The First Facile Synthesis of Some 1,2*a*,3,8*b*-Tetrahydro-2*H*-Cyclobuta[*c*] Chromenes Through Intramolecular Alkylation of an Aromatic Ring by a Cyclobutanone

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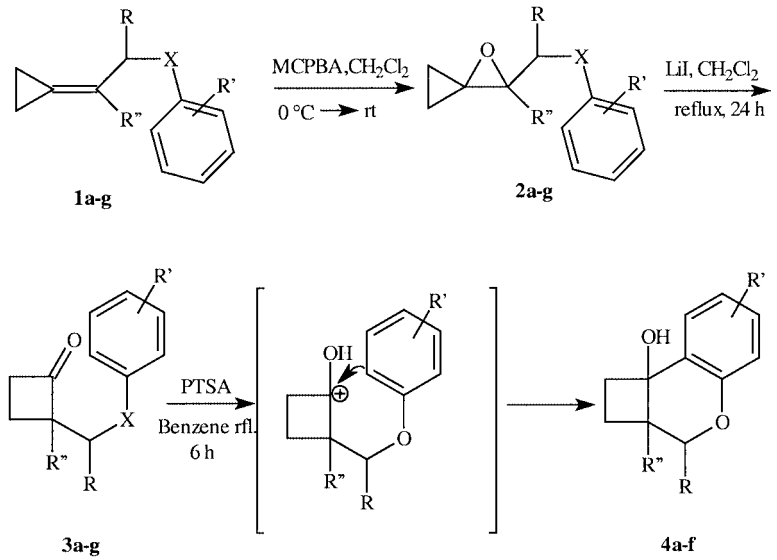
Abstract: Starting from cyclobutanones several new chromenes containing a cyclobutane ring are prepared. Ring fission of these derivatives gives easy access to functionalized 3-isoflavenes.

Key words: cyclopropanes, cyclobutanones, electrophilic aromatic substitutions, ring opening, kinetic resolution

Cyclobutanones are the basic structure of several natural products and are useful intermediates in the synthesis of many natural products and different molecules.[1,2] While they are mostly synthesized by [2+2] cycloaddition reactions between ketene and olefins, much effort is now being devoted to methods that use as starting material suitably substituted cyclopropanes.[2,3] The most common reactions using cyclobutanones as useful intermediates include their transformation into γ- lactones, pyrrolidones, cyclopentanones and cyclohexanones.[1] They undergo easily the Favorskii[4] rearrangement to give cyclopropanecarboxylic acids and react very easily with vinyl metals to give the corresponding 1-vinylcyclobutanols that can undergo many useful transformations.[1]

We now report a new use of the cyclobutanone ring as an intramolecular alkylating reagent of an oxygen substituted aromatic ring, to give access to a new versatile class of benzopyrans. As a matter of fact the cyclobutanones **3** have been prepared by lithium iodide induced ring enlargement[5] of the oxaspiropentane **2**,[6] obtained by epoxidation of the easily accessible[7] alkylidenecyclopropanes **1** (Scheme 1). Treating **3a–f** with PTSA in refluxing benzene for 6 h the new derivatives **4a–f** were obtained in 30–70% yields (Table) probably through protonation of the oxygen atom of the cyclobutanone and consequent alkylation of the activated aromatic ring.[8] Activation of the aromatic ring is necessary as demonstrated by the unreactivity of the cyclobutanone **3g** lacking the oxygen atom. The stereochemistry of the R″ and the OH group in the derivatives **4a–f** was demonstrated to be *cis* by NOE experiments.

In the case of derivative **3e** the corresponding compound **4e** was formed together with some amount of the isoflavene **5e** carrying a two carbon chain with a terminal tosyloxy group, probably coming from the ring fission of the



Scheme 1

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Table Reaction of Cyclobutanones **3a–g** with PTSA.

3	X	R	R′	R″	Yield **4** (%)[a]
a	O	H	H	CH_3	50
b	O	H	*p*-OCH_3	CH_3	70
c	O	H	*p*-Cl	CH_3	65
d	O	H	*m*-CH_3	CH_3	70[b]
e	O	H	H	C_6H_5	60
f	O	CH_3	H	CH_3	30[c]
g	CH_2	H	H	CH_3	0

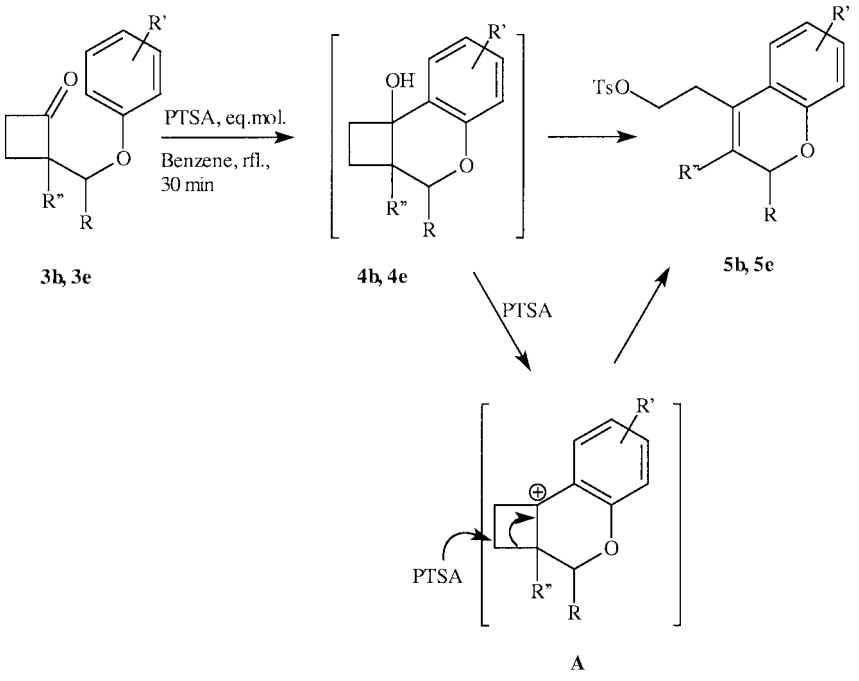
[a] Isolated yield.
[b] Yields referred to the two regioisomers **4d** and **4d′** formed in the 4:5 ratio.
[c] Only one diastereoisomer has undergone cyclization, (vide infra).

intermediate cyclobutyl cation **A** by PTSA (Scheme 2). Using an equimolar amount of PTSA, derivatives **3b** and **3e** were completely transformed, after 30 min into **5b** and **5e** in satisfactory yields (50% and 60% respectively) (Scheme 2).

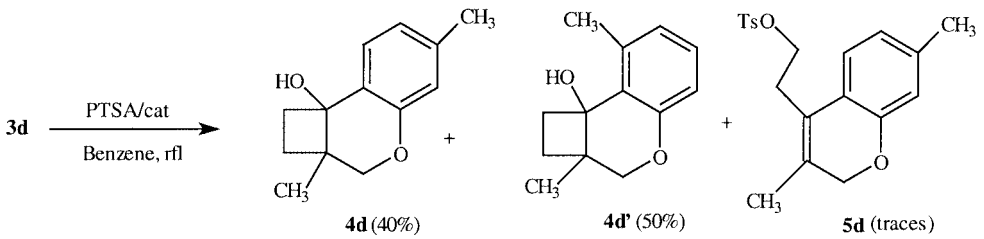
Derivative **3d** gave the two possible regioisomers **4d** and **4d′** in roughly the same quantities, accompanied by small quantities of the chromene **5d** coming from the cyclobutyl ring fission of the derivative **4d** (Scheme 3).

Derivative **3f** prepared as a mixture (60:40) of the two possible diastereoisomers, is particularly interesting for what concerns the stereochemistry of the corresponding ring closure product. In fact using catalytic amounts of PTSA in refluxing benzene, after 6 h it was possible to isolate from the reaction mixture only the cyclobutanol **4f** accompanied by small amounts of the chromene **5f** and the most abundant unreacted diastereoisomer of the starting cyclobutanone, through a kinetic resolution (Scheme 4).

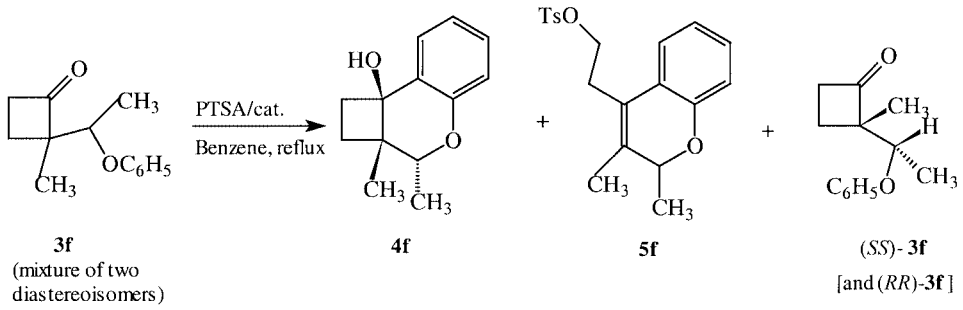
The stereochemistry of the cyclobutanol **4f**, assigned on the basis of NOE experiments, shows that the relative position of the two methyl groups is *trans*, while the apical methyl group, at 1.24 ppm, and the alcoholic OH are in relative *cis* position. On the basis of the steric constraints present during the cyclization step only the diastereoisomer with the *SR* configuration, and of course its *RS* enantiomer can give rise to the chromene **4f** with the found stereochemistry. The unreacted recovered **3f** will therefore have the *SS* and *RR* stereochemistry and its unreactiv-



Scheme 2



Scheme 3



3f (mixture of two diastereoisomers) **4f** **5f** (*SS*)- **3f** [and (*RR*)-**3f**]

Scheme 4

ity could be explained with the unfavorable steric hindrance present in the generation of the other possible chromene, that should have all the three groups in relative *cis* position.

In conclusion we have reported a synthesis of a new class of chromenes containing the cyclobutane ring that is susceptible to be opened as a consequence of its strain to new functionalized chromenes. This transformation is particularly important as it represents a versatile access to the family of the isoflav-3-enes bearing a 2*H*-1-benzopyran nucleus that are gaining increasing importance for their antiestrogen activity.[9] Chiral non racemic version of this reaction is being studied and the results will be presented in due course.

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Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and by the University of Cagliari (National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni') and from C.N.R. (Italy) is gratefully acknowledged.

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(6) It has not been possible to isolate the oxaspiropentane **2e**, as it is transformed to the corresponding cyclobutanone **3e** during the epoxidation reaction.

(7) Some derivatives have been previously reported. For **1a–e, g** see: (a) Bernard, A. M.; Piras, P. P. *Synth. Commun.* **1997**, *27*, 709. (b) Bernard, A. M.; Piras, P. P. *Synlett* **1997**, *5*, 585. (c) Brandi, A.; Carli, S.; Goti, A. *Heterocycles* **1988**, *27*, 17. (d) For **2a**,**b**, **3a** see: Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P. *Synlett* **1998**, 668. (e) For **3b** see: Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P. *Tetrahedron* **2000**, *56*, 4555.

(8) Typical procedure for the preparation of chromenes **4a**–**f**: A stirred solution of cyclobutanone **3** (2.7 mmol) and *p*-toluenesulfonic acid (0.27 mmol, 0.046 g) in benzene (10 mL) was refluxed for 6 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to remove the solvent. The residue was purified by chromatography on silica gel with Et_2O–light petroleum (1:1) as eluent.
All new compounds have been fully characterized by ^1H NMR (300 MHz), ^{13}C NMR (75.4 MHz) and mass spectra (70 eV). Analytical data for some representative derivatives are reported. **1f:** colorless oil; yield: 70%. ^1H NMR ($CDCl_3$) δ: 1.00–1.22 (m. 4 H), 1.52 (d, 3 H, *J* = 6.6 Hz), 1.84 (s, 3 H), 5.05 (q, 1 H, *J* = 6.6 Hz), 6.90–7.28 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ: 1.14, 2.76, 15.10, 19.71, 78.56, 115.65, 118.76, 120.65, 124.74, 129.12, 158.16. **3e:** yellow oil; yield: 85%. ^1H NMR ($CDCl_3$) δ: 2.48–2.58 (m, 1 H), 2.73–2.82 (m, 1 H), 2.98–3.10 (m, 1 H), 3.18–3.30 (m, 1 H), 3.97, 4.23 (AB q, 2 H, *J* = 9 Hz), 7.22–7.44 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ: 21.09, 44.09, 72.06, 72.54, 114.58, 121.25, 126.58, 127.50, 128.69, 129.43, 137.83, 158.43, 210.17. IR (neat, cm^{-1}) : 1782. MS *m/z*: 252 [M^+ (0.4)], 209(5), 195(9), 159(100), 131(23), 117(60). **4e:** yellow oil; yield 60%. ^1H NMR ($CDCl_3$) δ: 2.13–2.27 (m, 1 H), 2.19 (br s, 1 H), 2.26–2.33 (m, 2 H), 2.54–2.61 (m, 1 H), 4.05,4.14 (AB q, 2 H, *J* = 11.4 Hz), 6.85–7.65 (m, 9 H). ^{13}C NMR ($CDCl_3$) δ: 19.94, 36.76, 52.91, 71.74, 72.68, 117.29, 122.08, 127.22, 127.32, 127.58, 128.57, 128.79, 129.73, 138.37, 154.17. IR (neat, cm^{-1}) : 3450. MS *m/z*: 252 [M^+(6)], 234(5), 224(8), 121(100). **5e:** red oil; yield 56%. ^1H NMR ($CDCl_3$) δ: 2.41 (s, 3 H), 2.81 (t, 2 H, *J* = 7.5 Hz), 3.99 (t, 2 H, *J* = 7.5 Hz), 4.78 (s, 2 H), 6.81–7.64 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ: 21.55, 26.98, 68.19, 69.39, 116.19, 121.51, 122.60, 123.25, 124.00, 127.69, 127.78, 128.02, 128.77, 128.91, 129.69, 132.69, 134.34, 13.44, 144.54, 153.89. IR (neat, cm^{-1}): 1160,1350.

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