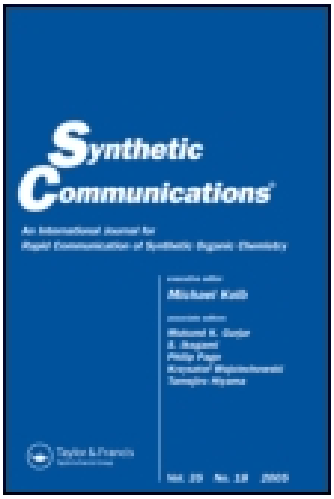

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Syntheses of 4-Aryl Chromanes: A Rearrangement Approach

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DOI: 10.1080/00397911.2015.1015140

SYNTHESES OF 4-ARYL CHROMANES: A REARRANGEMENT APPROACH

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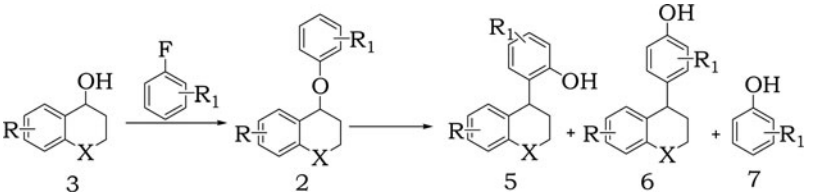
[2]*Department of Chemistry, Sri Krishnadevaraya University, Ananthapur, Andhra Pradesh, India*

GRAPHICAL ABSTRACT



Abstract *4-Aryl chromanes are synthesized from 4-Aryloxy chromanes via a rearrangement methodology.*

Keywords 4-Aryl chromanes; 4-aryloxy chromanes; 4-hydroxy chromanes; rearrangement

INTRODUCTION

Chroman(3,4-dihydro-2H-benzopyran) is an important structural moiety in many natural products with interesting biological and pharmaceutical significance.[1] In this class the 4-aryl chromans have gained considerable attention because of the interest in their biological activities such as antiestrogenic and antifertility,[2] α-adrenoreceptor-sub-type inhibition,[3] polymerase β-inhibition and COX-2 inhibition,[4] and inhibition of prostaglandin synthesis.[5] Interesting synthetic methods have been developed for the construction of the chroman unit.[6] Similarly, 4-aryl thiochromans also have shown interesting biological activities.[7]

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Address correspondence to A. V. Reddy, Research and Development Center, Suven Life Sciences Ltd., Plot No. 18, Phase III, Jeedimetla, Hyderabad 500055, India. E-mail: reddyvenis@rediffmail.com
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

RESULTS AND DISCUSSION

The retrosynthetic analysis of 4-aryl chromanes (both oxa and thia) is shown in Scheme 1.

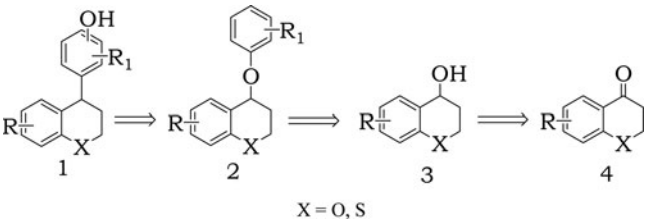
Oxa and thia chromanes **1** leads to ethers **2**, which are prepared from chromanones **4** as shown in Scheme 1. Sufficient literature is available for the preparation of chromanones **4.**[8]

We recently reported ether rearrangements of acyclic biphenyl methanols and similar aryl methanols to produce natural products and drug intermediates.[9] When the ethers of type **2** are subjected to acidic conditions they undergo rearrangement to give compounds of type **1**. The alcohols (chromanols) **3** are prepared by $NaBH_4$ reduction of chromanones **4**. Chromanols are reacted with fluoro aromatics in the presence of NaH/dimethylsulfoxide (DMSO) or KOH/DMSO to give ethers **2**.[10] Both fluoronaphthalene and fluorotoluenes are reacted with **3** to give differently substituted ethers. The ethers **2** are rearranged in the presence of $BF_3 \cdot OEt_2$ to give rearranged 4-aryl chromanes. During the rearrangement it is observed that two products, **5** and **6**, are formed invariably as depicted in Scheme 2.

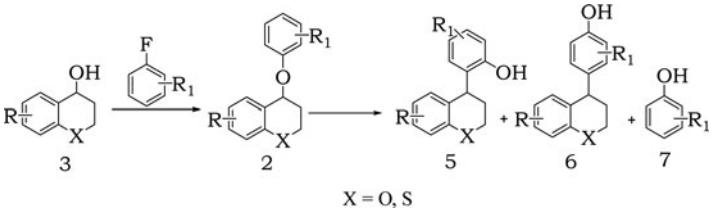
Using the optimized procedure, chromanol ethers **2** are prepared from chromanols (**3**) with different fluoro compounds under basic conditions in good yields.

Chromanol (oxa and thia) ethers when subjected to acidic rearrangement conditions gave 4-aryl chromanes **5** and **6** along with phenolic compounds. The phenolic compounds are cleaved aromatic part of ethers as shown in Scheme 2. Both aryl chromanes and phenols were separated on a silica-gel column. Mostly 4-aryl chromanes are crystalline solids (Table 1); if not, nosyl derivatives are prepared in some cases to characterize them. The structure of nosylate of **6a** was confirmed by x-ray analysis (Fig. 1).

In summary, the acid-catalyzed ether rearrangement technique is useful in producing different substituted 4-aryl oxa and thia chromanes. This method is

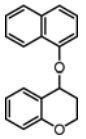
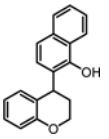
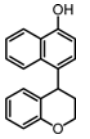
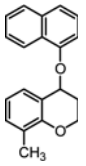
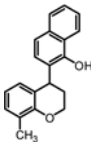
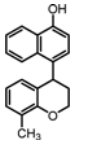
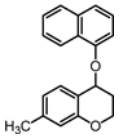
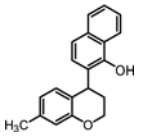
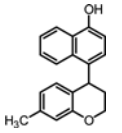
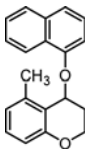
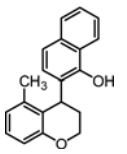
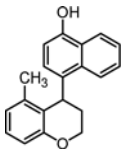
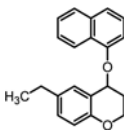
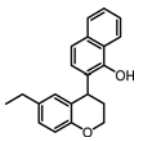
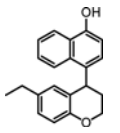
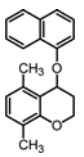
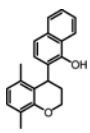
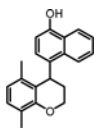
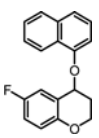
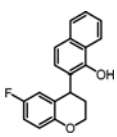
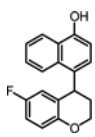
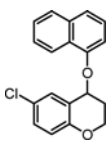
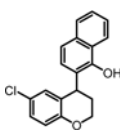
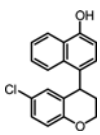


Scheme 1. Retrosynthetic analysis of chromanes via ether rearrangement method.



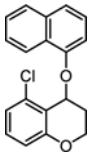
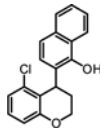
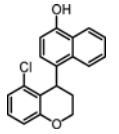
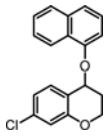
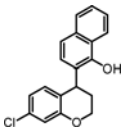
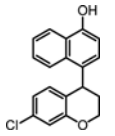
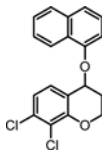
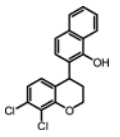
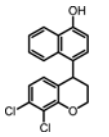
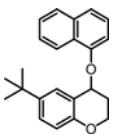
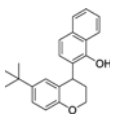
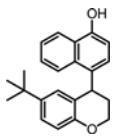
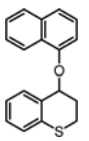
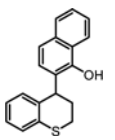
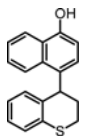
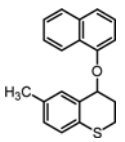
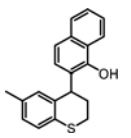
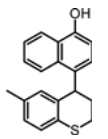
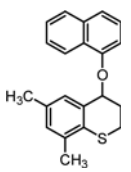
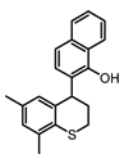
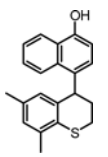
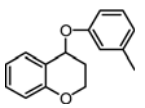
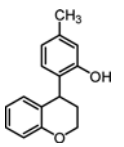
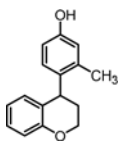
Scheme 2. Rearrangement of ethers to give 4-aryl chromanes.

Table 1. Rearrangement of ethers to give 4-aryl chromanes

		Products		Isolation		HPLC ratio (%)		
Entry	Ether (**2**)	*ortho*-Isomer (**5**)	*para*-Isomer (**6**)	**5**	**6**	**5**	**6**	**7**
A				As nosyl salt	As nosyl salt	45.6	29.8	12.7
b				As nosyl salt	Phenol	45.15	28.8	9.69
c				Phenol	Phenol	30.2	51.8	7.7
d				Phenol	Phenol	34.8	49.0	6.81
e				As nosyl salt	As nosyl salt	29.16	55.1	2.34
f				As nosyl salt	Phenol	29.82	54.8	5.52
g				As nosyl salt	Nosyl salt	45.63	27.6	10.03
h				Phenol	As nosyl salt	28.0	51.2	11.8

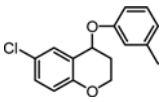
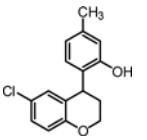
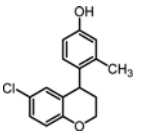
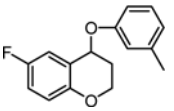
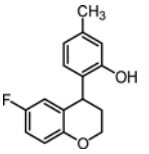
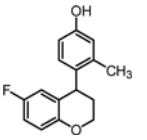
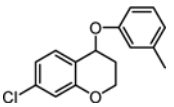
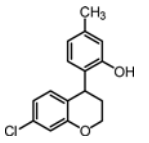
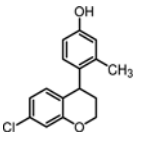
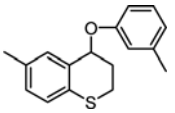
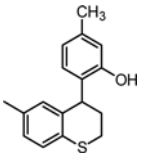
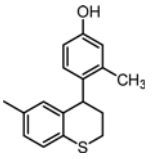
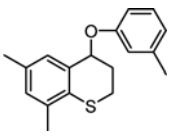
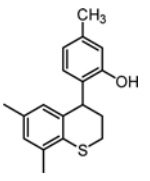
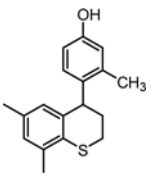
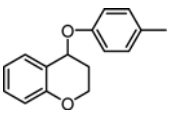
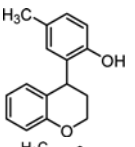
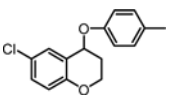
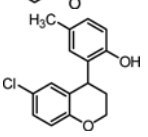
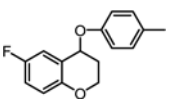
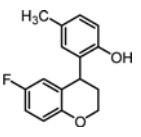
(*Continued*)

Table 1. Continued

Entry	Ether (**2**)	Products: *ortho*-Isomer (**5**)	Products: *para*-Isomer (**6**)	Isolation: **5**	Isolation: **6**	HPLC ratio (%): **5**	**6**	**7**
i				Phenol	Phenol	48.37	27.0	8.75
j				As nosyl salt	As nosyl salt	28.77	34.4	10.51
k				As nosyl salt	Phenol	50.02	25.4	11.44
l				As nosyl salt	As nosyl salt	43.14	28.3	10.33
m				As nosyl salt	Phenol	24.36	44.3	11.0
n				Phenol	Phenol	26.8	44.8	8.7
o				As nosyl salt	As nosyl salt	25.5	63.7	7.68
P				As nosyl salt	As nosyl salt	**5** 41.6	**6** 28.8	m-cresol 8.6

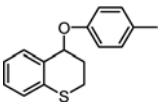
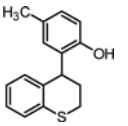
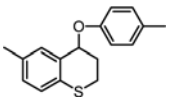
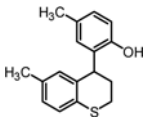
(Continued)

Table 1. Continued

Entry	Ether (**2**)	Products: *ortho*- Isomer (**5**)	Products: *para*- Isomer (**6**)	Isolation: **5**	Isolation: **6**	HPLC ratio (%): **5**	HPLC ratio (%): **6**	HPLC ratio (%): **7**
Q				As nosyl salt	As nosyl salt	30.6	32.8	5.8
R				As nosyl salt	As nosyl salt	24.4	23.6	11.6
S				As nosyl salt	As nosyl salt	38.2	29.3	4.8
T				As nosyl salt	As nosyl salt	26.8	44.8	8.7
U				As nosyl salt	As nosyl salt	25.5	63.7	7.68
V				**5** As nosyl salt	**6** —	**5** 58.8		P-cresol 11.2
W				As nosyl salt	—	61.7		8.8
X				As nosyl salt	—	60.97		14.6

(*Continued*)

Table 1. Continued

Entry	Ether (**2**)	Products: *ortho*-Isomer (**5**)	Products: *para*-Isomer (**6**)	Isolation: **5**	Isolation: **6**	HPLC ratio (%): **5**	HPLC ratio (%): **6**	HPLC ratio (%): **7**
Y				As nosyl salt	—	60.2		8.8
Z				As nosyl salt	—	61.2		12.2

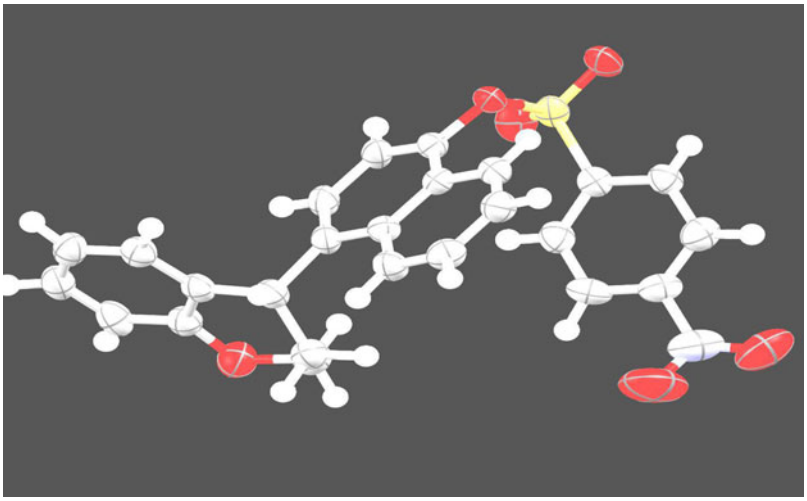


Figure 1. X-ray structure of **6a** nosylate.

practical and convenient to provide a 4-aryl chromanes from readily available 4-aryl chromanones.

EXPERIMENTAL

Most of the reagents used in this work were obtained from commercial suppliers and were of laboratory reagent or analytical reagent grade. Solvents were purified before use by standard procedures. Melting points were determined using open capillary tubes on a Polmon melting-point apparatus (model 96) and are uncorrected. ^{1}H (400-MHz) and ^{13}C (100-MHz) NMR spectra were recorded by using a Bruker 400 spectrometer with tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR spectrophotometer as KBr pellets or with the neat products. Mass spectra

were recorded on an API 2000 LCMS/MS Applied Bio Systems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240 CHN elemental analyzer. Analytical thin-layer chromatography (TLC) was conducted on E-Merck 60F254 aluminium-packed plates of silica gel (0.2 mm). Developed plates were visualized by using ultraviolet light or in an iodine chamber. High-performance liquid chromatography (HPLC) was performed by using a Shimadzu 2010 instrument.

General Procedure for Synthesis of 2a–2o: 4-(Naphthalen-1-yloxy)-chroman (2a)

A mineral oil suspension of 60% sodium hydroxide (NaH) (12.0 g, 0.3 mol) was taken in a round-bottomed flask and DMSO (200 mL) was added in 10 min at rt under a nitrogen atmosphere and stirred for 5 min. The temperature was raised to 60–65 °C and maintained for 30 min; after 30 min it was cooled to rt. A solution of **3a** (30 g, 0.2 mol in 100 mL DMSO) was added over 25 min and fluoro naphthalene (43.8 g, 0.3 mol) was also added over 10 min at rt. The temperature of the reaction mixture was raised to 60–65 °C, the mixture was stirred for 4 h, and after completion of the reaction (monitored by TLC) the reaction mass was cooled to rt. Then 10 ml of methanol was added to the reaction mixture and finally quenched into DM water (550 mL) and extracted with ethyl acetate (3×200 mL). The combined organic layer was washed with brine solution (200 mL), dried over sodium sulfate, and concentrated under reduced pressure to obtain the crude product. The crude product was purified by silica-gel chromatography to give pure **2a** (27.5 g, 60%), a white solid. Mp: 70.8–73.8 °C; IR (In KBr, cm^{-1}) 3051.5, 2879.42, 1626.0, 1578.41, 1397, 1267.75; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 2.47$ (m, 2H), 4.50 (m, 2H), 5.61 (t, 1H, $J = 5.8$ Hz), 7.0 (d, 1H, $J = 4.1$ Hz), 7.04 (d, 1H, $J = 7.8$ Hz), 7.12 (d, 1H, $J = 7.35$ Hz), 7.57 (m, 6H), 7.89 (d, 1H, $J = 7.98$ Hz), 8.31 (d, 1H, $J = 8.21$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 27.57$, 62.44, 106.14, 117.15, 118.12, 120.62, 120.94, 121.27, 122.46, 125.41, 125.79, 126.60, 127.54, 131.10, 130.93, 134.89, 153.14, 155.30. Mass for $C_{19}H_{16}O_2$: 277.0. Anal. calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.61; H, 5.80.

General Procedure for Synthesis of 5a–5z and 6a–6z: 3-Chroman-4-yl-naphthalen-2-ol (5a) and 4-Chroman-4-yl-naphthalen-1-ol (6a)

$BF_3 \cdot OEt_2$ (20 mL) was added over 10 min to a cooled and stirred solution (10–15 °C) of **2a** (20.0 g, 0.07 mol) in ethyl acetate (200 mL), and the reaction mass allowed to come to rt and stirred for 3 h. After completion of the reaction (monitored by TLC), the reaction mass was quenched in DM water (150 mL) and the organic layer was separated. The aqueous layer was again extracted with ethyl acetate (100 mL), and the combined organic layers were washed with brine solution (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to get the crude product. The crude product was purified with silica-gel column chromatography. On eluting with 20% ethyl acetate in hexane, **5a** (3-chroman-4-yl-naphthalen-2-ol) was obtained as a red liquid. Compound **6a** (4-chroman-4-yl-naphthalen-1-ol) was obtained later as a brown liquid.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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