The BHC Company

Synthesis of Ibuprofen[1]

A Greener Synthesis of Ibuprofen Which Creates Less Waste and Fewer Byproducts

Overview

Pharmaceutical drugs are a booming business with estimated U.S. sales of $124.6 billion in 1998. These sales have more that quadrupled since 1985.[2] Analgesics (pain killers) are a very well known group of drugs that include aspirin, acetaminophen (Tylenol), and ibuprofen (Motrin, Advil, and Medipren). In addition to their analgesic properties, ibuprofen and aspirin are members of the nonsteroidal antiinflammatory (NSAI) group of drugs and are thus used to reduce swelling and inflammation.

Problem.** **The traditional industrial synthesis of ibuprofen was developed and patented by the Boots Company of England in the 1960s (U.S. Patent 3,385,886). This synthesis is a six-step process and results in large quantities of unwanted waste chemical byproducts that must be disposed of or otherwise managed. Much of the waste that is generated is a result of many of the atoms of the reactants not being incorporated into the desired product (ibuprofen) but into unwanted byproducts (poor atom economy/atom utilization).

Solution.** **The BHC Company has developed and implemented a new greener industrial synthesis of ibuprofen that is only three steps (U.S. Patents 4,981,995 and 5,068,448, both issued in 1991).[3] In this process, most of the atoms of the reactants are incorporated into the desired product (ibuprofen). This results in only small amounts of unwanted byproducts (very good atom economy/atom utilization)[4–10] thus lessening the need for disposal and mediation of waste products.

(from Cann, M.C.; and Connelly, M.E. *Real World Cases in Green Chemistry*, American Chemical Society: Washington, DC, 2000)

Company Profile

- **The BHC Company was a joint venture of the Hoechst Celanese (now Celanese) Corporation and the Boots Company. BASF purchased the Boots Company and Celanese sold its interest in the BHC Company to BASF. Celanese operates the ibuprofen manufacturing facility in Bishop, TX, for BASF.**

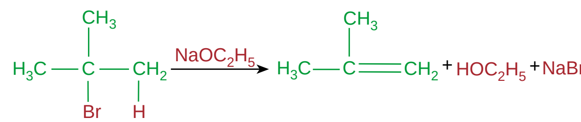
Background

Aspirin, acetaminophen, and ibuprofen are some of the most commonly used over-the-counter analgesics. Ibuprofen is perhaps best known as an active ingredient in the brand name drugs Motrin, Advil, Nuprin, and Medipren.

The Boots Company PLC of Nottingham, England (discoverers of ibuprofen) patented a synthesis of ibuprofen (hereafter known as the brown synthesis) in the 1960s (U.S. Patent 3,385,886) that has been the method of choice for the industrial preparation of ibuprofen for many years. This synthesis has not only resulted in the preparation of millions of pounds of ibuprofen over the past four decades, but concomitantly it has also produced millions of pounds of unwanted, unutilized, and unrecycled waste chemical byproducts that must be disposed of or otherwise treated.

One of the major ways that chemists have traditionally measured the efficiency of a reaction (or a synthesis) is by the percentage yield of the product (moles of the desired product/moles of limiting reagent × 100). What student of the chemistry lab has not done a reaction and had to calculate the percent yield of the product with a portion of his or her grade dependent upon it? However, nowadays what one does not produce from a chemical reaction is almost as important as what one does produce. Chemists have become much more conscious about the formation of unwanted byproducts (oftentimes hazardous wastes) that are produced in chemical reactions because they are usually treated as waste and must be disposed of properly or otherwise managed.

Chemists must not only strive to develop reactions that produce high yields, but these same reactions must also aim for incorporation of all the atoms of the reactants into the desired products, thus eliminating the production of unwanted byproducts. This concept has led to two similar terms, *atom economy*[4,7,8,10] (Barry Trost of Stanford University) and *atom utilization*[5,6,9] (Roger Sheldon of Delft University). To illustrate the atom economy/utilization of a reaction, consider the following dehydrohalogenation reaction of 2-bromo-2-methylpropane, with sodium ethoxide to produce methylpropene, the desired product.



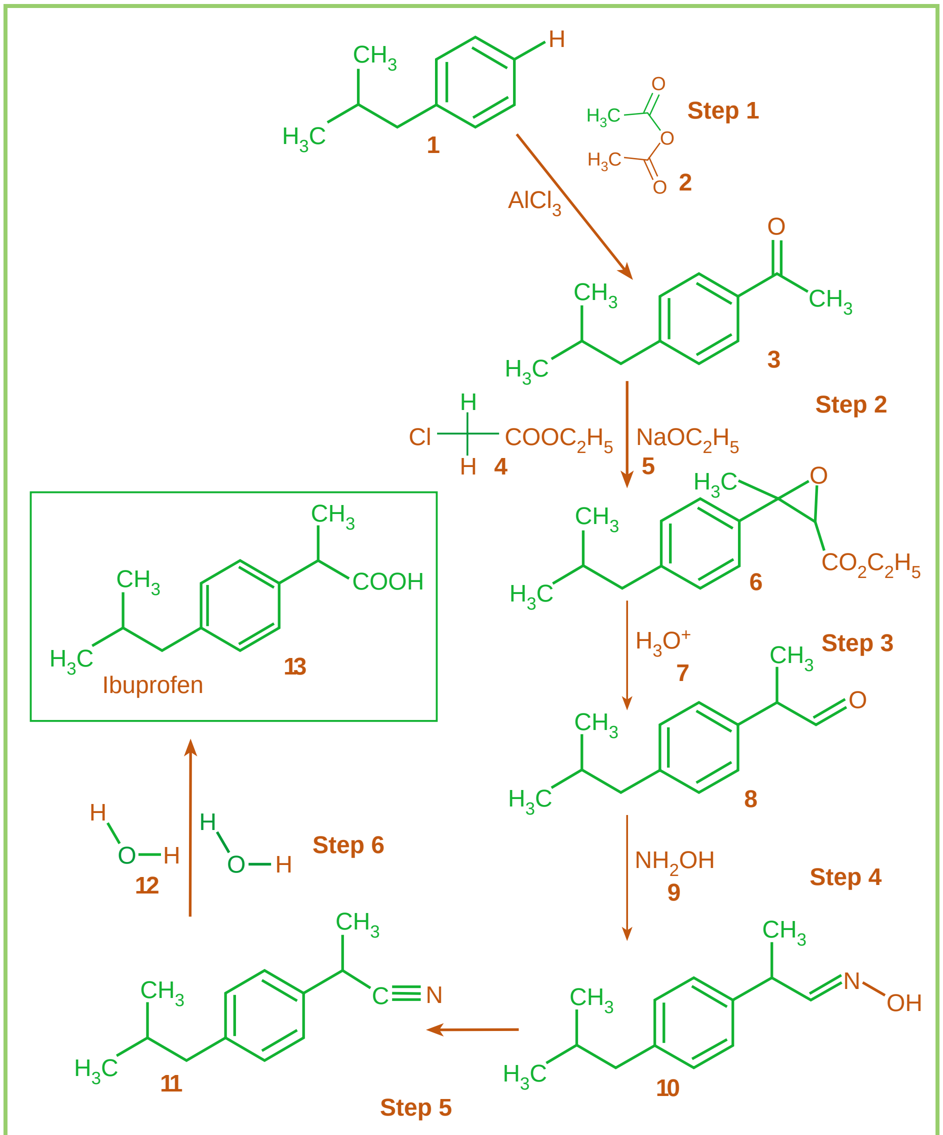
Notice that all of the atoms of the reactants that are ultimately incorporated or utilized in the methylpropene (shown in green) are indicated in green. On the other hand, all the atoms of the reactants that are shown in brown end up in the unwanted byproducts (also shown in brown) ethanol and sodium bromide. These brown atoms are not incorporated or utilized in the desired product and thus contribute to the poor atom economy/utilization of this reaction. Percentage atom utilization may be calculated by dividing the molecular weight of the desired product by the molecular weights of all the products generated in a reaction.[5,6] Using this formula, this dehydrohalogenation reaction exhibits only 27% atom utilization.

Percentage atom utilization = MW of propene/MW (propene + ethanol + sodium bromide) × 100 = 56/(56 + 46 + 103) × 100 = 27%

Even if this reaction were to proceed with 100% yield, only 27% (by weight) of the atoms of the reactants are incorporated into the desired product, with 73% of the reactant atoms ending up as unwanted byproducts. Because it is often difficult to determine the identity of all the byproducts, the term *percentage atom economy* may be determined by dividing the formula weight of the desired product by the sum of the molecular weights of all the reactants used in the reaction × 100.[11] This equation will be used throughout the remainder of this case.

If we now return to the traditional synthesis of ibuprofen as developed by the Boots Company (Scheme 1), we can now calculate the percentage atom economy of this synthesis.[5,6]

The atoms of the reactants that are incorporated or utilized in the final product (ibuprofen) are again indicated in green, while the atoms that end up in byproducts, or are unutilized, are indicated in brown. From a cursory glance at Scheme 1, it is clear that many of the reactant atoms are not incorporated into the ibuprofen. Table 1 drives this point home even more dramatically where the percentage atom economy of 40% is calculated.[11] Thus the majority, 60% (by weight), of all the reagent atoms in this synthesis are incorporated into unwanted byproducts or waste. Since about 30 million lb of ibuprofen are produced each year, this translates into more than 35 milion lb of waste generated each year from the synthesis of ibuprofen!



SCHEME 1. The Boots Company Synthesis of Ibuprofen—The Brown Synthesis

TABLE 1. Atom Economy in the Brown Synthesis of Ibuprofen

Reagent			**Utilized in ibuprofen**		**Unutilized in ibuprofen**	
	Formula	FW	Formula	FW	Formula	FW
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
2	$C_4H_6O_3$	102	C_2H_3	27	$C_2H_3O_3$	75
4	$C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
5	C_2H_5ONa	68		0	C_2H_5ONa	68
7	H_3O	19		0	H_3O	19
9	NH_3O	33		0	NH_3O	33
12	H_4O_2	36	HO_2	33	H_3	3
Total			**Ibuprofen**		**Waste products**	
	$C_{20}H_{42}N0_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5

Percentage Atom Economy = (FW ibuprofen/FW all reactants) × 100 = (206/514.5) × 100 = 40%

Green Chemistry: The BHC Company Synthesis of Ibuprofen—A Greener Synthesis of Ibuprofen

In the mid-eighties when the patent on ibuprofen was about to run out and the FDA had approved ibuprofen for over-the-counter use, other companies recognized the potential financial rewards that the synthesis of this drug could reap, and they set out to develop new synthetic methods and build their own plants to produce ibuprofen. During this time, the Hoechst Celanese Corporation (Somerville, NJ; now known as the Celanese Corporation) and the Boots Company agreed to a joint venture resulting in the BHC Company. The purpose of this joint venture was to develop and to put into practice a new green synthesis of ibuprofen and to market the product. The focus of the Celanese group was to develop the more efficient and environmentally sensitive green chemistry/technology for this new synthesis, while the Boots group was to market the ibuprofen prepared by this new method, using their considerable experience in this area.

The BHC Company synthesis of ibuprofen (hereafter known as the green synthesis) is shown in Scheme 2 (U.S. Patents 4,981,995 and 5,068,448).[3] The atoms of the reactants that are incorporated into the final product (ibuprofen) are again shown in green while the unutilized reactant atoms are shown in brown. Even from a cursory glance at the three-step green synthesis (Scheme 2) and at the six-step brown synthesis (Scheme 1), it is patently evident that the green synthesis provides for a far greater atom economy than the brown synthesis. The percentage atom economy for the green synthesis (as calculated in Table 2) is 77%, which climbs to 99% if one considers that the acetic acid generated in Step 1 is recovered.

These figures are in marked contrast to the previously discussed 40% atom economy of the brown synthesis. Thus, the preparation of ibuprofen by the green synthesis can prevent the formation of millions of pounds of waste chemical byproducts each year and reduce, by millions of pounds, the amount of reactants needed.

There are other environmental advantages to the green synthesis versus the brown synthesis, not the least of which is the fact that the green synthesis is a three-step catalytic synthesis, while the brown synthesis generally requires auxiliary reagents in stoichiometric amounts. For example, the very first step in each process yields the same product 3 via acylation of isobutylbenzene. However, the brown synthesis uses aluminum trichloride in stoichiometric amounts (not accounted for in Table 1) for this step, which generates large amounts of aluminum trichloride hydrate as a waste byproduct that is generally landfilled. By contrast, the green synthesis uses hydrogen fluoride as a catalyst that is recovered and reused repeatedly. It should also be noted that the Raney nickel and the palladium catalysts in Steps 2 and 3 of the green synthesis are recovered and reused.

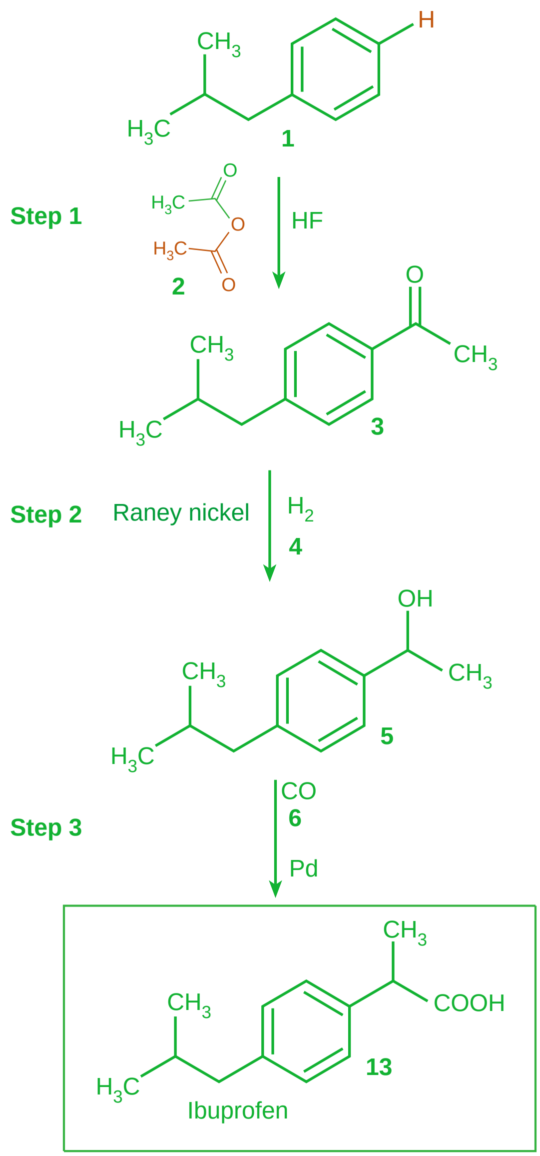
In addition to the elimination of large quantities of waste, by virtue of only requiring three steps, the green synthesis offers the advantage of a greater throughput compared with the six-step brown synthesis. This translates into the ability to produce larger quantities of ibuprofen in less time and with less capital expenditure, resulting in significant economic benefits to the company. Thus, the green synthesis is a win–win situation with both the environment and the bottom line benefiting.

Not only did the development of the BHC Company synthesis (the green synthesis) of ibuprofen win a prestigious Presidential Green

TABLE 2. Atom Economy in the Green Synthesis of Ibuprofen

Reagent			Utilized in ibuprofen		Unutilized in ibuprofen	
	Formula	FW	Formula	FW	Formula	FW
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
2	$C_4H_6O_3$	102	$C_2H_3O_1$	43	$C_2H_3O_2$	59
4	H_2	2	H_2	2	—	0
6	CO	28	CO	28	—	0
Total			**Ibuprofen**		**Waste Products**	
	$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60

Percentage Atom Economy = (FW ibuprofen/ FW of all reactants) × 100 = (206/266) × 100 = 77%



SCHEME 2. The BHC Company Synthesis of Ibuprofen—The Green Synthesis

Chemistry Challenge Award in 1997, it also won the coveted Kirpatrick Chemical Engineering Achievement Award in 1993.[12] This award recognizes outstanding group efforts in developing and commercializing process technology and is given out every two years by *Chemical Engineering* magazine.

Green Chemistry in Action

On October 15, 1992, the green synthesis was put into practice on an industrial scale at one of the largest ibuprofen manufacturing facilities in the world in Bishop, TX.[3] This plant is operated by the Celanese Corporation for BASF and currently produces approximately 20–25% (more than 7 million lb) of the world's yearly supply of ibuprofen. This translates into enough ibuprofen to produce about 6 billion tablets of pain medication, which is sold to 25 pharmaceutical companies who market ibuprofen products as generic or branded products such as Advil, Motrin, Nuprin, and Mediprin. Bishop might be considered the pain capital of the world, given that Celanese also produces 20 million lb of acetaminophen (the active ingredient in Tylenol) in this Texas town.

QUESTIONS

1. In assessing how green a reaction or a synthesis is, there are several other factors that one must consider other than the percentage yield and the percentage atom economy.[13] Discuss the following considerations.

   a) A reaction that uses methylene chloride as a solvent, versus one that uses water, versus one that uses no solvent.

   b) A reaction that uses a stoichiometric amount of a reagent versus one that uses a catalytic amount of the same reagent.

   c) A reaction that takes place at 200 ^{o}C versus one that takes place at room temperature.

   d) A reaction that requires the use of a drying agent versus one that does not require a drying agent.

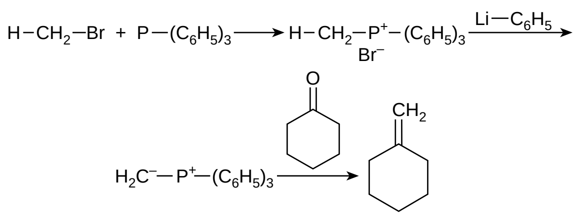
   e) A reaction that requires purification of the product by column chromatography or recrystallization versus one that requires no purification of the product.

   f) A synthesis that uses starting material that is produced from crude oil versus one that uses biomass-derived starting material.

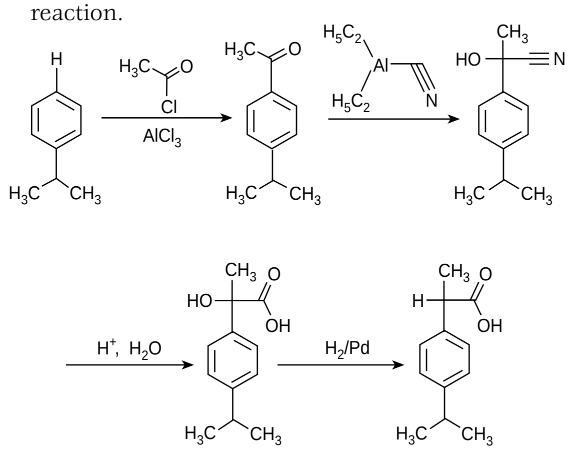
2. From the point of view of atom utilization or atom economy, certain types of organic reactions are inherently greener than others. Apply this statement to addition reactions versus substitution reactions.

3. Supply the mechanism for the first step (acylation) of the green synthesis (Scheme 2).

4. Shown below is the synthesis of methylene cyclohexane via a Wittig reaction (Wittig won the Nobel Prize in 1979 in part for the development of this reaction). Calculate the overall percentage atom utilization of this synthesis. (Use the combined molecular weights of the reactants, not products, for your calculation.) To facilitate your calculation, set up a table similar to Tables 1 and 2.



5. What byproducts are formed in Step 2 of Scheme 1? Provide a mechanism for this reaction.
6. Supply a mechanism for the conversion of 11 to 13 in Scheme 1.
7. The ethyl synthesis, shown below, is another synthesis by which ibuprofen is manufactured. Calculate the percentage atom economy for this reaction.



8. Consider a reaction that you have done in the lab. What wastes were generated in this reaction? In your answer, consider not only waste byproducts but also solvents and auxiliary agents such as drying agents and chromatographic materials used to purify your products.
9. The BHC Company Synthesis of Ibuprofen won the Presidential Green Chemistry Challenge in 1997. Look up the three focus areas for the Presidential Green Chemistry Challenge (download the *Presidential Green Chemistry Challenge Brochure* at http://epa.gov/greenchemistry/presgcc.htm; accessed Dec 1999) and decide which focus area (or areas) this case study best fits.
10. Following the Twelve Principles of Green Chemistry can lead to more environmentally benign technologies (see inside front cover).[13] Which principle(s) are used in "The BHC Company Synthesis of Ibuprofen"?

REFERENCES AND NOTES

1. This case is based on the work of the BHC Corporation, which received a 1997 Presidential Green Chemistry Challenge Award for its synthesis of ibuprofen. For more information on the Awards Program, please visit the program Web site at www.epa.gov/greenchemistry (accessed Dec 1999) or contact the U.S. EPA Green Chemistry Program at 202-260-2659.
2. PhRMA Web site. Facts & Figures. www.searchforcures.com/facts/phfacts/1_98b.html (accessed Dec 1999).
3. The BHC Company. The BHC Company Ibuprofen Process, a proposal submitted to the Presidential Green Chemistry Challenge Awards Program, 1997.
4. Trost, Barry M. The Atom Economy—A Search for Synthetic Efficiency. *Science* **1991,** *254,* 1471–1477.
5. Sheldon, Roger A. Organic Synthesis—Past, Present and Future. *Chem. Ind. (London),* **1992,** (Dec), 903–906.
6. Sheldon, Roger A. Consider the Environmental Quotient. *CHEMTECH* **1994,** *24* (3), 38–47.
7. Trost, Barry M.; Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem., Int. Ed. Engl.* **1995,** *34,* 259–281.
8. Rouhi, A. Maureen. Atom Economical Reactions Help Chemists Eliminate Waste. *Chem. Eng. News* **1995,** (June 19), 32–35.
9. Sheldon, Roger A. Catalysis and Pollution Prevention. *Chem. Ind.* **1997,** (Jan 6), 12–15.
10. See the case study in this series called "The Concept of Atom Economy: How Many Reactant Atoms Are Incorporated into the Desired Product and How Many Are Wasted?"
11. The percentage atom economy is an extension of Trost's concept of atom economy.
12. Westheimer, T. The Award Goes to BHC. *Chem. Eng.* **1993,** (Dec), 84–95.
13. Anastas, Paul T.; Warner, John C. *Green Chemistry: Theory and Practice;* Oxford University Press: New York, 1998.