# A Quick, Clean and Green Synthesis of Methylenedioxyprecocene and other Chromenes over Basic Montmorillonite K10 Clay

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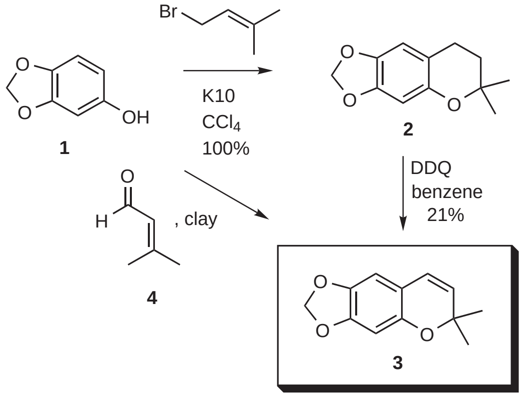
This manuscript is dedicated to Adam T. Rzepka.

**Abstract:** The microwave-assisted, clay-catalyzed condensation of sesamol and other phenols with 3-methyl-2-butenal to give methylenedioxyprecocene **3** and other chromenes, is described.

**Key words:** green chemistry, natural products, Montmorillonite clay, microwave-assisted, chromenes

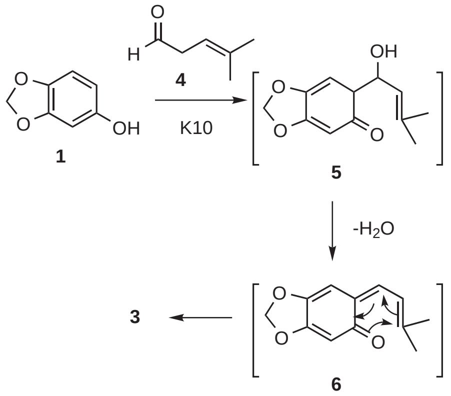
As topics like green chemistry[1] and diversity-oriented synthesis[2] continue to shape the way chemists think about the construction of physiologically active compounds, the development of synthetic methods that promote faster and cleaner reactions, with regard to selectivity, atom economy and waste reduction, is pivotal. Environmentally benign clays, naturally abundant, inorganic catalysts, are ideally suited for advancing modern synthetic chemistry: they are inexpensive, nontoxic, chemically diverse, and recyclable.[3] While clays have already been shown to effectively catalyze a wide range of chemical reactions, their application in the synthesis of diverse libraries of compounds is far from exhausted.[4] The use of microwave irradiation to promote quicker and cleaner chemical reactions is similarly well suited for the advancement of more environmentally friendly synthesis,[5] especially when used in combination with clays and under solvent-free conditions.[6] Herein, we report a quick, clean and green synthesis of methylenedioxyprecocene (**3**), an insecticide that exhibits anti-juvenile hormone activity in some insects.[7] Our synthesis features the microwave-assisted condensation of sesamol with 3-methyl-2-butenal (**4**) over dry clay.

In a recent communication, we reported a facile, clay-catalyzed, one-pot synthesis of 2,2-dimethylbenzopyrans (e.g. **2**, Scheme 1) from phenols, which promises to be of practical application in the construction of natural and non-natural products containing this particular functional motif.[8] Synthesis of the insecticide methylenedioxyprecocene (**3**), for example, was accomplished by K10 clay-catalyzed conversion of sesamol (**1**) to the corresponding 2,2-dimethylbenzopyran (**2**) in quantitative yield, followed by oxidation of **2** by DDQ (Scheme 1).[9] The second step of this synthesis, neither high yielding nor environmentally friendly, prompted us to consider a more direct route to **3** from **1**: clay-catalyzed condensation with 3-methyl-2-butenal (**4**).



Scheme 1 Synthesis of methylenedioxyprecocene **3**

Given its widespread occurrence in physiologically active natural products, synthesis of the 2,2-dimethyl-2*H*-chromene ring system is fairly well precedented,[10] though the direct condensation of readily available phenols and α,β-unsaturated aldehydes on clays has not been reported previously. At the outset of this investigation we presumed that acidic Montmorillonite K10 clay might promote electrophilic aromatic addition of 3-methyl-2-butenal to sesamol to give intermediate **5** (Scheme 2). Further, at elevated temperature and with the aid of a Dean–Stark trap, dehydration of **5** might ensue, followed by an intramolecular hetero-Diels–Alder reaction of the incipient *o*-quinone methide species **6** to give the desired chromene **3** (Scheme 2).



Scheme 2 Proposed mechanism of the clay-catalyzed conversion of sesamol to **3**

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**Table 1** Conversion of Sesamol (**1**) to Methylenedioxyprecocene (**3**) under Various Conditions

| | Conditions | | | | Product distribution (%)[a] | | |
|---|---|---|---|---|---|---|---|
| Entry | Catalyst | Solvent | Temp (°C)/energy | Time (min) | **3** | **1** | Other[b] |
| 1 | K10 | Toluene | Reflux | 30 | 19 | 9 | 72 |
| 2 | K10 | None | 110 | 120 | 7 | 3 | 90 |
| 3 | K10 | None | 23 | 45 | 3 | 97 | 0 |
| 4 | K10 | None | MWI | 8 | 29 | 2 | 69 |
| 5 | K10-$K^+$ | None | 110 | 60 | 91 | 0 | 9 |
| 6 | K10-$K^+$ | None | MWI | 8 | 84 | 16 | 0 |
| 7 | None | None | MWI | 8 | 2 | 98 | 0 |
| 8 | $K_2CO_3$ | None | MWI | 10 | 67 | 31 | 2 |
| 9 | $Na_2CO_3$ | None | MWI | 10 | 66 | 34 | 0 |
| 10 | $Li_2CO_3$ | None | MWI | 10 | 28 | 66 | 6 |
| 11 | $CaCO_3$ | None | MWI | 10 | 7 | 92 | 1 |

[a] Assessed by GC-MS analysis of crude reaction mixture.
[b] Unidentified.

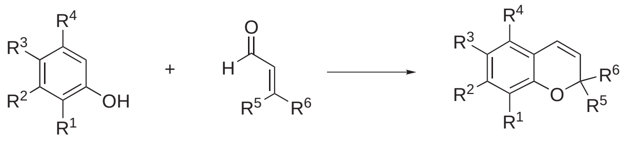
Upon refluxing a mixture of Montmorillonite K10 clay, sesamol (**1**), and 3-methyl-2-butenal (**4**) in toluene for 30 minutes (with Dean–Stark trap), however, we observed only 19% conversion to the desired chromene **3** (measured by GC-MS, Table 1, entry 1). Running the experiment neat, heating the dry reaction mixture in an oven at 110 °C was also unsuccessful, giving even less conversion to the desired chromene and a greater amount of other unidentified products (Table 1, entry 2). We found that the reaction was much cleaner when run neat at room temperature, resulting in a 3% conversion to the desired product after only 45 minutes, with no 'other' products observed (Table 1, entry 3). Thus, it appeared that selective conversion of sesamol (**1**) to **3** could be achieved, but that prolonged exposure of the reaction mixture to heat resulted in the generation of unwanted by-products.

We reasoned that if we could get the reaction to go more quickly, that it would also proceed more selectively. Hence we considered replacing conventional heating with microwave irradiation (MWI), which had been shown to greatly enhance rates of reaction for a variety of other systems.[6] Indeed, exposure of a mixture of Montmorillonite K10 clay, sesamol, and 3-methyl-2-butenal to MWI for 8 minutes resulted in a somewhat quicker and cleaner generation of **3** (Table 1, entry 4), though this hardly constituted an improvement over existing methodologies.[10] At this point we considered altering the chemical reactivity of the clay, which ultimately led to success.

In its natural form, Montmorillonite K10 clay is Brønsted acidic, but it can be easily made basic by washing with a saturated aqueous basic solution (potassium carbonate for instance). We reasoned that conducting the reaction on basic K10, either at elevated temperature or in the presence of microwave irradiation, might allow for a quicker and cleaner synthesis of **3** since others had shown this reaction to proceed well in the presence of other (less environmentally friendly) bases.[10] Indeed, we observed a dramatic improvement by running the reaction on basic clay (K10-$K^+$); conversion of **1** to **3** (neat, 110 °C) was complete after one hour with only a small amount of by-product generated (Table 1, entry 5). The reaction was similarly successful when run neat in the microwave, proceeding to near completion after only eight minutes with no undesired by-products detected by GC-MS analysis of the crude reaction mixture (Table 1, entry 6). Minimal reaction was observed in a control experiment in which the two reactants were exposed to microwave irradiation in the absence of any catalyst (Table 1, entry 7). Although the reaction proceeded relatively well in the presence of a series of carbonate bases alone (MWI/10 min, Table 1, entries 8–11) it was neither as complete nor as clean as with the K10-$K^+$. Evidently, the success of this particular reaction may be attributed to a synergistic effect between the basic clay and microwave irradiation; under these conditions the reaction proceeds most quickly and cleanly. Organic products are separated from the clay by extracting with methylene chloride and/or methanol. The clay is recycled by treatment with excess saturated aqueous $K_2CO_3$, filtered and dried in an oven at 110 °C for 1–2 hours.

In an effort to explore the general scope of this reaction under the optimized conditions, sesamol was reacted with other aldehydes, and a variety of other phenols were reacted with 3-methyl-2-butenal (Table 2). Exposure of a mixture of sesamol, crotonaldehyde, and K10-$K^+$ to microwave irradiation for eight minutes resulted in about

**Table 2** Reaction Scope



**7** **8** **9**

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | Product distribution (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **9** | **7** | Other |
| 1 | H | -O($CH_2$)O- | | H | H | $CH_3$ | 48 (**9a**)[11] | 11 | 41 |
| 2 | H | -O($CH_2$)O- | | H | H | H | 7 (**9b**)[12] | 10 | 83 |
| 3 | H | $OCH_3$ | $OCH_3$ | H | $CH_3$ | $CH_3$ | 18 (**9c**)[11] | 68 | 14 |

a 50% conversion to the desired chromene, with only about 10% unreacted sesamol and 40% by-product (Table 2, entry 1). Exposure of a mixture of sesamol, acrolein, and K10-$K^+$ to microwave irradiation for eight minutes resulted in less than 10% conversion to the desired chromene, with only about 10% unreacted sesamol and more than 80% by-product (Table 2, entry 2). In both of the above cases the by-products, not surprisingly, appeared to result from Michael addition of the phenol to the unsaturated aldehyde species. The reaction appeared to be somewhat more general with a variety of phenols and 3-methyl-2-butenal (entries 3–7 in Table 2), though in most cases the formation of other, unidentified products was also observed.

In spite of the obvious irony of targeting an insecticidal compound to demonstrate an example of green synthesis, the methodology reported herein indeed represents a quicker and cleaner route to methylenedioxyprecocene (**3**). Conditions for the reaction were optimized for the synthesis of **3** only, but were applied to the construction of analogous compounds with reasonable success (Table 2). It is likely that this methodology (solvent-free, basic clay-mediated, microwave-assisted condensation of phenols with α,β-unsaturated aldehydes) will be of general applicability in the synthesis of an even wider variety of chromene-containing compounds, but that conditions will need to be optimized for each individual system. We are currently investigating other clay-catalyzed, microwave-assisted reactions for application in the greener synthesis of physiologically active natural and non-natural products.

$^1$H and $^{13}$C NMR spectra were collected at 300 MHz and 75 MHz, respectively. The proton signal of residual, nondeuterated solvent ($\delta$ = 7.26 ppm for $CHCl_3$) was used as an internal reference for $^1$H NMR spectra. For $^{13}$C NMR spectra, chemical shifts are reported relative to the $\delta$ = 77.23 ppm resonance of $CDCl_3$. Coupling constants are reported in Hz. IR were recorded as thin films on a Nicolet Avatar 360. GC analysis was performed on a Hewlett Packard 5890 Series II gas chromatograph with a 5971 Series mass selective detector. Column chromatography was performed using Selecto Scientific (70-150 mesh) silica gel. All reagents and solvents were used as purchased from the manufacturer, without further purification.

**General Experimental Procedure for the Synthesis of Methylenedioxyprecocene (3)**

A slurry of 500 mg of Montmorillonite K10 clay (Aldrich) in 10 mL of sat. aq $K_2CO_3$ was stirred at r.t. for 1 h. After the clay was allowed to settle, most of the aqueous phase was decanted off, and the remaining clay isolated by vacuum filtration. The wet clay was washed successively with acetone (to remove excess water) and $CH_2Cl_2$ (to remove residual acetone), then transferred to a round-bottom flask and evaporated for about 30 min. The dry clay was transferred to a clean watch glass, where it was spread out and further dried in an oven at 110 °C for a period of 1–2 h. The clay was transferred to a vial, which was fitted with a rubber septum and allowed to cool under nitrogen. In another vial, sesamol (138 mg, 1 mmol) was dissolved in 3-methyl-2-butenal (106 μL, 1.1 mmol). To this dark solution was added the dried clay and the mixture evenly distributed using a metal spatula. The vial was placed in the center of the carousel platform of a household grade microwave oven and subjected to microwave irradiation for a period of 8 min. The reaction mixture (which had visibly darkened in color) was allowed to cool to r.t., taken up in 5 mL of $CH_2Cl_2$, and filtered to remove the clay, washing with excess $CH_2Cl_2$. Product distribution was measured by GC-MS analysis. The filtrate was evaporated under vacuum to afford a dark oil (176 mg). The crude product was purified by column chromatography with silica gel, eluting with 90% hexanes–EtOAc to give **3** as a dark yellow oil (81 mg, 64% yield based on recovered starting phenol).

**Methylenedioxyprecocene (3)**:[10f] IR: 3041, 2975, 2892, 2775, 1718, 1645, 1605, 1502, 1482, 1458, 1372, 1361, 1265, 1254, 1199, 1158, 1112, 1069, 1039, 904, 859, 818, 776, 757 $cm^{-1}$. $^1$H NMR ($CDCl_3$): $\delta$ = 6.49 (s, 1 H), 6.40 (s, 1 H), 6.22 (d, $J$ = 9.75 Hz, 1 H), 5.90 (s, 2 H), 5.50 (d, $J$ = 9.75 Hz, 1 H), 1.49 (s, 6 H). $^{13}$C NMR ($CDCl_3$): $\delta$ = 148.2, 147.6, 141.4, 128.2, 122.3, 114.3, 105.6, 100.9, 99.1, 76.0, 27.4. GC-MS (70 eV): $t_R$ = 9.521 min, $m/z$ (%) = 204, (33) [$M^+$], 189 (100) [M – 15]$^+$.

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