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Improved Procedure for 3,4-Dihydro-1H-2-Benzopyran Ring Closure. A General Access to 3-Substituted Isochromanes.

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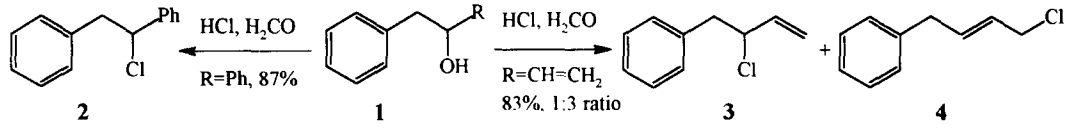
Abstract: A general method for the ring closure of 1-substituted 2-(-hydroxymethyl)-phenylethanols to 3-substituted isochromanes using *p*-TsOH supported on silica gel is reported.

In the course of studies on selective oxidation by dimethyldioxirane[2] we needed a method to prepare 3-arylisochromanes from readily available substrates in good yields with a variety of substituents on the aromatic rings, reported syntheses[3,4,5] being limited in that they are not applicable to isochromanes with an aromatic substituent at C-3. For example the procedure by Singh[4] for 3-alkylisochromanes fails in the synthesis of 3-aryl and 3-vinyl isochromanes, the chloroderivative **2** being the main product obtained from 1-phenyl-2-phenylethanol, and **3** and **4** from 1-vinyl-2-phenylethanol (scheme 1).

Scheme 1



2 **1** **3** **4**

A recent procedure by Azzena[5] and co-workers allowed us to prepare 3-phenylisochromane in good yield, but when the reaction was carried out with diols which are endowed with electron rich aryl groups (i.e. R= (*p*-OCH_3-aryl), the second step resulted in a dehydration process.[6]

Since the procedure of Azzena allows the preparation of a wide range of diaryl diols in moderate-good yields, starting from phthalane and readily available substituted benzaldehydes, our target was to find a general procedure for cyclisation of such diols.

Preceeding studies[7] prompted us to consider the possibility of performing the reaction using toluene *p*-sulfonic acid supported on silica gel, since the proximity between the two carbinol groups should

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promote intramolecular substitution vs elimination, as for a general acid catalysis.[3]

As reported in Table 1, the *p*-TsOH/SiO_2 system was very efficient and general, leading to alkyl, alkenyl or aryl isochromanes in very good yields and short reaction times.

Table 1.

Entry	R	Method[a]	Temperature	Time	Yield%[b]
1	C_6H_5	*p*-TsOH/SiO_2	r.t	8 h	83
2		*p*-TsOH	r.t.	2 days	69
3	*p*-$OCH_3C_6H_4$	*p*-TsOH /SiO_2	r.t.	15 min	94
4		*p*-TsOH	r.t.	15 min	95
5	*p*-FC_6H_4	*p*-TsOH /SiO_2	reflux	1.5 h	83
6		*p*-TsOH	reflux	10 h	77
7	*m*-FC_6H_4	*p*-TsOH /SiO_2	reflux	2 h	80
8	*p*-$NO_2C_6H_4$	*p*-TsOH /SiO_2	reflux	4 h	64
9	(*E*)CH=CH-CH_3[c]	*p*-TsOH /SiO_2	r.t.	5 min	93
10		*p*-TsOH	r.r.	30 min	81
11	$(CH_2)_4CH_3$	*p*-TsOH /SiO_2	reflux	3 h	76

[a]A mixture of *p*-TsOH and silica gel was prepared dissolving 1.5 g of acid in $CHCl_3$ and adding 9 g of SiO_2 (200-400 mesh, Merck); diols were dissolved in 4 ml $CHCl_3$ and treated with 150 mg of this mixture in the reported conditions. [b]Yields are of isolated product. [c]The (*E*) isomer was produced.

In certain cases *p*-TsOH alone was also effective, but the process was generally much slower, pointing out the catalytic effect of silica gel and confirming our concerns about the reaction pathway, in which the absorption step is crucial.

The rate of this method is strongly dependent on the substituents on the aromatic ring at C-1: electron-donating groups on the *para* position favour the reaction (entry 3), while electron-withdrawing groups make the process slower (entries 5,7,8). Worthy of note is the case of (*E*) 1-(2-hydroxymethyl)phenylpent-3-en-2-ol (entry 9), which reacted with an extraordinary efficiency, affording the corresponding 3-crotylisochromane in just few minutes.

Experiments performed under the same conditions using molecular sieves instead of silica gel did not give the same results.

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