Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 26 Jun 2013.

To cite this article: Sean Stokes & Keith T. Mead (2013): Synthesis of Quinolines from N-Tosyl-1-azadienes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:19, 2627-2633

To link to this article: http://dx.doi.org/10.1080/00397911.2012.726388

Synthetic Communications®, 43: 2627–2633, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.726388

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SYNTHESIS OF QUINOLINES FROM *N*-TOSYL-1-AZADIENES

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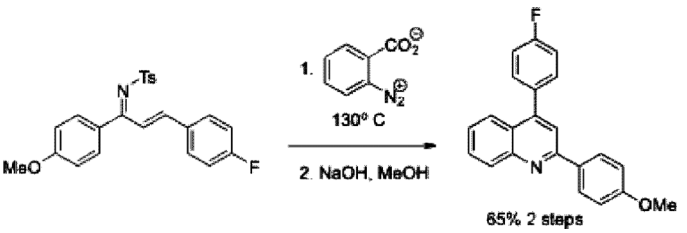
GRAPHICAL ABSTRACT



Abstract *A route to aryl-substituted quinolines from* N-*tosyl 1-azadienes is described. The key steps are a [4 + 2] cycloaddition with benzyne followed by base treatment of the 1,4-dihydroquinoline product. The* N-*tosyl 1-azadienes were prepared from readily accessible cinnamaldehyde and chalcone substrates by condensation with* p-$TsNH_2$.

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Keywords 1-Azadienes; benzyne; [4 + 2] cycloaddition; quinoline synthesis

INTRODUCTION

The extraordinary contribution of quinoline synthesis to medicine and agriculture has been extensively acknowledged and reviewed.[1,2] Despite these advances, new synthetic method development in this area continues to be a focal point of high interest.

Aryl-substituted quinolines represent a subclass of structures known for their pharmacological properties, particularly those that are aryl substituted at the 2- or 4-position.[3] By contrast, routes to 2,4-diarylquinolines have received less attention.[4]

We recently reported a new route to 1,4-dihydroquinolines by reacting *N*-substituted 1-azadienes with benzyne generated from benzene diazonium carboxylate (BDC).[5] This provided a new entry into biologically active 4-arylquinoline-2-one derivatives such as the fungal metabolite 3-*O*-methylviridicatin.[6] The purpose

Received July 23, 2012.

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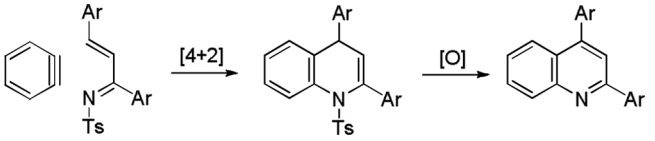


Scheme 1. Strategy for synthesizing quinolines from 1-azadienes.

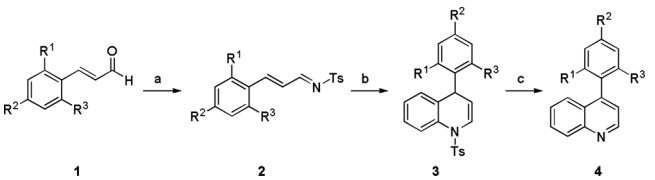
of the current study was to see if *N*-tosyl-protected 1-azadienes could provide an efficient route to aryl-substituted quinolines (Scheme 1). We reasoned that aromatization of the cycloadduct could be achieved by either base-induced elimination of *p*-toluenesulfinic acid[7] or tosyl group hydrolysis followed by air oxidation.[8–10]

RESULTS AND DISCUSSION

Initial studies focused on the synthesis of 4-arylquinolines, which required the preparation of a series of *N*-tosyl 4-aryl-1-azadienes **2** (Scheme 2). This was achieved by condensing cinnamaldehyde precursors **1** with *p*-$TsNH_2$ following the method described by Raghavan and Rajender.[11] Each azadiene derivative was then subjected to our two-step protocol, which involved reaction with BDC at 130 °C followed by treatment of the 1,4-dihydroquinoline product **3** with NaOH in refluxing MeOH.

BDC was synthesized from anthranilic acid using trichloroacetic acid (TCA) and isoamyl nitrite according to known procedures.[12] However, some modifications were made to ensure that both water and acid were excluded to avoid decomposition of the azadiene in the cycloaddition step. First, a solution of TCA in tetrahydrofuran (THF) was made and stored over molecular sieves for at least 24 h prior to use. Next, when BDC precipitated out of solution, it was filtered and made into a suspension in the reaction solvent (PhCl) and used as a slurry. This ensured that the BDC never dried out and therefore did not pose an explosion risk. Finally, to remove trace amounts of acid from this suspension, isobutylene oxide was added.

Cycloaddition reactions of derivatives **2** with benzyne generated under these conditions proceeded in good to moderate yields when the azadiene aryl group was either *p*-substituted (Table 1, entries 2, 3, and 6) or mono ortho-substituted (Table 1, entry 5), but not ortho-disubstituted (Table 1, entry 4). With compound **2d**, only slow decomposition of the imine was observed, as monitored by thin-layer



Scheme 2. Reagents and conditions: (a) $TsNH_2$, $BF_3 \cdot OEt_2$, benzene, Dean–Stark;(b) BDC, chlorobenzene, reflux; (c) NaOH, MeOH, reflux.

Table 1. Results of the reactions shown in Scheme 2

Entry	1–4	R^1	R^2	R^3	Yield of **2**[a] (%)	Yield of **3**[a] (%)	Yield of **4**[a] (%)
1	**a**	H	H	H	77	57	90
2	**b**	H	MeO	H	67	70	93[b]
3	**c**	H	NO_2	H	80	64	87
4	**d**	MeO	MeO	MeO	62	No Rxn	N/A
5	**e**	MeO	H	H	88	69	92
6	**f**	H	$(CH_3)_2N$	H	60	Not isolated[c]	56

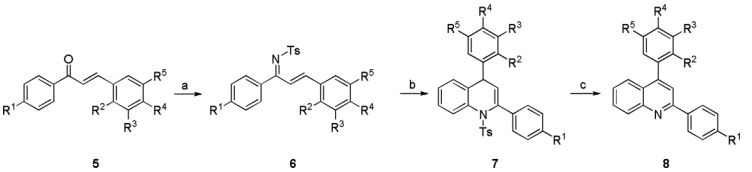
[a]Isolated yield.
[b]previously reported result.[5]
[c][4 + 2]reaction conditions gave the quinoline product directly.

chromatography (TLC). In contrast, the amine-containing 1-azadiene **2f** gave a quinoline product directly without isolation of the 1,4-dihydroquinoline intermediate (Table 1, entry 6). There are known examples of *N*-tosyl-1,2-dihydroquinolines undergoing elimination reactions to produce quinolines in the presence of a nitrogenous base.[7] It is possible that the dimethylamine functionality in **2f** acted as a base, causing the liberation of *p*-toluenesulfinate in 1,4-elimination.

Encouraged by our results, we next set out to extend this route to 2,4-diarylquinolines. This required condensing *p*-$TsNH_2$ with a series of chalcones **5**, which were prepared using the method of Ram and Khan[13] (Scheme 3). In every case, NMR showed formation of the azadiene product as a single isomer. Moreover, several derivatives crystallized, thereby allowing crystallographic analysis. The x-ray structure of azadiene **6b** revealed an *E,E* configuration for the diene with a preferred *s-trans* conformation (Figure 1).

The condensation of **5i** with *p*-$TsNH_2$ produced a viscous, brown oil that showed multiple products by TLC, and attempts at purification by column chromatography and crystallization were unsuccessful. As a result, no cycloadduct was observed for this derivative. In all other cases studied, however, our two-step protocol gave the expected 2,4-diarylquinoline product **8** (Table 2).

In summary, a two-step procedure for preparing aryl-substituted quinolines from aryl-substituted *N*-tosyl1-azadienes has been demonstrated. Crucial to the success of this approach is the elimination of trace amounts of water and TCA in the cycloaddition step.



Scheme 3. Reagents and conditions: (a) $TsNH_2$, $TiCl_4$, Et_3N, DCE, reflux; (b) BDC, chlorobenzene, reflux;(c) NaOH, MeOH, reflux.

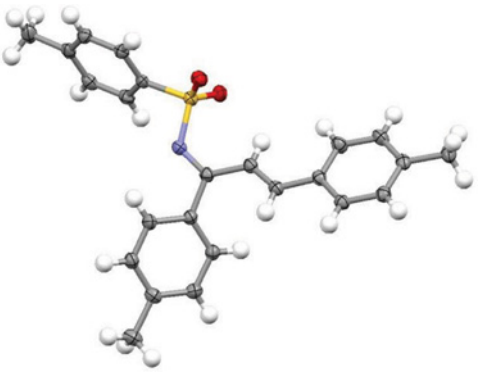


Figure 1. X-ray structure of azadiene **6b**. (Figure is provided in color online.)

Table 2. Results of the reactions shown in Scheme 3

Entry	5–8	R^1	R^2	R^3	R^4	R^5	Yield of 6 (%)	Yield of 7 (%)	Yield of 8 (%)
1	**a**	H	H	H	H	H	63	67	90
2	**b**	Me	H	H	Me	H	58	63	96
3	**c**	MeO	H	H	H	H	67	62	88
4	**d**	MeO	H	H	MeO	H	68	58	92
5	**e**	MeO	H	H	Cl	H	51	56	94
6	**f**	MeO	H	H	F	H	56	71	92
7	**g**	H	H	MeO	MeO	MeO	47	55	90
8	**h**	MeO	OBn	H	H	H	61	63	90
9	**i**	MeO	H	H	NO_2	H	No Rxn	N/A	N/A
10	**j**	MeO	H	NO_2	H	H	59	62	88
11	**k**	Br	H	H	MeO	H	66	65	91

EXPERIMENTAL

Synthesis of *N*-Tosyl 1-Azadiene (2a)

Cinnamaldehyde (1.32 g, 10 mmol) and *para*-toluenesulfonamide (1.71 g, 10 mmol) were dissolved in benzene (60 mL) and then $BF_3(OEt_2$(44 μL, 0.4 mmol) was added. The mixture was refluxed using a Dean–Stark apparatus for 2 h. The reaction was cooled to 0 °C and then EtOAc was added. The organic mixture was washed with cold 1 N NaOH, water, and brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure. The crude oil was mixed with petroleum ether and stored in a −10 °C freezer overnight. The resulting solid was recrystallized in a mixture of hexane and EtOAc: 2.2 g (77%); white solid; mp 201–203 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.80 (d, $J = 9.4$ Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 7.6$ Hz, 2H), 7.51 (d, $J = 15.8$ Hz, 1H), 7.47–7.43 (m, 3H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.00 (dd, $J = 9.4$ and; 15.8 Hz, 1H), 2.46 (s, 3H).

Synthesis of *N*-Tosyl-1,4-dihydroquinoline (3a)

Anthranilic acid (165 mg, 1.2 mmol) and trichloroacetic acid (1 mL, 0.03 mmol, 0.03 M in THF dried over crushed 4 Å molecular sieves) were dissolved in THF (2 mL) and cooled to 0 °C. Isopentyl nitrite (321 μL, 2.4 mmol) was added, stirred at 0 °C for 15 min, warmed to room temperature, 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 isobutylene oxide (213 μL, 2.4 mmol) and stirred for 15 min. This suspension was slowly added to a refluxing mixture of azadiene **2a** (114 mg, 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 room temperature 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: 82 mg (57%); orange oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (dd, $J = 0.9$ and 8.4 Hz, 1H), 7.56 (d, $J = 8.3$ Hz, 2H), 7.20–7.17 (m, 3H), 7.12–7.01 (m, 4H), 6.96 (dd, $J = 1.1$ and 7.9 Hz, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.61 (dd, $J = 1.2$ and 7.7 Hz, 2H), 5.39 (dd, $J = 4.4$ and 7.9 Hz, 1H), 4.35 (d, $J = 4.3$ Hz, 1H), 2.41 (s, 3H).

Synthesis of Quinoline (4a)

N-Tosyl-1,4-dihydroquinoline **3a** (51 mg, 0.14 mmol) was dissolved in MeOH (10 mL) and then NaOH (17 mg, 0.42 mmol) was added. The solution was refluxed overnight and then cooled to room temperature. The mixture was diluted with EtOAc and H_2O and then separated. The organic solution was washed with H_2O and brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude oil was subjected to column chromatography: 26 mg (90%); orange oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.96 (d, $J = 4.4$ Hz, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 7.93 (dd, $J = 1.1$ and 8.4 Hz, 1H), 7.77–7.71 (m, 1H), 7.55–7.49 (m, 6H), 7.35 (d, $J = 4.4$ Hz, 1H).

Synthesis of N-Tosyl 1-Azadiene (6a)

p-Toluenesulonamide (0.86 g, 5 mmol) and *trans*-chalcone (1.04 g, 5 mmol) were dissolved in DCE (20 mL) and then $TiCl_4$ (2.5 mL, 2.5 mmol, 1 M in DCM) was added, followed by Et_3N (1.4 mL, 10 mmol). The mixture was refluxed overnight and then cooled to room temperature. The organic solution was washed with dilute HCl, saturated $NaHCO_3$, water, and brine and then dried over Na_2SO_4. The solvent was removed and the brown syrup was left to crystallize overnight. The solid was recrystallized from a mixture of hexane and EtOAc: 1.14 g (63%); yellow solid; mp 149–151 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04–7.45 (m, 13H), 7.34 (d, $J = 7.9$ Hz, Hz, 2H), 7.10 (d, $J = 16.0$ Hz, 1H), 2.45 (s, 3H).

Crystal Data for 6b

$C_{26}H_{24}NO_2S$, FW = 414.52, crystal size: 0.23 mm × 0.27 mm × 0.30 mm, crystal system: triclinic, space group: P -1, a = 8.8684(8) Å, b = 10.0584(9) Å, c = 11.4737(11) Å, α = 89.6940(10)°, β = 80.7440(10)°, γ = 89.5130(10)°, V = 1010.11(16) Å^3, Z = 2, T = 100(2) K, reflections collected 12475 (0.74 Å resolution), 4766 independent (R_{int} = 0.0218), R_1 = 0.0371, wR_2 = 0.0985. The crystallographic data was deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 886372). The data can be obtained free of charge from www.ccdc.cam.ac.uk.

SUPPORTING INFORMATION

Full experimental details, ^{1}H and ^{13}C NMR spectra, and HRMS data for all new compounds can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

We thank the National Institutes of Health through Grant No. 1 R15 GM088780-01 for financial support of this research. The NMR data were made possible through NSF CRIF Award 0840220, which supported the acquisition of a 600-MHz NMR. We also thank Jonathan R. Frisch and the X-ray Crystallographic Laboratory at Mississippi State University for the structure of azadiene **6b**.

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