Montmorillonite K10 Clay Catalyzed Synthesis of 4-Aryltetrahydropyrans: A One-Pot, Multicomponent, Environmentally Friendly Prins–Friedel–Crafts-Type Reaction

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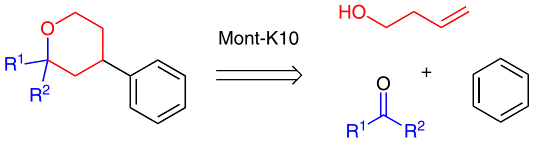
Abstract: The Montmorillonite K10 clay catalyzed synthesis of 4-aryltetrahydropyrans is presented as a one-pot, multicomponent, environmentally friendly Prins–Friedel–Crafts-type reaction.

Key words: aldehydes, cyclization, green chemistry, heterogeneous catalysis, multicomponent reaction

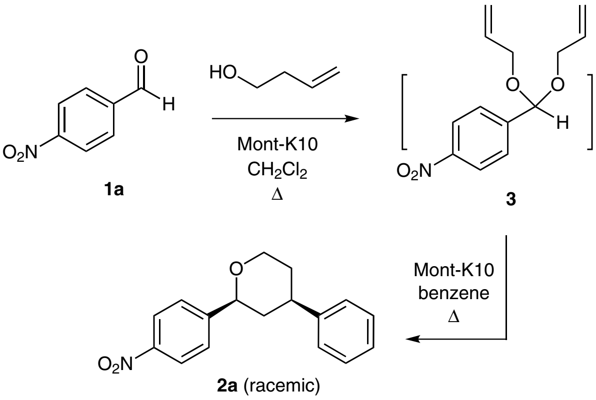


Scheme 1 Retrosynthesis

Advances in high throughput screening (HTS) technology for identification of new potential drugs has prompted researchers to develop more efficient synthetic routes to libraries of small organic molecules. Multicomponent reactions (MCR), which result in the breaking and forming of multiple bonds in a single step or in a single reaction flask, are considered ideal for the generation of new compound libraries for HTS.[1] The tetrahydropyran (THP) moiety is a naturally occurring and abundant heterocyclic motif that has been implicated in the physiological activity of a broad array of natural and synthetic products.[2] A host of synthetic approaches to THP compounds has been reported, including the one-pot MCR of carbonyls (**1**) with 3-buten-1-ol and arenes catalyzed by $BF_3{\cdot}OEt_2$.[3] Herein we report our investigation of a more environmentally friendly approach to the synthesis of THPs using Montmorillonite K10 clay (Mont-K10, Scheme 1) as a catalyst. In addition to being considerably less expensive than $BF_3{\cdot}OEt_2$, Mont-K10 clay is also nontoxic, noncorrosive, and much simpler to handle. Reactions catalyzed by $BF_3{\cdot}OEt_2$ must be conducted in rigorously dried glassware, under an inert environment, and they require aqueous workup steps, which invariably lead to the generation of waste products. Mont-K10 catalyzed reactions, on the other hand, can be conducted open to the air and workup typically involves only a filtration step; often, both the clay and the solvent can be recycled and reused.[4,5]

As concern for the environment continues to shape the way chemists think about the construction of physiologically active compounds, the development of synthetic methodologies that promote greener reactions is essential. Environmentally benign clays are ideally suited for the 'greening' of modern synthetic chemistry, and we have reported the effective application of Montmorillonite K10 clay as a catalyst for carbon–carbon bond-forming and other reactions.[6–12]

We chose to begin our investigation with *p*-nitrobenzaldehyde (**1a**) as the carbonyl substrate. We found that refluxing *p*-nitrobenzaldehyde with excess 3-buten-1-ol in dichloromethane in the presence of Mont-K10 clay gave the corresponding acetal **3**. When **3** was subsequently taken up in excess benzene and refluxed in the presence of additional Mont-K10, the corresponding tetrahydropyran product **2a** was generated in good yield (Scheme 2).



Scheme 2 Initial experiment

In an effort to simplify the procedure and avoid wasting a full equivalent of the 3-buten-1-ol, we next refluxed *p*-nitrobenzaldehyde with Mont-K10, 3-buten-1-ol (1.1 equiv), and methanol (5 equiv) in benzene for two hours. This modified procedure successfully resulted in the generation of **2a** in good yield, presumably via dimethyl acetal (or mixed acetal) intermediate **4**. We propose a mechanism in which **4** reacts subsequently with 3-buten-1-ol to give oxonium ion intermediate **5**, which in turn undergoes Prins cyclization to give carbocation **6**. Benzene then reacts with **6** via Friedel–Crafts alkylation to give **2a** (Scheme 3). This initial reaction was robust enough to be

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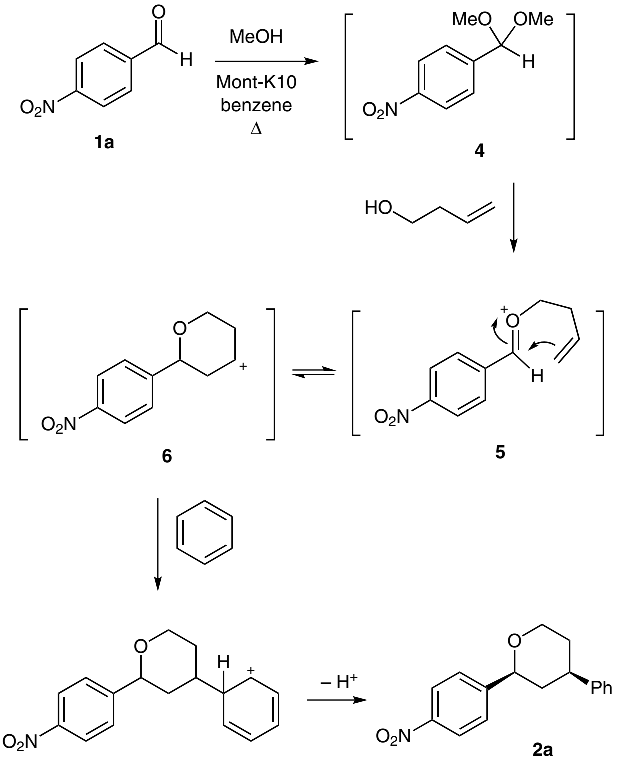
developed into an undergraduate organic chemistry laboratory discovery/research project, the details of which have been reported.[13]



Scheme 3 Proposed mechanism

We next set out to probe the scope of the reaction with a sample of readily available carbonyl compounds (Table 1). Our results, though far from exhaustive, are consistent with those reported by Reddy et al. using $BF_3{\cdot}OEt_2$.[3] Of particular note are the observed yields for the reactions with acetone and cyclohexanone (Table 1, entries 5 and 6, respectively), which are superior to previously reported values. Our methodology represents a much more environmentally and logistically friendly route to the target compounds, and further expands the repertoire of reactions successfully catalyzed by Montmorillonite K10 clay.[14]

Table 1 Reaction Scope

Entry	Carbonyl	R^1	R^2	Product	Yield (%)
1	**1a**	p-$O_2NC_6H_4$	H	**2a**[3,15]	90
2	**1b**	m-$O_2NC_6H_4$	H	**2b**[3]	88
3	**1c**	o-$O_2NC_6H_4$	H	**2c**[3]	99
4	**1d**	m-BrC_6H_4	H	**2d**[3]	91
5	**1e**	Me	Me	**2e**[3]	75
6	**1f**	$–(H_2C)_5–$		**2f**[3]	90

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(14) **Typical Procedure for the Mont-K10-Catalyzed Prins–Friedel–Crafts Reaction for the Synthesis of 2a**: In a 5-mL round-bottomed flask, equipped with a magnetic stir bar, the Mont-K10 clay (200 mg) and *p*-nitrobenzaldehyde (151 mg, 1 mmol) were combined with benzene (2 mL). Methanol (202 μL, 5 mmol) was added, followed by 3-buten-1-ol (94 μL, 1.1 mmol) and the reaction mixture was refluxed with vigorous stirring. Reaction progress was monitored by TLC (in 1:1 hexanes–EtOAc). When the reaction was complete, the mixture was allowed to cool to r.t. Then, the product mixture was vacuum filtered, washing with acetone, to separate the clay. The filtrate was concentrated under vacuum to give a pale yellow solid (255 mg, 90%). See ref. 15 for the experimental details and characteristic data.

(15) **Analytical Data for Compound 2a**: ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 100 MHz, respectively. The proton signal of residual, non-deuterated solvent ($\delta = 7.26$ ppm for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. ^{13}C NMR chemical shifts are reported relative to the $\delta = 77.23$ ppm resonance of $CDCl_3$. Coupling constants are reported in Hz. IR spectra were recorded as thin films on a Nicolet Avatar 360 instrument. GC analysis was performed on a Hewlett Packard 5890 Series II gas chromatograph with a 5971 Series mass selective detector. **Tetrahydro-2-(4-nitrophenyl)-4-phenyl-2*H*-pyran (2a)**: IR ($CDCl_3$): 3029, 2942, 1849, 1602, 1517, 1345, 1130, 1106, 1085, 850, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J = 8.8$ Hz, 2 H), 7.57 (d, $J = 8.8$ Hz, 2 H), 7.23–7.33 (m, 5 H), 4.60 (dd, $J = 11.2$, 2.0 Hz, 1 H), 4.30–4.36 (m, 1 H), 2.75–3.83 (m, 1 H), 2.95–3.05 (m, 1 H), 2.10 (dq, $J = 13.2$, 2.0 Hz, 1 H), 1.85–1.90 (m, 2 H), 1.70 (q, $J = 12.4$ Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.0$, 145.5, 142.9, 128.3, 127.4, 126.7, 126.4, 125.7, 79.8, 68.5, 42.0, 41.5, 33.3. GC–MS (70 eV; $t_R = 13.174$ min): m/z (%) = 283 (28) $[M^+]$, 205 (88) $[M - 78]^+$, 104 (100) $[M - 179]^+$, 91 (68) $[M - 192]^+$.