Preparation of Thioflavones via Thiophosphoryl Chloride Mediated Cyclodehydration and Thionation of 1-(2-Hydroxyphenyl)-3-arylpropane-1,3-diones

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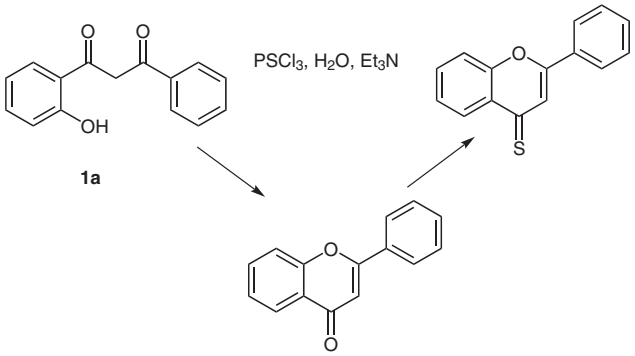
Abstract: A simple and convenient one-pot strategy for the preparation of thioflavones from 1,3-diketones is described. Cyclodehydration of a range of β-diketones and thionation of the resulting flavones was achieved using thiophosphoryl chloride ($PSCl_3$) which serves as both a catalyst and thionating agent.

Key words: β-diketones, flavones, thioflavones, thiophosphoryl chloride

Thioflavones, sulfur analogues of flavones, have been found to exhibit a wide spectrum of biological activity.[1] However, these compounds have been studied in far less detail than their oxygen-containing counterparts due to the limited availability of methods for their synthesis. Most of the current procedures for the synthesis of thioflavones are based on the thionation of flavones.[2]Although a number of efforts have been reported for the preparation of flavones,[3] their synthesis from β-diketones[4] is the most commonly accepted method. As part of our drug development program, we required a fast and efficient method for the preparation of structurally diverse thioflavones starting from β-diketones. The preparation of thioflavones from β-diketones is typically a two-step procedure involving: (i) acid-catalyzed cyclodehydration of a diketone to a flavone, and (ii) thionation of the flavone using a thionating reagent.[2] To date, both of these steps have been carried out independently using different sets of reagents and various reaction conditions.[5]In terms of reagent economy and a greener synthesis of thioflavones from β-diketones, a single reagent-driven, one-pot preparation should prove superior. In our previous work, we demonstrated that thiophosphoryl chloride ($PSCl_3$), in combination with water and triethylamine, could be used as a thionating agent for carbonyl compounds, and as an acid catalyst.[6] As part of our continued interest in the application of thiophosphoryl chloride in organic transformations, we have examined its applicability for the direct transformation of β-diketones into thioflavones, and our results are reported herein.

We envisaged that thiophosphoryl chloride would initially mediate cyclization of the β-diketone into the corresponding flavone, which would then undergo subsequent thionation by the same reagent to yield the thioflavone (Scheme 1). 1-(2-Hydroxyphenyl)-3-phenylpropane-1,3-dione (**1a**) was selected as a model substrate for this transformation.



Scheme 1 Thiophosphoryl chloride ($PSCl_3$) mediated synthesis of thioflavones from 1,3-diketones

A mixture of **1a** and thiophosphoryl chloride (one equivalent each) was stirred at 80 °C under solvent-free conditions. However, even after three hours, no appreciable cyclization of **1a** into the corresponding flavone was observed; increasing the reaction temperature did not improve the outcome. Based on our previous experience,[6] we investigated the same reaction using activated thiophosphoryl chloride (i.e., partially hydrolyzed with water and triethylamine). Thus diketone **1a** (1 mmol) was treated with thiophosphoryl chloride (1 mmol), water (1 mmol) and triethylamine (1.5 mmol) with stirring, and the mixture heated to 80 °C. As the reaction progressed, the mixture became colored and the intensity of the color increased with time. After 15 minutes, the mixture was analyzed by TLC and was found to contain the corresponding flavone and thioflavone, a considerable amount of side product and traces of the starting diketone. To prevent side-product formation the reaction was studied under various conditions (temperature, order of reagent addition and solvent). The optimized conditions required initial treatment of thiophosphoryl chloride with water (1 mmol) and triethylamine (1 mmol) resulting in a highly acidic reaction medium, followed by addition of the diketone and stirring at 80 °C. Analysis of the reaction mixture after 15 minutes indicated formation of the flavone and thioflavone, but no side product was present. To enable complete conversion of the flavone into the thioflavone, addition of a second equivalent of the reagent com-

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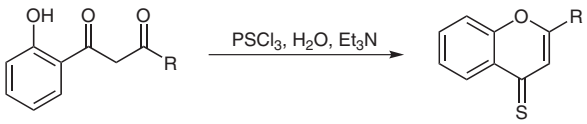
Table 1 Conversion of Various 1-(2-Hydroxyphenyl)-3-arylpropane-1,3-diones into Thioflavones[a]



Entry	R	Time (min)[b]	Yield (%)[c]	Ref.
1	Ph	90	88	2c
2	4-ClC_6H_4	90	83	2g
3	4-MeC_6H_4	90	81	2e
4	4-FC_6H_4	90	83	2e
5	4-$MeOC_6H_4$	90	78	2c
6	4-$O_2NC_6H_4$	90	82	2e
7[d]	3.4.5-$(MeO)_3C_6H_2$	110	69	2h
8	2,5-$(O_2N)_2C_6H_3$	100	94[e]	2e
9	2-thienyl	90	52	–

[a] Reactions were carried out under solvent-free conditions on 5 mmol scale.
[b] Reactions were monitored by TLC (SiO_2, hexane–EtOAc, 8:2).
[c] Yield of isolated product.
[d] Reaction facilitated by addition of $MeNO_2$ (500 µl).
[e] Conversion determined by GC–MS.

bination was required and the reaction was continued at the same temperature until complete.

The applicability of this protocol with other aryl-substituted 1,3-diketones was studied. After careful adjustments of the reaction parameters, a range of 1,3-diketones with functionalities such as halide, nitro, alkyl, alkoxy and thienyl was found undergo this transformation (Table 1). No significant difference in the reactivities of substrates containing electron-donating or electron-withdrawing groups was observed. However, the bulky substrate 1-(2-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propane-1,3-dione (entry 7, Table 1) required a longer reaction time, with enhanced side product formation resulting in a lower overall yield. A few drops of nitromethane were added to this particular reaction in order to maintain efficient mixing of the reagents. Only a moderate 52% yield of 2-(thiophen-2-yl)-4*H*-chromene-4-thione (entry 9, Table 1) was obtained. Further efforts to optimize the reaction conditions for such substrates were not undertaken. All the products gave satisfactory IR, NMR and mass spectral data and were in accord with those reported in the literature.

In conclusion, we have developed a simple convenient one-pot strategy for the preparation of thioflavones via cyclodehydration of β-diketones and subsequent thionation of the intermediate flavones. The thiophosphoryl chloride–water–triethylamine ($PSCl_3$–H_2O–Et_3N) reagent system has been utilized as a dual purpose reagent for both the cyclization and thionation steps.

Column chromatography was performed using silica gel (Spectrochem 230–400 mesh) and TLC was carried out using Merck 25 DC-Alufolien Kieselgel GF254 silica gel plates. Melting points were obtained using a Scientific MP-DS melting point apparatus. IR spectra were recorded on a Thermo Electron FTIR- 6700 spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained using a Bruker Avance DPX instrument with $CDCl_3$ as the solvent. Low-resolution electron impact (EI) mass spectra were recorded using an Agilent 5975C spectrometer. Elemental analyses were obtained using an Elementar vario Micro cube instrument.

Thioflavones; General Procedure

Et_3N (5 mmol) was added slowly to a stirred mixture containing H_2O (5 mmol) and $PSCl_3$ (5 mmol) at 30 °C. The resulting mixture was heated at 60 °C for 5 min, the β-diketone (5 mmol) added, and the mixture stirred at 80 °C for 15 min. At this point, cyclodehydration was complete and partial thionation of the flavone had also occurred (TLC, hexane–EtOAc, 8:2). To complete the thionation reaction, additional $PSCl_3$ (5 mmol) and H_2O (5 mmol) were added followed by dropwise addition of Et_3N (7.5 mmol), and heating was continued at 80 °C. On completion of the reaction (indicated by TLC), silica gel (ca. 1 g) was added and the mixture was purified by silica gel column chromatography (hexane–EtOAc, 9:1) to afford the expected thioflavone as a colored solid.

2-(Thiophen-2-yl)-4*H*-chromene-4-thione (Entry 9, Table 1)

Dark green crystals; mp 126–127 °C.

IR (KBr): 1598, 1553, 1506, 1420, 1382, 1170, 727 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (dd, J_1 = 1.6 Hz, J_2 = 6.8 Hz, 1 H), 7.77 (dd, J_1 = 1.2 Hz, J_2 = 0.8 Hz, 1 H), 7.70–7.66 (m, 1 H), 7.63–7.61 (m, 2 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.41–7.37 (m, 1 H), 7.23–7.17 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.31, 151.18, 150.40, 134.76, 134.05, 131.21, 129.79, 129.23, 128.90, 128.74, 126.21, 119.30, 118.21.

MS (EI, 70 eV): *m/z* = 244 [M^+], 200, 171, 126, 108, 100, 69.

Anal. Calcd for $C_{13}H_8OS_2$: C, 63.90; H, 3.30; S, 26.25. Found: C, 64.04; H, 3.14; S, 26.33.

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(5) A literature survey revealed a report in which the direct preparation of 2-methylchromone-4-thione from the corresponding β-diketone by refluxing in P_2S_5–pyridine was described, see: Coombers, R. C.; Fenton, D. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **1983**, *14*, 139. For comparison with our protocol, this system was utilized for the preparation of 2-phenyl-4*H*-chromene-4-thione from 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (**1a**), as a model substrate. The reaction was monitored by TLC and GC–MS, but only formation of the corresponding flavone was observed, even after stirring for 4 h.

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