Efficient Synthesis of *N*-(9-Xanthyl)-4-Toluenesulfonamides Enabled by an Addition–Cyclization Cascade of Arynes

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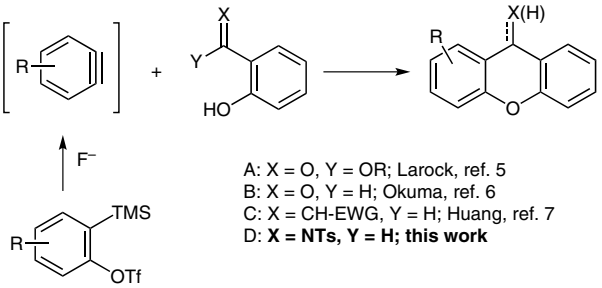
Received: 27.12.2012; Accepted after revision: 04.02.2013

Abstract: An efficient synthesis of *N*-(9-xanthyl)-4-toluenesulfonamides is described in which salicyl *N*-tosylimines react with silylaryl triflates in the presence of CsF. This mild process involves an addition–cyclization cascade in which arynes are generated and trapped in situ.

Key words: *N*-(9-xanthyl)-4-toluenesulfonamides, salicyl *N*-tosylimines, arynes, addition–cyclization, cascade

Arynes are highly reactive intermediates widely used in organic transformations to construct 1,2-disubstituted arenes and other useful compounds containing aryl groups.[1] Ever since Kobayashi's pioneering work on fluoride-mediated aryne formation from silylaryl triflates,[2] these intermediates have usually been generated and captured under very mild reaction conditions. Synthetic chemists have taken advantage of this mild protocol to significantly extend the scope of aryne-trapping reaction partners, leading to numerous useful methods for synthesizing a variety of skeletons bearing at least one aryl group.[3]

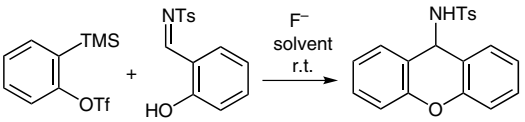
Aryne intermediates are usually captured using molecules containing both electrophilic and nucleophilic sites.[4] In 2006, Larock and co-workers reported an addition–cyclization of arynes with salicylates to form xanthone (Scheme 1, reaction A).[5] Similar reaction pathways were later described involving salicylaldehydes or phenols bearing an *ortho*-Michael acceptor to provide, respectively, 9-hydroxyxanthenes[6] or 9-spiroxanthenes[7] (Scheme 1, reactions B and C). We envisaged that *N*-tosylimines derived from salicyaldehydes would likewise react with arynes to afford *N*-(9-xanthyl)-4-toluenesulfonamides (Scheme 1, reaction D). In this reaction, the aryl carbanion intermediate would be trapped not by the carbonyl groups and Michael acceptor as in the examples above, but by the azomethine group functioning as an electrophile. In this way, the anticipated products, which are useful precursors for benzylation,[8] could be prepared more simply than through conventional reactions involving relatively complex molecules such as xanthones[8] or 9-hydroxyxanthenes.[9] Here we present our results on the facile synthesis of *N*-(9-xanthyl)-4-toluenesulfonamides via an addition–cyclization cascade of salicyl *N*-tosylimines and silylaryl triflates in the presence of CsF.



Scheme 1 Salicyl *N*-tosylimine, which serves as a reaction partner of arynes

As a starting point for our studies, we used salicyl *N*-tosylimine (**2a**) to trap the benzyne intermediate generated in situ from 2-(trimethylsilyl)phenyl triflate (**1a**) in the presence of CsF in acetonitrile at room temperature (Table 1, entry 1). The cascade reaction occurred smoothly and afforded the anticipated product *N*-(9-xanthyl)-4-toluenesulfonamide (**3a**) in high yield (92%).[10] In this process, the nucleophilic phenolic oxygen of **2a** added to the benzyne generated in situ, creating a new O–C bond and a

Table 1 Screening of Solvents and Sources of Fluoride Ion in the Reaction of **1a** with **2a**[a]



1a **2a** **3a**

Entry	Fluoride source	Solvent	Time (h)	Yield (%)[b]
1	CsF	MeCN	6	92
2	CsF	CH_2Cl_2	7	77
3	CsF	THF	7	54
4	TBAF	MeCN	7	70
5	KF	MeCN	7	66
6	TBAT	MeCN	9	58

[a] Reactions were performed using 1.3 equiv of **1a**, 1.0 equiv of **2a**, and 2.5 equiv of fluoride source at r.t.
[b] Isolated yields after silica gel chromatography.

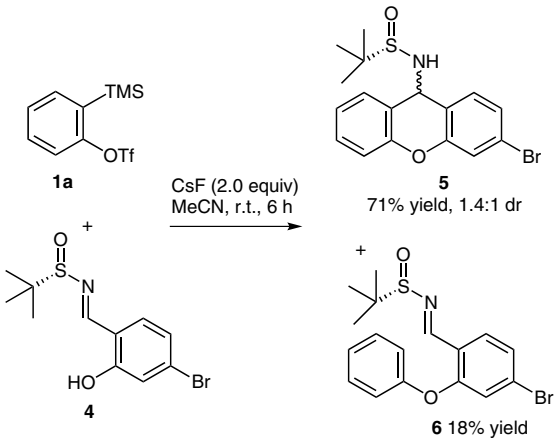
SYNLETT 2013, 24, 0640–0644
Advanced online publication: 20.02.2013
DOI: 10.1055/s-0032-1318311; Art ID: ST-2012-W1105-L

carbanion intermediate, which underwent intramolecular cyclization with an imine group to furnish the product **3a**. The yield of this aryne-based transformation was not improved by using other commonly used solvents (CH_2Cl_2, THF; Table 1, entries 2 and 3) or sources of fluoride ion (TBAF, KF, TBAT; Table 1, entries 4–6). Therefore, the initial reaction conditions (1.3 equiv of **1a**, 1.0 equiv of **2a**, 2.5 equiv of CsF, MeCN, r.t.) were used to investigate the substrate scope.

A range of salicyl *N*-tosylimines **2a**–**i** (Table 2, entries 1–9) could participate in the reaction, providing a variety of *N*-(9-xanthyl)-4-toluenesulfonamides **3** substituted at various positions on the aryl ring with electron-donating or electron-withdrawing groups. Yields were moderate to good (59–92%). The reaction tolerated halogen substitutions (**3b**,**d**,**e**,**g**,**h**), allowing structurally diverse products to be prepared.[5b] To test the suitability of the reaction of **1a** with **2a** for preparative synthesis, the reaction was scaled up to one gram. The scaled-up reaction provided **3a** in higher yield than the microscale reaction (Table 2, entry 1, 99% vs. 92%).

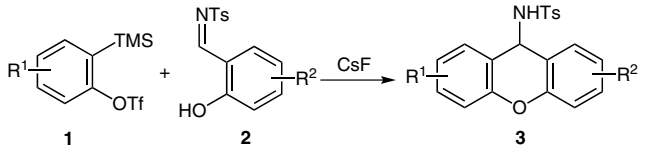
The substrate scope was further investigated using a variety of aryne precursors (Table 2, entries 10–13). Substituted aryl triflates **1b**–**d** underwent addition–cyclization and gave products in good yield (72–83%). Only one regioisomer was obtained in the reaction of 3-methoxy-2-(trimethylsilyl)phenyl triflate (**1c**, Table 2, entry 11), while low regioselectivities were obtained using aryne precursors **1d** (1.5:1, Table 2, entry 12) and **1e** (1.5:1, Table 2, entry 13). These different results are because the arynes generated from **1d** and **1e**, unlike that derived from **1c**, lack strong steric and electronic biases.[1e,12]

Our interest in applying *N*-*tert*-butanesulfinyl imines (*t*-BS imines) to the asymmetric synthesis of nitrogen-containing compounds[13] led us to test the feasibility of using *t*-BS imines in this addition–cyclization cascade. Similar to the results obtained with *N*-tosylimines **2**, the *t*-BS imine **4** derived from 4-bromo-salicyladehyde reacted with **1a** to give *N*-*tert*-butanesulfinyl amide **5** in 71% yield with poor diastereoselectivity (1.4:1 dr, Scheme 2). It also generated the O-arylation product **6** in 18% yield; this product formed when the nucleophilic addition of the phenol group to the benzyne intermediate was followed by protonation instead of cyclization. Attempts to improve yield using Lewis acids to activate the imine were unsuccessful. In fact, adding one equivalent of $Yb(OTf)_3$, $In(OTf)_3$, or $Ti(O\textit{i}\text{-}Pr)_3Cl$ to the reaction reduced the yield to 52–56%. In addition, the Lewis acids did not affect the diastereoselectivity.



Scheme 2 Reaction of silylphenyl triflate **1a** with *N*-*tert*-butanesulfinyl imines **4**

Table 2 Synthesis of *N*-(9-Xanthyl)-4-Toluenesulfonamides from Salicyl *N*-Tosylimines and 2-(Trimethylsilyl)aryl Triflates[a]



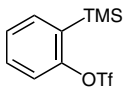
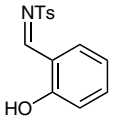
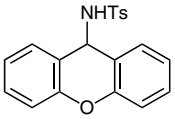
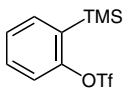
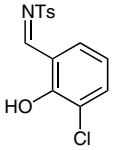
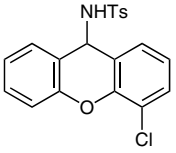
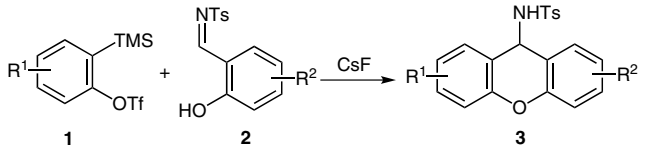
Entry	*N*-Tosylimines	Silylaryl triflates	Time (h)	Products	Yield (%)
1	 **1a**	 **2a**	6	 **3a**	92 (99[b])
2	 **1a**	 **2b**	10	 **3b**	90

Table 2 Synthesis of *N*-(9-Xanthyl)-4-Toluenesulfonamides from Salicyl *N*-Tosylimines and 2-(Trimethylsilyl)aryl Triflates[a] (continued)



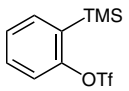
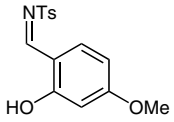
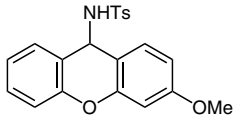
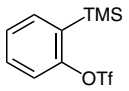
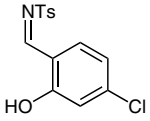
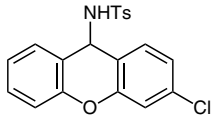
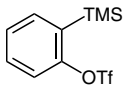
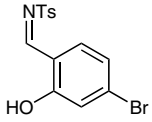
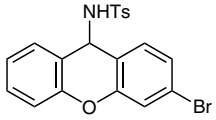
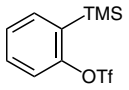
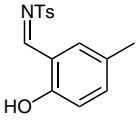
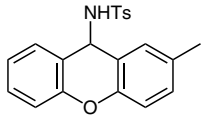
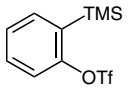
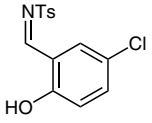
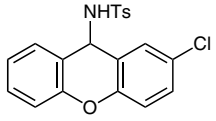
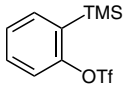
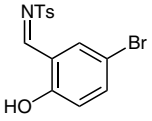
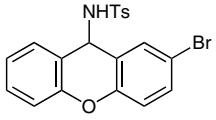
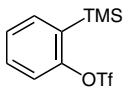
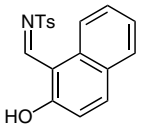
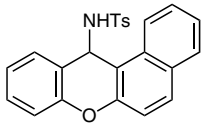
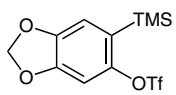
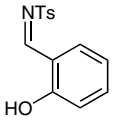
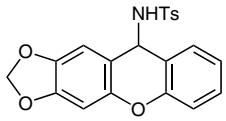
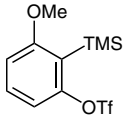
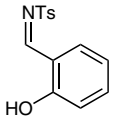
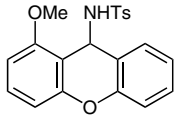
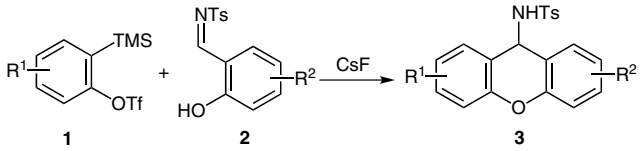
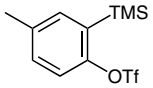
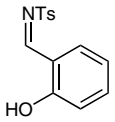
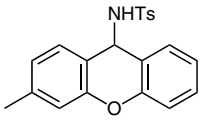
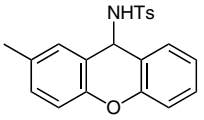
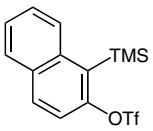
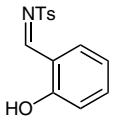
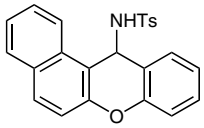
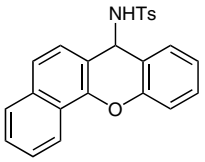
Entry	*N*-Tosylimines	Silylaryl triflates	Time (h)	Products	Yield (%)
3	 **1a**	 **2c**	12	 **3c**	84
4	 **1a**	 **2d**	8	 **3d**	70
5	 **1a**	 **2e**	7	 **3e**	59
6	 **1a**	 **2f**	4	 **3f**	75
7	 **1a**	 **2g**	9	 **3g**	70
8	 **1a**	 **2h**	9	 **3h**	72
9	 **1a**	 **2i**	5	 **3i**	83
10	 **1b**	 **2a**	6	 **3j**	83
11	 **1c**	 **2a**	9	 **3k**	88

Table 2 Synthesis of *N*-(9-Xanthyl)-4-Toluenesulfonamides from Salicyl *N*-Tosylimines and 2-(Trimethylsilyl)aryl Triflates[a] (continued)



1 **2** **3**

Entry	*N*-Tosylimines	Silylaryl triflates	Time (h)	Products	Yield (%)
12	 **1d**	 **2a**	10	 **3l**  **3l'**	72 (**3l**/**3l′** = 1.5:1)[c]
13	 **1e**	 **2a**	6	 **3m**  **3m'**	83 (**3m**/**3m′** = 1.5:1)[c]

[a] All reactions were carried out in MeCN using 1.3 equiv of **1**, 1.0 equiv of **2** and 2.5 equiv of CsF at r.t.
[b] Reaction on 1-gram scale.
[c] Regioisomeric ratios were determined by ^{1}H NMR spectroscopy; **3l′** = **3f**; **3m** = **3i**.

In summary, a new general method has been developed that allows a wide range of *N*-(9-xanthyl)-4-toluenesulfonamides to be constructed. The process involves the in situ generation of aryne intermediates, which then participate in an addition–cyclization cascade with salicyl *N*-tosylimines.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (20972182 and 21172251) and the Chinese Academy of Sciences.

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

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(10) **General Procedure for the Preparation of *N*-(9-Xanthyl)-4-Toluenesulfonamides Synthesized from Salicyl *N*-Tosylimines and 2-(Trimethylsilyl)aryl Triflates**
To a solution of salicyl *N*-tosylimine[11] (0.38 mmol, 1.0 equiv) and triflate (0.49 mmol, 1.3 equiv) in MeCN (5 mL) was added CsF (0.95 mmol, 2.5 equiv) in one portion. After stirring at r.t. for the indicated time (Table 2), the reaction mixture was poured into 10% aq Na_2CO_3 (5 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were dried over Na_2SO_4, filtered, and evaporated to give a crude product, which was purified by silica gel column chromatography using elution with EtOAc–PE to afford *N*-(9-xanthyl)-4-toluenesulfonamide. The general procedure was followed using salicyl *N*-tosylimine (**2a**, 105 mg, 0.38 mmol), silylaryl triflate **1a** (146 mg, 0.49 mmol), and CsF (144 mg, 0.95 mmol). The reaction mixture was stirred for 6 h and purified by silica gel chromatography using PE–EtOAc (5:1) as eluent to give cyclization product **3a** (122 mg, 92% yield) as a white solid; mp 196–198 °C (lit.[9] mp 197–197.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.1 Hz, 2 H), 7.37–7.20 (m, 4 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.08 (d, *J* = 8.2 Hz, 2 H), 6.99 (t, *J* = 7.5 Hz, 2 H), 5.77 (d, *J* = 8.6 Hz, 1 H), 4.87 (d, *J* = 8.6 Hz, 1 H), 2.47 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.5, 143.8, 138.8, 130.0, 129.7 (overlap, 2 C), 127.4, 123.8, 120.6, 116.9, 49.4, 21.8. ESI-HRMS: *m/z* calcd for $C_{20}H_{17}NO_3SNa$ $[M + Na]^+$: 374.0821; found: 374.0825. See the Supporting Information for experimental details and characterization data for all new compounds.
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