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Faculty Research and Development Grant Proposal, 2005

Application of Green Chemistry in the Synthesis of HIV-1 Protease Inhibitors

Budget Narrative

A salary stipend is requested to support my continued, full-time efforts in the research and development of green chemistry in the synthesis of physiologically active natural (and non-natural) products during the summer of 2005. No additional funding is requested, and no other internal funding (for the PI) will support this work during the summer of 2005.

Project Description

Application of Green Chemistry in the Synthesis of HIV-1 Protease Inhibitors

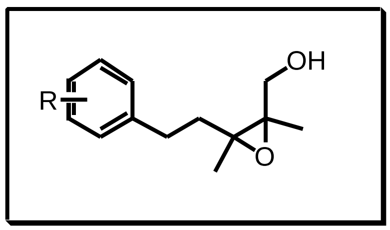
Background, Importance, and Specific Objectives

In the process of developing synthetic routes to physiologically beneficial compounds like drugs, industrial and academic research laboratories also generate a significant amount of chemical waste that is hazardous to the environment. Since the Pollution Prevention act was passed in 1990, however, chemists have attempted to minimize waste by designing new, more environmentally friendly methods for organic synthesis. This movement, often referred to as "green chemistry," has resulted in the development of an array of new technology, including the use of clays as catalysts.[1] A catalyst is a chemical species that induces a chemical reaction (a chemical transformation) to occur at a reasonable rate, without itself being consumed in the process. Application of naturally benign substances like clays as catalysts for chemical reactions constitutes an exciting component of green chemistry and promises to reduce the amount of hazardous waste associated with carrying out important laboratory research.[2] The use of microwave irradiation to promote faster and cleaner chemical reactions is also an important component of green chemistry, especially when used in combination with clays and other solvent-free conditions.[3] The proposed project is aimed at contributing to green chemistry through the application of clays and microwave irradiation in the synthesis of compounds that have been shown to inhibit HIV-1 protease, one of the key enzymes responsible for proliferation of the virus that is known to cause AIDS.[4] Furthermore, the simplicity of this work, in terms of its execution, makes it highly accessible to participation by undergraduate students and affords them an excellent opportunity to gain first-hand experience in research.

In the most general sense, clays are a type of fine-grained earth, primarily composed of aluminum and silicate minerals.[2] Montmorillonite clays, the class of clays that I have been working with for the past several years while at DePaul, 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 from 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, including as catalysts for a broad range of chemical reactions.[2]

Another important development in the green chemistry movement is the use of microwave irradiation (in ordinary household microwave ovens) as an energy source for speeding up chemical reactions. Reactions that proceed in a matter of hours or days when heated by conventional means have been shown to go to completion in several minutes when exposed to microwaves.[3] Speeding up a chemical reaction to this degree is not only much more energy efficient, but often also results in much cleaner processes—i.e. the development of unwanted byproducts that may form when a reaction is heated for extended periods of time are reduced or eliminated completely. The combination of conducting chemical reactions using clay catalysts and microwave irradiation is extremely promising, and based on our preliminary results will contribute substantially to the development of more environmentally friendly routes to the synthesis of drugs and other useful chemical compounds, such as the targeted HIV-1 protease inhibitors. A two-dimensional rendering of the general molecular structure of the targeted HIV-1 protease inhibitors is shown in the below (Figure 1).

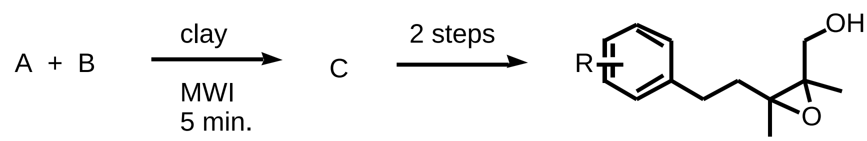
Figure 1. The general molecular structure of the targeted HIV-1 protease inhibitor compounds



Methods and Approaches

The target compounds will be prepared in the laboratory via a novel 3-step synthetic scheme that is illustrated in a simplified manner in Figure 2. The first is the key step, in which two reactants (A and B) are mixed with a small amount of powdered Montmorillonite clay in a glass vial and microwaved for a period of 5 minutes. The resulting product (C) is then extracted from the clay using a solvent (such as acetone), isolated and purified. In two successive subsequent steps intermediate C is converted to the target compound(s). The real beauty and elegance of the scheme is that a wide variety of reactants can be coupled in the first step (other than A and B) to give a variety of "C-type" intermediates. These intermediates, then, can be converted by the same two-step sequence to give an array of compounds that have the general molecular structure of the target compound, but each with subtle differences. Subtle differences in molecular structure can result in dramatic differences in physiological activity. Hence, it is conceivable that the proposed route will result in the generation of a whole “library” of new compounds that have varying levels of interaction (inhibitory activity) with HIV-1 protease.

Figure 2. Proposed synthetic scheme (simplified)



Expected Specific Outcomes

This research will ultimately lead to the publication of several peer-reviewed journal articles within the 2005-2006 academic year with participating undergraduate students as co-authors and/or co-presenters. Relevant journals include *Tetrahedron Letters*, *Organic Letters*, *Synlett*, *Synthesis*, and *Green Chemistry*. Preliminary results will be presented at the national meeting of the American Chemical Society (ACS) in March, 2005 (San Diego, CA) by three undergraduate students and myself. Successful completion of the proposed project will constitute a significant contribution to green chemistry, and may also result in the generation of potentially new and more effective compounds for the treatment of HIV and AIDS.

Relevance to Previous Work

My research group and I have been investigating the use of clays as catalysts for chemical reactions at DePaul for the past two years, and we have been generously supported by previous internal grants (URAP, URC, FRD). Our work has been presented in several peer-reviewed journal articles[5] and national ACS meetings.[6] In the past four and a half years I have, in fact, mentored nearly 15 undergraduate research students, 11 of whom have appeared as co-authors or co-presenters in published or presented work. Our previous work has laid the foundation for the proposed project, preliminary results of which are very encouraging.

References

1. Eissen, M.; Mazur, R.; Quebbemann, H.-G.; Pennemann, K.-H. *Helv. Chim. Acta* **2004**, *87*, 524.
2. (a) Laszlo, P. *Science* **1987**, *235*, 1473, and references therein. (b) Nagendrappa, G. *Resonance* **2002**, 64.
3. (a) Giguere, R. J.; Bray, T. L.; Duncan, S. M. *Tetrahedron Lett.* **1986**, *27*, 4945. (b) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279
4. Abell, A. D.; Hoult, D. A.; Bergman, D. A.; Fairlie, D. P. *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 2853.
5. (a) Dintzner, M. R.; McClelland, K. M.; Morse, K. M.; Akroush, M. H. *Synlett* **2004**, *11*, 2028. (b) Dintzner, M. R.; Morse, K. M.; McClelland, K. M.; Coligado, D. M. *Tetrahedron Lett.* **2004**, *45*, 79. (c) Dintzner, M. R.; Lyons, T. W.; Akroush, M. H.; Wucka, P. *Synlett* **2005**, *submitted.*
6. (a) 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, **2004**; American Chemical Society: Washington, DC; ORGN-132. (b) Dintzner, M. R.; McClelland, K. M.; Coligado, D. Progress toward the synthesis of an anti-inflammatory acetophenone glucoside." *Abstracts of Papers*, 225th National Meeting of the American Chemical Society, New Orleans, LA, **2003**; American Chemical Society: Washington, DC; ORGN-429. (c) Dintzner, M. R.; Lyons, T. W.; Akroush, M. H. "Progress toward the synthesis of *Z*-2,3-epoxy-5-phenylpentan-1-ol derivatives, precursors to potential HIV-1 protease inhibitors." *Abstracts of Papers*, 229th National Meeting of the American Chemical Society, San Diego, CA, **2005**; American Chemical Society: Washington, DC; *abstract submitted.*

Project Summary

Application of Green Chemistry in the Synthesis of HIV-1 Protease Inhibitors

The principles and techniques of “green chemistry,” or chemistry that is environmentally friendly, will be applied to the synthesis of a family of compounds with potential HIV-1 protease inhibitory activity. The key features of the proposed project involve using natural clays as chemical catalysts and conducting experiments in a microwave oven, both of which promote quicker, cleaner, and more environmentally friendly chemistry.