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An Unexpected Thermal [1,3]-[1,3]-*para* Rearrangement of Chromone-3-ylmethyl Aryl Ethers: Mechanism and Application of the Intercepted [1,3]-Rearranged Intermediates to the Synthesis of *cis*-Homopterocarpans

Krishnan Devarajan,[1] Somasundaram Devaraj,[1] Kalpattu K Balasubramanian,[2] and Shanmugasundaram Bhagavathy*[1]
[1]*Department of Chemistry, B. S. Abdur Rahman University, Seethakathi Estate, Vandalur, Chennai 600 048, India*
[2]*Shasun Pharmaceuticals Ltd., Vandalur Kelambakkam Road, Vandalur, Chennai 600 048, India*

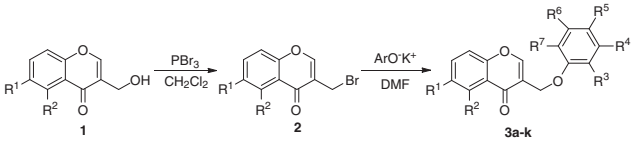
(E-mail: bhagavathy@bsauniv.ac.in)

Chromone-3-ylmethyl aryl ethers with unsubstituted *ortho*-positions have been found to undergo a novel domino [1,3]-[1,3]-rearrangement to give 4′-hydroxyhomoisoflavones under thermal conditions while the *para*-substituted ethers lead to 2′-hydroxyhomoisoflavones involving an *O*- to *C*-[1,3]-migration, instead of the expected Claisen rearrangement. A few *cis*-homopterocarpans have been synthesized using the 2′-hydroxyhomoisoflavones obtained from the thermal [1,3]-rearrangement of chromene-3-ylmethyl aryl ethers.

Despite the passage of more than ten decades, Claisen rearrangement[1] continues to receive wide attention for its synthetic applications as well as for its mechanistic aspects.[2] The aromatic Claisen rearrangement which involves a [3,3]-sigmatropic shift provides a convenient entry to *ortho*-allylphenols, precursors to a variety of heterocycles such as chromans, coumarins, etc. The intervention of *O*- to *C*-[1,3]-migration is very rarely encountered in an uncatalyzed thermal aromatic Claisen rearrangement,[3] though this is frequently observed under conditions of acid catalysis and transition-metal catalysis.[2a,2c,4] The *para*-Claisen rearrangement typically follows a domino pathway viz., *ortho*-Claisen rearrangement, which involves a [3,3]-sigmatropic shift followed by a Cope rearrangement that is also a [3,3]-sigmatropic shift. But, there are hardly any examples of *para*-Claisen rearrangements involving a domino [1,3]-[1,3]-migration.[5] During the course of our study on the thermal Claisen rearrangement of chromone-3-ylmethyl aryl ethers **3**, we encountered an unexpected and rare *para*-Claisen rearrangement that we describe in this paper. Thermally, the aryl ether **3** with unsubstituted *para*-position and at least one unsubstituted *ortho*-positions leads to the formation of 4′-hydroxyhomoisoflavones **4** via a novel domino [1,3]-[1,3]-rearrangement, while the *para*-substituted aryl ether leads to 2′-hydroxyhomoisoflavones **6** via a direct [1,3]-shift. We also report the synthesis of a few homopterocarpans using our [1,3]-*ortho* rearrangement strategy.

Our initial attempts to synthesize the chromone-3-ylmethyl aryl ethers **3** via the Buchwald–Hartwig coupling reaction of the alcohol[6] **1** with aryl halides led only to the formation of trimeric compounds.[7] Hence, the aryl ethers **3a**–**3k** were prepared in very good yields from the respective alcohol **1** by the standard sequence of reactions as depicted in Scheme 1 (Table 1).

Thermal rearrangement of the ether **3a** was investigated in different solvents like DMF, *o*-dichlorobenzene, *N*,*N*-diethylaniline, diphenyl ether, etc. Among these, diphenyl ether (Ph_2O) turned out to be the best solvent which led to a relatively faster reaction (4 to 5 h) with good yields. Refluxing the ether **3a** in Ph_2O for 4 h led to the product **4a**, product of *para*-rearrangement (Scheme 2). The structure was also confirmed by characterizing its acetate derivative **5a**. A few other *para*-unsubstituted ethers **3b**–**3g** also underwent similar rearrangements to afford the corresponding 4′-hydroxyhomoisoflavones **4b**–**4g** (Table 2).

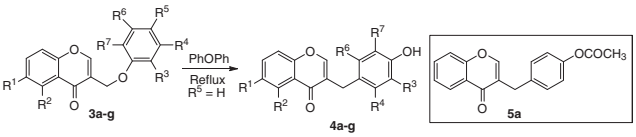


Scheme 1. Synthesis of aryl ethers **3**.

Table 1. Synthesis of chromone-3-ylmethyl aryl ethers **3**

Entry	Ether **3**	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield[a]/%
1	**3a**	H	H	H	H	H	H	H	82
2	**3b**	–CH=CH–CH=CH–		H	H	H	H	H	69
3	**3c**	H	H	Cl	H	H	H	H	76
4	**3d**	H	H	Me	H	H	H	H	66
5	**3e**	H	H	H	Me	H	Me	H	69
6	**3f**	–CH=CH–CH=CH–		Me	H	H	H	H	73
7	**3g**	H	H	Me	H	H	H	Me	76
8	**3h**	H	H	H	H	Me	H	H	80
9	**3i**	H	H	H	H	Cl	H	H	71
10	**3j**	H	H	H	H	Et	H	H	71
11	**3k**	H	H	H	H	OMe	H	H	68

[a]Isolated yield after column chromatography.



Scheme 2. Thermal rearrangement of *para*-unsubstituted aryl ethers **3a**–**3g**.

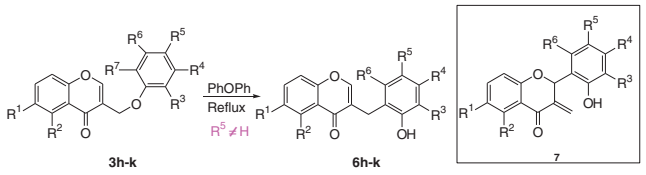
But, the *para*-substituted aryl ether **3h** upon refluxing in Ph_2O afforded the 2′-hydroxyhomoisoflavone **6h**,[8] a product of formal [1,3]-shift. It is to be noted here that we did not observe the product due to [3,3]-shift viz., **7** (Scheme 3 and Table 2), in any of the cases.

Recently, Hou et al.[3] had observed that thermal rearrangement of aryl cinnamyl ethers gave rise to a mixture of products due to normal [3,3]-shift and formal [1,3]-shift. These authors have shown that the formal [1,3]-shift product actually stems from a domino process due to migration of the aryloxy moiety

Table 2. Thermal rearrangement of chromone-3-ylmethyl aryl ethers **3** in Ph_2O

Entry	Substrate	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Pdt	Yield[a] /%
1	**3a**	H	H	H	H	H	H	H	**4a**	84
2	**3b**	–CH=CH–CH=CH–		H	H	H	H	H	**4b**	73
3	**3c**	H	H	Cl	H	H	H	H	**4c**	72
4	**3d**	H	H	Me	H	H	H	H	**4d**	71
5	**3e**	H	H	H	Me	H	Me	H	**4e**	66
6	**3f**	–CH=CH–CH=CH–		Me	H	H	H	H	**4f**	76
7	**3g**	H	H	Me	H	H	H	Me	**4g**	68
8	**3h**	H	H	H	H	Me	H	H	**6h**	83
9	**3i**	H	H	H	H	Cl	H	H	**6i**	73
10	**3j**	H	H	H	H	Et	H	H	**6j**	69
11	**3k**	H	H	H	H	OMe	H	H	**6k**	65

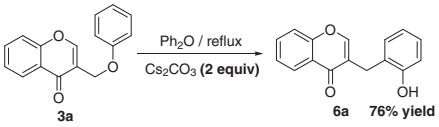
[a]Isolated yields after column chromatography.



Scheme 3. Thermal rearrangement of *para*-substituted aryl ethers **3h**–**3k**.

from α- to γ-position of the allyl group (*C*- to *C*-[1,3]-shift), designated by them as O[1,3] shift, followed by a [3,3]-shift. Majumdar et al. observed that thermal rearrangement of coumarin-3-ylmethyl aryl ethers led to *para*-migration products when the *para*-position is unsubstituted and *ortho* [1,3]-products when the *para*-position is blocked.[9] They speculated that the *para*-rearrangement proceeds through a direct migration of the allyl moiety involving a [1s,5s]-shift (which is geometrically not feasible) and the *ortho*-rearrangement via a [1s,3s]-shift. In view of these reports, we investigated the mechanism of our transformation of the ethers **3** to the aryl chromones **4** and **6** in detail.

We observed that the thermal transformation of the ether **3a** to chromone **4a** was inhibited neither when the reaction was performed in *N*,*N*-diethylaniline, which is known to be a good free radical inhibitor,[10] nor in the presence of free radical inhibitors like Tempo or BHT in Ph_2O. The possibility of a breakage of the ether **3** into its ion pairs and recombination of the ion pairs within the solvent cage is ruled out, as there was no change in the course of the reaction on going from nonpolar Ph_2O to a mixture of Ph_2O and dipolar aprotic *N*-methyl-2-pyrrolidone, as monitored by HPLC. The findings from a crossover experiment conducted with ethers **3b** and **3d** ruled out the possibility of a breakage and recombination mechanism. When an equimolar mixture of the ethers **3b** and **3d** was refluxed in Ph_2O and the crude products analyzed by HPLC, we could detect only the phenols **5b** and **5d** and no evidence could be found for the presence of the crossover products **5a** and **5f**. In addition, we did not find any evidence for the formation of *bis*-alkylated products,[4a] which rules out the mechanism based on breakage and ion pair recombination outside the solvent cage. It is known that $CaCO_3$ can stop the Claisen rearrangement at the



Scheme 4. Rearrangement of ether **3a** in the presence of Cs_2CO_3.

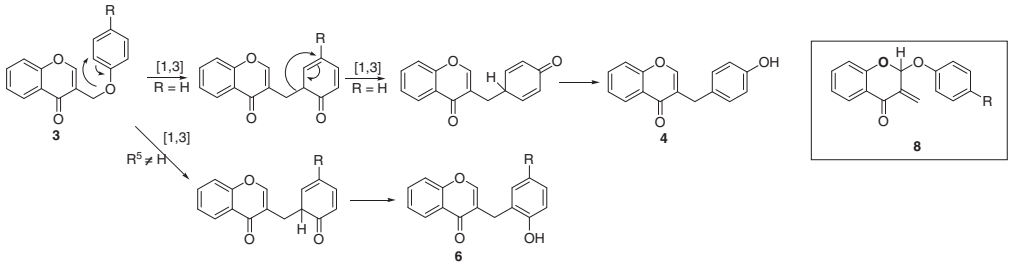
ortho stage by bringing about the rapid enolisation of the *ortho*-dienone.[11] We found no change in the course of the reaction upon refluxing the ether **3a** in Ph_2O in the presence of $CaCO_3$, and the same *para*-migration product **4a** was isolated. Interestingly, the rearrangement of aryl ether **3a** to the phenol **6a**, which is the product of [1,3] migration could be achieved by using Cs_2CO_3 (Scheme 4). Further, in a control experiment, it was observed that the phenolic product of *ortho* [1,3]-rearrangement **6a** was stable under thermal conditions and did not get converted to the *para*-rearrangement product **4a**. These findings reveal that the first intermediate in the *para*-rearrangement arises out of a direct migration of the chromenylmethyl moiety from *O*- to *ortho* carbon, viz., *O* to *C*-[1,3]-shift.

When the progress of the reaction in the case of **3a** was followed by HPLC, no evidence could be seen for the formation of *ortho*-dienone intermediate or for the phenol **6a** indicating that *para*-rearrangement is much faster compared to the initial *ortho*-migration and enolisation of the *ortho*-dienone. Nor was there any indication for the intermediate **8** (Scheme 5).[3]

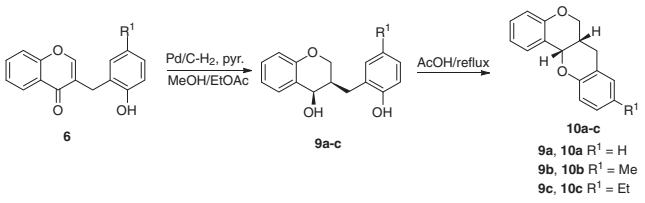
In the case of the rearrangement of *para*-substituted ether **3h**, HPLC and NMR reaction monitoring again did not reveal the formation of any intermediate. The NMR spectra of the samples taken in the early stages were devoid of the signals due to the exomethylene protons and acetal protons, characteristic of **8**, which is a crucial intermediate in the mechanistic pathway based on the work of Hou et al.[3] Thus, the HPLC and NMR reaction monitoring of this rearrangement clearly rules out a domino *C*- to *C*-[1,3] and *O*- to *C*-[3,3]-pathway for the *ortho*-rearrangement. Based on the above data, we propose that the *ortho*-rearrangement proceeds through a concerted *O*- to *C*-[1,3]-shift, while the *para*-rearrangement proceeds through a domino *O*- to *C*-[1,3]-rearrangement and *C*- to *C*-[1,3]-shifts as outlined in Scheme 5.

Following this, we applied our strategy towards the synthesis of *cis*-homopterocarpans via a simplified route. Homopterocarpans possessing the benzopyrano-[4,3-*b*]-[1]-benzopyran system are biologically active compounds homologous to the second largest group of natural isoflavonoid pterocarpans.[12] So far, only a few syntheses have been reported for *cis*-homopterocarpans.[13] We could successfully convert the 2′-hydroxyhomoisoflavones **6** to the respective *cis*-homopterocarpans **10** as outlined in Scheme 6. Palladium-catalyzed hydrogenation of **6** in the presence of pyridine yielded *cis*-chromanol **9** in 69% to 78% yields. Our attempts at the intramolecular Mitsunobu reaction of **9** did afford the *cis*-homopterocarpans **10**, but in very low yield. However, heating the chromanol **9** in acetic acid resulted in a smooth cyclodehydration, furnishing the *cis*-homopterocarpans **10** in good yield. The NMR spectral data of **10** were in accordance with those reported in literature.[13a]

In conclusion, we describe an unusual *ortho* rearrangement involving a rare [1,3]-shift and a novel *para*-rearrangement involving a domino [1,3]-[1,3]-migration of chromone-3-ylmethyl



Scheme 5. Mechanistic pathway for the thermal rearrangement of chromone **3**.



Scheme 6. Synthesis of *cis*-homopterocarpans **10**.

aryl ethers under thermal conditions. *cis*-Homopterocarpans have been synthesized using the 2′-hydroxyhomoisoflavones. Our method provides yet another entry to homoisoflavonoids, which allows variation in both the aromatic rings. The 3-benzylchromones (homoisoflavones) **4** and **6** are known to possess anti-inflammatory, antioxidant, antiproliferative, antifungal, antiviral, and antimutagenic activities.[14,15] Comparative biological studies on these homopterocarpans and homoisoflavones are in progress.

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Supporting Information is available electronically on J-STAGE.

References and Notes

1 L. Claisen, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157.

2 a) *The Claisen Rearrangement: Methods and Applications*, ed. by M. Hiersemann, U. Nubbemeyer, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2007**. doi:10.1002/9783527610549. b) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, **2005**. c) A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939. d) K. C. Majumdar, R. K. Nandi, *Tetrahedron* **2013**, *69*, 6921. e) R. P. Lutz, *Chem. Rev.* **1984**, *84*, 205. f) S. J. Rhoads, N. R. Raulins, in *Organic Reactions*, John Wiley & Sons, New York, **1975**, Vol. 22, p. 1. doi:10.1002/0471264180.or022.01.

3 S. Hou, X. Li, J. Xu, *J. Org. Chem.* **2012**, *77*, 10856.

4 a) N. Geetha, K. K. Balasubramanian, *Tetrahedron Lett.* **1998**, *39*, 1417. b) E. J. Corey, L. I. Wu, *J. Am. Chem. Soc.* **1993**, *115*, 9327. c) F. X. Talamás, D. B. Smith, A. Cervantes, F. Franco, S. T. Cutler, D. G. Loughhead, D. J. Morgans, Jr., R. J. Weikert, *Tetrahedron Lett.* **1997**, *38*, 4725.

5 There is no well-documented example for *para*-Claisen rearrangement involving a domino [1,3]-[1,3]-migration.[2a,2f]

6 a) R. Araya-Maturana, J. Heredia-Moya, H. Pessoa-Mahana, B. Weiss-López, *Synth. Commun.* **2003**, *33*, 3225. b) C. K. Ghosh, S. Bhattacharyya, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, *36*, 267.

7 K. Devarajan, K. K. Balasubramanian, S. Bhagavathy, *Synth. Commun.* **2013**, *43*, 2165.

8 F. M. Dean, M. Malki, L. J. O'Keeffe, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2675.

9 K. C. Majumdar, G. H. Jana, S. K. Ghosh, S. Saha, *Monatsh. Chem.* **1997**, *128*, 641.

10 A. W. Burgstahler, L. K. Gibbons, I. C. Nordin, *J. Chem. Soc.* **1963**, 4986.

11 a) R. Irie, K. Noda, Y. Ito, T. Katsuki, *Tetrahedron Lett.* **1991**, *32*, 1055. b) R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron: Asymmetry* **1991**, *2*, 481.

12 a) L. Jiménez-González, M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Phytochem. Rev.* **2008**, *7*, 125. b) C. Selvam, S. M. Jachak, R. G. Oli, R. Thilagavathi, A. K. Chakraborti, K. K. Bhutani, *Tetrahedron Lett.* **2004**, *45*, 4311.

13 a) P. Da Re, P. Velenti, L. Cateni, P. L. Barili, *Tetrahedron Lett.* **1976**, *17*, 71. b) A. Rampa, A. Bisi, F. Belluti, S. Gobbi, L. Piazzi, P. Valenti, A. Zampiron, A. Caputo, K. Varani, P. A. Borea, M. Carrara, *IL Farmaco* **2005**, *60*, 135. c) P. Valenti, G. Fabbri, A. Rampa, A. Bisi, F. Belluti, *Farmaco* **1997**, *52*, 13.

14 a) T. M. Hung, C. V. Thu, N. T. Dat, S.-W. Ryoo, J. H. Lee, J. C. Kim, M. Na, H.-J. Jung, K. Bae, B. S. Min, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2412. b) V. Siddaiah, M. Maheswara, C. V. Rao, S. Venkateswarlu, G. V. Subbaraju, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1288.

15 a) S. Malhotra, V. K. Sharma, V. S. Parmar, *J. Chem. Res.* **1988**, *179*, 22. b) J. Andrieux, D. H. R. Barton, H. Patin, *J. Chem. Soc., Perkin* **1977**, *1*, 1359. c) V. M. Rao, G. L. V. Damu, D. Sudhakar, V. Siddaiah, C. VenkataRao, *ARKIVOC* **2008**, 285. d) V. Siddaiah, C. V. Rao, S. Venkateswarlu, G. V. Subbaraju, *Tetrahedron* **2006**, *62*, 841.