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Thallium(III) *p*-tosylate (TTS) mediated oxidative rearrangement of 2-naphthyl and 2-heteroarylchromanones

Chidvilas Kurapati[a], M Muthukrishnan[b], Om V Singh[a#] & Rambabu Gundla*[a]

[a] Department of Chemistry, School of Science, GITAM Deemed to be University, Hyderabad, Telangana 502 329, India

[b] Division of Organic Chemistry-Technology, CSIR-National Chemical Laboratory, Pune 411 008, India

E-mail: rgundla@gitam.edu, om@dev-synthesis.com

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A practical and effective approach towards the synthesis of 3-hetroaryl-4*H*-chromen-4-ones by the oxidative rearrangement of the respective 2-hetroaryl chroman-4-ones using thallium(III) *p*-tosylate is described. The oxidative rearrangement of α and β-naphthyl and thiophene behave like aryl groups. However, pyridyl groups give only the dehydrogenated product.

Keywords: Oxidative rearrangements, thallium(III) *p*-tosylate, dehydrogenation, thallium(III) acetate, 2- and 3-(β-naphthyl) chromones, 2- and 3-(2-theinyl)chromones, 2- and 3-(3-theinyl)chromones, 2-(3-pyridyl)chromones, 2-(4-pyridyl)chromones

Isoflavonoids and their derivatives are sometimes referred to as phytoestrogens, as many isoflavonoid compounds have biological effects *via* the estrogen receptor. The Isoflavones can be synthesized from the conventional methods like Suzuki couplings using bromo counterparts. Here we tried to synthesis the Iso flavones containing different substituted aryl groups at 3rd position and with different electron donating and withdrawing groups at 6th and 7th positions from flavanones[1] using thallium(III) *p*-tosylate (TTS). Flavanones can be synthesized by the usual methods from the respective chalcones[2]. The substituted chalcones can be prepared from the aldehyde and 2′-hydroxyacetophenones which are commercially available.

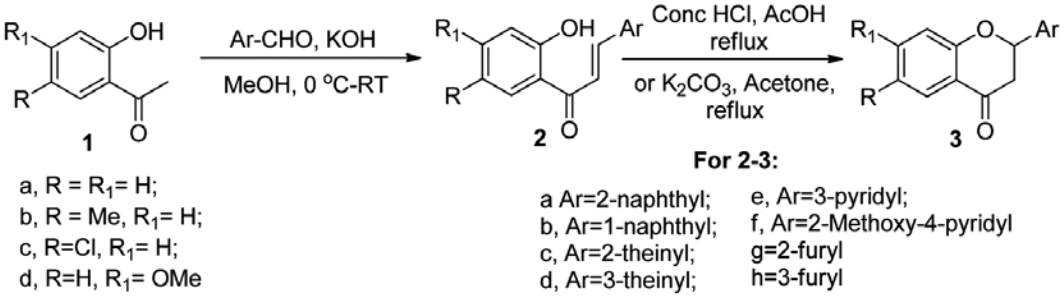
Thallium(III) salts are versatile reagents for the oxidation of a wide variety of enolic and olefinic groups[3,4] either by oxidative rearrangements[5] or with the nucleophilic displacement of the thallium substituent in the intermediate oxy- or-C-thallation adduct yielding to un-rearranged products[6,7]. Thallium(III) *p*-tosylate (TTS) was prepared *in situ* by the reaction of thallium(III) acetate (TTA) and the *p*-toluene sulfonic acid. Thallium(III) acetate (TTA) was prepared by the reaction of thallium oxide and acetic acid. TTS have been utilized for oxidative rearrangement of flavanones to isoflavones[8-11]. This biomimetic approach for the synthesis of isoflavones with hetero aryl groups was first time developed in the laboratory. The effects of different substituents at the aryl ring (electron donating and electron withdrawing groups) and have been studied and observed that electron withdrawing groups have reduced the migratory aptitude of aryl groups significantly. In these cases, dehydrogenated products were obtained as major products and oxidative rearranged as minor (20-30%, nitro group). Later on we have demonstrated that thallium(III) perchlorate (prepared *in situ* by reacting thallium(III) oxide with perchloric acid worked well with electron withdrawing groups[8] and oxidative rearranged were obtained as major products (>90%).

The objective of the present study is to further explore the scope and limitation of TTS. In this study we have used α-naphthyl, β-naphthyl and few heterocycles such as 2-theinyl, 3-theinyl, 3-pyridyl and 4-pyridyl in place of aryl ring at the 2-position of chromanones and their oxidation with TTA and TTS has been studied.

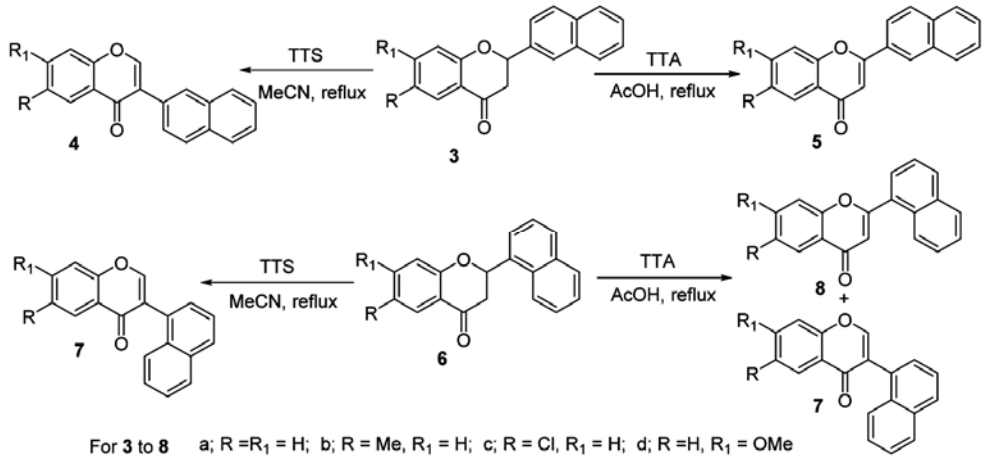
Results and Discussion

The requisite 2-substitueted chromanones were synthesized from respective 2′-hydroxyacetophenones

Present Address: Om V Singh, Devsynthesis India Pvt Ltd, Plot No 56, Ground and First floor, Tech Park, IDA Nacharam, Hyderabad, Telangana 500 076, India. E-mail: om@dev-synthesis.com



Scheme I — 2-Hetroarylchromanones

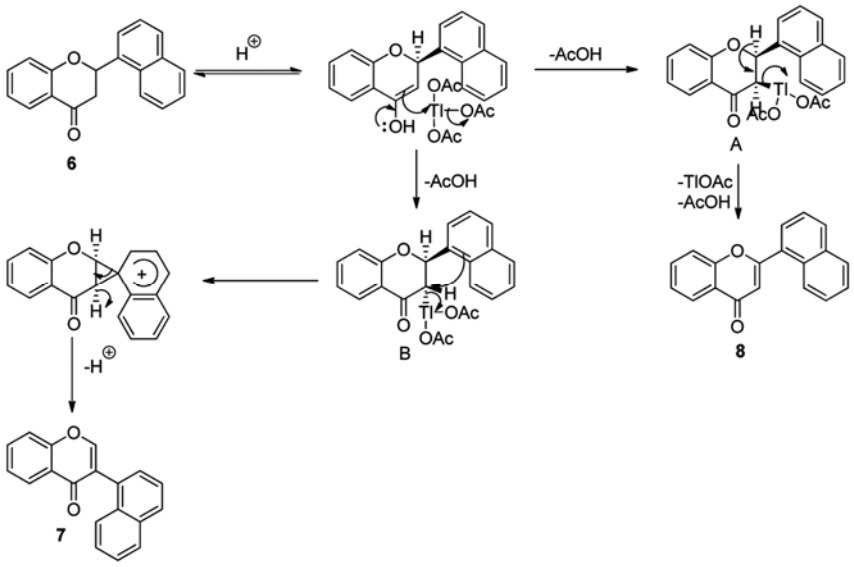


Scheme II — Oxidative rearrangement of α- and β-naphthalenes

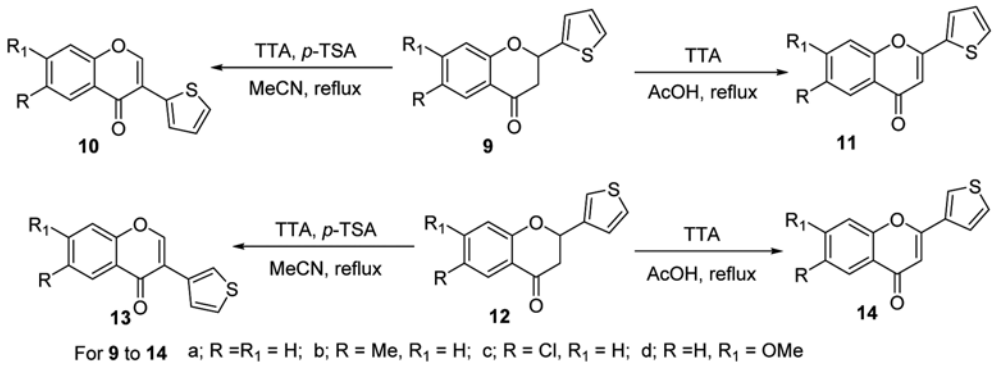
in 3 steps as outlined in Scheme I. The Claisen condensation of 2′-hydroxyacetophenones **1a-d** with substituted aromatic/heteryl aldehydes in presence of potassium hydroxide in methanol afforded the corresponding chalcone derivatives **2** in good yields (~80%). Cyclization of these chalcones under acidic or mildly basic conditions afforded respective 2-substituted chromanones **3** in 60-70% yields.

Initially, we studied the oxidation of 2-(α and β-naphthyl) chromanones (**3a-d** and **6a-c**) with TTS and TTA as depicted in Scheme II. The oxidation of 2-(β-naphthyl) chromanones **3a-d** with TTA in refluxing acetic acid gave dehydrogenated products 2-(β-naphthyl) chromones **4a-d** in excellent yield. The oxidation of **3a-d** with TTS gave only rearranged products *i.e*. 3-(β-naphthyl chromones **5a-d** in excellent yield by oxidative 2,3-aryl rearrangement as has been demonstrated in case of aryl ring. However, the oxidation of 2-(α-naphthyl) chromanones **6a-d** with TTA in refluxing acetic acid gave a mixture of 2-(α-naphthyl) chromones **8a-c** and 3-(α-naphthyl) chromones **7a-c** in almost 1:1 ratio by dehydrogenation and oxidative rearrangement, respectively. Both compounds were separated by column chromatography and characterized. We have, for the first time observed the formation of oxidative rearrangement products with TTA. Further oxidation of **6a-c** with TTS in refluxing acetonitrile gave only **7a-c** by oxidative rearrangement.

The formation of oxidative rearranged products **7a-c** during the oxidation of 2-(α-naphthyl) chromanones **6a-c** with TTA could be explained as depicted in Scheme III. The initial electrophilic attack of TTA at enolic form of 2-(α-naphthyl) chromanones would provide a mixture of intermediate **A** (*cis* C_3-thallated product) and **B** (*trans* C_3-thallated product). The formation of intermediate **A** and **B** could be explained by steric hindrance created by α-naphthyl group which would force the thallium(III) to attack at the enolic form of **6** from the back side also to generate the mixture of intermediate **A** and **B**. The reductive elimination of thallium(I) acetate from intermediate **A** would furnish 2-(α-naphthyl) chromones **8**, however, reductive elimination of thallium(I) acetate from intermediate **B** would furnish 3-(α-naphthyl) chromones **7**. This is the first time we have observed the



Scheme III — Probable mechanistic approach for the oxidative rearrangement



Scheme IV — Oxidative rearrangement for thiophene

formation of oxidative rearranged product with TTA. Hence, bulky aryl group could provide oxidative rearranged products by oxidation of chromanones with TTA as in the case of α-naphthyl group.

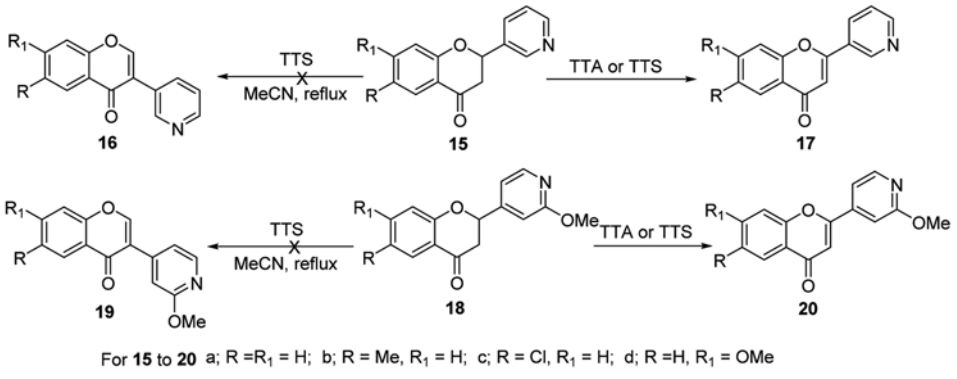
The oxidation of 2-(theinyl)chromones, 3-(theinyl)chromones with TTA and TTS have been outlined in Scheme IV. The oxidation of 2- and 3-(theinyl)chromones, with TTA in acetic acid under refluxing conditions gave the dehydrogenated products[10] (**11a-c** and **14a-c**) in excellent yields whereas oxidation with TTS in refluxing acetonitrile gave oxidative rearranged products[9] (**10a-c** and **13a-c**) in similar manner as in case of simple aryl groups.

The same methodology was also studied on 3-(pyridyl) and 4-(pyridyl) chromones (**15a-c** and **18a-b**) with TTA and TTS (Scheme V). In both the conditions, only the formation of oxidative products (**17a-c** and **20a-b**) was observed, respectively and no oxidative rearranged product was observed. It may be because of electron withdrawing nature of pyridine ring, which is much higher under acidic conditions (*p*-TSA). Similar results have been obtained when aryl ring has nitro group at *para*-position[8].

The same reactions were studied with 2- and 3-(furyl)chromones. In these reactions, no expected oxidative rearranged products were observed and compounds were decomposed under the reactions conditions, most probably due to opening of furan ring.

Experimental Section

The chemicals and solvents were purchased from Aldrich and used as received. Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectral data were recorded on a Shimadzu IR-460 instrument using the KBr self-supported pellet technique. ^{1}H and ^{13}C NMR spectra:



Scheme V — Oxidative rearrangement for pyridyl group

Bruker 400 MHz instruments using $CDCl_3$ and DMSO-d_6 (as described) as applied solvent; δ in ppm, *J* in Hz. Mass spectra obtained on a Agilent and Waters instruments at ionization potential of 70 eV. Progress of reaction was monitored by TLC and LC-MS. Thin-layer chromatography was performed using silica gel 60F 254 Al backed foils. The purifications were done by using combiflash automated system and preparative TLC.

General procedure for the oxidation of 2-substituted chromanones with Thallium(III) acetate

To a solution of 2-substitutedchromanones (**3a-d**, **6a-c**, **9a, 12a, 15a-c** or **18a** and **18c**; 1.0 eq) in acetic acid (10 vol.) was added thallium(III) acetate (1.4 eq.) and the resultant mixture was refluxed on hot plate for 2 h. The reaction mixture was cooled to RT, poured into water and extracted with dichloromethane (2 × 50 mL). The organic phase was washed with water (2 × 50 mL) followed by saturated sodium bicarbonate solution (25 mL) and dried over anhydrous sodium sulfate. The solvent was distilled off and the residue was purified by combiflash automated purification system using ethyl acetate-hexane (1: 9) as eluent to afford 2-substitutedchromones (**5a-d, 8a-c, 11a-c, 14a-c, 18a-c** and **20a-c**).

2-(2′-Naphthyl) chromone, 5a [12]: The compound was obtained as off-white solid. Yield 81%. m.p.156-158°C; ^{1}H NMR ($CDCl_3$): δ 8.49 (brs, 1H), 8.26 (dd, 1H, *J*=1.60 and 7.94 Hz), 7.99–7.87 (m, 4H), 7.62–7.56 (m, 4H), 7.45 (dd, 1H, *J*=1.54 and 8.06 Hz), 6.96 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 179.01, 163.29, 155.21, 134.01, 133.07, 132.90, 129.38, 128.30, 128.35, 127.90, 124.12, 123.52, 122.74, 118.10 and 108.01; HRMS (ESI): Calcd for $C_{19}H_{12}O_2$ $[M+ H]^+$: 273.0831. Found: 273.0926. Data was consistent with the literature reported data.

General procedure for the oxidation of 2-substitutedchromanones with thallium(III) *p*-tosylate

To a solution of (**3a-d**, **6a-c**; **9a-c, 12a-c, 15a-c** or **18a** and **18c**; 1.0 eq) in acetonitrile (10 vol.) was added thallium(III)*p*-tosylate (1.2 eq.) and the resultant mixture was refluxed on hot plate for 2 h. The reaction mixture was cooled to RT, poured into water and extracted with dichloromethane (2 × 10 mL). The organic phase was washed with water (2 × 10 mL) followed by saturated sodium bicarbonate solution (5 mL) and dried over anhydrous sodium sulfate. The solvent was distilled off and the residue was purified by combiflash automated purification system using ethyl acetate-hexane (1: 9) as eluent to afford dehydrogenated (**17a-c**, **20a** and **20c**) or oxidative rearranged products (**4a-d, 7a-c, 10a-c** and **13a-c**) and their characterization data are given in supporting information.

7-Methoxy-3-(thiophen-3-yl)-4*H*-chromen-4-one, 13c: The compound was obtained as white solid. m.p.181-183°C. Yield 65%. ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, *J*=8.8 Hz), 8.14 (s, 1H), 7.98 (t, 1H, *J*=2.0 Hz), 7.37 (d, 2H, *J*=2.0 Hz), 6.99 (dd, 1H, *J*=2.4 Hz, 8.8 Hz), 6.85-6.84 (d, 1H, *J*=2.4 Hz), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ_C 175.4, 164.09, 157.7, 152.1, 131.7, 127.9, 126.3, 125.4, 124.2, 120.3, 118.39, 114.7, 100.1 and 55.8; HRMS (ESI): Calcd for $C_{14}H_{10}O_3S$ $[M+ H]^+$: 259.0421. Found: 259.0510.

Conclusions

We have demonstrated that β-naphthyl group behaves just like phenyl group during the oxidation of 2-(β-naphthyl) chromanones with TTA and TTS and gives 2-(β-naphthyl) chromones and 3-(β-naphthyl) chromones, respectively in excellent yields. However, α-naphthyl group behaves differently and provides

3-(α-naphthyl) chromones when oxidized with TTS and a mixture of 2-(α-naphthyl) chromones and 3-(α-naphthyl) chromones with TTA. Further 2-theinyl and 3-theinyl groups also behave just like phenyl during the oxidation with TTA and TTS. However, 3-pyridyl and 4-pyridyl groups gave only dehydrogenated products irrespective of thallium(III) salts (TTA or TTS) and no rearranged product could be observed. With the 2-furyl and 3-furyl groups, none of the expected products (oxidised /oxidative rearranged products) could be observed. The furan ring opened-up during the course of reaction.

The applicative part of the present work was initiated in our lab for the synthesis of biologically active natural products. This will give a novel lead for the synthesis of natural products and will be published in the near future.

Supplementary Information

Full experimental details and, ^{1}H and ^{13}C NMR spectral data for the new compounds is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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Disclosure statement

It is stated that none of the authors have any conflict of interest in the context of this communication.

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