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Lewis Acid-Catalyzed Annulative Partial Dimerization of 3-Aryloxyacrylates to 4-Arylchroman-2-ones: Synthesis of Analogues of Tolterodine, RORγ Inhibitor and a GPR40 Agonist

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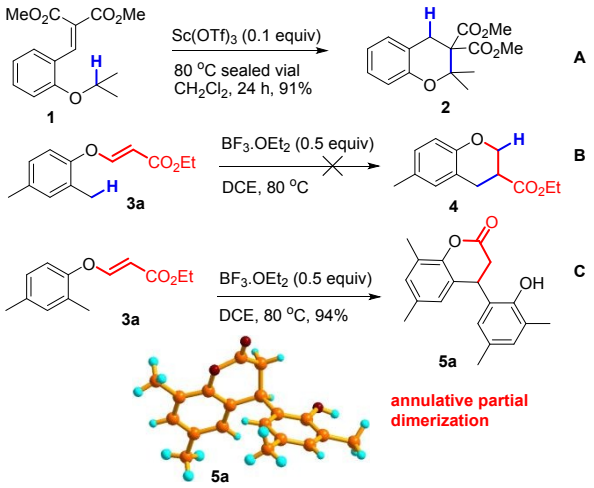
A beguiling annulative partial dimerization of 3-aryloxyacrylates to 4-arylchroman-2-ones catalyzed by Lewis acid (BF_3·OEt_2) has been developed. The reaction involves two molecules of 3-aryloxyacrylate, resulting in the loss of one propiolate molecule to furnish 4-arylchroman-2-one, an important structural motif found in many natural products. This methodology has been elaborated to synthesize analogues of tolterodine, RORγ inhibitors and a GPR40 agonist.

The molecular rearrangements occupy an important niche in synthetic organic chemistry[1] and are important for building unusual complexities in the products from rather simple substrates or easy-to-make starting materials. Many natural products and valuable compounds have been synthesized by molecular rearrangements.[1,2] Acid-catalyzed rearrangements offer a unique opportunity in cascade reactions, leading to several bonds being formed in a single operation. Such reactions are sought after for being atom economic and highly resource conservative. Atkinson and co-workers had shown a remarkable 1,5-hydride shift in acyclic systems containing α,β-unsaturated ketones, creating an intermediate enolate that cyclized with the benzylic cation to give a cyclic product.[3a] Latter, Reinhoudt *et al.*[3b] described a similar 1,5-hydride shift, to produce fused heterocycles. Noguchi *et al.*[3c] also reported similar chemistry for preparing fused pyridine compounds. Extensive work by Dalibor Sames and co-workers[4] on such hydride transfer cyclization (called HT-cyclization) has opened a new avenue for several types of substrates to be employed for 1,5-hydride shift and subsequent cyclization. In their work, the aryl-alkyl ether **1** failed to rearrange initially when BF_3·OEt_2 was used, but the desired HT-cyclized product **2** was obtained with $Sc(OTf)_3$ in a sealed tube (Scheme 1A).[4c] We believed that, an aryl methyl group would also provide an active hydride to the pendant aryloxyacrylate in compound **3a**, followed by in-situ enolate cyclization to give benzopyran **4** (Scheme 1B). However, to our delight, it delivered an annulative partially dimerized/ rearranged product 4-arylchroman-2-one **5a** with two molecules of **3a** being involved with a concomitant loss of one propiolate molecule (Scheme 1C). Such an annulative partial dimerization is hitherto unknown to the best of our knowledge and much to our astonishment that several substrates underwent the HT-cyclization in the seminal work of Sames *et al.*[4] Product **5a** was characterized by ^1H and ^{13}C NMR and HRMS data. Further the structure was confirmed unambiguously by single crystal XRD (Scheme 1).[5]



Scheme 1 Hydride transfer cyclization and a new partial annulative dimerization.

This method is simple, and 4-arylchroman-2-ones (4-aryldihydrocoumarin),[6] an important structural motif found in many natural products[7,8] (Figure 1, for e.g. the calomelanols **6a-h**,[7a-c] poinsettifolactone **6i**[7d] and gnetumontanin C **6j**[7f]), could be obtained in one step from the substrates of type **3**. Further, the 4-arylchroman-2-ones could serve as intermediates for drugs and bioactive compounds like tolterodine **7**,[9] the GPR40 agonists **8**[10] and the RORγ inhibitor (–)-ML209 **9**[8e] (Figure 1).

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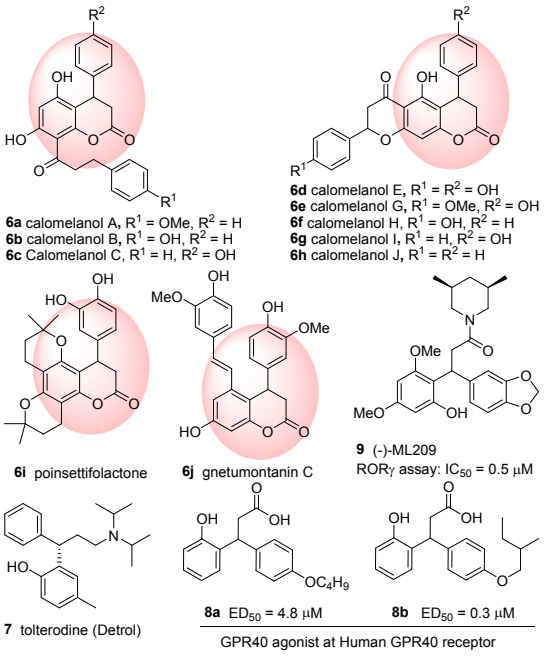
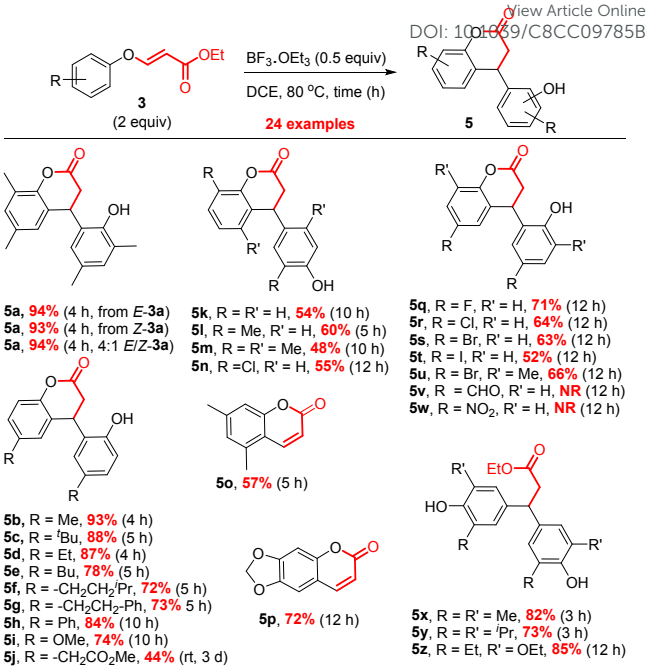


Fig. 1 4-Aryldihydrocoumarin natural products and related drug molecules.



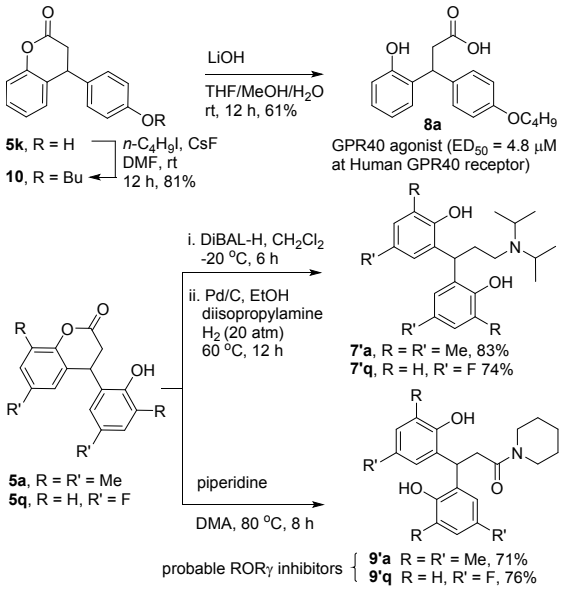
Scheme 2 Annulative partial dimerization/rearrangement of various ethyl 3-aryloxyacrylates **3**. NR = No reaction.

The reaction of **3a** as model compound with various Lewis and Brønsted acids was first optimized to reveal that $BF_3{\cdot}OEt_2$ (0.5 equiv) in 1,2-dichloroethane (DCE) at 0.02 M concentration and 80 °C were optimum requirement giving the product **5a** in 94% yield in 4 h (see Table 1 in SI for details). The minor *Z*-acrylates (*Z*-**3**) obtained during the preparation of **3** were found to provide the same product **5**. Thus, the reaction does not necessitate the separation of the two geometric isomers of the 3-aryloxyacrylates. With the optimized conditions, the scope and limitations of the annulative partial dimerization was investigated as shown in Scheme 2, to furnish the 4-arylchroman-2-ones **5** in good to excellent yields. The reaction worked well with alkyl, aryl, methoxy or methylacetate substituents on the aryloxy part of the substrate **3a-j** to give 4-arylchroman-2-ones **5a-j** in 44-94% yields. The product **5j** required 3 days for the complete consumption of **3j** and was obtained in moderate yield (44%, a reaction at 80 °C gave poor yields). It can be noted that since the para-position in **3a-j** was blocked, the electrophilic substitution occurred at the ortho-position. When the para- and/or ortho-position was free e.g., in **3k-n**, the reaction resulted in substitution exclusively at the para-position to give **5k-n** respectively. The trend in yields could be a result of increased nucleophilicity of phenol because of the alkyl groups or due to steric crowding. This was more evident for **3o** and **3p**, which gave coumarins **5o** and **5p**, respectively, through oxonium-arylation and 4-aryloxy elimination rather than O-C migration. Halide substituted substrates also reacted well to give 4-arylchroman-2-ones **5n** and **5q-u** in good yields of 52-71%. The halide group can be used as handle for various coupling reactions for molecular diversity. The aryl ring needs to be nucleophilic enough for the electrophilic substitution. Hence, substrates with electron-withdrawing groups, **3v** and **3w**, did not undergo this reaction. When the ortho positions were blocked, the substrates **3x-z** gave un-cyclized β,β-bis-arylacetates **5x-z** in good yields, because of no ortho-hydroxy group for lactonization.

We further considered synthetic modifications of the 4-aryldihydrocoumarins. The 4-arylchroman-2-one **5k** was elaborated efficiently to **8a**, a GPR40 agonist by first phenolic OH alkylation to **10** and then lactone hydrolysis (Scheme 3).[9,10] GPR40 is a G-protein-coupled receptor primarily expressed in pancreatic β-cells. It is an attractive therapeutic target to control type 2 diabetes. GPR40 agonists are known to stimulate insulin secretion and reduce circulating glucose levels in a glucose dependent manner.[11] Compound **8a** showed ED_{50} = 4.8 μM at the Human GPR40 receptor.[10] The DiBAL-H reduction of **5a** and **5q** to the lactols and further one-pot reductive amination gave tolterodine analogues **7'a** and **7'q** in good yields (Scheme 3).[9,12] Tolterodine, traded as detrol is an antimuscarinic drug[13a] that is used for the treatment of urinary incontinence and acts on M2 and M3 subtypes of muscarinic receptors.[13b] The 4-aryldihydrocoumarins **5a** and **5q** were converted to **9'a** and **9'q** by reacting with piperidine (Scheme 3). RORγt, a retinoic acid-related orphan receptor plays a key role in the differentiation of TH17 cells. Antagonizing the activity of RORγt transcription is a potential means to treat TH17-related autoimmune diseases.[14] Littman *et al.*[8e] prepared several diphenylpropanamides and found (–)-ML209 **9** (Figure 1) as a significant RORγ inhibitor (RORγ essay: IC_{50} = 0.5 μM).

We further considered mechanistic studies for ascertaining the series of intermediary steps. A reaction on two different, mixed substrates was carefully examined (Scheme 4), with one chosen to have both ortho-positions substituted to avoid cyclization, thus expecting to give three products instead of four if there was cross-over of aryl groups. Indeed the reaction delivered three products as expected. For example, the reaction

of equimolar amounts of **3x** and **3b** (Scheme 4, entry 1) provided aromatization gives **23** via the enol **22**. The loss of D^2 in the deuterium experiment could be due to the reversible enolization (**22** to **23**). The lactonization of **23** gives **5**. The O-C

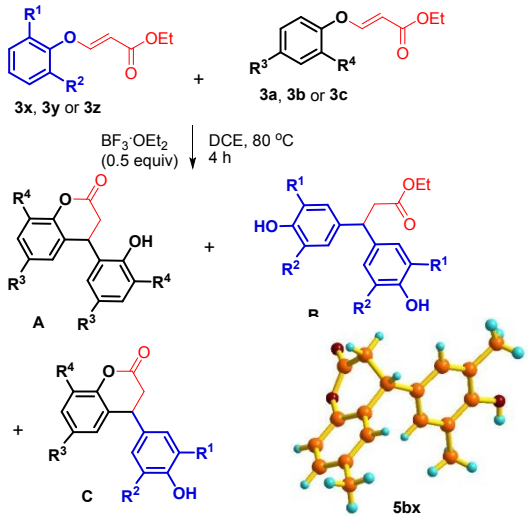


Scheme 3 Synthesis of GPR40 agonist **8a**, tolterodine analogues (**7'a** & **7'q**) and probable RORγ inhibitors (**9'a** & **9'q**).

5b (27%), **5x** (25%) and the aryl group cross-over product **5bx** (37%, structure confirmed by single crystal XRD).[5] Similarly, compounds **5by**, **5ay**, **5cy** and **5az** (entries 2-5) were obtained as cross-over products and is an extension of this method to obtain compounds with two different aryl moieties. It also indicated the cleavage of C3-O aryloxy-acrylate bond.

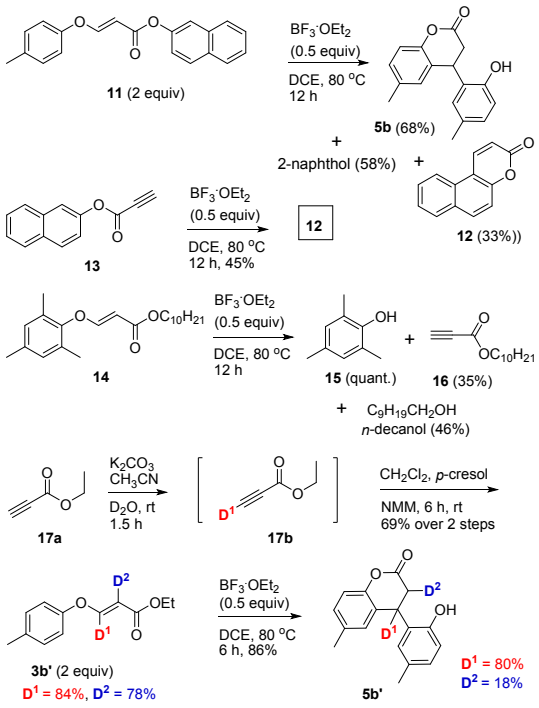
The cleavage of C3-O bond was further supported by the reaction of compound **11** (Scheme 5), to give the usual product **5b** (68%) and the fused naphthyl coumarin **12** (33%), which arises from the naphthyl propiolate that is formed by the cleavage of C3-O bond. 2-Naphthol (58%) was also isolated from this reaction. This was similar to compounds **5o** and **5p** (Scheme 2). To substantiate this claim we prepared separately 2-naphthyl propiolate **13**, and reacted it with $BF_3{\cdot}OEt_2$ to give **12** in 45% yield. Further, the reaction of *n*-decyl 3-aryloxyacrylate **14** with $BF_3{\cdot}OEt_2$ gave the phenol **15** (quant), *n*-decylpropiolate **16** (35%) and *n*-decanol (46%). This clearly indicated the cleavage of the C3-O bond. A deuterium labelling study was also conducted (Scheme 5). The di-deuterated 3-aryloxyacrylate **3b'**, obtained in good yield with deuterium incorporation as D^1 (84%) and D^2 (78%) was treated with $BF_3{\cdot}OEt_2$ (0.5 equiv) to provide compound **5b'**. This had D^1 (80%), while there was loss at D^2 (18%). The loss at D^2 could be attributed to the reversible enolization (see reaction mechanism, Scheme 6). It also indicated that the β-hydrogen of the acrylate that corresponds to D^1 is not involved.

Considering the various experiments and results, the mechanism as shown in Scheme 6 is proposed. Co-ordination of $BF_3{\cdot}OEt_2$ with the carbonyl group of **3** gives the oxo-carbenium ion **18**. The C3-O bond cleavage of another molecule of **3** gives the $^+BF_3$-phenoxide **19** that undergoes electrophilic substitution with **18** to produce **21**. Next, the O- to C-aryl migration and



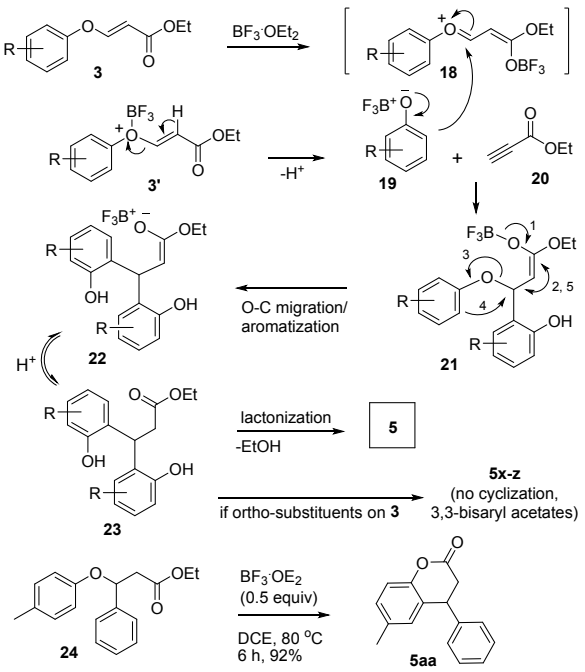
entry	R^1, R^2, R^3, R^4 (**3**)	yield **A**	yield **B**	yield **C**
1	$R^1 = R^2 = R^3 = Me$, $R^4 = H$	**5b**, 27%	**5x**, 25%	**5bx**, 37%
2	$R^1 = R^2 = i$-Pr, $R^3 = Me$, $R^4 = H$	**5b**, 30%	**5y**, 25%	**5by**, 35%
3	$R^1 = R^2 = i$-Pr, $R^3 = R^4 = Me$	**5a**, 32%	**5y**, 21%	**5ay**, 32
4	$R^1 = R^2 = i$-Pr, $R^3 = t$-Bu, $R^4 = H$	**5c**, 28%	**5y**, 23%	**5cy**, 34%
5	$R^1 = Et$, $R^2 = OEt$, $R^3 = R^4 = Me$	**5a**, 27%	**5z**, 24%	**5az**, 32%

Scheme 4 Cross-over experiments of mixed 3-aryloxyacrylates.



Scheme 5 Experiments to ascertain C3-O bond cleavage in 3-aryloxyacrylates and deuterium labelling study.

aryl-migration was proved by the reaction of **24** (prepared separately) to give the product **5aa** in 92% yield (Scheme 6). The presence of ortho-substituents directs the electrophilic substitution at para position. This prevents cyclization, giving the 3,3-bis-arylacetates **5x**-**z** as there is no ortho-hydroxyl group for lactonization.



Scheme 6 Plausible mechanism.

In summary, we have developed a beguiling annulative partial dimerization/rearrangement of 3-aryloxyacrylates under Lewis-acid conditions to 4-arylchroman-2-ones (4-aryldihydrocoumarins), which are important structural motifs in many natural products. The reaction occurs through C3-O aryloxy bond cleavage, electrophilic aromatic substitution, O-C aryl-migration and lactonization. This method is important, as addition of a phenol to alkyl/aryl propiolate delivers **3** and in one step would further provide 4-arylchroman-2-ones **5**.

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Conflicts of interest

There are no conflicts of interest to declare.

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