ChemPubSoc Europe

DOI: 10.1002/ejoc.201600531

EurJOC European Journal of Organic Chemistry

Communication

Arene Prenylation

Iron-Catalyzed Arene Prenylation

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Abstract: The syntheses of prenylated arenes and 2,2-dimethylchromans using a Friedel–Crafts-type coupling between activated arenes and isoprene is reported. A combination of catalytic amounts of $FeCl_3$ and $AgBF_4$ promotes a regioselective prenylation event followed by a cyclization to form a 2,2-dimethylchroman structure. The method avoids isoprene polymerization and allows the facile late-stage derivatization of biologically active motifs.

Introduction

Prenylated arenes and the related 2,2-dimethylchroman moiety represent intriguing scaffolds in therapeutic development. Naturally occurring[1] and synthetic prenylated arenes[2] display a range of biological activity (Figure 1). Additionally, the incorporation of an isoprene unit into bioactive molecules increases lipophilicity, which is shown to increase potency in many cases.[3] The importance of accessing these structures has driven the development of many methods to incorporate prenyl groups into substituted arenes.[4] Catalytic installation of the isoprene unit represents the most utilized method for arene prenylation, where the catalysts include precious metals[5] and Lewis acids.[6] Additionally, the isoprene unit is often derived from prenyl surrogates such as prenyl halides[6a] and organometallic reagents.[5,6b] The most efficient and atom-economic route to prenylated arenes and 2,2-dimethylchromans is the direct implementation of isoprene. This strategy is rare but can be realized using catalytic amounts of metal triflates[7] or zeolites;[8] however, inherent complications exist using this approach. First, the reaction often produces a mixture of mono- and polyprenylated products. Second, for non-phenolic substrates, it is challenging to isolate the linear prenylated arene without subsequent cyclization to an indane product.[7d] The development of a complimentary catalytic method to access prenylated arenes or 2,2-dimethylchromans would be a valuable addition to the synthetic chemist's toolbox for the synthesis of biorelevant prenylated arenes.

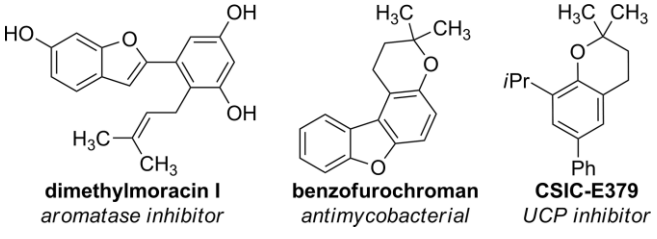
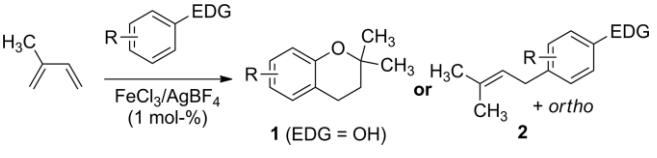


Figure 1. Structures of biologically active prenylated arenes.

Isoprene activation using iron is known in the context of hydrovinylations[9] and polymerizations;[10] however, these processes are presumed to operate under a low-valent iron center during catalysis. To the best of our knowledge, isoprene functionalization using a high-valent, or cationic, iron species has not been reported. Iron-catalyzed processes are becoming more sophisticated as new methods unveil novel reactivity patterns.[11] These recent advances and our interest in atom-economic processes led us to investigate the Lewis -acidic properties of iron as a catalyst for this Friedel–Crafts (FC) type reaction.[12] An intrinsic issue with FC chemistry is the employment of organohalides and/or an excess of metal salts, which limits FC-type reactions on an industrial scale.[13] A recent surge in methods to circumvent these issues have been reported through the use of catalytic, nontoxic metals[7c,7d,12d] and activated alcohols[12a,12d] or π-components[7c,7d,12b] in lieu of organohalides. The method described herein utilizes an iron/silver co-catalyst system to promote the efficient and selective prenylation of activated arenes (Scheme 1).



Scheme 1. Iron-catalyzed arene prenylation.

Results and Discussion

We began our investigations by studying various iron sources as catalysts for the prenylation of 2,6-dimethylphenol and 4-chlorophenol (Table 1). A thorough screening of iron sources and additives (not shown) determined that iron(II) or iron(III) halides in combination with silver salts were most effective at producing the desired prenylated arenes or 2,2-dimethylchromans in high yields while minimizing isoprene oligomer byproduct formation. Ferrous bromide (1 mol-%) and $AgBF_4$

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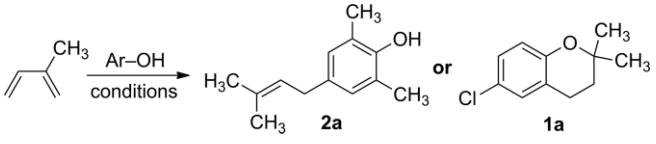
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.201600531.

(2 mol-%) were effective in the production of prenylated product **2a** (Entry 1); however, ferric chloride proved to be a more active catalyst, allowing for higher conversion to **2a** (Entry 2). Lowering the catalyst loading or removing the iron source did not provide beneficial results (Entries 3 and 4). Reducing the $AgBF_4$ loading to 1 mol-% did not diminish reactivity (Entry 5), and increasing the amount of isoprene to 2 equiv. afforded higher conversion to **2a** (Entry 6). Finally, removing the silver resulted in suppressed activity (Entry 7). Applying the best conditions to 4-chlorophenol provided low conversion to 2,2-dimethylchroman product **1a** (Entry 8). Ultimately, increasing the temperature to 60 °C offered the highest conversion to the product (Entry 9), which we then employed as our optimized conditions. Performing the reaction in the presence of 2,6-di-*tert*-butylpyridine (DTBP) or potassium carbonate resulted in reduced reactivity (Entries 10 and 11).[14] Because we still observe moderate conversion to the chroman product in the presence of these Brønsted bases, we hypothesize that a combination of Brønsted acid activation and Lewis acid activation is operative.[14b,14c] The phenolic proton and/or adventitious water are likely sources for the acidic media. To corroborate this hypothesis, we performed the reaction with 1 mol-% HBF_4•Et_2O in place of the Fe/Ag system and achieved 52 % yield of the chroman (Entry 12). This result shows that the $FeCl_3/AgBF_4$ combination is a more effective catalyst through slow generation of acidic media, which is optimal for this reaction.[14c]

Table 1. Optimization of reaction conditions.

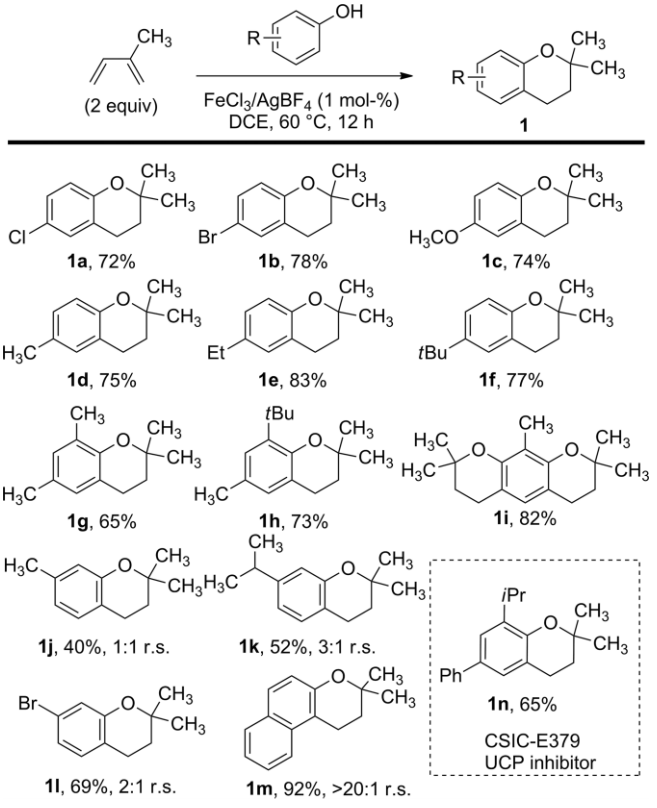


Entry[a]	Phenol	Fe source (amount [mol-%])	$AgBF_4$ [mol-%]	GC conversion [%][b]
1	2,6-dimethyl	$FeBr_2$ (1)	2	22
2	2,6-dimethyl	$FeCl_3$ (1)	2	51
3	2,6-dimethyl	$FeCl_3$ (0.5)	1	25
4	2,6-dimethyl	–	1	<5
5	2,6-dimethyl	$FeCl_3$ (1)	1	53
6[c]	2,6-dimethyl	$FeCl_3$ (1)	1	53
7[c]	4-chloro	$FeCl_3$ (1)	1	71
8[c]	4-chloro	$FeCl_3$ (1)	1	39
9[c,d]	4-chloro	$FeCl_3$ (1)	1	80
10[c,d,e]	4-chloro	$FeCl_3$ (1)	1	72
11[c,d,f]	4-chloro	$FeCl_3$ (1)	1	53
12[c,d,g]	4-chloro	–	–	52

[a] Reactions performed with isoprene/Ar–OH (1:1) in 1,2-dichloroethane (1 M) at 23 °C for 12 h. [b] GC conversion based on crude integration of product and starting Ar–OH. [c] Reaction performed with isoprene/Ar–OH (2:1). [d] Reaction performed at 60 °C. [e] Reaction performed with 2 mol-% of 2,6-di-*tert*-butylpyridine. [f] Reaction performed with 1 equiv. of K_2CO_3. [g] Reaction performed with 1 mol-% of HBF_4•Et_2O.

The substrate scope of this method for the synthesis of 2,2-dimethylchroman products is summarized in Table 2. Phenols containing *para*-substitution afforded the chroman product in high yields with a range of electron-donation ability (**1a**–**1h**). Interestingly, reaction of 2-methylresorcinol proceeded to give bis(chroman) product **1i** in high yield. To probe the regioselectivity of the process, we subjected 3-substituted phenols to our reaction conditions. As expected, increasing the size of the substituent resulted in an increase in regioselectivity (1:1 to 3:1) of chroman products **1j**–**1k**. 3-Bromophenol provided a 2:1 mixture of regioisomers (**1l**), however in increased yield. 2-Naphthol provided the best result where a > 20:1 regioselectivity was observed in 92 % yield (**1m**). The incorporation of Lewis-basic sites on the substrates, such as 4-hydroxybenzamide, resulted in unproductive reactivity, which is a common problem for these types of reactions.[12d] Fortunately, products **1a**, **1b**, and **1l** allow further functionalization through cross-coupling chemistry such as Ullmann[15] or Buchwald–Hartwig aminations.[16] Additionally, increasing catalyst loading for low-yielding substrates did not result in higher yields, but rather increased formation of diprenylated products and isoprene oligomers. Finally, we were interested in the application of this method to the synthesis of known UCP inhibitor CSIC-E379 (**1n**).[2b] This method afforded the desired product in 65 % yield, demonstrating the utility of the method in the synthesis of bioactive molecules.

Table 2. Reaction scope for 2,2-dimethylchroman products.[a]

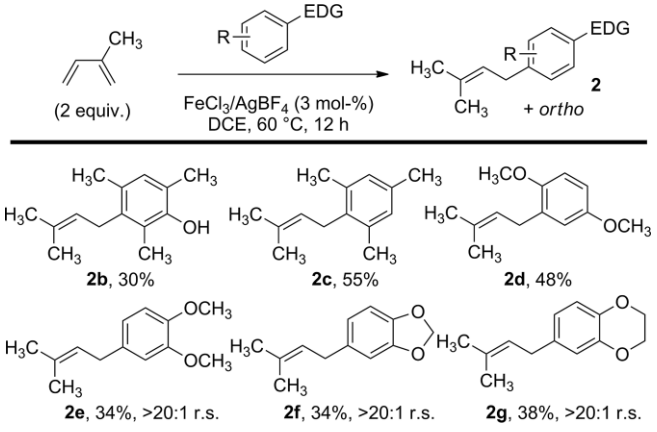


[a] Isolated yields are an average of two reactions on a 1 mmol scale. Products **1j**–**1m** isolated as a mixture of regioisomers where the regioselectivity (r.s.) was determined by ^1H NMR spectroscopy of the crude reaction mixture.

Employing our method to substrates that are only capable of producing the linear prenylated product is depicted in Table 3. Using slightly more catalyst (3 mol-%), substituted phenols were capable of providing prenylated arene **2b** in moderate yield. Prenylmesitylene (**2c**) was synthesized in 55 % yield. Additionally, dimethoxybenzenes were effective as substrates in

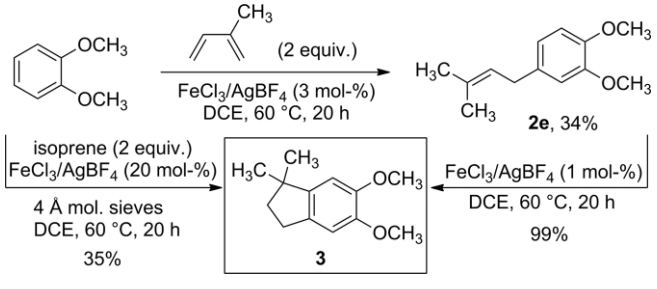
the production of compounds **2d** and **2e**. We then examined 1,3-benzodioxole and benzo-1,4-dioxane for the synthesis of prenyl products **2f** and **2g**. Each substrate produced the desired product in low yield. However, excellent regioselectivity was observed. It is important to note that when employing $Bi(OTf)_3$ as a catalyst for this reaction, complete cyclization to an indane product is observed in 79 % yield.[7d] The ability to truncate the reaction at the linear prenylated arene under our conditions demonstrates the unique reactivity of the $FeCl_3/AgBF_4$ catalyst system. Additionally, the low to moderate yields for this process is comparable to those of other systems, which underscores the challenge of this reaction.[7c]

Table 3. Reaction scope for prenylated arene production.[a]



[a] Isolalted yields are an average of two reactions on a 1 mmol scale. Regioselectivity (r.s.) was determined by ^1H NMR spectroscopy of the crude reaction mixture.

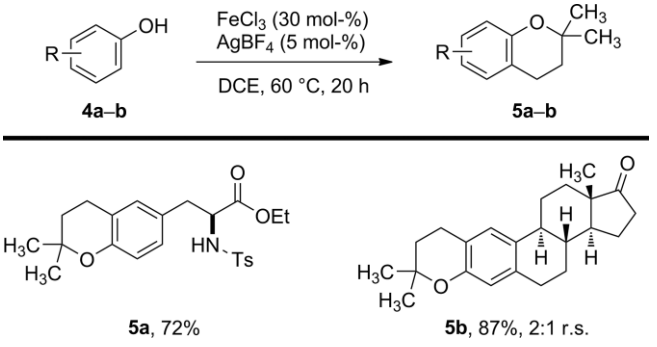
During our examination of veratrole, we observed the formation of small quantities of indane product **3**. We explored the selective formation of these potentially useful products using a modified $FeCl_3/AgBF_4$ catalyst system (Scheme 2). Subjecting **2e** to our original prenylation conditions afforded indane product **3** in 99 % yield. Direct conversion to the indane was possible by increasing the catalyst loading to 20 mol-% $FeCl_3$ and $AgBF_4$. Using this direct prenylation/cyclization protocol, 35 % of **3** was obtained. These results demonstrate the unique ability of the $FeCl_3/AgBF_4$ system to stop the reaction at prenylated arene product **2**, and its ability to produce indane products under modified conditions.



Scheme 2. Selective formation of indane products.

To explore the application of the iron-catalyzed process to the prenylation of privileged scaffolds, we pursued the prenylation of protected tyrosine **4a** and estrone (**4b**) (Table 4). The direct prenylation of these molecules has potential applications in the medicinal chemistry and chemical biology arenas. Upon allowing protected tyrosine **4a** to react under our optimized conditions, low reactivity was observed presumably due to the Lewis-basic functional groups. Increasing the loading to 30 mol-% $FeCl_3$ and 5 mol-% $AgBF_4$, we were pleased to observe the formation of derivatized tyrosine **5a** in a 72 % yield. To the best of our knowledge, this chroman-functionalized tyrosine has not been explored as an amino acid derivative in chemical synthesis. This new product represents an interesting scaffold in peptide and peptidomimetic syntheses. This procedure was also effective in the prenylation of estrone (**4b**) to obtain 87 % yield of **5b** in a 2:1 regioisomeric ratio. These reactions exhibit the applicability of the iron-catalyzed prenylation process for natural product diversification.

Table 4. Prenylation of L-tyrosine and estrone.[a]



[a] Regioselectivity (r.s.) was determined by ^1H NMR spectroscopy of the crude reaction mixture.

Conclusions

We report a mild and selective iron catalyst system for the production of a variety of highly useful 2,2-dimethylchroman and prenylated arene products. This method avoids the use of stoichiometric Lewis/Brønsted acids and employs isoprene directly, which makes the process 100 % atom-economic. We applied the method to the synthesis of a known UCP inhibitor and to the functionalization of a new tyrosine derivative that has potential utility in peptide synthesis. Efforts to employ this catalyst system to additional Friedel–Crafts and other atom-economic processes are ongoing in our laboratory.

Experimental Section

Representative Procedure: In an oven-dried 4 mL vial was added $FeCl_3$ (1.6 mg, 0.01 equiv.), $AgBF_4$ (2.0 mg, 0.01 equiv.), and 4-chlorophenol (135.0 mg, 1.0 mmol). The flask was purged with N_2 and the mixture diluted with freshly distilled 1,2-dichloroethane (DCE) (1.0 mL). Isoprene (200 μL, 2.0 mmol) was added dropwise to the stirred reaction mixture over the course of 1 min. Completion of the reaction was determined by GC–MS, after which the reaction mixture was placed in a separatory funnel, diluted with ethyl acetate, and washed with a saturated brine solution. The organic layer was then washed with 1 M NaOH and again with brine solution.

The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was then subjected to bulb-to-bulb distillation in vacuo to afford 149 mg of product as a colorless oil (74 % yield).

Supporting Information: Representative procedures for linear prenylated compounds and analytical data for new compounds.

Acknowledgments

This work was supported by Loyola University Chicago. Professor Karl Scheidt (Northwestern University) is acknowledged for insightful discussions. We thank Northwestern University ChemCore for purification of the prenylated tyrosine and estrone materials.

Keywords: Iron · Homogeneous catalysis · Aromatic substitution · Terpenoids

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Received: April 28, 2016
Published Online: May 30, 2016