An Environmentally Benign Synthesis of Octahydro-2*H*-chromen-4-ols via Modified Montmorillonite K10 Catalyzed Prins Cyclization Reaction

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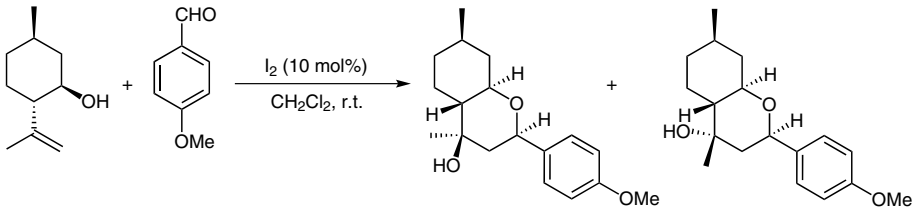
Abstract: (–)-Isopulegol undergoes Prins cyclization reaction in the presence of 20 wt% of acid-treated montmorillonite K10 to produce octahydro-2*H*-chromen-4-ols in good yields and with high *cis* selectivities under solvent-free conditions. The solid-acid catalyst can be reused without loss of its activity.

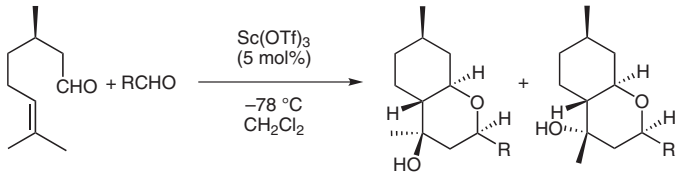
Key words: (–)-isopulegol, Prins cyclization, H-K10 mont, octahydro-2*H*-chromen-4-ols, reusability

Saturated six-membered heterocycles bearing oxygen are a common structural motif of many biologically active natural products such as avermectins, aplysiatoxin, oscillatoxins, latrunculins, talaromycins, acutiphycins, apicularens, phorboxazoles, and bryostatins.[1] The construction of six-membered oxygen heterocycles in a single-step chemical reaction is of particular interest to synthetic organic chemists, and among all existing methods the Prins cyclization[2] has emerged as a powerful single-step reaction for the synthesis of this type of heterocycle. There have been many reports in the literature where the Prins cyclization reaction was employed in the key step of several total syntheses of natural products.[3] Generally, Lewis acids and Brønsted acids promote this important consecutive C–O and C–C bond-forming coupling reaction of homoallylic alcohols with aldehydes and ketones to produce a wide range of tetrahydropyran derivatives under mild conditions.[4,5] Although there have been many methods reported in the literature on this important reaction, most of them possess at least one drawback; among these are the need for stoichiometric excess of the promoting acid catalysts, use of an additive such as TMSCl, requirement for the homoallylic alcohol or the aldehyde to be used in excess, need for anhydrous reaction conditions and/or inert atmosphere, and limitation to aldehydes as the carbonyl component. The synthesis of octahydro-2*H*-chromen-4-ols from isopulegol via Prins cyclization reaction is limited to one example reported by Silva Jr. et al. where they used molecular iodine as a homogeneous catalyst to catalyze the Prins cyclization of (–)-isopulegol with *p*-anisaldehyde[6] (Scheme 1). Recently, Yadav et al. also described an efficient method for the synthesis of octahydro-2*H*-chromen-4-ol from (*R*)-citronellal and aldehydes via direct ene-Prins reaction using a catalytic amount of $Sc(OTf)_3$ under mild conditions (Scheme 2).[7] In the former case the authors only reported one example; whereas in the latter they used $Sc(OTf)_3$ as catalyst at low temperature. The increasing demand for environmentally friendly and sustainable chemical processes prompted us to develop a novel catalytic system for the Prins cyclization to synthesize a variety of octahydro-2*H*-chromen-4-ols.

Recently, modified montmorillonite K10 solid-acid catalysts have received much attention in organic synthesis due to their unique properties including their ability to exchange cations in the interlayers, expandable interlayer



Scheme 1 Prins cyclization of (–)-isopulegol with *p*-anisaldehyde using I_2[6]



Scheme 2 Ene-Prins cyclization of (*R*)-citronellal with aldehydes using $Sc(OTf)_3$[7]

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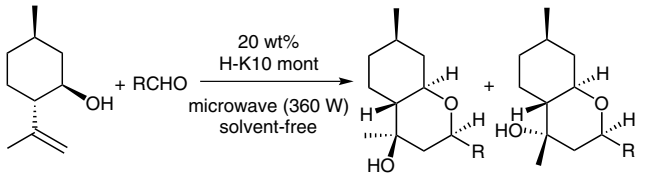
space, and tunable acidity.[8] Ease of catalyst separation and reutilization properties of modified montmorillonite K10 solid-acid catalysts make the chemical process very simple and also environmentally benign. Recent reports by Wang et al.[9] and Wallis et al.[10] have established the efficacy of acid-treated montmorillonite K10 (H-K10 mont).

As an alternative to classical heating conditions, researchers have used microwave irradiation under solvent-free conditions to carry out a range of chemical processes.[11,12] To the best our knowledge, there have been no reports in the literature on the use of H-K10 mont as catalyst under solvent-free and microwave-irradiation conditions for this important cylization reaction. We report herein the first example of H-K10 mont catalyzed Prins cylization of (–)-isopulegol to produce octahydro-2*H*-chromen-4-ol derivatives (Scheme 3).

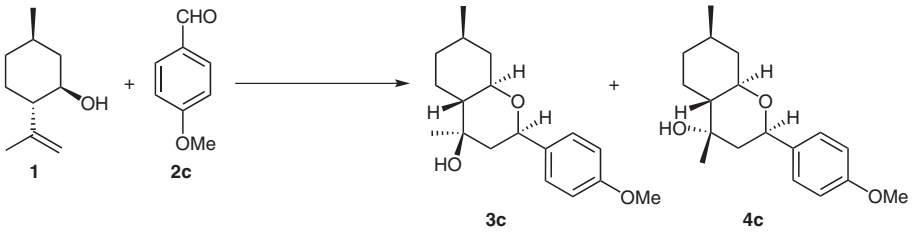


Scheme 3 Prins cyclization of (–)-isopulgol with aldehydes using H-K10 mont under microwave irradiation and solvent-free conditions

Our initial studies began with the search for optimal reaction conditions for the synthesis of octahydro-2*H*-chromen-4-ol derivatives. Initially, we performed the reaction of isopulegol (**1**) and *p*-anisaldehyde (**2c**) in the presence of 10 wt% of H-K10 mont under solvent-free conditions at room temperature for six hours. These conditions led to a 42% yield of a diastereomeric mixture of octahydro-2*H*-chromen-4-ols **3c** and **4c** (Table 1, entry 1). Repeating the reaction at 80 °C for three hours failed to enhance the yield of the product (Table 1, entry 2). However, when the same mixture was irradiated with microwaves for three minutes (Table 1, entry 3), a significant acceleration of the reaction rate was observed leading to a 70% yield of the corresponding cyclized product with excellent diastereoselectivity (20:1). In search of further improvement, we found that 20 wt% of H-K10 mont smoothly catalyzed the reaction to give 86% yield under microwave irradiation. Finally, the reaction was also performed at different powers. Thus, we performed the Prins cyclization reaction of (–)-isopulegol (**1**, 1.0 mmol) and *p*-anisaldehyde (**2c**, 1.2 mmol) at 180 W, 360 W, and 500 W power for three minutes using 20 wt% of H-K10 mont (Table 1, entries 4–6). However, the products were obtained with almost similar diastereomeric ratios, although the reaction performed at 180 W afforded the product in comparatively lower yield. Thus, the optimal reaction conditions involved the use of 20 wt% of H-K10 mont catalyst, isopulegol (**1**, 1.0 mmol) and aldehyde **2** (1.2 mmol) under microwave irradiation (360 W) and solvent-free conditions.

After optimization of the reaction conditions, the general applicability of this protocol was explored with various aromatic, heteroaromatic, and aliphatic aldehydes and also with ketone to produce a variety of substituted octahydro-2*H*-chromen-4-ol. The results of this protocol are summarized in Table 2. Initially, we explored the Prins cyclization reaction of (–)-isopulegol with various aromatic aldehydes. It was observed that yields and diastereoselectivities of products were strongly variable according to the nature of the substituent present in the arene ring.

Table 1 Reaction Conditions Optimization Studies Using (–)-Isopulegol (**1**) and *p*-Anisaldehyde[a]



Entry	Catalyst (wt%)[b]	Conditions	Time	Yield (%)[c]
1	10	25 °C	6 h	42
2	10	80 °C	3 h	46
3	10	MW (360 W)	3 min	70
4	20	MW (360 W)	3 min	86
5	20	MW (180 W)	3 min	60
6	20	MW (500 W)	3 min	65
7	0	MW (360 W)	3 min	0

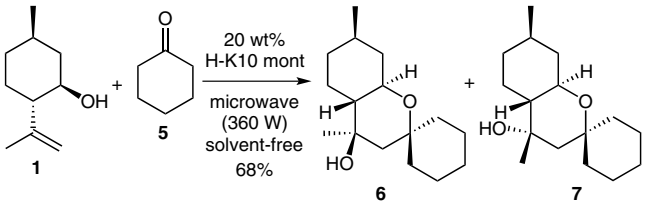
[a] Reaction performed with **2c** (1.2 mmol) and **1** (1 mmol).
[b] Solid-acid catalyst H-K10 mont prepared by reported method.[9,13]
[c] Isolated yield.

Aldehydes with electron-donating substituents at the *para* position gave very good yields and excellent diastereoselectivites of the corresponding Prins products (Table 2, entries 3 and 5); whereas *o*-anisaldehyde afforded an inseparable mixture of products **3d** and **4d** in a 6.5:1 diastereomeric ratio as determined by ^{1}HNMR spectroscopic analysis (Table 2, entry 4). Aldehydes with electron-withdrawing groups also underwent cyclization, but their corresponding octahydro-2*H*-chromen-4-ol derivatives were obtained in lower yields and diastereoselectivities (Table 2, entries 6–13). Unsubstituted aromatic aldehydes such as benzaldehyde and 2-napthaldehyde also underwent smooth cyclization with the yield of the chromenol derivative for the latter being higher than the former (Table 2, entries 1 and 2). Diastereoselectivities in both cases were found to be very good.

Next, we extended our studies to heteroaromatic aldehydes. When 2-furfuraldehyde and 2-thiophene carbaldehyde were reacted with (–)-isopulegol under the same reaction conditions, the corresponding chromen derivatives were obtained in good yields but with poor diastereoselectivities (Table 2, entries 14 and 15). Pyridine-2-carbaldehyde and pyridine-3-carbaldehyde did not undergo reaction (Table 2, entries 16 and 17).

To extend the utility of this protocol further, various aliphatic aldehydes were investigated. Propanal and 3-phenylpropanal underwent smooth cyclization to give their corresponding chromen derivatives in good yields and good diastereoselectivities (Table 2 entries 18 and 19).

Finally, the efficacy of the catalyst has also been tested with cyclohexanone **5** under the same reaction conditions to afford a 4:1 diasteromeric mixture of products **6** and **7** in 68% yield (Scheme 4).

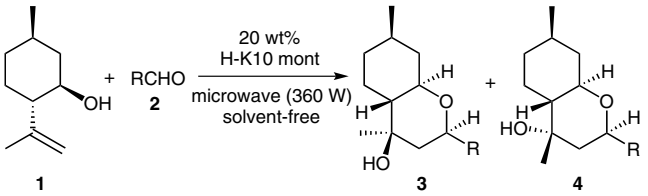


Scheme 4 Prins cylization of (–)-isopulegol with cyclohexanone

Concerning the recovery and reuse of the catalyst we observed that the catalyst can be reused up to five times without loss of any significant catalytic activity. After completion of the reaction of (–)-isopulegol with *p*-tolualdehyde the catalyst was recovered from the reaction mixture by a simple filtration process. The solid residue was washed with ethyl acetate, dried under vacuum, and kept in oven at 100 °C before its use for another cycle. The same method was applied for subsequent other three cycles. The results are summarized in Table 3.

The efficiency of other solid-acid catalysts such as montmorillonite K10, amberlyst-15, PPA-silica, and silica sulfuric acid was also examined, and the results are presented in Table 4.

Table 2 Synthesis of Octahydro-2*H*-chromen-4-ols via Prins Cyclization of (–)-Isopulegol with Different Aldehydes[a]

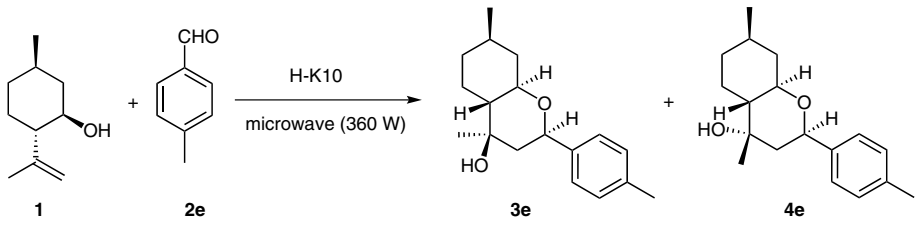


Entry	R	Product	Ratio of **3**/**4**[a]	Yield (%)[b]
1	Ph	**3a** + **4a**	9:1	76
2	2-naphthyl	**3b** + **4b**	10:1	80
3	4-$MeOC_6H_4$	**3c** + **4c**	20:1	86
4	2-$MeOC_6H_4$	**3d** + **4d**	6.5:1[c]	76
5	4-MeC_6H_4	**3e** + **4e**	25:1	82
6	4-ClC_6H_4	**3f** + **4f**	5:1	78
7	2,4-$Cl_2C_6H_3$	**3g** + **4g**	4:1	72
8	4-BrC_6H_4	**3h** + **4h**	9:1	78
9	3-BrC_6H_4	**3i** + **4i**	3:1	65
10	2-BrC_6H_4	**3j** + **4j**	2:1	70
11	4-FC_6H_4	**3k** + **4k**	3:1	64
12	2,4,5-$F_3C_6H_3$	**3l** + **4l**	1:1	50
13	3-$O_2NC_6H_4$	**3m** + **4m**	3:1	64
14	2-furfuryl	**3n** + **4n**	3:1	56
15	2-thiophenyl	**3o** + **4o**	2:1	50
16	2-pyridinyl	n.r.	–	
17	3-pyridinyl	n.r.	–	
18	Pr	**3r** + **4r**	5:1	70
19	3-phenylpropyl	**3s** + **4s**	4:1	76

[a] Diastereomeric ratios obtained from the isolated yield of the products.
[b] Isolated yield.
[c] Determined by ^{1}HNMR analysis; n.r.: no reaction.

In summary, a variety of aldehydes with both electron-donating and electron-withdrawing substituents undergo H-K10 mont promoted Prins cyclization reaction with (–)-isopulegol to generate a library of octahydro-2*H*-chromen-4-ols under microwave irradiation and solvent-free conditions. (–)-Isopulegol also underwent Prins cyclization with cyclohexanone to afford a spiro chromenol derivative under the same reaction conditions. This protocol offers an environmentally benign synthesis of chromen derivatives using reusable and eco-friendly clay catalyst and it can also be utilized as an effective alternative method over the two existing classical methods.

Table 3 Reusability of H-K10 Mont in the Synthesis of **3e** and **4e**[a,b]



Run	Yield (%)[c]
1	82
2	80
3	80
4	78
5	75

[a] Reaction performed with **2e** (1.2 mmol) and **1** (1.0 mmol).
[b] Solid-acid catalyst: 20 wt% H-K10 mont.
[c] Isolated yield.

Table 4 A Comparative Study[a] of Different Solid-Acid Catalysts for the Synthesis of **3c** and **4c**

Entry	Catalyst (20 wt%)	Yield (%)[b]
1	H-K10 mont	86
2	K-10 mont	15
3	Amberlyst-15	–[c]
4	PPA-silica	–[c]
5	silica sulfuric acid	–[c]

[a] Reaction conditions: Aldehyde **2c** (1.2 mmol) and (–)-isopulegol (1 mmol) and catalyst. Microwave irradiation at 360 W for 3 min under solvent-free conditions.
[b] Isolated yield.
[c] Complex mixture of products.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Experimental Procedure and Analytical Data**

Preparation of the Catalyst H-K10 Mont

A slurry of commercially available montmorrilonite K10 (5 gm) in 1 M HCl (100 mL) was stirred vigorously at 80 °C for 6 h. The solid was filtered out and washed several times with deionized H_2O to remove Cl^- completely. The solid residue was then dried at 120 °C for 12 h to afford the catalyst.

General Procedure for the Synthesis of Octahydro-2*H*-chromen-4-ol Derivatives

A mixture of (–)-isopulegol (**1**, 1 mmol), an aldehyde **2** (1.2 mmol), and H-K10 mont [20% (wt/wt of **1**] were irradiated in a closed vessel in the absence of any solvent in a Synthos 3000 microwave reactor at 360 W for 3 min. After 3 min of reaction time EtOAc was added to the crude reaction mixture, and the mixture was filtered. The residue was further washed with EtOAc to completely remove any product. The EtOAc layer was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel using EtOAc–hexane (3:7) as the eluent to furnish pure the chromenol derivatives **3** and **4**. The solid acid catalyst was dried under vacuum and kept in oven at 100 °C before its use for another cycle. The sturctures of the compounds **3a**, **4a**, **3c**, **4c**, **3e**, **4e**, **3f**, **4f**, **3h**, **4h**, **3r**, **4r**, **3s**, and **4s** were confirmed by comparison of their analytical data with those reported in the literature.[7] The analytical data of all new compounds are given in the Supporting Information.

Selected Analytical Data

Compound **3g**: viscous liquid. IR ($CHCl_3$): 3376, 2949, 2924, 2869, 1590, 1562, 1473, 1455, 1377, 1092, 942, 824, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, 1 H, *J* = 8.4 Hz), 7.32 (d 1 H, *J* = 1.9 Hz), 7.24 (m, 1 H), 4.76 (dd, 1 H, *J* = 1.4, 11.4 Hz), 3.27 (dt, 1 H, *J* = 4.2, 10.4 Hz), 2.08–1.93 (m, 2 H), 1.75 (m, 1 H), 1.60 (br s, 1 H, OH), 1.45–1.30 (m, 3 H), 1.32 (s, 3 H), 1.27–0.98 (m, 4 H), 0.94 (d, 3 H, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 133.3, 131.8, 128.8, 128.2, 127.4, 77.6, 73.0, 70.8, 52.1, 48.6, 41.4, 34.3, 31.4, 23.0, 22.2, 21.0. ESI-MS: *m/z* = 330 $[M + 1]^+$. Anal. Calcd for $C_{17}H_{22}Cl_2O_2$: C, 62.01; H, 6.73. Found: C, 61.96; H, 6.80.

Compound **4g**: viscous liquid. IR ($CHCl_3$): 3481, 2926, 2854, 1589, 1563, 1472, 1455, 1375, 1251, 1095, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, 1 H, *J* = 8.4 Hz), 7.31 (d 1 H, *J* = 2.0 Hz), 7.23 (d, 1 H, *J* = 1.9 Hz), 5.12 (dd, 1 H, *J* = 1.7, 11.4 Hz), 3.59 (dt, 1 H, *J* = 4.0, 11.0 Hz), 1.99–1.94 (m, 2 H), 1.85–1.65 (m, 2 H), 1.55 (br s, 1 H, OH), 1.50–1.40 (m, 2 H), 1.25 (s, 3 H), 1.23–0.96 (m, 4 H), 0.94 (d, 3 H, *J* = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.3, 133.1, 132.0, 128.8, 128.3, 127.3, 75.8, 71.2, 69.4, 49.5, 46.6, 41.3, 34.4, 31.2, 28.1, 22.5, 22.2. ESI-MS: *m/z* = 330 $[M + 1]^+$.

Compound **3i**: white solid; mp 97 °C. IR ($CHCl_3$): 3387, 2923, 2867, 1597, 1569, 1454, 1376, 1354, 1321, 1206, 1102, 1034, 781, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.32 (dd, 1 H, *J* = 1.4, 3.1 Hz), 7.18 (d, 1 H, *J* = 1.5 Hz), 7.10 (d, 1 H, *J* = 7.7 Hz), 4.33 (dd, 1 H, *J* = 2.0, 11.7 Hz), 3.53 (dt, 1 H, *J* = 4.2, 10.5 Hz), 1.84–1.96 (m, 1 H), 1.82 (dd, 1 H, *J* = 2.3, 12.8 Hz), 1.20–1.76 (m, 5 H), 1.23 (s, 3 H), 0.95–1.19 (m, 3 H), 0.87 (d, 3 H, *J* = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.3, 130.2, 129.8, 129.0, 124.6, 122.5, 75.6, 74.0, 69.4, 49.3, 48.1, 41.2, 34.4, 31.3, 28.2, 22.5, 22.2. ESI-MS: *m/z* = 362 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{23}BrO_2$: C, 60.18; H, 6.83. Found: C, 60.14; H, 6.81.

Compound **4i**: semi-solid. IR ($CHCl_3$): 3455, 2927, 2869, 1597, 1570, 1476, 1455, 1424, 1375, 1327, 1253, 1162, 1097, 1063, 1036, 901, 782, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 1 H), 7.38 (dd, 1 H, *J* = 1.2, 2.9 Hz), 7.32 (d, 1 H, *J* = 1.5 Hz), 7.15 (d, 1 H, *J* = 7.7 Hz), 4.75 (dd, 1 H, *J* = 2.1, 11.6 Hz), 3.53 (dt, 1 H, *J* = 4.1, 11.0 Hz), 1.98 (m, 1 H), 1.70–1.80 (m, 1 H), 1.35–1.76 (m, 3 H), 1.24 (s, 3 H), 1.05–1.19 (m, 3 H), 0.96 (d, 3 H, *J* = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.3, 130.2, 129.8, 129.0, 124.6, 122.5, 75.6, 74.0, 69.4, 49.3, 48.1, 41.2, 34.4, 31.3, 28.2, 22.5, 22.2. ESI-MS: *m/z* = 362 [M + Na].