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One-Pot Oxidative Heteroannulations of *N*-Sulfonylanilines with Styrenes for the Construction of 5-Aminocoumaran Derivatives

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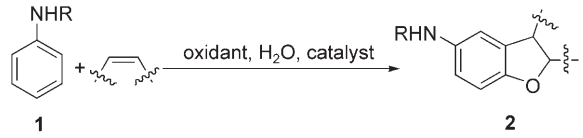
Abstract: An efficient one-pot oxidative heteroannulation of *N*-sulfonylaniline derivatives with styrene derivatives for the rapid construction of 5-aminocoumaran derivatives is reported. Copper trifluoromethanesulfonate was found to be an excellent catalyst for the oxidative heteroannulation reactions with low reactive styrenes.

Keywords: aromatic substitution; cycloaddition; heterocycles; hypervalent compounds; oxidation

Introduction

The widespread availability and inherent functionality of aniline derivatives makes them attractive substrates in organic synthesis. Oxidative functionalization reactions of phenols are well-known and useful synthetic processes,[1] and the elegance of these strategies prompted us to contemplate the possibilities for the oxidative functionalizations of aniline derivatives.[2] As a part of our work on the synthetic application of sulfonamides in the presence of hypervalent iodine,[3] in this communication, we present an efficient one-pot oxidative heteroannulation of *N*-sulfonylaniline derivatives with styrene derivatives for the rapid construction of 5-aminocoumaran derivatives.

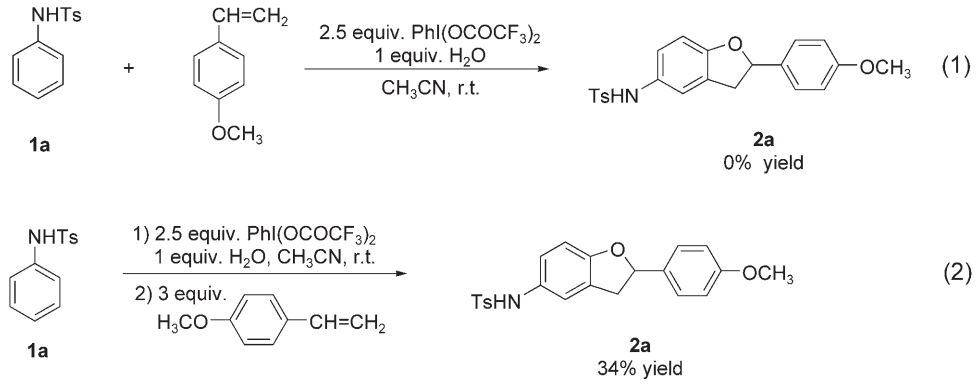
Compounds which have the 5-aminocoumaran (5-amino-2,3-dihydrobenzofuran) structure are reported to be efficient antioxidants and to have protective effects against central nervous system trauma and ischemia.[4] The general synthetic pathways for the preparation of 5-aminocoumaran derivatives have involved multi-step procedures or relatively harsh reaction conditions. Our one-pot oxidative heteroannulation strategy, which involves an oxidative carbon-oxygen bond-forming reaction[5] and an oxidative carbon-carbon bond-forming reaction[6] of aniline derivatives, is shown in Scheme 1. The oxidation of aniline derivatives normally depends on the nature of the oxidant.[2] Iodobenzene bis(trifluoroacetate) [$PhI(OCOCF_3)_2$] was initially elected as the oxidant for the one-pot oxidative heteroannulation due to its similar oxidative properties to those of Tl(III), Hg(II), and Pb(IV) derivatives, but without the toxic and concomitant environmental problems of these heavy metal analogues.[7] Moreover, trifluoroacetic acid, the metabolite of $PhI(OCOCF_3)_2$, will not affect the oxidative carbon-oxygen bond-forming reaction due to its lower nucleophilicity.



Scheme 1. One-pot oxidative heteroannulation of aniline derivatives with alkenes to construct 5-aminocoumaran derivatives.

Results and Discussion

In testing this strategy, a one-pot reaction was tested but failed [Scheme 2, Eq. (1)]. *N*-Tosylaniline **1a** was recovered in 96% yield from the reaction, and some oxidation products of 4-methoxystyrene were isolated as the by-products. Since *N*-tosylaniline showed a lower reactivity toward the $PhI(OCOCF_3)_2$, to avoid the consumption of oxidant by 4-methoxystyrene, the one-pot oxidative heteroannulation reaction was then carried out in a stepwise way. $PhI(OCOCF_3)_2$ was added into the solution of *N*-tosylaniline **1a** and H_2O in acetonitrile. After *N*-tosylaniline had disappeared, the reaction mixture was then treated with 4-methoxystyrene. We were delighted to find that the



Scheme 2.

reaction was completed in 30 min and afforded 5-aminocoumaran **2a** in 34% yield [Scheme 2, Eq (2)].

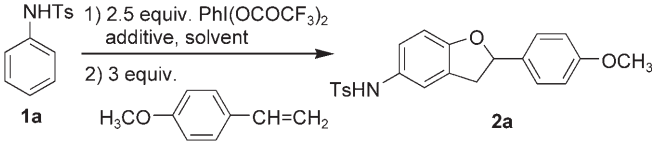
This promising result encouraged us to optimize the reaction conditions. Additional water was not necessary since the trace of water in solvent could play the role (Table 1, entry 1). No product **2a** was detected when acetone, MeOH, *t*-BuOH, DMSO, DMF and EtOAc were used as the solvent while the reaction could proceed with varied efficiency in THF, $ClCH_2CH_2Cl_2$ and toluene (Table 1, entries 2–10). Lower temperatures were better for the first-step oxidation, but not for the second-step heteroannulation (Table 1, entries 11–13). Since some oligomers of *N*-tosylaniline were isolated as by-products, the influence of the concentration on the reaction was investigated (Table 1, entries 14–16). A lower concentration inhibited the deleterious side reactions, but slowed down the intermolecular heteroannulation.

In order to understand the reaction pathway, several control experiments were done. When 4 Å molecular sieves were introduced into the reaction, a complicated reaction was observed. The reaction gave **2a** in a lower yield but oligomers of *N*-tosylaniline in higher yields (Table 1, entry 17). Only a trace amount of product **2a** was formed when 4 equivalents of *t*-BuOK were added to the reaction mixture before 4-methoxystyrene (Table 1, entry 18). When $PhI(OCOCH_3)_2$ was used instead of $PhI(OCOCF_3)_2$ as the oxidant, the reaction was complicated. Acetate-substituted *N*-tosylaniline derivatives were isolated as by-products (Table 1, entry 19).

A proposed reaction pathway for the one-pot oxidative heteroannulation of *N*-tosylaniline with 4-methoxystyrene is outlined in Scheme 3. *In situ* oxidation of *N*-tosylaniline in the presence of H_2O gives an intermediate **A**, which undergoes aromatization to form *N*-tosyl-*p*-aminophenol. This is followed by further oxidation to afford an electrophilic intermediate *p*-quinone monosulfonimide **C**.[8] With the catalysis of the CF_3COOH generated in the oxidation reactions, 5-aminocoumaran is constructed from the Michael addition of intermediate **C** with 4-methoxystyrene and a subsequent intramolecular cyclization.[9]

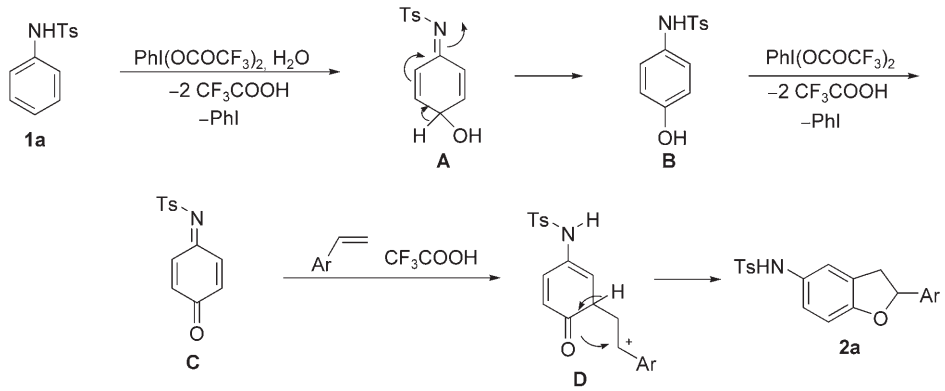
Trace amounts of *N*-tosyl-*p*-aminophenol were detected during the oxidation reaction. Analysis of the reaction mixture of the first-step oxidation by

Table 1. Optimization of the one-pot oxidative heteroannulation.



Entry	Solvent	Temp. [°C]	Time	Yield [%][a]
1	CH_3CN	25	30 min	36
2	Acetone	25	30 min	0
3	MeOH	25	30 min	0
4	*t*-BuOH	25	30 min	0
5	DMSO	25	30 min	0
6	DMF	25	30 min	0
7	EtOAc	25	30 min	0
8	THF	25	30 min	10
9	$ClCH_2CH_2Cl$	25	30 min	24
10	Toluene	25	30 min	18
11[b]	CH_3CN	0–25	1 h	46
12[b]	CH_3CN	−10–25	3 h	58
13[b]	CH_3CN	−20–25	10 h	51
14[c]	CH_3CN	−10–25	3 h	65
15[d]	CH_3CN	−10–25	4 h	75
16[e]	CH_3CN	−10–25	5 h	72
17[d,f]	CH_3CN	−10–25	4 h	32
18[d,g]	CH_3CN	−10–25	6 h	trace
19[d,h]	CH_3CN	−10–25	4 h	25

[a] Isolated yield base on the *N*-tosylaniline.
[b] The concentration of *N*-tosylaniline was 0.25 M.
[c] The concentration of *N*-tosylaniline was 0.125 M.
[d] The concentration of *N*-tosylaniline was 0.063 M.
[e] The concentration of *N*-tosylaniline was 0.031 M.
[f] 4 Å molecular sieve was added.
[g] 4 equivalents of *t*-BuOK were added.
[h] $PhI(OCOCH_3)_2$ was used instead of $PhI(OCOCF_3)_2$.

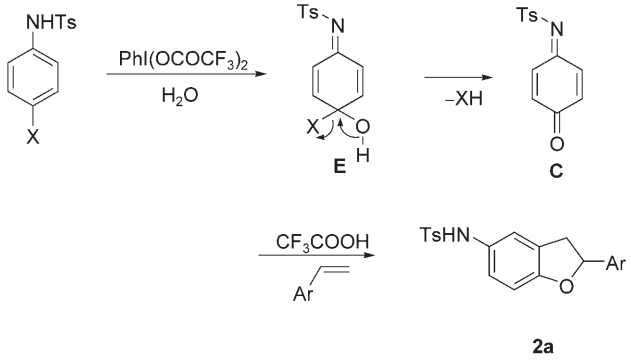


Scheme 3. A proposed pathway for the oxidative heteroannulation of *N*-tosylaniline with 4-methoxystyrene.

^{1}H NMR spectroscopy indicated the formation of *p*-quinone monosulfonimide.[10] The oxidative heteroannulation of *N*-tosyl-*p*-aminophenol proceeded smoothly even using 1.2 equivalents of PhI(OCOCF$_3$)$_2$, and gave product **2a** in a nearly quantitative yield.

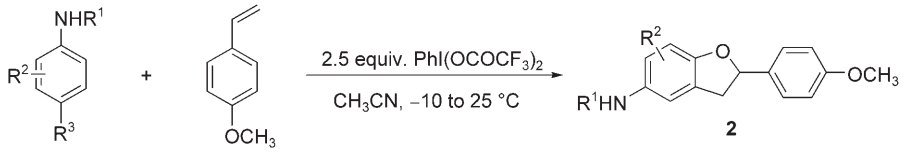
When the C-4 position of *N*-tosylaniline was blocked with a methyl group, the reaction was very complicated, and did not give any isolable amounts of product (Table 2, entry 1). However, it was noteworthy that the reaction of *N*-tosyl-4-anisidine proceeded very well and gave product **2a** in 95% yield (Table 2, entry 2). No indoline product was isolated from the reaction.[11]

The influence of C-4 substitution of the *N*-tosylaniline on the reaction was investigated. The reactivity



Scheme 4. A proposed pathway for the oxidative heteroannulation of C-4 substituted *N*-tosylaniline derivatives with 4-methoxystyrene.

Table 2. One-pot oxidative heteroannulation of various aniline derivatives with 4-methoxystyrene.



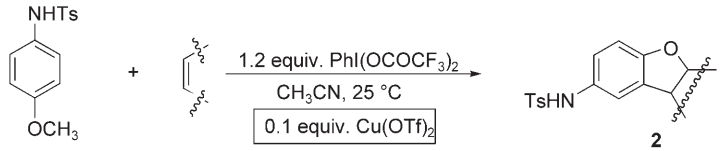
Entry	R^1	R^2	R^3	Product	Yield [%][a]
1	*p*-$CH_3C_6H_4SO_2$	H	*p*-CH_3	-	0
2	*p*-$CH_3C_6H_4SO_2$	H	*p*-MeO	**2a**	95
3	*p*-$CH_3C_6H_4SO_2$	H	*p*-BuO	**2a**	85
4	*p*-$CH_3C_6H_4SO_2$	H	*p*-$PhCH_2O$	**2a**	88
5	*p*-$CH_3C_6H_4SO_2$	H	*p*-CH_3COO	**2a**	44
6	*p*-$CH_3C_6H_4SO_2$	H	*p*-Cl	**2a**	70
7	*p*-$CH_3C_6H_4SO_2$	H	*p*-Br	**2a**	73
8	*p*-$CH_3C_6H_4SO_2$	H	*P*-F	-	0
9	*p*-$CH_3C_6H_4SO_2$	*o*-MeO	H	**2b**	35
10	*p*-$CH_3C_6H_4SO_2$	*m*-MeO	H	**2c**	18
11	*p*-$CH_3C_6H_4SO_2$	2,6-di-CH_3	H	-	0
12	*p*-$NO_2C_6H_4SO_2$	H	H	**2d**	70
13	CH_3SO_2	H	H	**2e**	78
14	PhCO	H	H	-	0
15	CF_3CO	H	H	-	0

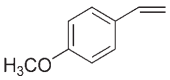
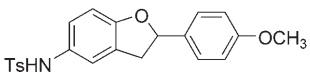
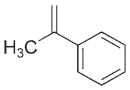
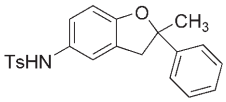
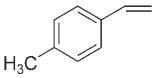
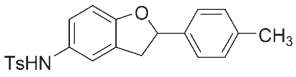
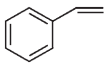
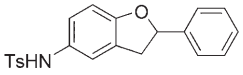
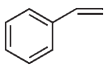
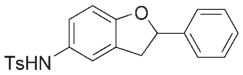
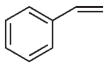
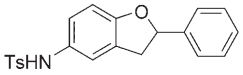
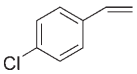
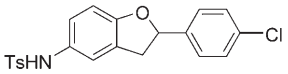
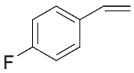
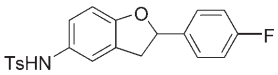
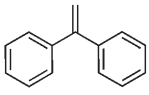
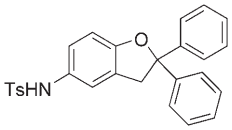
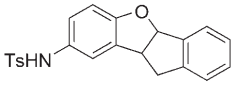
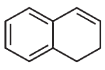
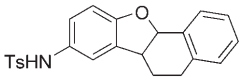
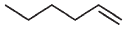
[a] Isolated yield base on the *N*-tosylaniline derivative.

of 4-butoxy- or 4-benzyloxy-substituted derivative was similar to that of *N*-tosyl-4-anisidine (Table 2, entries 3 and 4). Acetate substitution resulted in a slower reaction and a lower yield of **2a** (Table 2, entry 5). More notably, 4-chloro- and 4-bromo-substituted *N*-tosylaniline derivatives were found to be effective substrates. Their reactions also afforded *N*-tosyl-2,3-dihydro-5-benzofuranamine **2a** in good yields (Table 2, entries 6 and 7). No reaction occurred in the case of *N*-(4-fluorophenyl)-4-methylbenzenesulfonamide (Table 2, entry 8).

When *N*-tosyl-2-anisidine and *N*-tosyl-3-anisidine were used as the substrates, the reactions were complicated. The corresponding *N*-tosyl-2,3-dihydro-5-benzofuranamine derivatives were isolated in low yields (Table 2, entries 9 and 10). Sterically hindered *N*-(2,6-dimethylphenyl)-4-methylbenzenesulfonamide showed no reactivity toward the oxidant (Table 2, entry 11). Sulfonyl protection of the aniline was important for the oxidative heteroannulation since neither *N*-phenylbenzamide nor 2,2,2-trifluoro-*N*-phenyl-

Table 3. One-pot oxidative heteroannulation of *N*-(4-*m*ethoxyphenyl)-4-methylbenzenesulfonamide with various alkenes.



Entry	$Cu(OTf)_2$ (equivalents)	Alkene	Product		Yield [%][a]
1	0			**2a**	92
2	0			**2f**	91
3	0			**2g**	81
4	0			**2h**	trace
5[b]	0			**2h**	28
6	0.1			**2h**	80
7	0.1			**2i**	72
8	0.1			**2j**	75
9	0.1			**2k**	84
10	0.1			**2l**	72
11	0.1			**2m**	65
12	0.1		no reaction		
13	0.1		no reaction		

[a] Isolated yield.
[b] The reaction mixture was warmed up to reflux after the addition of styrene.

acetamide gave the corresponding cycloaddition product (Table 2, entries 12–15).

A proposed reaction pathway for the oxidative heteroannulation of C-4 substituted *N*-tosylaniline derivatives is outlined in Scheme 4. *In situ* oxidation of C-4 substituted *N*-tosylaniline derivatives in the presence of H_2O gives an intermediate **E**, which undergoes elimination of an XH to form intermediate *p*-quinone monosulfonimide **C** (Scheme 4). Although acetate, chloride and bromide are better leaving groups than ethers, electron-withdrawing substitution decreases the reactivity of the corresponding *N*-tosylaniline derivatives towards the oxidant.

The scope of the oxidative heteroannulation with respect to the alkenes was then investigated. In the presence of 1.2 equivalents of $PhI(OCOCF_3)_2$, the reactions of *N*-tosyl-4-anisidine with electron-rich styrenes proceeded smoothly even at room temperature. The corresponding *N*-tosyl-2,3-dihydro-5-benzofuranamine derivatives were obtained in high yields (Table 3, entries 1–3). Under the same conditions, styrene showed a lower reactivity (Table 3, entry 4). Although the heteroannulation occurred at a higher temperature, product **2h** was formed in a low yield (Table 3, entry 5).

Based on the tentative reaction pathway, Lewis acid-promoted heteroannulations were tested. Various Lewis acids were examined, and $Cu(OTf)_2$ was finally found to be the best catalyst for the heteroannulation of styrene. In the presence of 10 mol% $Cu(OTf)_2$, the reaction was completed in 2 h at room temperature, and afforded product **2h** in 80% yield (Table 3, entry 6). Further investigation indicated that even electron-poor or sterically hindered styrene derivatives were effective substrates in $Cu(OTf)_2$-catalyzed oxidative heteroannulation (Table 3, entries 7–9). It was noticeable that tetracyclic products **2l** and **2m** could be formed when bicyclic indene and 1,2-dihydronaphthalene were employed (Table 3, entries 10 and 11). The structure of compound **2m** was determined with the help of a single-crystal diffraction analysis[12] which clearly showed the *cis* junction of the dihydrobenzofuran and the tetrahydronaphthalene ring (Figure 1). We next applied our optimized $Cu(OTf)_2$-catalyzed oxidative heteroannulation conditions to aliphatic olefins. Unfortunately, neither cyclic nor acyclic aliphatic olefins gave a corresponding product (Table 3, entries 12 and 13).

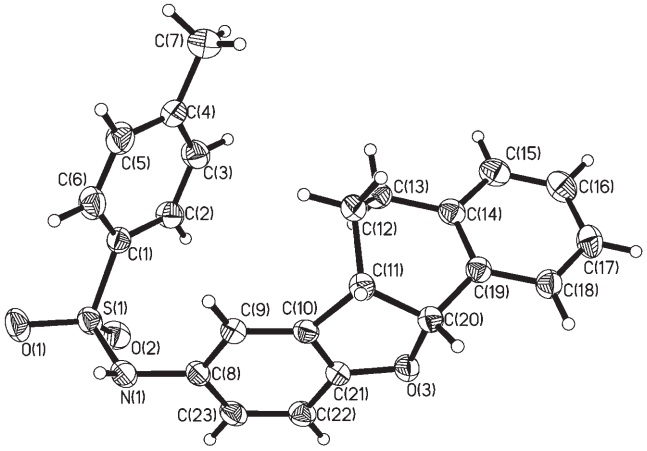


Figure 1. ORTEP view of the crystal structure of **2m**.

Conclusions

In summary, we report here an efficient one-pot oxidative heteroannulation of *N*-sulfonylaniline derivatives with styrene derivatives for the rapid construction of 5-aminocoumaran derivatives. $Cu(OTf)_2$ was found to be an excellent catalyst for the oxidative heteroannulation reactions with low reactive styrenes. The potential of this reaction system can be evaluated by its mild conditions and simple process. The scope, mechanism, synthetic application, and $Cu(OTf)_2$-catalyzed asymmetric reactions are the subject of ongoing investigations and will be reported in due course.

Experimental Section

Typical Experimental Procedure

$PhI(OCOCF_3)_2$ (1.25 mmol) was added to the solution of *N*-tosylaniline **1a** (0.5 mmol) in acetonitrile (8 mL) at −10 °C. The mixture was allowed to stir at −10 °C. Upon completion as shown by TLC, the reaction mixture was treated with 4-methoxystyrene (1.5 mmol). This was then allowed to stir at 25 °C for 15 min. The reaction was then quenched with saturated $NaHCO_3$, and extracted by ethyl acetate (100 mL × 3). The organic layer was dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product. The characterization data are available in the Supporting Information file.

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[12] CCDC 664013 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336033.

