

Application of Chemical Informatics to Alternatives Assessment

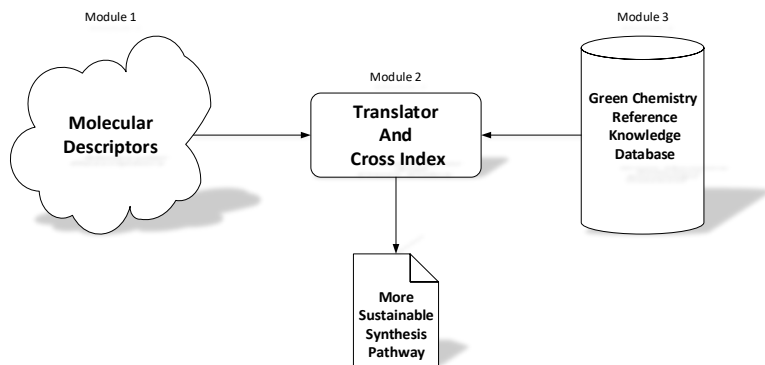
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Applications of Cheminformatics to Environmental Science
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Disclaimer

The views expressed in this presentation are those of the author[s] and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

Basis for the Framework



- Based upon the way that a chemist views synthetic chemistry.
- Combine knowledge of organic reactions and the 12 Principles of Green Chemistry.
- Incorporate the concept of scale and chemical engineering processing.

- Impact of selected choices we make at the molecular level.
- Focus on conveying sustainable chemistry knowledge through automated framework.
- Advance the state of green and sustainable chemistry in the design, synthesis, and production of alternatives to CoCs.

Gonzalez, M. A.; Takkellapati, S.; Tadele, K.; Li, T.; Varma, R. S., Framework towards more Sustainable Chemical Synthesis Design – A Case Study of Organophosphates. *ACS Sustainable Chemistry & Engineering* submitted.

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Research Article
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Framework toward More Sustainable Chemical Synthesis Design—A Case Study of Organophosphates

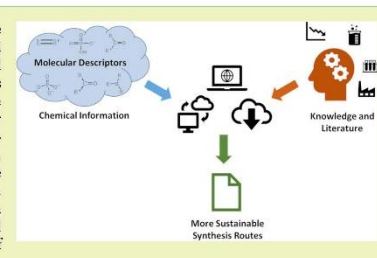
Michael A. Gonzalez,^{*,†} Sudhakar Takkellapati,[‡] Kidus Tadele,[‡] Tao Li,[†] and Rajender S. Varma[†]

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 Supporting Information

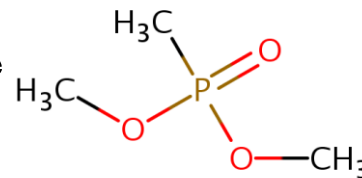
ABSTRACT: In recent years, the advancement of sustainable chemistry concepts and approaches along with their demonstrated application has become a central part of the design, synthesis, and manufacture of a chemical. Sustainable chemistry not only utilizes the principles of green chemistry, but also expands to incorporate economic, societal, and environmental aspects. This is further elucidated by the incorporation of life cycle assessment/thinking to include the raw material production, manufacture, processing, use, and disposal stages, allowing for a comprehensive evaluation of the environmental and human health impacts attributed to a chemical. This contribution outlines an approach for the development of a preliminary framework for the sustainable synthesis of a chemical that is identified as an alternative for an existing chemical of concern. The framework is introduced concurrently with a case



What the application does...

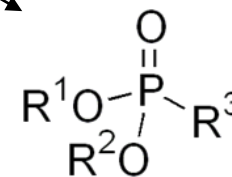
Enter Molecule's
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Step 1: Construct Molecule

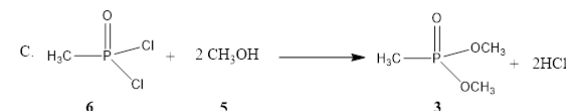
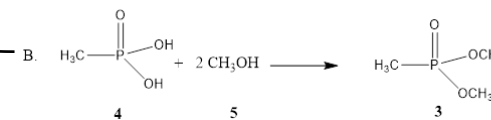
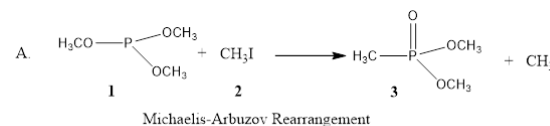


Step 2:
Identify Functional Group

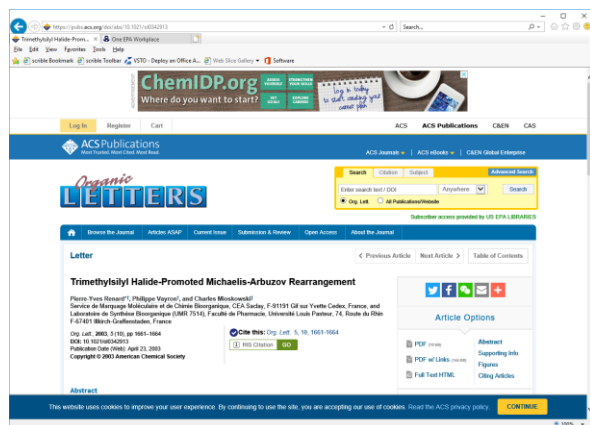
Dimethyl methylphosphonate



Step 3:
Look Up Reactions

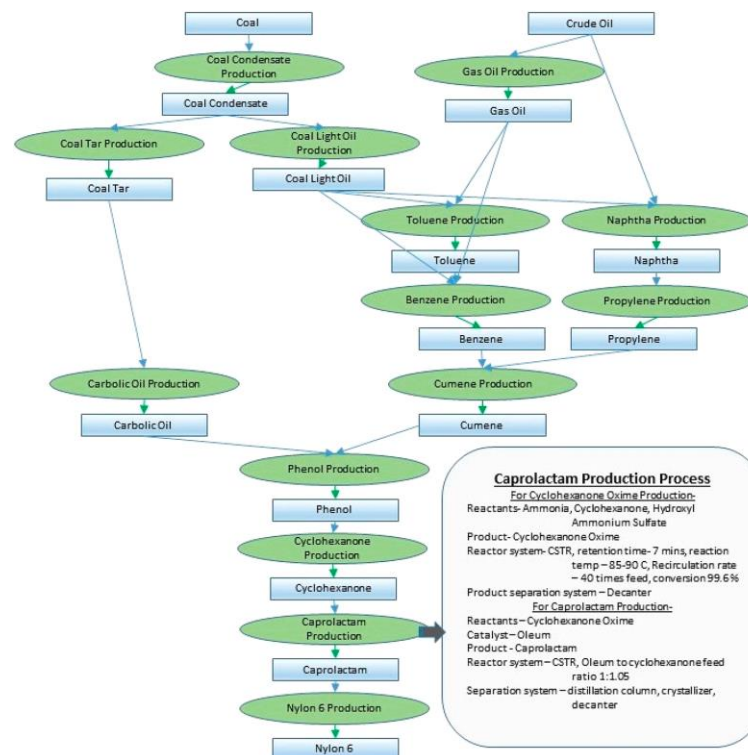


Step 4: Obtain References



Chemical Lineage

- Chemical lineage represents the synthetic pathway from commodity chemicals to the final, manufactured chemical product.
- A chemical compound (child) is produced by a chemical reaction from reactants (parents).
- The parent compounds are produced from their parents.
- Forms a lineage where a chemical has ancestors.
- Life Cycle Inventory (LCI) information for a chemical can be obtained by aggregating the LCI information for its ancestors combined with the emissions that occur during the chemical's manufacture.
- Ancestor chemicals can be evaluated as CoCs and alternatives identified.

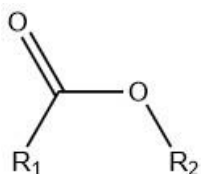


EPA Chemical Manufacturing Ontologies

- **Chemical Lineage Ontology:**
 - **Traces and identifies synthesis steps for producing a chemical from raw materials (e.g. crude oil, coal, natural gas).**
 - **Synthesis steps are typically name chemical reactions (e.g. Diels–Alder reaction).**
 - **For each step of the reaction sequence, a chemical has parents (reactants) and children (products).**
 - **Reaction conditions for each step are part of the ontology.**
- **Process Ontology**
 - **Unit operations that are required to carry out each of the synthesis steps.**
 - **Includes reactors, separation processes, storage, etc.**
 - **Emissions can be evaluated for each process step.**

Functional Group

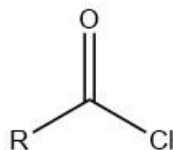
- Arrangement of atoms and bonds within a molecule with well characterized reaction properties.
- Examples:



Ester

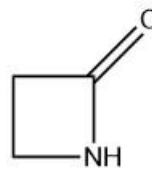
SMARTS

C(=O)OC



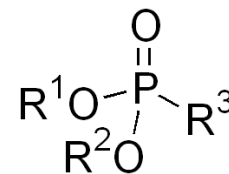
Acyl halide

C(=O)X



Lactam

C(=O)NC
In a ring



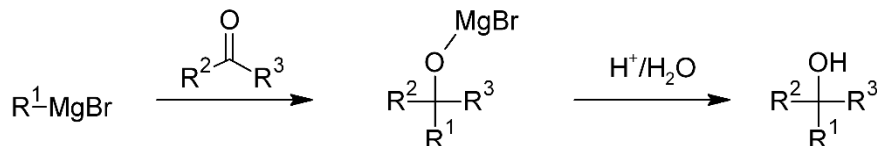
Phosphonate

COP(C)(=O)OC

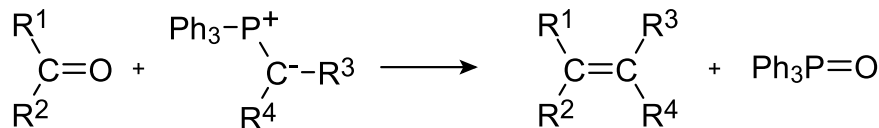
- Functional groups usually undergo the same or similar reactions typically regardless of the remainder of the molecule.
- Allows for systematic identification of reactions associated with a functional group.

Named Chemical Reaction

- General class of chemical reactions.
- Represent the mechanism used to produce a class of chemicals from a class of reactants under similar conditions.
- Involves formation of one functional group from one or more other functional groups.
- Examples:
 - Grignard reaction – alkylation of a carbonyl group.



- Wittig reaction – alkene from carbonyl group.

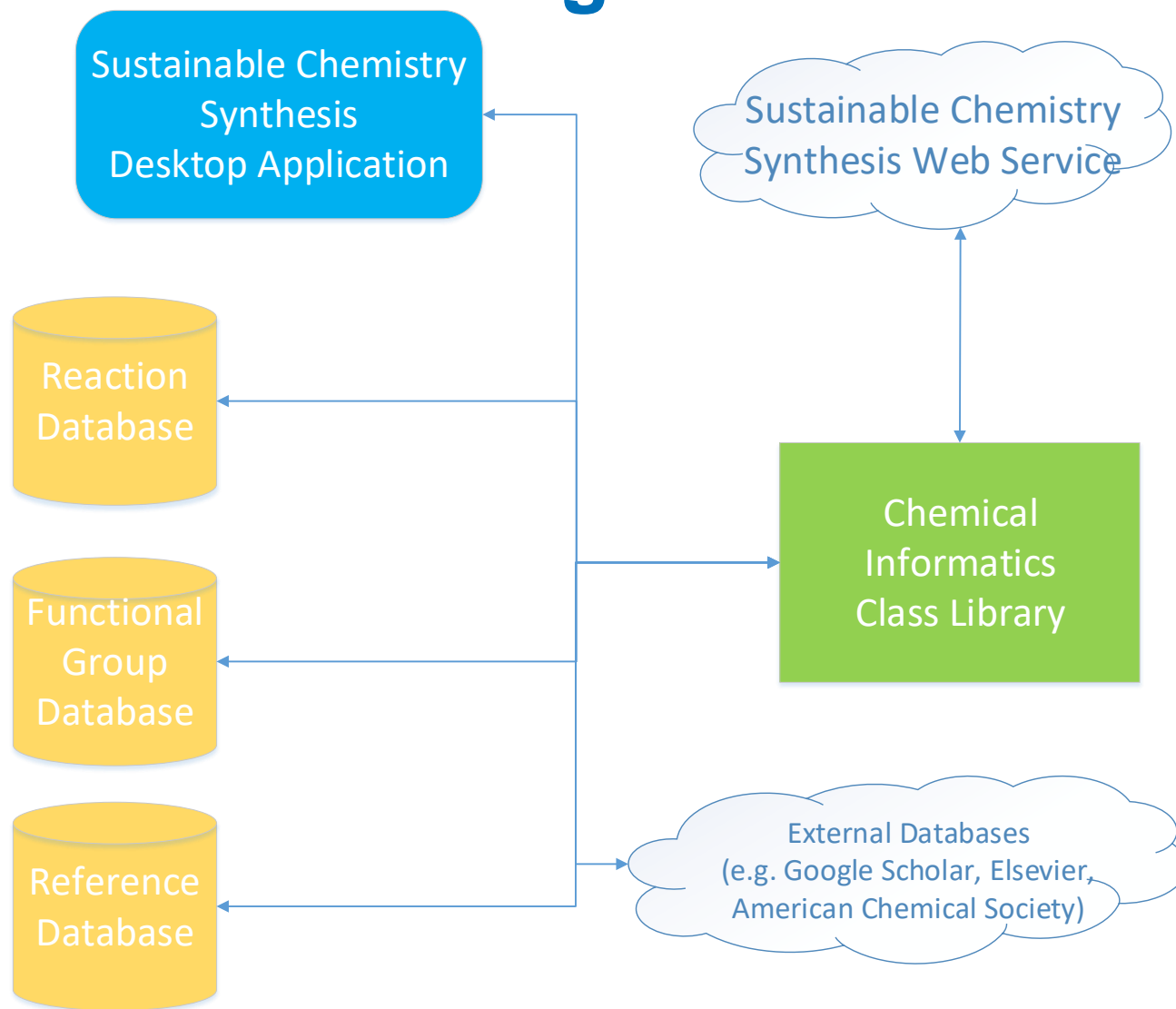


- Our current database contains about 200 named reactions.

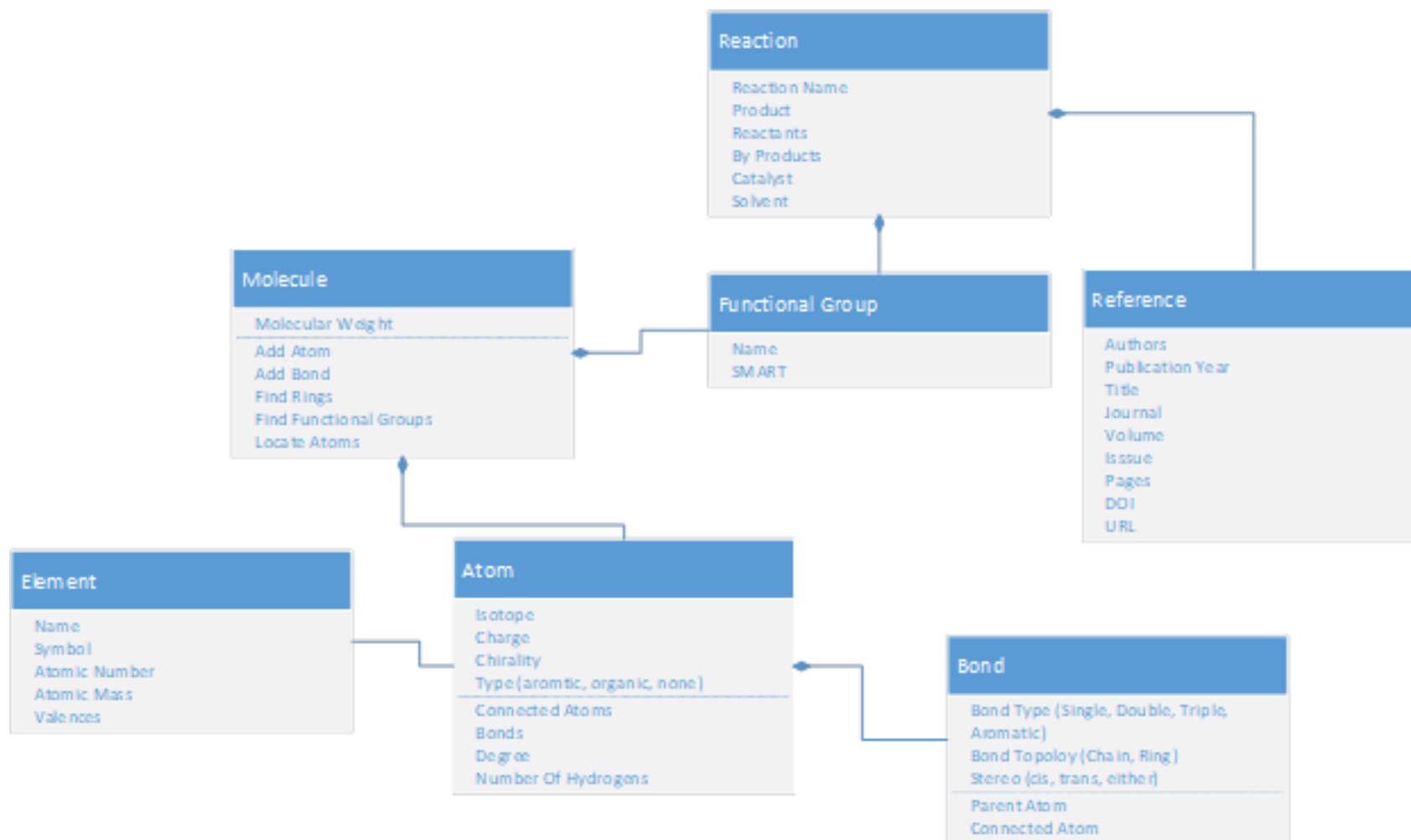
Application Overview

- Includes a Chemical Informatics class library.
- Class library can be exposed as a web service that allows users to obtain a list of functional groups and named chemical reactions associated with the functional groups within an identified chemical structure.
- C# ASP .NET Core Web Application.
- Testbed C# Windows Forms Desktop Application.
- Input is a structural representation of the molecule
 - Simplified Molecular-Input Line-Entry System (SMILES)
 - Chemical table (MOL) file from TEST.
- Output can either be a JSON serialized set of results or a web page.

Application Block Diagram



Chemical Informatics Class Diagram



Application Overview

- **Atom Class**
 - Nodes of the molecule graph.
 - Contains a collection of connected atom objects and bonds.
 - Obtains information about atom from Element Class.
- **Element Class**
 - Chemical Element Information from Blue Obelisk Data Repository (<https://sourceforge.net/projects/blueobelisk/>).
- **Bond Class**
 - Edges of the molecule graph.
 - Bond type (single, double, triple, aromatic)
 - Stereo orientation (cis/trans)

Application Overview

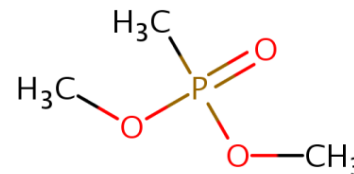
- **Molecule Class**
 - Contains a collection of Atom objects.
 - Ring Identification using Tarjan Depth First Search
 - SMILES/SMARTS matching using VF2 Subgraph Isomorphism Algorithm
 - Aromaticity detection/Kekulization.
- **SMILES/SMARTS Parser**
 - Converts SMILES/SMARTS into an instance of the Molecule Class.
 - Grammar based upon OpenSMILES (<http://opensmiles.org/>)
 - Built using ANTLR4 (www.antlr.org).
- **MOL File Parser**
 - Used to import TEST output

Application Overview

- **Functional Group Class**
 - **SMiles ARbitrary Target Specification (SMARTS) string** representing the functional group's structural subgraph of atoms/bonds.
- **Named Reaction Class**
 - List of reactant and product functional groups.
 - Associated with the desired functional group.
 - Keywords to enable online search using Google scholar, etc.
- **Reference Class**
 - Contains information for journal article associated with a reaction.
 - Input as an Endnote (RIS) file that can be obtained from the journal.
 - Has URL/DOI to enable access of the article from journal web site.

Case Study

- **Brominated flame retardants**
 - **Persistent/Bioaccumulative**
 - **Toxic to humans**
 - **Banned by the European Union**
 - **No longer produced by some US manufacturers**
- **Proposed Alternative**
 - **Dimethyl methylphosphonate**



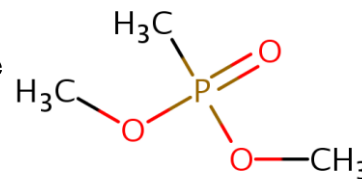
Covaci, Adrian, Stuart Harrad, Mohamed A. E. Abdallah, Nadeem Ali, Robin J. Law, Dorte Herzke, and Cynthia A. de Wit. 2011. 'Novel brominated flame retardants: A review of their analysis, environmental fate and behaviour', *Environment International*, 37: 532-56.

van der Veen, Ike, and Jacob de Boer. 2012. 'Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis', *Chemosphere*, 88: 1119-53

What the application does...

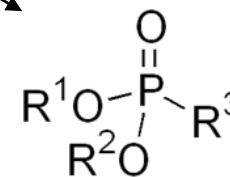
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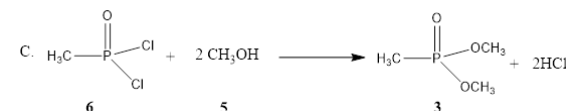
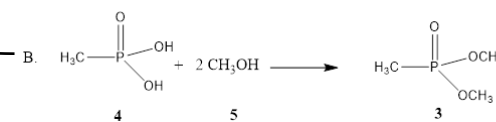
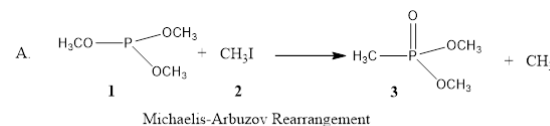


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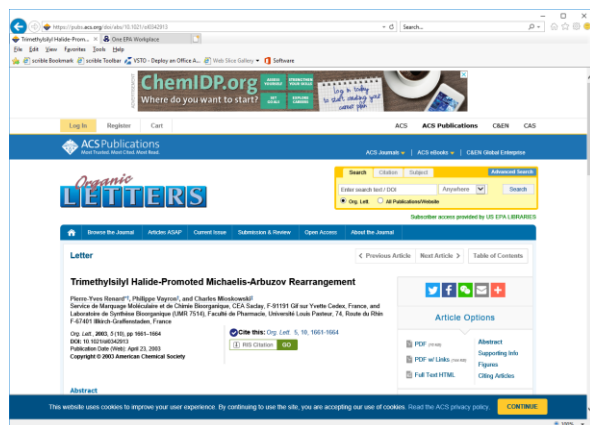
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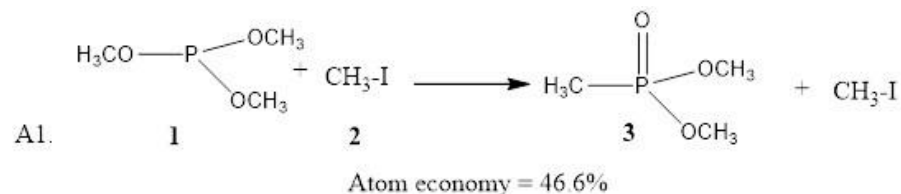


Step 4: Obtain References

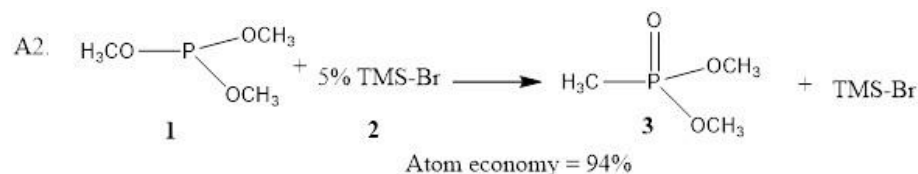


Synthesis of Dimethyl Methylphosphonate

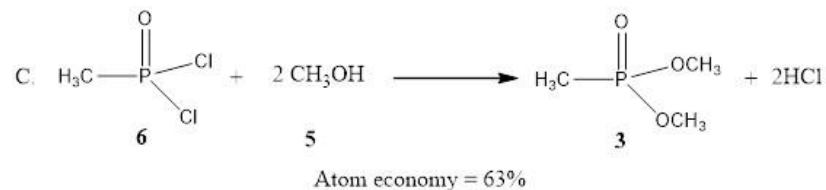
Michaelis-Abruzov Reaction



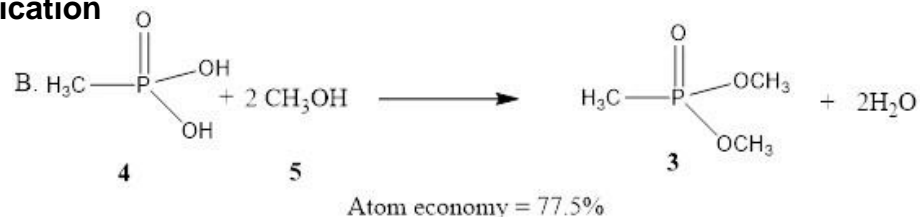
TMS-promoted Michaelis-Abruzov



Solid phase



Alkylphosphonic acid esterification



Evaluation of Synthesis Sustainability

- **Based on the Twelve Principles of Green Chemistry and Green Engineering**
- **Emphasizes reduce or eliminate environmental impacts by reducing or eliminating the use and generation of hazardous materials in the design, manufacturing, and application of chemical products**

Synthesis Sustainability Metrics

- **Atom Economy** - simplest green chemistry metric.
 - Ratio of the mass of the reactants that is incorporated into the final desired product.
 - Does not consider solvents, catalysts, or auxiliaries.
- **E-Factor** - Ratio of the mass of waste to mass of product.
- **Effective Mass Yield (EMY)** - percentage of the mass of the product relative to the mass of all non-benign materials used in the synthesis.
- **Process Mass Intensity (PMI)** - ratio of the quantity of raw materials input to the quantity of bulk product output

Trost, B. M. 1991. 'The atom economy--a search for synthetic efficiency', *Science*, 254: 1471.

Sheldon, Roger A. 1992. 'Organic synthesis - past, present and future. (advantages of incorporating catalysis to organic synthesis)', *Chemistry and Industry*, 23: 903-06.

Hudlicky, Tomas, Dean A. Frey, Lukasz Koroniak, Christopher D. Claeboe, and Larry E. Brammer Jr. 1999. 'Toward a 'reagent-free' synthesis', *Green Chemistry*, 1: 57-59.

ACS GCI PR. 2018. 'Tools for Green Chemistry & Engineering', ACS GCI Pharmaceutical Roundtable

Chemical Alternatives Assessment

- **Involves comparing the potential human health and environmental effects of an identified alternate to a chemical of concern (CoC) throughout their life cycle.**
- **Focus of this work is identifying sustainable chemical synthesis routes that can be used for manufacturing of an identified alternate chemical.**
- **Inputs (reactants, catalysts and other reaction aids), as well as outputs (desired products and by-products) can be identified based upon the type of reaction used.**
- **The life cycle risk evaluation of a candidate manufacturing process can then be developed based upon the reaction participants throughout the lineage.**

Application Screen Shot

Form1

File

Functionality

Tests

References

Data

Atoms

Functionalities

JSON Output

Test Page

Functional Group:

PHOSPHONATE ESTER

Named Reaction:

Michaelis-Arbusov

H₃CO—P

OCH₃

OCH₃

1

+

CH₃-I

2

→

H₃C—P

O

OCH₃

OCH₃

3

+

CH₃-I

A1.

Atom economy = 46.6%

Renard, Pierre-Yves, Vayron, Philippe, Leclerc, Eric, Valleix, Alain, Mioskowski, Charles (2003). "Lewis Acid Catalyzed Room-Temperature Michaelis-Arbusov Rearrangement". *Synthesis* 2003, 1155-1158.

Gandavaram Syam Prasad, Manubolu Manjunath, Kachi Reddy Kishore Kumar Reddy, Obulam Vijaya Sarathi Reddy, Cirandur Suresh Reddy (2006). "Synthesis and antibacterial activity of phosphonate esters". *Journal of Chemical Sciences* 118, 1155-1158.

Kiddle, James J., Gurley, Alison F. (2000). "MICROWAVE IRRADIATION IN ORGANOPHOSPHORUS CHEMISTRY 1: THE MICHAELIS-ARBUZOV REACTION." *Phosphorus* 2000, 115-118.

Yadav, Veejendra K. (1990). "A Practical Approach to Homo Trialkyl Phosphonates: A Catalytic Michaelis-Arbusov Reaction." *Synthetic Communications* 20, 239-246.

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Alternatives Assessments Dashboard Hazard Profiles for the Synthesis of Dimethyl Methyl Phosphonate

	Acute Mammalian Toxicity Oral	Acute Mammalian Toxicity Inhalation	Acute Mammalian Toxicity Dermal	Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Neurotoxicity Repeat Exposure	Neurotoxicity Single Exposure	Systemic Toxicity Repeat Exposure	Systemic Toxicity Single Exposure	Skin Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation
121-45-9 Trimethyl phosphite	M	N/A	M	N/A	L	L	H	H	N/A	N/A	M	N/A	N/A	H	H	L	N/A	L	L
74-88-4 Methyl iodide	H	H	M	VH	H	L	N/A	N/A	N/A	N/A	N/A	M	N/A	H	VH	VH	VH	H	L
2857-97-8 Bromotrimethylsilane	M	L	N/A	N/A	N/A	L	N/A	N/A	N/A	N/A	N/A	N/A	N/A	VH	VH	N/A	N/A	N/A	N/A
993-13-5 methyl phosphonic acid	M	N/A	N/A	N/A	L	L	N/A	H	N/A	N/A	N/A	N/A	N/A	N/A	N/A	M	N/A	N/A	L
67-56-1 Methanol	H	H	H	N/A	H	H	H	H	N/A	N/A	H	H	N/A	N/A	H	L	N/A	H	L
676-97-1 methyl phosphonic dichloride	VH	VH	N/A	N/A	L	L	N/A	H	N/A	N/A	N/A	N/A	N/A	N/A	N/A	L	N/A	N/A	L
67-56-1 Methanol	H	H	H	N/A	H	H	H	H	N/A	N/A	H	H	N/A	N/A	H	L	N/A	H	L

Summary

- **Named reactions can be identified as a starting point for the production of chemicals based upon functional groups present in a molecule.**
- **Chemical lineage information, including required reactants, by-products, catalysts, reaction conditions, etc. can be determined for each of the named reactions.**
- **Synthesis pathways can be built from the named reactions.**
- **Alternative assessment of the manufacturing phase of the chemical life cycle can then be performed.**