Synthesis of Aryl-Substituted 1,4-Dihydroquinolines by [4+2] Cycloaddition of Benzyne with 1-Azadienes

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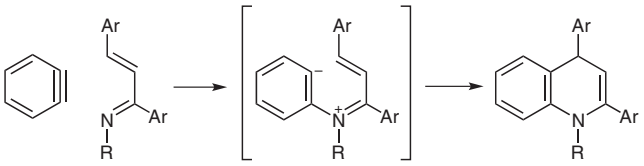
Abstract: The synthesis of aryl-substituted 1,4-dihydroquinolines can be achieved using a [4+2] cycloaddition between benzyne and various aryl-substituted 1-azadienes. The conditions are tolerated by *N*-aryl-, alkyl-, tosyl-, and *tert*-butoxycarbonyl-protected 1-azadienes. A short synthesis of the fungal metabolite 3-*O*-methylviridicatin is reported.

Key words: benzyne, dihydroquinolines, azadienes, cycloaddition, 3-*O*-methylviridicatin

Aryl-substituted quinolines and quinoline derivatives are structural motifs common to a broad range of chemotherapeutic agents, including HMG-CoA reductase inhibitors,[1] antimicrobials,[2] cytotoxic compounds,[3] and antitumor agents.[4] Not surprisingly, then, many groups have been inspired to develop new methods for their synthesis.[5] We decided to investigate [4+2] cycloadditions of 1-azadienes with benzyne as a route to 1,4-dihydroquinolines that could be used to target derivatives that are aryl-substituted at C-2 and/or C-4, depending on the azadiene employed (Scheme 1). Previously, these derivatives have been prepared by aryllithium and aryl Grignard additions to quinolinium ions.[6] Mild oxidation methods have been used to convert 1,4-dihydroquinolines into quinolines.[7] However, we saw other possibilities for further functionalization of these products, including oxidative additions to the enamine π-system.[8] The requisite azadiene substrates are conveniently accessible from chalcone or cinnamaldehyde precursors by standard condensation procedures.



Scheme 1 Proposed [4+2] route to aryl-substituted 1,4-dihydroquinolines

Several groups have previously reported [4+2] cycloaddition reactions of arynes with a variety of donor–acceptor reagents. In addition to the voluminous work of the Larock group,[9] this includes 1,3-dienes,[10] furans,[11] *N*-acyl enamines,[12] β-amino carbonyls,[13] and *o*-quinone methides.[14] To the best of our knowledge, reactions of arynes with 1-azadienes have not been reported,[15] and prior examples of reactions initiated by imine additions to arynes are rare.[15–21] Singal and Kaur have reported that benzyne reacts with azomethines to give 1,2-diarylbenzazetidines via [2+2] cycloaddition.[16] However, Yoshida and coworkers were able to trap imine-generated aryl anions with CO_2, which led to the formation of benzo-1,3-oxazine-4-ones.[17]

Azadiene **1a** was prepared by condensation of *p*-methoxy cinnamaldehyde with aniline and reacted with excess benzyne generated from benzenediazonium-2-carboxylate (BDC) under different conditions (Table 1). In refluxing DCE (Table 1, entry 1), the desired compound **2a** was isolated in 33% yield, along with two other products. The first of these was identified as compound **3**, the result of a [2+2] cycloaddition of product **2a** with benzyne. The other product was identified as compound **4**, arising from a [2+2] cycloaddition between the imine group of azadiene **1a** and benzyne, as observed by Singal and Kaur.[16] Fortunately, by using chlorobenzene as the solvent and conducting the reaction at higher temperature, we were able to completely eradicate the formation of compound **4** (Table 1, entry 2). Moreover, the unwanted formation of compound **3** was minimized by adding BDC in divided doses (Table 1, entry 3). Thus, azadiene **1a** was refluxed overnight with three equivalents of BDC, and then an additional three equivalents were added over three hours with TLC monitoring. Under these conditions, we were able to isolate compound **2a** in 67% yield, 71% based on recovered starting material. The only other significant product was the benzyne dimer, but being very nonpolar this was easily separable from the [4+2] product by column chromatography.

The use of fewer equivalents of BDC resulted in higher amounts of recovered starting material. Inferior yields of compound **2a** were observed when benzyne was generated from 2-trimethylsilylphenyltriflate using CsF, MeCN (45%), TBAF, THF (38%), and KF, THF, 18-crown-6 (30%). However, for optimum yields, steps had to be taken to eliminate both moisture and acid from BDC.

In an attempt to better understand the absence of benzoazetidine **4** in the product mixture at high temperature, this [2+2] product was heated under reflux in chlorobenzene overnight to see if it was equilibrating to **2a**. However, the result was a 50% conversion to a compound

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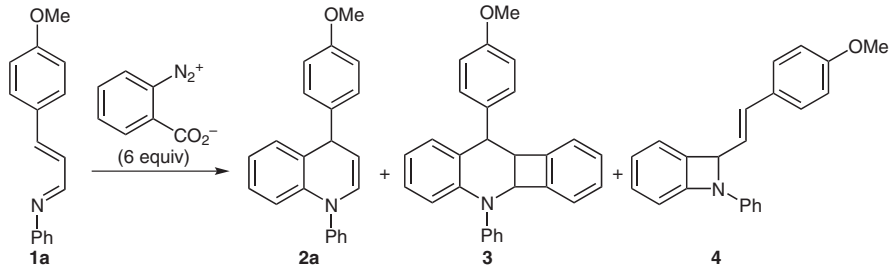
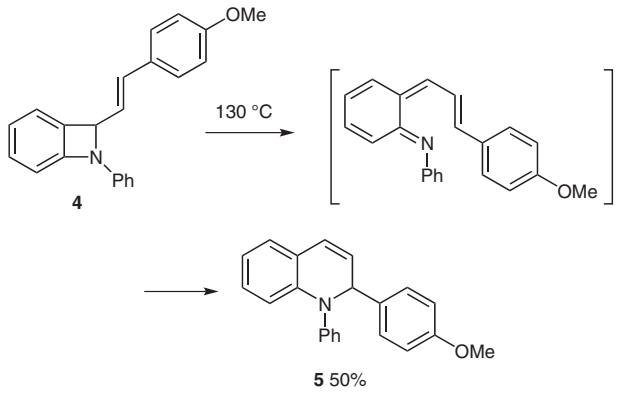
Table 1 Effects of Solvent and Temperature on Reaction Outcome



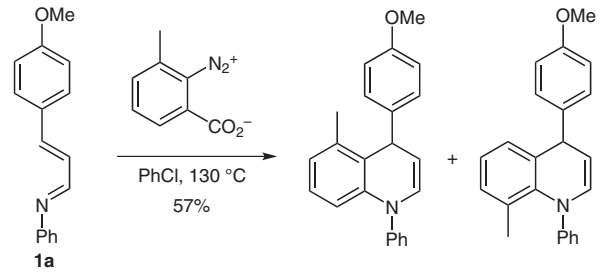
Entry	Solvent	Temp (°C)	Yield of **2a** (%)	Yield of **3** (%)	Yield of **4** (%)
1	DCE	84	33	8	19
2	PhCl	130[a]	52	13	–
3	PhCl	130[b]	67	<5	–

[a] BDC added in a single dose.
[b] BDC added in stages.

showing a similar, but clearly nonidentical, ^{1}H NMR spectrum to that of **2a**. Based on well-established literature precedent of related benzoazetidines,[22] we identified this structure as the 1,2-diaryl-1,2-dihydroquinoline **5** presumably formed by electrocyclic ring opening of **4** followed by intramolecular [4+2] cycloaddition of the azaxylylene intermediate (Scheme 2). This result strongly suggests that at 130 °C, a [4+2] cycloaddition of **1a** occurs to the exclusion of the [2+2] path, given the absence of compound **5** in the product mixture.



Scheme 2 Formation of 1,2-dihydroquinolines from benzoazetidines



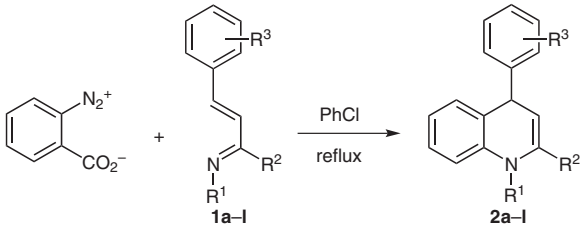
Scheme 3 Evidence for aryne formation

To test whether cycloadditions of 1-azadienes are actually occurring via benzyne formation and not a 2-carboxyphenyl cation intermediate generated from stepwise decomposition of BDC,[23] azadiene **1a** was reacted with the arenediazonium carboxylate derived from 2-amino-3-methylbenzoic acid to see if we would observe scrambling of the methyl group in the product. Indeed, in refluxing chlorobenzene an inseparable 1:1 mixture of regioisomeric 1,4-dihydroquinolines resulted (Scheme 3), consistent with aryne formation.

The generality of this reaction was investigated by varying the substitution pattern on the azadiene (Table 2). Overall, yields of [4+2] products were good to moderate, and in most cases a small amount of starting material was recovered. As expected, 2,4-diaryl-substituted derivatives were accessible (see Table 2, entries 2 and 12), although additional electron donation at the 2-position did not translate to a higher yield (Table 2, compare entries 1 and 2). For the synthesis of *N*-aryl products, reactions tended to be cleaner when the azadiene was N-substituted with an electron-withdrawing group (Table 2, compare entries 3 and 4). When this electron demand was reversed, slow addition of BDC was necessary to avoid further reaction of the 1,4-dihydroquinoline product with benzyne. Surprisingly, additional methoxy groups on the C4-aryl ring did not improve yields (Table 2, compare entries 4 and 5), perhaps due to steric influences. By comparison, *N*-benzyl azadienes were found to be less stable than their *N*-aryl counterparts, and were often prone to decomposition. Compound **2g**, for example, was eventually prepared in acceptable yield only when all traces of acid and moisture were excluded from the reaction. In contrast, both *N*-Boc- and *N*-tosyl-protected azadienes were more stable to the conditions employed, and gave the expected products **2h–l** without noticeable decomposition.

To illustrate an application of this method, 3-*O*-methylviridicatin (**9**) was chosen as a suitable target (Scheme 4). This is one of several 4-arylquinolin-2(1*H*)-ones which

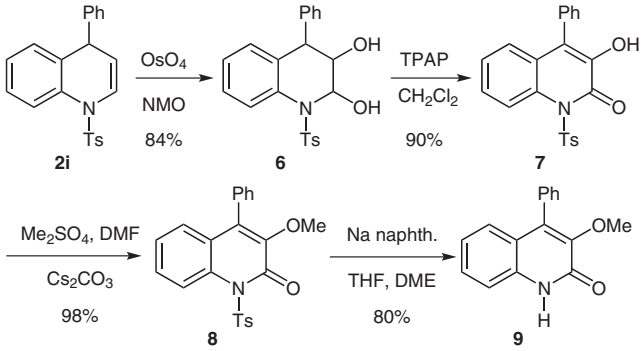
Table 2 Synthesis of 1,4-Dihydroquinolines from Azadienes[a]



Entry	Azadiene	R^1	R^2	R^3	Product	Yield (%)
1	**1a**	Ph	H	4-MeO	**2a**	67[b] (71)[c]
2	**1b**	Ph	4-$MeOC_6H_4$	4-MeO	**2b**	63[b]
3	**1c**	4-$O_2NC_6H_4$	H	4-MeO	**2c**	73[b]
4	**1d**	4-$MeOC_6H_4$	H	4-MeO	**2d**	55[b] (64)[c]
5	**1e**	4-$MeOC_6H_4$	H	2,4,6-$(MeO)_3$	**2e**	48[b] (58)[c]
6	**1f**	3,4,5-$(MeO)_3C_6H_2$	H	2,4,6-$(MeO)_3$	**2f**	58[b] (72)[c]
7	**1g**	Bn	H	4-MeO	**2g**	64[b]
8	**1h**	Boc	H	4-MeO	**2h**	53[b]
9	**1i**	Ts	H	H	**2i**	41[b] (57)[c]
10	**1j**	Ts	H	4-MeO	**2j**	61[b] (70)[c]
11	**1k**	Ts	H	4-O_2N	**2k**	64[b]
12	**1l**	Ts	Ph	H	**2l**	59[b] (67)[c]

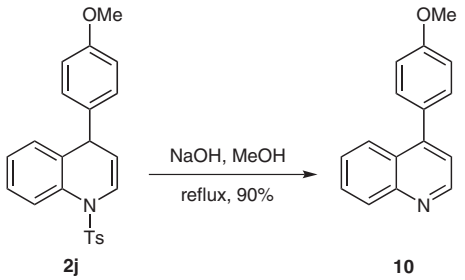
[a] Reaction conditions: **1** (0.4 mmol), BDC (3–6 equiv), PhCl (3 mL), 130 °C, 12–18 h.
[b] Yield of isolated product.
[c] Yield based on recovered starting material.

have attractive considerable attention in recent years for their biological activities.[24] Isolated as a fungal metabolite in 1964,[25] 3-*O*-methylviridicatin was shown to inhibit the replication of HIV induced by tumor necrosis factor-α.[26] Working on the hypothesis that it functions by inhibiting the signaling of NF-κB, Désaubry and colleagues recently designed analogues of this natural product that showed promise as potential anti-inflammatory agent.[27] Compound **2i** was oxidized to the 2,3-diol **6** and then to the corresponding dione which tautomerized to **7**. Following near-quantitative methylation of **7**, standard detosylation of **8** gave the desired product **9** in 59% overall yield from **2i**.



Scheme 4 Synthesis of 3-*O*-methylviridicatin

Finally, N-tosylated products of cycloaddition provided additional confirmation of structure assignments. Base treatment of **2j**, for example, gave the quinoline **10** (Scheme 5) which correlated with the spectral data of the known compound.[28]



Scheme 5 Synthesis of quinolines from *N*-tosyl-protected products of [4+2] cycloaddition

In summary, the [4+2] cycloaddition of benzyne with azadienes has been shown to be a useful route to aryl-substituted 1,4-dihydroquinolines. The oxidation of these products to biologically active 4-arylquinoline-2-ones and

their conversion into aryl-substituted quinolines have been demonstrated.

General Method for Preparing the Aryl-Substituted 1,4-Dihydroquinolines

Anthranilic acid (165 mg, 1.2 mmol) and TCA (1 mL, 0.03 mmol, 0.03 M in THF dried over crushed 4 Å MS) were dissolved in THF (2 mL) and cooled to 0 °C. Isopentyl nitrite (321 μL, 2.4 mmol) was added and stirred at 0 °C for 15 min then warmed to r.t. and stirred for 45 min. The precipitate was filtered and washed with chlorobenzene (Caution: use a plastic spatula when handling the diazonium salt). The diazonium salt was added to chlorobenzene (3 mL) and 1,2-epoxy-2-methylpropane (213 μL, 2.4 mmol) and stirred for 15 min. This suspension was slowly added to a refluxing mixture of azadiene (0.4 mmol) in chlorobenzene (3 mL) (Caution: use a Teflon-coated needle and plastic syringe to add suspension). The solution was refluxed overnight. TLC was used to determine when the reaction was complete. If the azadiene was still present, another batch of diazonium salt in suspension was created and added periodically over several hours. Once TLC showed that significant amounts of product had formed, the reaction was cooled to r.t., and the solvent was removed under reduced pressure. The crude oil was subjected to flash gradient column chromatography on neutral alumina using hexane–EtOAc mixtures as the eluting solvents.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References

(1) Nobuhide, M.; Yoshinobu, Y.; Hiroshi, I.; Yoshio, O.; Tamejiro, H. *Tetrahedron Lett.* **1993**, *24*, 8263.
(2) Metwally, K. A.; Abdel-Aziz, L. M.; Lashine, E.-S. M.; Husseiny, M. I.; Badawya, R. H. *Bioorg. Med. Chem.* **2006**, *14*, 8675.
(3) Lai, Y.-Y.; Huang, L.-J.; Lee, K.-H.; Xiao, Z.; Bastow, K. F.; Yamori, T.; Kuo, S.-C. *Bioorg. Med. Chem.* **2005**, *13*, 265.
(4) Chen, Y.-L.; Huang, C.-J.; Huang, Z.-Y.; Tseng, C.-H.; Chang, F.-S.; Yang, S.-H.; Lin, S.-R.; Tzeng, C.-C. *Bioorg. Med. Chem.* **2006**, *14*, 3098.
(5) (a) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177. (b) Schramm, O. G.; Oeser, T.; Kaiser, M.; Brun, R.; Mueller, T. J. J. *Synlett* **2008**, 359. (c) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427. (d) Stone, M. T. *Org. Lett.* **2011**, *13*, 2326. (e) Li, L.; Seidel, D. *Org. Lett.* **2010**, *12*, 5064.
(6) (a) Hilgeroth, A.; Voigt, B. *Heterocycles* **2003**, *60*, 2223. (b) Rezgui, F.; Mangeney, P.; Alexakis, A. *Tetrahedron Lett.* **1999**, *40*, 624. (c) Meyers, A. I.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1135. (d) Moudam, O.; Ajamaa, F.; Ekouaga, A.; Mamlouk, H.; Hahn, U.; Holler, M.; Welter, R.; Nierengarten, J.-F. *Eur. J. Org. Chem.* **2007**, 417.
(7) (a) Bennasar, M. L.; Roca, T.; Monerris, M.; García-Díaz, D. *J. Org. Chem.* **2006**, *71*, 7028. (b) Bennasar, M. L.; Roca, T.; Monerris, M.; García-Díaz, D. *Tetrahedron Lett.* **2005**, *46*, 4035.
(8) (a) Rudler, H.; Denise, B.; Xu, Y.; Parlier, A.; Vaissermann, J. *Eur. J. Org. Chem.* **2005**, *17*, 3724. (b) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812. (c) Schmidt, A.; Michalik, D.; Rotzoll, S.; Ullah, E.; Fischer, C.; Reinke, H.; Goerls, H.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 2804. (d) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261.
(9) (a) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340. (b) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2011**, *76*, 4980. (c) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234. (d) Kivrak, A.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 7381. (e) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 2289. (f) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180. (g) Shi, F.; Mancuso, R.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4067. (h) Rogness, D. C.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003. (i) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409. (j) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.
(10) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028.
(11) (a) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96. (b) Sygula, A.; Sygula, R.; Rabideau, P. W. *Org. Lett.* **2006**, *8*, 5909.
(12) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.
(13) Yoon, K.; Ha, S. M.; Kim, K. *J. Org. Chem.* **2005**, *70*, 5741.
(14) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049.
(15) Castedo and co-workers have reported the intramolecular [4+2] cycloadditions of arynes with benzylidene amines. See: González, C.; Guitián, E.; Castedo, L. *Tetrahedron Lett.* **1996**, *37*, 405.
(16) Singal, K. K.; Kaur, J. *Synth. Commun.* **2001**, *31*, 2809.
(17) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040.
(18) Nakayama, J.; Midorikawa, H.; Yoshida, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1063.
(19) Aly, A. A.; Mohamed, N. K.; Hassan, A. A.; Mourad, A.-F. E. *Tetrahedron* **1999**, *55*, 1111.
(20) Fishwick, C. W. G.; Gupta, R. C.; Storr, R. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2827.
(21) Shou, W.-G.; Yang, Y.-Y.; Wang, Y. G. *J. Org. Chem.* **2006**, *71*, 9241.
(22) For examples, see: Wojciechowski, K. *Eur. J. Org. Chem.* **2001**, 3587.
(23) Buxton, P. C.; Fensome, M.; Heaney, H.; Mason, K. G. *Tetrahedron* **1995**, *51*, 2959.
(24) Kobayashi, Y.; Harayama, T. *Org Lett.* **2009**, *11*, 1603; and references cited therein.
(25) Austin, D. J.; Myers, M. B. *J. Chem. Soc.* **1964**, *1*, 1197.
(26) Heguy, A.; Cai, P.; Meyn, P.; Houck, D.; Russo, S.; Michitsch, R.; Pearce, C.; Katz, B.; Bringmann, G.; Feineis, D.; Taylor, D. L.; Tyms, A. S. *Antiviral Chem. Chemother.* **1998**, *9*, 149.
(27) Ribeiro, N.; Tabaka, H.; Peluso, J.; Fetzer, L.; Nebigil, C.; Dumont, S.; Muller, C. D.; Désaubry, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5523.
(28) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177.

