was prolonged (16–20 h vs. 3–5 h) or a higher catalyst loading was used (10 mol % CuCl for **4m** vs. 5 mol % CuCl). Thus, the yields of products **4j**–**4n** were moderate.

The resulting 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones can be transformed to other valuable synthetic building blocks. For example, the phenylsulfonyl group on the product was easily cleaved under radical reduction conditions to form 2,3-dihydro-4(1*H*)-quinolinones as illustrated in Scheme 2.[11] Treatment of **4a** or **4h** with *n*-Bu_3SnH and azobisisobutyronitrile (AIBN) provided the corresponding desulfonylated products **5** and **6** in 90–92% yield.

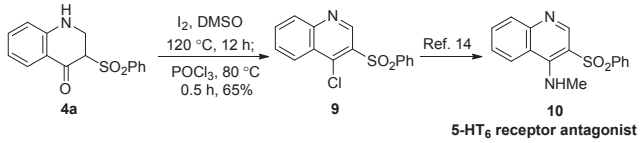
The synthetic utility of this methodology was demonstrated by the synthesis of the 5,6-dihydrophenanthridine derivative **8**, which is a useful structural motif found in biologically active molecules and natural products (Scheme 3).[12] After *N*-Boc-protection of **4h**, conjugate addition of β-keto sulfone to methyl vinyl ketone in the presence of triethylamine afforded the desired Michael addition product **7** in 86% yield. An intramolecular aldol reaction of **7** was then carried out under pyrrolidine and acetic acid conditions, followed by the elimination of water and phenylsulfonic acid using *p*-TsOH to give pyrrolidine-substituted 5,6-dihydrophenanthridine **8** in 50% yield.[13]



Scheme 2. Desulfonylation of 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones.



Scheme 3. Aromatization via Michael addition and aldol reactions.



Scheme 4. The synthesis of 4-chloro-3-(phenylsulfonyl)quinolone.

Finally, the result displayed in Scheme 4 shows that the 3-(phenylsulfonyl)-2,3-dihydro-4(1*H*)-quinolinones can be used as building-blocks used to prepare a serotonin 5-HT_6 receptor antagonist.[14] When 2,3-dihydro-4(1*H*)-quinolinone **4a** was treated with I_2 in DMSO, a dehydrogenation reaction occurred to generate 3-(phenylsulfonyl)-4-quinolinol, which was subsequently transformed to 4-chloro-3-(phenylsulfonyl)quinoline (**9**) using $POCl_3$ at 80 °C in 65% yield. Chloro-substituted quinoline **9** could serve as a precursor for amine-substituted quinoline **10**, which showed higher antagonist activity against 5-HT_6 receptors than compound **9**.

In summary, we have investigated a facile and mild synthetic protocol used to prepare new versatile 3-sulfonyl-substituted-2,3-dihydro-4(1*H*)-quinolinones. The synthesis involves a one-pot Cu-catalyzed aza-Michael addition and base-mediated intramolecular cyclization reaction sequence. The use of readily available methyl 2-aminobenzoates and vinyl sulfone, the use of an inexpensive Cu catalyst system and the synthetic utility of the products make this new methodology attractive. Further study towards the expansion of substrate scope to other types of olefins is in progress.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.160772.

References and Notes

1 a) N. S. Gill, A. Kaur, R. Arora, V. Dhawan, M. Bali, *Curr. Res. Chem.* **2012**, *4*, 88. b) S. Chandrasekhar, S. N. C. V. L. Pushpavalli, S. Chatla, D. Mukhopadhyay, B. Ganganna, K. Vijeender, P. Srihari, C. R. Reddy, M. J. Ramaiah, U. Bhadra, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 645. c) Y. Xia, Z.-Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S.-C. Kuo, E. Hamel, T. Hackl, K.-H. Lee, *J. Med. Chem.* **1998**, *41*, 1155.
2 For a review, see: B. Nammalwar, R. A. Bunce, *Molecules* **2014**, *19*, 204.
3 a) M. Layek, M. A. Reddy, A. V. D. Rao, M. Alvala, M. K. Arunasree, A. Islam, K. Mukkanti, J. Iqbal, M. Pal, *Org. Biomol. Chem.* **2011**, *9*, 1004. b) Y. Gong, K. Kato, *J. Fluorine Chem.* **2004**, *125*, 767. c) V. Y. Mitskyavichyus, *Chem. Heterocycl. Compd.* **1996**, *32*, 456.
4 a) J. Lange, A. C. Bissember, M. G. Banwell, I. A. Cade, *Aust. J. Chem.* **2011**, *64*, 454. b) K. W. Anderson, J. J. Tepe, *Org. Lett.* **2002**, *4*, 459. c) K. W. Anderson, J. J. Tepe, *Tetrahedron* **2002**, *58*, 8475.
5 a) R. Dhiman, S. Sharma, G. Singh, K. Nepali, P. M. S. Bedi, *Arch. Pharm.* **2013**, *346*, 7. b) R. A. Bunce, B. Nammalwar, *J. Heterocycl. Chem.* **2011**, *48*, 613.
6 a) R. A. Bunce, J. E. Schammerhorn, J. Sigle, *J. Heterocycl. Chem.* **2013**, *50*, 373. b) R. A. Bunce, T. Nago, *J. Heterocycl. Chem.* **2009**, *46*, 623.
7 a) K. Kanagaraj, K. Pitchumani, *J. Org. Chem.* **2013**, *78*, 744. b) S. Chandrasekhar, K. Vijeender, C. Sridhar, *Tetrahedron Lett.* **2007**, *48*, 4935.
8 a) X. Liu, Y. Lu, *Org. Lett.* **2010**, *12*, 5592. b) T. Nemoto, T. Fukuda, Y. Hamada, *Tetrahedron Lett.* **2006**, *47*, 4365.
9 a) K. Okuro, H. Alper, *J. Org. Chem.* **2012**, *77*, 4420. b) R. Grigg, A. Liu, D. Shaw, S. Suganthan, D. E. Woodall, G. Yoganathan, *Tetrahedron Lett.* **2000**, *41*, 7125.
10 S. Kim, S. Kang, G. Kim, Y. Lee, *J. Org. Chem.* **2016**, *81*, 4048.
11 M. S. Wilson, A. Padwa, *J. Org. Chem.* **2008**, *73*, 9601.
12 a) W.-I. Lee, J.-W. Jung, J. Jang, H. Yun, Y.-G. Suh, *Tetrahedron Lett.* **2013**, *54*, 5167. b) J. Éles, G. Beke, I. Vágó, É. Bozó, J. Huszár, Á. Tarcsay, S. Kolok, É. Schmidt, M. Vastag, K. Hornok, S. Farkas, G. Domány, G. M. Keserű, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3095. c) X.-J. Yang, F. Miao, Y. Yao, F.-J. Cao, R. Yang, Y.-N. Ma, B.-F. Qin, L. Zhou, *Molecules* **2012**, *17*, 13026.
13 a) S. Kiren, A. Padwa, *J. Org. Chem.* **2009**, *74*, 7781. b) C. J. Stearman, M. Wilson, A. Padwa, *J. Org. Chem.* **2009**, *74*, 3491.
14 A. V. Ivachtchenko, E. S. Golovina, M. G. Kadieva, O. D. Mitkin, I. M. Okun, *Pharm. Chem. J.* **2015**, *48*, 646.