Green Chemistry: Application of Montmorillonite Clays in Organic Synthesis

List of pending support for leave

I have not applied for external support for this leave request.
I will apply for a Cottrell College Science award from Research Corporation for summer funding (summers 2004 and 2005).

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Status of tenure clock

I request that my tenure clock not be stopped if the proposed leave is granted.

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Abstract

Montmorillonite clays are mined in regions all over the world and have been found to effectively catalyze a broad range of chemical reactions. Although these clays have demonstrated such success, they are somewhat under-exploited in organic synthesis, perhaps because their specific modes of action are not entirely understood. Given their natural availability, low cost, and ease of use, however, application of clays in organic synthesis comprises an attractive topic for further investigation. This project, which is proposed to be carried out during autumn quarter, 2004, is aimed at investigating the uses of Montmorillonite clays in organic synthesis. Specific synthetic targets are physiologically active quinoline compounds.

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Project Description

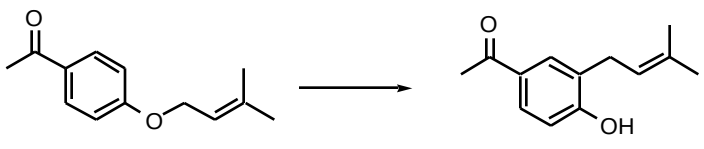
In efforts aimed at the development of new drug compounds, pharmaceutical companies and academic research labs also generate a significant amount of chemical waste that is hazardous to the environment. Since the Pollution Prevention Act of 1990 was passed, however, chemists have attempted to minimize waste by designing new, more environmentally friendly methods for synthesizing useful organic compounds. This movement, often referred to as "Green Chemistry," has produced an array of improved methodologies, including the use of clays as chemical catalysts.[1] This project is focused on contributing to Green Chemistry through the application of environmentally benign Montmorillonite clays in organic synthesis.

In the most general sense, clays are a type of fine-grained earth, primarily composed of aluminum and silcate minerals.[1] Montmorillonite clays are thought to have formed from volcanic ash during the Jurassic and later periods, and were named for the location of their discovery, Montmorillon, France, in the 1800s. These clays are now mined in regions all over the world, including Europe, Africa, Asia, South and North America, with U.S. mines in Florida, Georgia, Illinois and Texas. Montmorillonite clays have a wide variety of uses and have recently been found to have the ability to catalyze a wide range of chemical reactions.[1] A catalyst is a chemical species that induces a chemical reaction to occur at a reasonable rate, without itself being consumed in the

process; the catalyst can typically be recovered and reused. Development of naturally benign substances like clays as catalysts for chemical reactions constitutes an exciting breakthrough in Green Chemistry and promises to reduce the amount of hazardous waste associated with the synthesis of new drug compounds.

While my scholarly interests have always been aimed at the synthesis of physiologically active natural products, I have only recently become interested in Green Chemistry. In the context of a synthesis project[2] that was initiated during the summer of 2002, my research group and I discovered a novel catalytic use for Montmorillonite clays that has laid the groundwork for our foray into the realm of Green Chemistry and will be further developed and established in the proposed work.

About a year ago, my research group and I had occasion to use Montmorillonite clay as a catalyst for a key reaction in an ongoing project aimed at the total synthesis of one such molecule of life.[2] The target compound was a naturally-occurring anti-inflammatory, and our designed synthesis of it involved a very challenging chemical transformation (conversion of **1** to **2**, Figure 1).

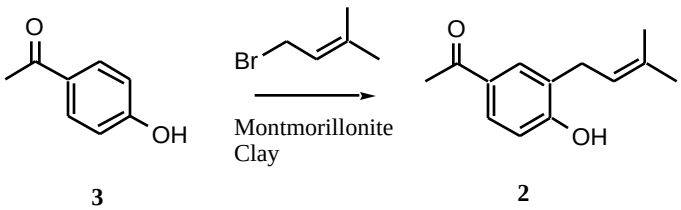


1 **2**

Figure 1. Conversion of **1** to advanced intermediate **2**

After a thorough review of the literature, we came upon an analogous reaction that had been successfully carried out in the presence of Montmorillonite clay.[3] Attempted duplication of this reaction with our system, however, turned out to be significantly more challenging, so we set out to more thoroughly investigate the original reaction and determine the optimal conditions for its success. This study led to several important observations about the clay-catalyzed rearrangement of compounds like **1** to give products like **2**, which we recently reported in the literature[4] and will present at the upcoming national meeting of the American Chemical Society (April, 2004).[5]

In addition to optimizing the conditions for the clay-catalyzed rearrangement of **1** to **2** we also discovered a novel way of making systems like compound **2** (conversion of **3** to **2**, Figure 2).



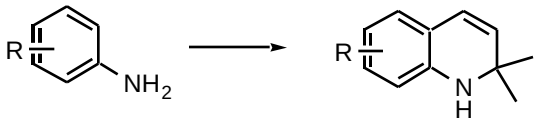
3 **2**

Figure 2. Conversion of **3** to **2**

This new process is also clay-catalyzed, but is much more flexible, in terms of substrate scope, and more efficient with respect to yield of product. Our new approach is the topic of a second paper that is currently in preparation[6] and will also be presented at the 2004

ACS meeting.[5] The success of this new reaction has prompted us to consider additional uses for Montmorillonite clays in the synthesis of physiologically active natural products.

The compounds that we're interested in targeting during the course of the proposed leave are called quinolines, such as compound **5** shown in Figure 3, below.



4 **5**

Figure 3. Clay-catalyzed synthesis of quinolines **5**

Quinolines are ubiquitous in nature and have been shown to exhibit a range of physiological benefits, such as anti-inflammatory activity.[7] A preliminary experiment conducted in my lab during the summer of 2003 demonstrated that treatment of a substituted aniline compound (like compound **4** in Figure 3 above) with prenyl bromide (an alkylating agent) in the presence of Montmorillonite K10 clay, results in successful generation of the corresponding quinoline product (**5** in Figure 3). I am confident that we will be able to generate a variety of substituted quinoline compounds through this and other clay-catalyzed reactions. This would be a significant accomplishment since existing technology for synthesizing quinolines in the laboratory involves much more abrasive, less environmentally benign conditions.[7]

It has been said that "the molecules of life actually developed in sedimentary clays."[1] Whether or not this is true, it is surely a promising pursuit to study the use of clays in the synthesis of physiologically beneficial compounds. In addition to being environmentally benign and reducing the amount of waste that is generated from chemical laboratories, there are other incentives for using clays in research. Clays are commercially available and very inexpensive (less than $0.03 per gram!), as well as extremely easy to use and safe to handle, even for undergraduate researchers. Use of clays as catalysts allows for them to be recycled, which further increases their economic efficiency. Furthermore, reactions that are catalyzed by clay are extremely easy to "work-up;" since the clay does not dissolve in the reaction medium (solvent), it must simply be filtered away when the reaction is complete.

Projected outcomes

At least one paper and one presentation will result from the work to be carried out during the proposed leave. More importantly this work will further establish my research program in the area of Green Chemistry, as we build on the foundation that has been laid during the previous two summers. In addition to the synthesis of useful and interesting quinoline compounds, we anticipate that the proposed work will lead to other applications of clays in organic synthesis, for future exploration.

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References

1. Nagendrappa, G. "Organic synthesis using Clay Catalysts, Clays for 'Green Chemistry," *Resonance* **2002**, 64-77.
2. Dintzner, M. R.; McClelland, K. M.; Coligado, D. M. "Progress toward the synthesis of an anti-inflammatory acetophenone glucoside," *Abstracts of Papers*, 225th National Meeting of the American Chemical Society, New Orleans, LA; American Chemical Society: Washington, DC, **2003**; ORGN 429.
3. Dauben, W. G.; Cogen, J. M.; Behar, V. "Clay Catalyzed Rearrangement of Substituted Allyl Phenyl Ethers: Synthesis of Ortho-Allyl Phenols, Chromans and Coumarans," *Tetrahedron Lett.* **1990**, *31*, 3241.
4. Dintzner, M. R.; Morse, K. M.; McClelland, K. M. "Investigation of the Montmorillonite Clay-Catalyzed [1,3] Shift Reaction of 3-Methyl-2-Butenyl Phenyl Ether," *Tetrahedron Lett.* **2003**, *in press.*
5. Dintzner, M. R.; McClelland, K. M.; Morse, K. M. "Application of Montmorillonite clay in natural products synthesis" *Abstracts of Papers*, 227th National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, **2004**; submitted.
6. Dintzner, M. R., McClelland, K. M., Morse, K. M. "Montmorillonite Clay-Catalyzed Conversion of Phenols to 2,2-Dimethylbenzopyrans," *Organic Letters* **2004**, *in preparation.*
7. Dillard, R. D.; Pavey, D. E.; Benslay, D. N. "Synthesis and anti-inflammatory activity of some 2,2-dimethyl-1,2-dihydroquinolines" *J. Med. Chem.* **1973**, *16*, 251.

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10-week timeline

Week	Activity
1	Montmorillonite K10-catalyzed reaction of *p*-methoxyaniline with prenyl bromide; reaction monitored by GCMS and product(s) isolated, purified, and analyzed (IR, NMR)
2	Montmorillonite K10-catalyzed reaction of *p*-methoxyaniline with 3-methyl-2-butenal; reaction monitored by GCMS and product(s) isolated, purified, and analyzed (IR, NMR)
3	Montmorillonite K10-catalyzed rearrangement of N-prenylated-*p*-methoxyaniline with prenyl bromide; reaction monitored by GCMS and product(s) isolated, purified, and analyzed (IR, NMR)
4	Decide which of the above reactions is most successful and optimize conditions (solvent, temperature, concentration, etc.); if all reactions are successful, conditions for each will be optimized
5	Apply optimized conditions to several pre-selected, substituted anilines; reactions monitored by GCMS and products isolated, purified, and analyzed (IR, NMR)
6	Apply optimized conditions to several pre-selected, substituted anilines; reactions monitored by GCMS and products isolated, purified, and analyzed (IR, NMR)
7	Apply optimized conditions to several pre-selected, substituted anilines; reactions monitored by GCMS and products isolated, purified, and analyzed (IR, NMR)
8	Apply optimized conditions to several pre-selected, substituted anilines; reactions monitored by GCMS and products isolated, purified, and analyzed (IR, NMR)
9	Prepare all relevant samples for elemental analysis; begin writing experimental section of paper(s)
10	Continue writing paper(s) for submission by December 31, 2004

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Publications and presentations relevant to this application

- Dintzner, M. R.; McClelland, K. M.; Coligado, D. M. "Progress toward the synthesis of an anti-inflammatory acetophenone glucoside," *Abstracts of Papers,* 225th National Meeting of the American Chemical Society, New Orleans, LA; American Chemical Society: Washington, DC, **2003**; ORGN 429.

- Dintzner, M. R.; Morse, K. M.; McClelland, K. M. "Investigation of the Montmorillonite Clay-Catalyzed [1,3] Shift Reaction of 3-Methyl-2-Butenyl Phenyl Ether," *Tetrahedron Lett.* **2003**, *in press.*

- Dintzner, M. R.; McClelland, K. M.; Morse, K. M. "Application of Montmorillonite clay in natural products synthesis" *Abstracts of Papers,* 227th National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, **2004**; submitted.