

ENVIRONMENTALLY BENIGN “GREEN” SYNTHESIS OF MEDICINALLY IMPORTANT COMPOUNDS

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Abstract: A type of chemical compound called dihydropyrimidinones can be used to combat malaria, heart arrhythmia and prostate inflammation. Dihydropyrimidinones have been prepared previously, but with varying degrees of success and using methods that require and produce unnecessary hazardous chemicals. The focus of the proposed research is to develop a “green” (environmentally benign) method that can be used to produce these future medications in a responsible manner.

Background

Making Molecules: The Chemical Industry

Synthesis is a term used by chemists to refer to a process in which existing molecules are converted into new molecules. The existing molecules are called *starting materials* and the new molecules are known as *products*. The use of these terms is not accidental; chemical techniques have been used to manufacture products as like cosmetics, pharmaceuticals and plastics for hundreds of years.

The chemical industry will contribute 2.5% contribution to the US GDP in 2007.¹ This contribution will require the energy equivalent of 2.98 million barrels of crude oil per day and approximately \$5 billion to meet emissions, waste disposal and safety standards.² The petroleum resources will never be replaced, and the waste that must be disposed will be incinerated or buried in landfills. The reliance of the chemical industry on nonrenewable resources and on processes that use or generate hazardous waste cannot feasibly continue. A new approach is needed if our society continues to rely on the important products of the chemical industry.

Green Chemistry: A New Way of Producing New Molecules

Green Chemistry was conceived as an approach to reduce the use and generation of hazardous compounds, and to reduce the amount of energy needed to conduct chemical processes. It “involves inventing new methods to reduce chemical hazards while producing superior products in a more efficient and more economical fashion.”³

The ideal “green” chemical process would be **specific**, producing only the desired product and no other substances (e.g.-no generation of hazardous waste). A green process would also be **benign**, employing no hazardous compounds, and it would require **no energy input**. The twelve principles of green chemistry followed by conscientious practitioners are included as an appendix to this proposal.⁴ These principles will be followed in conducting the proposed research.

¹ William J. Storck, “Industry Outlook: United States,” Chemical & Engineering News, 85(2), January 8, 2007, pp. 14-17.

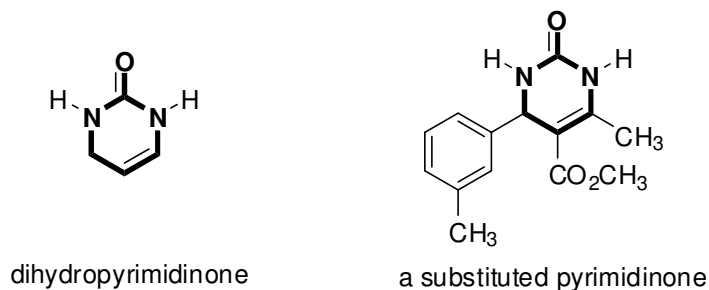
² Data are reported by the American Chemistry Council and summarized by the industry group Chemical Industry Vision 2020: “Important to our Economy and to the Way We Live The U.S. Chemical Industry” <http://www.chemicalvision2002.org>. Accessed Jan 20, 2007.

³ Doxsee, K.M. and Hutchison, J.E., “Green Organic Chemistry: Strategies, Tools and Laboratory Experiments,” Thomson/Brooks-Cole: California, 2004.

⁴ Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, 1998, p.30.

The compounds that are of interest to us are called dihydropyrimidinones. The molecular structure of these compounds is shown below in Figure 1. Compounds that contain similar arrangements of atoms as part of their molecular structure are called *substituted* dihydropyrimidinones.

Figure 1.



Substituted dihydropyrimidinones are currently used as medicinal compounds for the treatment of heart arrhythmia⁵ and have also been shown to be useful in the treatment of malaria and prostate inflammation under controlled laboratory conditions.⁶ These compounds have so far been prepared using traditional chemical techniques.

One of the traditional ways in which the preparation of chemical compounds is evaluated is by calculating a quantity known as the percent yield. This calculation determines the extent to which a chemical compound is produced from starting materials, but does not consider the efficiency or the hazards involved in doing so. A process that produces a product with a yield of 100% might generate enormous amounts of waste and involve high degree of risk. A more realistic calculation that takes hazard and efficiency into account is the *overall atom efficiency*. For example Monastrol, a promising anticancer dihydropyrimidinone that is undergoing clinical trials, is prepared with an overall atom efficiency of 15%.⁷ The significance of this is that 85% of the materials used to prepare monastrol are discarded as waste. Part of this waste is due to the use of a potentially carcinogenic additive.

Project Description:

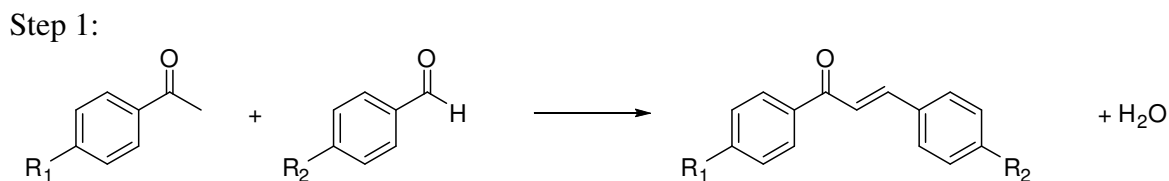
It should be possible to prepare monastrol and similar compounds using greener, more efficient methods outlined below in Figures 2-4. The overall approach meets several of the important criteria for green chemical processes. At the start of the synthesis no additives are used, and processes of this type have been shown to proceed with very high efficiency.⁸

⁵ A) Kappe, C.O. "Biologically Active Dihydropyrimidinones of the Bignelli Type- A Literature Survey" *Eur. J. Med. Chem.* **2000**, *35*, 1043-1052.

⁶ a) Agarwal, A.; Srivastave, K.; Puri, S.K.; Chahuan, Prem M.S. "synthesis of 4-pyrido-6-aryl-2-substituted Amino Pyrimidines As a New Class of Antimalarial Agents" *Bioorg. Med. Chem.* **2005**, *13*, 6226-6232. b) Dondoni, A.; Massi, A.; Sabbatini, S. "Improved Synthesis and Preparative Scale Resolution of Racemic Monastrol" *Tetrahedron Lett.* **2002**, *43*, 5913-5916. c) Bryzgalov, A.O.; Dolgikh, M.P.; Sorokina, I.V.; Tolstokova, T.G.; Sedova, V.F.; Shkurko, O.P "Antiarrhythmic Activity of 4,6-di(het)aryl-5-nitro-3,4-dihydropyrimidin-(1-*H*)-2-ones and Its Effects on Arterial Pressure in Rats" *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1418-1420. d) Sedova, V.F.; Voevoda, T.V.; Tolstikova, T.G.; Shkurko, O.P "Synthesis and Antiarrhythim Effect of 4-Aryl-5-nitro-6-phenyl-3,4-dihydro-(1-*H*)-pyrimidinones" *Khim. Farm. Zh.* **2002**, *36*, 4-7.

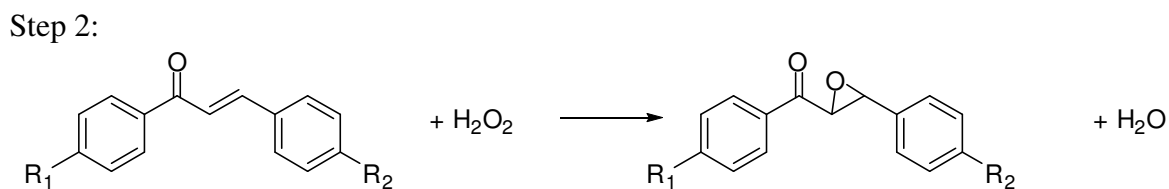
⁷ Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. "X-Ray Structure, Conformational Analysis, Enantioseparation, and Determination of Absolute Configuration of the Mitotic Kinesin Eg5 Inhibitor Monastrol" *Tetrahedron* **2000**, *56*, 1859.

⁸ Palleros, D.R. "Solvent-Free Synthesis of Chalcones" *J. Chem. Ed.* **2004**, *81*, 1345-1347.

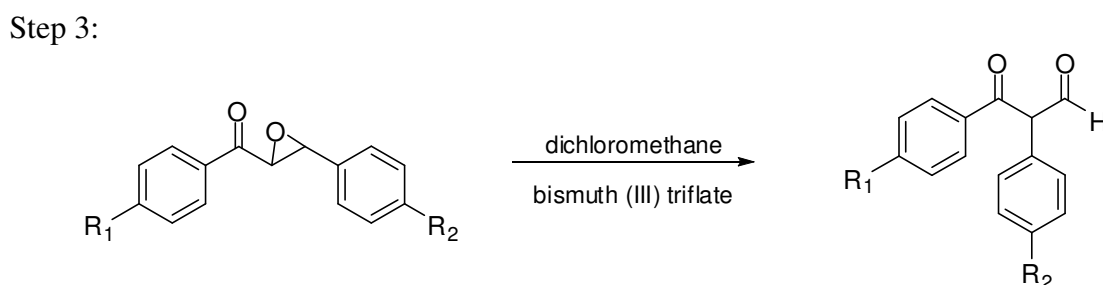
Figure 2

The byproduct of this first process is water. No energy input is required. The overall atom efficiency is 95%, which is less than the theoretical maximum of 100% efficiency only because water is formed as a byproduct. “R” refers to a chemical “wildcard” that can represent one or more atoms (like “x” can represent many different values in algebraic equations). By varying the identity of the R group, a large number of unique but related compounds can be produced using the same method.

The products of the first chemical process will be subjected to a second process in which they are modified using hydrogen peroxide, an environmentally benign chemical compound that is the same “peroxide” used to treat cuts and scrapes. The overall atom efficiency for the second process is again 95%. No energy input is required, and the only byproduct is water.

Figure 3

Once the products of this second process have each been isolated they will be further modified into new molecules using a process called *rearrangement* in which all atoms of the starting molecules are “shuffled” to give a product that is chemically distinct from the starting material.⁹ Rearrangement processes proceed with 100% overall atom efficiency.

Figure 4

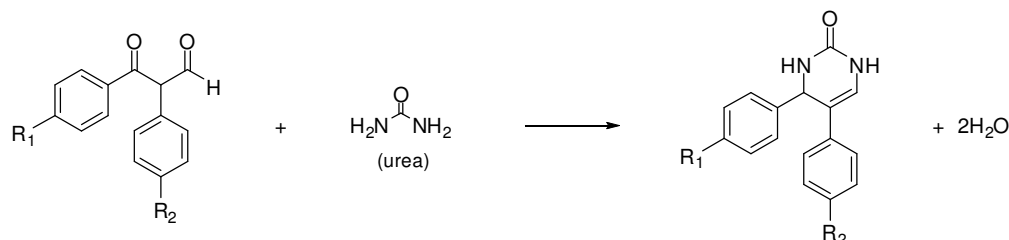
Two additives are required for the third process and appear over the arrow in Figure 4. Dichloromethane can easily be recovered, recycled and reused. The second, bismuth triflate, is used in extremely small

⁹ Kaushik, A.B.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R.S. “A Facile and Efficient Method For the Rearrangement of Aryl-substituted Epoxides to Aldehydes and Ketones Using Bismuth Triflate” *Tetrahedron Lett.* **2001**, *42*, 8129-8132.

amounts but cannot be reused without the production of hazardous waste.¹⁰ Thankfully, chemical compounds of this type are naturally occurring and nonhazardous.¹¹ This makes them ideal compounds for use in green chemical applications.

The final step will produce pyrimidinones. To do this, the products of the third step will be reacted with urea, a chemical starting material that is found in nature.¹² When combined with urea the products of the previous step will be converted to dihydropyrimidinones and water will be produced as a byproduct.

Figure 5



Overall, using a series of four consecutive steps and employing green chemistry principles, it will be possible to synthesize an important type of compound with an overall atom efficiency of 88%. This level of efficiency is less than the theoretical 100%, but is due to the repeated formation of a harmless byproduct, water. One benefit of the proposed series of synthetic steps is that it could also be modified to prepare molecules other than dihydropyrimidinones.

The results of this research will be presented at Wittenberg poster sessions and at the Ohio Academy of Science annual meeting. It has a strong potential to be published in chemistry journals. If other researchers see the benefit of our responsible approach, they can and use green chemistry principles to modify their own research.

Budget

The budget for this project will be used to purchase the chemicals needed to conduct the research. They will be purchased from Fisher Scientific or the Aldrich Chemical Company. The total reported is less than the \$250 amount to allow for shipping costs.

Compound	Cost
3,4-dihydroxybenzaldehyde	\$31.20
bismuth trifluoromethanesulfonate	\$44.00
3'-methylacetophenone	\$18.00
4'-methoxyacetophenone	\$14.80
4-chloroacetophenone	\$17.40
2-acetylpyridine	\$22.80
4-acetylpyridine	\$26.80
2-pyridinecarboxaldehyde	\$19.30
2-furaldehyde	\$32.20
total	\$226.50

¹⁰ The development of a bismuth additive that can be easily recycled would be of interest to the chemical community, but is beyond the scope of this proposal.

¹¹ For example, a chemical compound known as bismuth subsalicylate is the active ingredient in Pepto-Bismol®

¹² Urea is a waste product formed when proteins are digested by living organisms.

Schedule

The ten week project will take place in Dr. Hanson's research lab.

Week	Tasks
1	Order reagents, review additional literature.
2	Perform step 1, optimize
3	Continue step 1, use to make new compounds
4	Characterize newly prepared compounds, test and optimize step 2
5	Apply findings of week 4 to the preparation of additional molecules.
6	Summarize experimental procedures to date, begin step 3
7	Continue step 3
8	Apply step 4 to obtain target compounds.
9	Complete step 4, summarize results, tie up loose ends
10	Summarize research, write report.

The Twelve Principles of Green Chemistry

1. Prevention

It is better to prevent waste than to treat or clean up waste after it has been created.

2. Atom Economy (atom Efficiency)

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less Hazardous Chemical Syntheses

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Designing Safer Chemicals

Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. Safer Solvents and Auxiliaries

The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. Design for Energy Efficiency

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce Derivatives

Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

From: Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, 1998, p.30.