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Competitive cascade cyclization of 2′-tosyloxychalcones: An easy access to thioflavones and thioaurones

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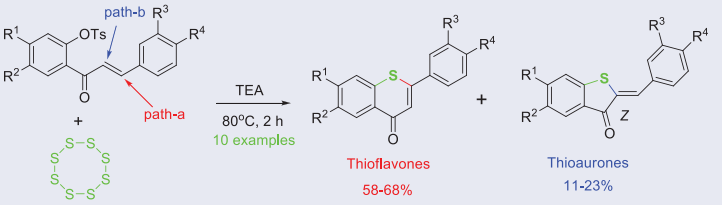
ABSTRACT

A new and efficient approach for the synthesis of thioflavones and thioaurones by competitive cascade cyclization of 2′-tosyloxychalcones has been developed. 2′-Tosyloxychalcones were smoothly converted into thioflavones and thioaurones by incorporation of sulfur atom using elemental sulfur and triethylamine in DMSO with good yields. The advantages of the methodology are the formation of both thioflavones and thioaurones in a single step. Easily accessible substrates, mild reaction conditions and compatibility with a broad range of functional groups make this protocol clean and inexpensive.

GRAPHICAL ABSTRACT



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Cyclization; sulfur; thioaurone; thioflavone; 2′-tosyloxychalcone

Introduction

Thioflavones and thioaurones are the sulfur incorporated isosteres of the flavones and aurones respectively, core constituents of natural product class of compounds[1,2] (Fig. 1). These two sulfur class of compounds have a wide range of biological activities and commercial applications. Thioflavone derivatives exhibit anti-malaria,[3] and anti-microbial activities.[4] Besides this they have inhibitory effects of steroid sulfate (STS)[5] and have specific inhibitions of ERK-MAP kinase signaling path way.[6] Moreover, substituted thioflavones exhibit highly potent antitumor and anti-carcinogenic effects.[7] Thioaurones have valuable commercial applications, as these scaffolds are used in dyes[2] and cosmetic industry.[8] Recently growing attention is to their applications in photo responsive devices and photoswitches.[9] They are also served as useful

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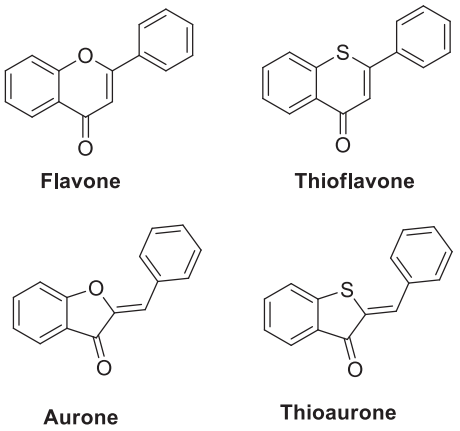


Figure 1. Structures of flavone, thioflavone and aurone, thioaurone.

intermediates for other bioactive sulfur containing molecules.[10] Thioflavones have more of biological applications whereas thioaurones are known for their commercial applications.

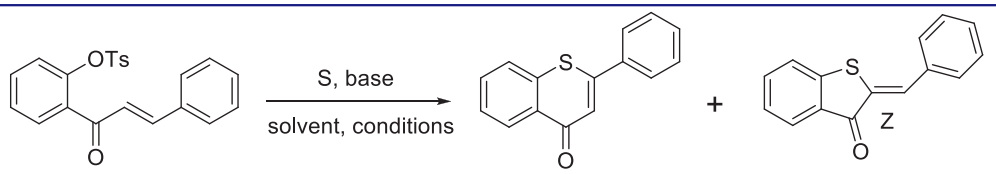
There are several methods for the synthesis of thioflavones and limited methods for the synthesis of thioaurones. Thioflavones can be synthesized starting from (a) thiosalicylic acid,[11a–d] or 2′-mercaptoacetophenone,[11e] (b) 2′-chloroacetophenones,[12] (c) 2-halobenzoyl chlorides,[13] (d) thiophenol,[14] (e) 2-(methylthio)benzoyl chloride,[15] (f) methyl 2-mercaptobenzoate,[16] (g) 2-halochalcones,[17] (h) 1-(2-(methylthio)phenyl-3-phenylprop-2-yn-1-one,[18a] and (i) thioisatins.[18b] Thioaurones can be synthesized by the general condensation method of benzothiophene-3-one with aromatic aldehydes. But it requires preparation of benzothiophene-3-one from the corresponding 2-mercaptoacetophenone.[2] Other multi-step methods are from 2-mercaptobenzoate[16] or metalation of 2-(methylthio)benzoic acid, ring closure, and aldol-type condensation[19] or 2′-nitrochalcones.[20] The above said methods have severe limitations including multistep synthesis, expensive starting materials/transition metal catalysts, and harsh reaction conditions. So, more general and simple route to synthesize thioflavones and thioaurones are still highly required.

As a part of our ongoing efforts toward the efficient synthetic methodologies of aurones and isoaurones,[21] here we report the synthesis of thioflavones and thioaurones by a cascade cyclization of 2′-tosyloxychalcones with elemental sulfur and triethylamine in DMSO.

Results and discussion

Conversion of 2′-tosyloxychalcones to either thioflavones or thioaurones would be an ideal method, as 2′-hydroxychalcones are easily accessible. We envisioned that the tosyl group is a good leaving group with sulfur nucleophile and further the rate of reaction is increased by the ortho carbonyl functionality. Then the cyclization onto enone via β and α attack could give either thioflavone or thioaurone, respectively. The 2′-tosyloxychalcones (**1**) were easily prepared[22] from the corresponding 2′-hydroxychalcones. The reaction of 2′-tosyloxychalcone (**1a**) with elemental sulfur was chosen as a model

Table 1. Optimization of the cyclization[a].



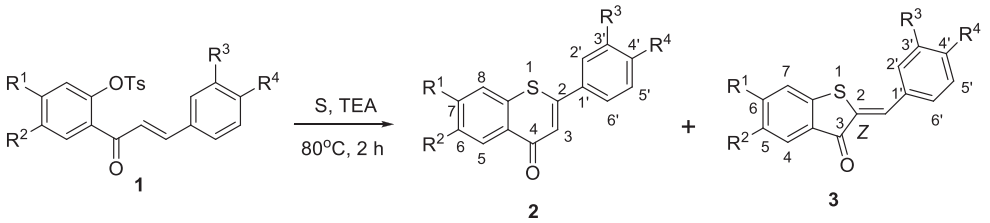
1a **2a** **3a**

						Yield[b] (%)	
Entry	Equiv. of sulfur	Base (Equiv.)	Solvent	Temp (°C)	Time (h)	Thioflavone (**2a**)	Thioaurone (**3a**)
1	1	TEA (1)	DMSO	80	6	10	2
2	2	TEA (2)	DMSO	80	5	50	8
3	3	TEA (3)	DMSO	80	2	60	10
4	5	TEA (5)	DMSO	80	2	66	14
5	10	TEA (10)	DMSO	80	2	50	5
6	5	TEA (5)	DMSO	rt	16	5	1.5
7	5	TEA (5)	DMSO	60	3	55	10
8	5		DMSO	80	4	0	0
9	5	TEA (5)	DMF	80	2	57	10
10	5	TEA (5)	PEG-400	80	4	50	10
11	5	DIPEA (5)	DMSO	80	2	40	9
12	5	DMAP (5)	DMSO	80	2	55	12
13	5	K_2CO_3 (5)	DMSO	80	4	56	10
14	5	Morpholine (5)	DMSO	80	2	20	2
15	5	NMP (5)	DMSO	80	3	60	13

[a]Reaction conditions: **1** (0.5 mmol), sulfur powder, base, and solvent (2 mL). [b]Isolated yield after column chromatography.

reaction to explore and optimize the cascade reaction, in the presence of various bases and solvents. The results were summarized in Table 1.

Cyclization of **1a** with elemental sulfur in the presence of triethylamine (TEA) at room temperature gave a low yield of products and the reaction is not completed even after 16 h (entry 6). Surprisingly at 80 °C, the cyclization proceeded cleanly and gave thioflavone (**2a**) as a major product and thioaurone (**3a**) as a minor product (entry 4) by the formation of two new C(sp^2)–S bonds from C(sp^2)–OTs aromatic bond and C(sp^2)–H vinylic bond. Formation of C–S bond via cleavage of C–O bond using sulfur and TEA is not known in the literature. Few initial experiments revealed that 5 Equiv. of sulfur is required for completion of the reaction. In the absence of base, the reaction is not progressing and hence, a base is essential for cyclization (entry 8). After establishing the role of base, the cascade reaction is checked with other bases such as N,N-diisopropylethylamine (DIPEA), 4-dimethylaminopyridine (DMAP), K_2CO_3, morpholine, and N-methylpiperidine (NMP) in DMSO. The reaction proceeds with all the above bases to give the desired products **2a** and **3a** but with lower yields than TEA/DMSO (entry 11–15). Then the cyclization with TEA is also checked with other solvents but obtained lower yields of products (entry 9, 10). Thus, cyclization of 2′-tosyloxychalcone (**1a**) with sulfur in presence of TEA in DMSO at 80 °C for 2 h gave thioflavone (**2a**) in 66% yield and thioaurone (**3a**) in 14% yield. The structures of **2a** and **3a** have been deduced from their spectroscopic data and finally confirmed by comparing them with that described in the literature.



Scheme 1. Thioflavones and thioaurones by cyclization of 2′-tosyloxychalcones.

Table 2. Formation of thioflavones and thioaurones by cyclization of **1**[a].

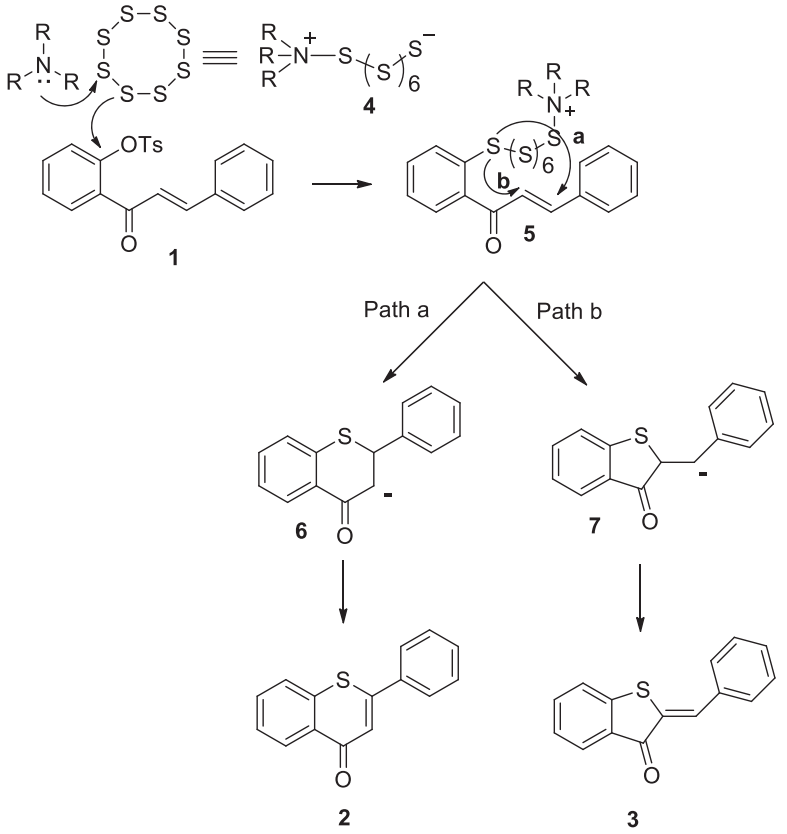
						Thioflavone (**2**)		Thioaurone (**3**)	
S. No.	Chalcone	R^1	R^2	R^3	R^4	Comp No.	Yield[b] (%)	Comp No.	Yield[b] (%)
1	**1a**	H	H	H	H	**2a**	67	**3a**	15
2	**1b**	H	H	H	OCH_3	**2b**	62	**3b**	12
3	**1c**	H	H	H	Cl	**2c**	63	**3c**	13
4	**1d**	H	H	H	CH_3	**2d**	66	**3d**	17
5	**1e**	H	H	NO_2	H	**2e**	64	**3e**	11
6	**1f**	H	H	H	$N(CH_3)_2$	**2f**	68	**3f**	23
7	**1g**	OCH_3	H	H	OCH_3	**2g**	67	**3g**	16
8	**1h**	OCH_3	H	H	Br	**2h**	58	**3h**	13
9	**1i**	H	Cl	H	OCH_3	**2i**	66	**3i**	13
10	**1j**	H	Cl	OCH_3	OCH_3	**2j**	63	**3j**	13

[a]Reaction conditions: **1** (1 mmol), sulfur powder (5 mmol), TEA (5 mmol), and DMSO (5 mL). [b]Isolated yields.

After having the optimized condition in hand, the scope and generality of the cyclization have been established as shown in Scheme 1. The generated substituted thioflavones (**2a**–**2j**) and thioaurones (**3a**–**3j**) were summarized in Table 2. A wide variety of substituents on both benzene rings of chalcone were tolerated including methoxy, methyl, nitro, and halogens. Further, there is no striking change in the ratio of formation of thioflavones and thioaurones by both electron donating and electron withdrawing substituents.

All the thioflavones (**2a**–**2j**) and thioaurones (**3a**–**3j**) were well characterized by their physical and spectroscopic data. The geometry of thioaurones was assigned as *Z*, based on the fact that the *Z*-isomer is thermodynamically more stable than *E*-isomer. Further, the chemical shift (δ) value of the vinylic proton, as well as carbon observed in the corresponding ^{1}H and ^{13}C NMR spectra are in line with the literature values.[1,2]

The mechanism of the cyclization is not very clear at this moment. In the present method, we assumed that the C–O bond is broke down by the sulfur nucleophile generated by the attack of triethylamine on sulfur powder. This concept is indirectly supported by the C–N bond cleavage with the sulfur nucleophile[20]. Hence, a cascade of sulfur nucleophilic substitution, cyclization and oxidation mechanism is described here. Initially ring opening of the cyclic octa sulfur (cyclic-S_8) by TEA leads to zwitterion **4**. The formed zwitterion (**4**) replaces highly labile aromatic tosyl group (also activated by the ortho carbonyl functionality) to give **5.** Sulfur is bivalent, so cyclization of **5** onto enone either by path-a (β-attack) or path-b (α-attack) gives dihydro-derivatives of thioflavone and thioaurone (**6** and **7**). Finally, dehydrogenation of **6** and **7** gives desired products thioflavone and thioaurone (**2** and **3**) respectively under reaction conditions as depicted in Scheme 2. Attempts to isolate any of the intermediates by carrying out the reaction at low temperatures were unsuccessful.



Scheme 2. Tentative mechanism of cyclization.

Experimental

General procedure for cyclization

To a solution of 2′-tosyloxychalcone (**1**, 1 mmol) in dry DMSO (5 mL) was added sulfur powder (160 mg, 5 mmol) and triethylamine (0.69 mL, 5 mmol) at room temperature. The mixture was stirred at 80 °C for 2 h and poured into ice cold water (40 mL). The mixture was stirred for 15 min and extracted with ethyl acetate (3 × 50 mL). The combined EtOAc layer was washed with water (50 mL), brine (50 mL), and dried over sodium sulfate. The solution was filtered and evaporated the solvent. The residue was chromatographed over silica gel column using hexane: ethyl acetate mixture as eluents to give thioaurone (**3**). Further elution of the column with the same solvent system gave thioflavone (**2**).

6-Chloro-2-(3,4-dimethoxyphenyl)-4H-thiochromen-4-one (2j)

Pale yellow color solid (210 mg, 63%), mp 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (1H, d, $J = 0.8$ Hz), 7.55–7.61 (2H, m), 7.30 (1H, dd, $J = 8.4$, 2.0 Hz), 7.21 (1H, s), 7.18 (1H, d, $J = 2.0$ Hz), 6.97 (1H, d, $J = 8.4$ Hz), 3.97 (3H, s), 3.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 153.0, 151.7, 149.7, 135.7, 134.3, 132.2, 131.9, 128.8, 128.2,

127.8, 122.1, 120.0, 111.5, 109.7, 56.1, 56.1; LC-MS (positive ion mode): *m/z* 333, 335 $(M+H)^+$; HRMS-(EI) (*m/z*): $(M+Na)^+$ calcd. for $C_{17}H_{13}ClO_3SNa$ 355.0171, 357.0142 found 355.0176, 357.0149.

(Z)-5-Chloro-2-(3,4-dimethoxybenzylidene)benzo[b]thiophen-3(2H)-one (3j)

Yellow color solid (42 mg, 13%), mp 182–184 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (1H, s), 7.85 (1H, d, $J=8.4$ Hz), 7.82 (1H, d, $J=2.0$ Hz), 7.77 (1H, dd, $J=8.4$, 2.0 Hz), 7.41 (1H, dd, $J=8.4$, 1.6 Hz), 7.38 (1H, d, $J=1.6$ Hz), 7.16 (1H, d, $J=8.4$ Hz), 3.86 (3H, s), 3.85 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 186.1, 151.4, 149.0, 143.6, 135.1, 134.7, 131.6, 131.0, 127.2, 126.3, 126.2, 125.6, 125.3, 114.0, 112.2, 55.8, 55.6; LC-MS (positive ion mode): *m/z* 333, 335 $(M+H)^+$; HRMS-(EI) (*m/z*): $(M+Na)^+$ calcd. for $C_{17}H_{13}ClO_3SNa$ 355.0171, 357.0142 found 355.0169, 357.0136.

Conclusions

In conclusion, we have demonstrated here a general and simple cascade method for the synthesis of thioflavones and thioaurones in a single reaction by using 2′-tosyloxychalcones as substrates with sulfur powder and triethylamine in DMSO. Readily accessible precursors, single step and mild reaction conditions make this protocol clean and inexpensive in economical view. Additionally, this protocol is devoid of multistep synthesis, malodorous sulfur substrates, and costly transition metal catalysts. We believe that this cyclization cascade for the formation of both thioflavones and thioaurones in a single reaction holds a potential value in the laboratory and industry in the near future.

General experimental details, characterization of compounds **2a–2i** and **3a–3i,** ^{1}H and ^{13}C NMR spectra of **2a–2j** and **3a–3j** are provided. This material can be found via the "Supplemental" section of this article's webpage.

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