聲明

本檔案之內容僅供下載人自學或推廣化學教育之非營利目的使用。並請於使用時註明出處。[如本頁取材自〇〇〇教授演講內容]。

綠色化學在化學與製藥工業之應用

2012 綠色/永續合成化學工作坊

November 30, 2012, 化學會年會，成功大學

國立中正大學　周德璋

Global Sustainability

The most critical challenge of today

"The challenges of global sustainability are most complex and definitionally the most consequential of any that civilization has or can encounter."

"The three elements of sustainability— environmental, social, *and* economic *must be recognized in the context shown in Fig.1."*

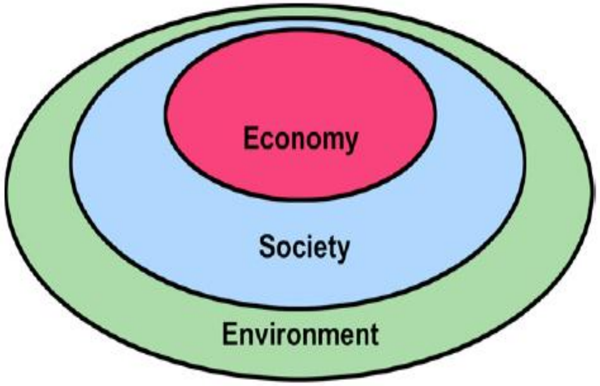


Fig. 1. A sustainable community [3].

"……., we must understand that the ***economy*** *exists within* ***society*** *and the society exists within the* ***environment****.*

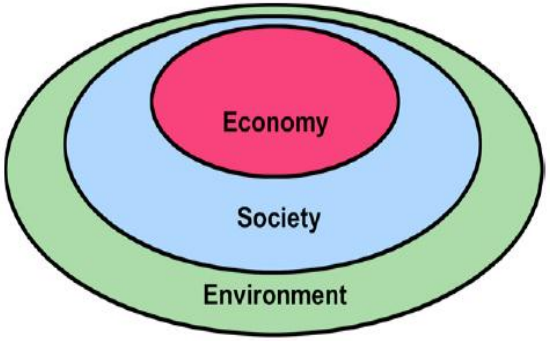


Fig. 1. A sustainable community [3].

"The true long-term goal must be to ensure that the goals of ***environment****,* ***society****, and* ***economy*** *are working in concert in a synergistic way."*

Toward→→→ **global sustainability**

J. B. Manley, P. T. Anastas, B. W. Cue Jr. *J. Cleaner Production* 16 (2008) 743.

Sustainable Development

Meeting the needs of today without compromising the ability of future generation to meet their needs.

Chemistry is a central science and technology!

永續化學

Sustainable Chemistry not only includes the concepts of **green chemistry**, but also expands the definition to a larger system than just the reaction. Also considers the effect of **processing**, materials, energy, and economics.

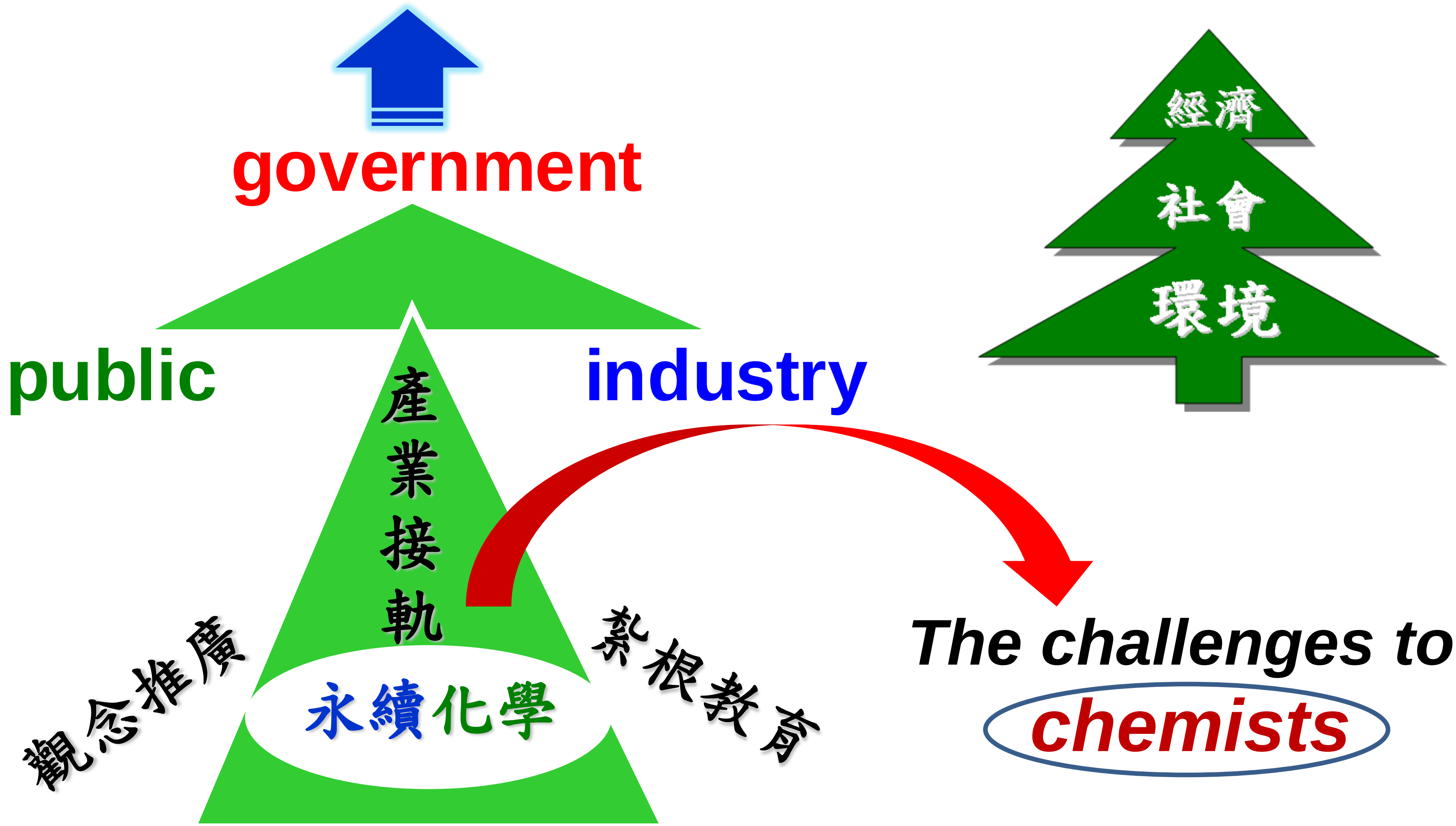
綠色化學

Green Chemistry is focused on the design, manufacture, and the use of chemicals and chemical processes that have little or no pollution potential or environmental risk.

Sustainable Development

"safeguarding human health and environment to allow for future generations to maintain the necessary resources to sustain life"

［**永續發展**：守護人類的健康和環境，讓子孫能持有永續其生命的必需資源。］



Paul T. Anastas

Professor of chemistry for the environment at Yale University,
Director of Yale's Center for Green Chemistry & Green Engineering,
Widely regarded as one of the fathers of "green chemistry,"
The Environmental Protection Agency assistant administrator for the Office of R&D,

"Why did you become a chemist?"
Some are excited by the **intellectual challenges of chemistry**. Others want to use chemistry and chemical engineering to solve problems and **make the world a better place**.

Anastas:
"The world needs both. Building a sustainable world is the most taxing intellectual exercise we have ever engaged in. It is also the most important for the future of the world."

Green Chemistry

The design, development, and implementation of chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment.

［為縮減或淘汰對人類健康和環境具有危害性的物質的使用與產生，而進行化學產品和製造過程的設計、開發與執行。］

Anastas PT, Warner JC, editors.
Green Chemistry: theory and practice.
Oxford: Oxford University Press; 1998.

Anastas PT, Kirchhoff MM,
Origins, Current Status, and Future Challenges of Green Chemistry
Acc. Chem. Res. 2002, 35. 686.

The Twelve Principals of Green Chemistry

1. Prevent waste
2. Design safer chemicals and products
3. Design less hazardous chemical syntheses
4. Use renewable feedstocks
5. Use catalysts, not stoichiometric reagents
6. Avoid chemical derivatives
7. Maximize atom economy
8. Use safer solvents and reaction conditions
9. Increase energy efficiency
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

Anastas PT, Warner JC, editors. *Green Chemistry: theory and practice.* Oxford: Oxford University Press; 1998.

"Underlying the Green Chemistry approach is the recognition that all we have to work with on Earth is matter and energy."［綠色化學方法之基礎是，認知到我們在地球上所能夠使用的，就是物質和能量。］

"Green Chemistry seeks to design and invent the next generation of matter (material) that is the basis of our society and our economy so that it minimizes adverse consequences to human health and the environment."［綠色化學的目的是，設計和發明下一代我們的社會和經濟能夠賴以立基，並能夠對人類健康和環境有最小不利後果的物質（材料）。］

J. B. Manley, P. T. Anastas, B. W. Cue Jr.
Frontiers in Green Chemistry: meeting the grand challenges for sustainability in R&D and manufacturing,
J. Cleaner Production 16 (2008) 743.

Webster's definition of chemistry,

"the study of matter and all of its transformations."

Transformations are carried out by **chemical synthesis**.

綠色化學的終極目的是縮減或淘汰對人類健康和環境具有危害性的物質的使用與產生，因此任何化學產品及其相關活動—製造過程的設計、開發、與實行，當然包含化學合成，都要秉持此認知而思考。

Anastas and Warner:
"In virtually every aspect in society,
it has long been acknowledged that preventing a problem
is superior to trying to solve it once it has been created."

Green Sustainable Synthesis **[綠色永續合成]**
seeks to reduce and prevent pollution at its source.

"Synthetic chemistry in the 21^{th} century is not just a great intellectual challenge, it is essential for addressing the many challenges that face humanity."[#]

［21世紀的合成化學並不只是一個重大的智力挑戰，有必要考慮到如何解決人類面臨的種種挑戰。］

[#] Prof. Peter B. Dervan, California Institute of Technology, 2009 Welch Symposium

Green
Sustainable
Synthesis

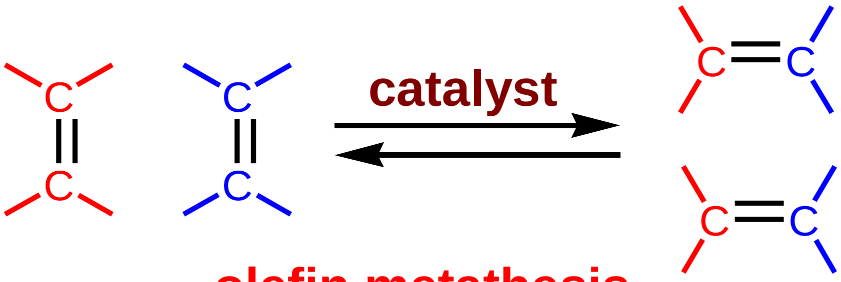
The challenges to all Chemists

Robert H. Grubbs, Richard R. Schrock, and France's Yves Chauvin



won the 2005 Nobel Award for their development of the **metathesis** method in organic synthesis.

"This represents a great step forward for **green chemistry**, reducing potentially hazardous waste through smarter production. **Metathesis is an example of how important basic science has been applied for the benefit of mankind, society, and the environment,……"**



olefin metathesis

產業接軌

To process chemists

Process chemists and engineers in industry generally feel that ***green chemistry*** *is an academic pursuit – until* ***green chemistry*** *considerations can lower the* ***cost of goods*** *(COG).*

Editorial: *Organic Process Research & Development* **2008,** *12,* 1019.

And provide good ***business opportunity****:*

Enhance Reputation; Prevent Product Liability; Increase Profitability; Ensure Compliance; Freedom to Innovate/Operate

John C. Warner

Research chemist at Polaroid (1988)
Professor at the UMass, Boston (1996),
-- established first doctoral program in green chemistry Professor at UMass Lowell (2004)
-- founded Center for Green Chemistry

Chief technology officer and chairman of the board of Warner Babcock Institute for Green Chemistry (2007)

產業接軌

"Green chemistry is the mechanics of doing sustainable chemistry,"

Warner:

"By focusing on green chemistry, it puts us in a different innovative space. It is a science that **presents industries with an incredible opportunity for continuous growth and competitive advantage."**

Chemical & Engineering News, 88(40), October 04, **2010**

Green Chemistry is Cost Efficient

	環 境 思 維	經 濟 思 維
Atom Economy	*Minimal by-product formation* 減低環境負擔	*More from less – incorporate total value of materials* 降低成本
Conver-gency	*increased process efficiency* 減低環境負擔	*Higher efficiency – fewer operations* 降低成本
Reagent Optimi-zation	*Catalytic, low stoichiometry, recyclable reagents minimize usage,* 減低環境負擔	Higher efficiency - higher selectivities 降低成本
Solvent Reduction	*Less solvent waste,* 減低環境負擔	Higher throughput, less energy, 降低成本

Green Chemistry is Cost Efficient

	環境思維	經濟思維
Energy Reduction	*from power generation, transport, and use* 減低環境負擔	*reflects increased efficiency, shorter process, mild conditions* 降低成本
In-situ Analysis	*Reduced possibility for exposure or release to the environment*	*Real-time data increases throughput and process efficiency, fewer reworks* 降低成本
Safety	*Non-hazardous materials reduce risk of exposure, release, explosions and fires*	*Worker safety and reduced down time, Reduced time on special control measures.* 降低成本

Organic Process Research & Development, ***2006***, *10, 315.*

Lower the Cost of Goods (COG) and the Environment

- Minimize waste
  - Achieving higher yields
    reduces the environmental quotient (EQ) of waste production.
  - Processing using fewer unit operations and under more concentrated conditions
    reduce waste, cycle times, and labor costs.
- Designing routes that require fewer steps
  require smaller quantities of starting materials, solvents, and reagents and less labor; less waste and reduced costs for waste disposal.

- Review and consider older approaches and replaced by new reactions and new technologies.
- Support new synthetic initiatives and encourage unbiased researchers from academia to invent new approaches to existing compounds.
- Provide feedback to drug discovery.
  - Is the most potent or bioavailable compound selected?
  - Can the compound be prepared in the fewest steps?
  - Is the chiral center of the prodrug really necessary?
- Selecting different starting materials through designing and redesigning routes to lower the COG

關照 COG　必也能關照我們的環境

E-Factor [Environmental factor]

$$E = \frac{\text{Total Waste (kg)}}{\text{Product (kg)}}$$

Products: target compounds (goods) and materials that are recovered.
Waste: Anything that enters and causes "burden" to the environment.

E Factors in Chemical Industry

Industry Sector	Product Tonnage	E factor
Oil refining	10^6 - 10^8	<0.1
Bulk chemicals	10^4 - 10^6	<1 - 5
Fine Chemicals	10^2 - 10^4	5 - 50
Pharmaceuticals	10 - 10^3	25 - 100

Sheldon, *Chem Tech*, ***1994***, *24*, 38; *Green Chemistry*, **2007**, *9*,1273.

Green Chemistry
in the
Chemical and Pharmaceutical Industry

Examples of Success

Case 1. **Pregabalin (Lyrica®)**

A Drug for the treatment of Neuropathic Pain

Case 2. **Sildenafil Citrate**

The Active pharmaceutical ingredient (API) in the PDE_5 Inhibitor Viagra™

Case 3. **Ibuprofen**

One of core non-steroidal anti-inflammatory medicines

Case 4. **Disodium iminodiacetate (DSIDA)**

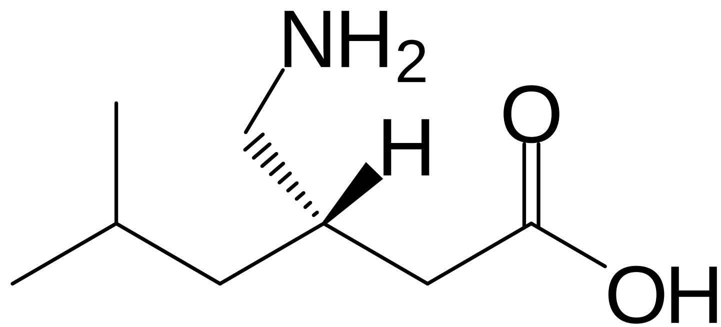
A key intermediate in the production of Roundup® herbicide

Case 1. 實例1

Pregabalin (Lyrica®)

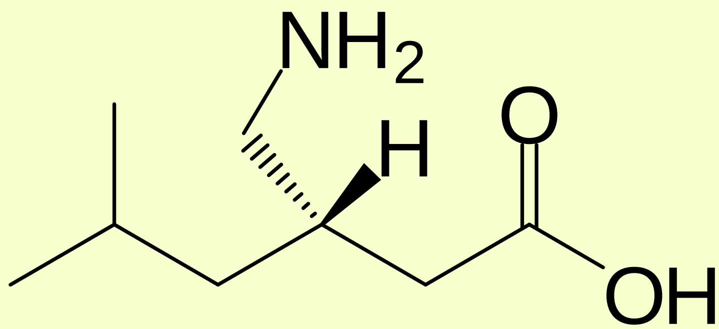
普瑞巴林

A Drug for the treatment of Neuropathic Pain



(*S*)-3-(aminomethyl)-5-methylhexanoic acid

What is Pregabalin (Lyrica®)?

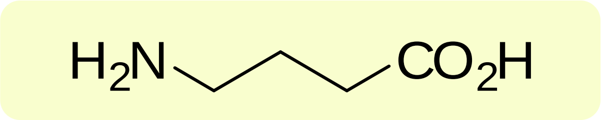


(*S*)-3-(aminomethyl)-5-methylhexanoic acid

- ✓ An anticonvulsant drug used for neuropathic pain.
- ✓ Marketed by Pfizer under the trade name **Lyrica®**.
- ✓ Was invented by medicinal chemist Richard Bruce Silverman at Northwestern University in the United States.

(Silverman, R. B.; Andruszkiewicz, R. U. S. Pat. 6,197,819 B1 -- "Gamma Amino Butyric Acid Analogs and Optical Isomers.". (March 6, 2001); expires in March 2018

- ✓ Pregabalin is an analogue of gamma-aminobutyric acid (GABA).



- ✓ Binds to the α–δ protein subunit of voltage-sensitive calcium channels, modifying calcium transduction and neurotransmitter release.
- ✓ Pregabalin acts as a agonist of GABA receptors.
- ✓ Increases GABA levels by increasing glutamic acid decarboxylase (GAD) activity.
- ✓ GAD is an enzyme that synthesizes glutamate to GABA in one step.

✓ **Lyrica®** launched in the US in September 2005.

- Sales in 2006 $ 1.16 billion
- Sales in 2007 $ 1.8 billion
- Sales in 2009 $ 2.84 billion
- Sales reached a record $3.063 billion in 2010.

✓ First drug approved by the US. FDA (2007) for wide spread pain of fibromyalgia.

✓ Approved in the European Union (2007) for treatment of generalized anxiety [憂慮] disorder.

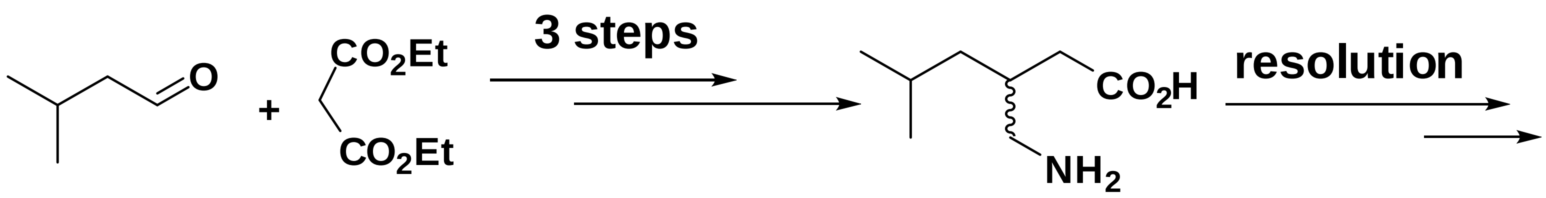
✓ Also treats epilepsy [羊癲瘋] and neuropathic [神經質的] pain disorders.

✓ Classified as a Schedule V drug in the U.S.

(low potential for abuse, and a limited dependence liability if misused)

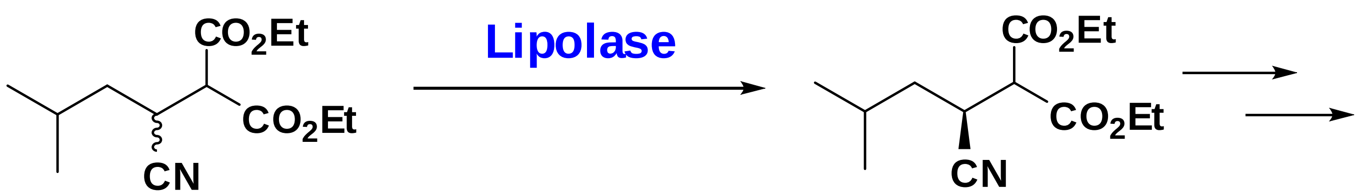
Manufacturing Process

● Launch Process -– Malonate route



M. S. Hoekstra, et.al. *Organic Process Research & Development* **1997**, *1*, 26-38

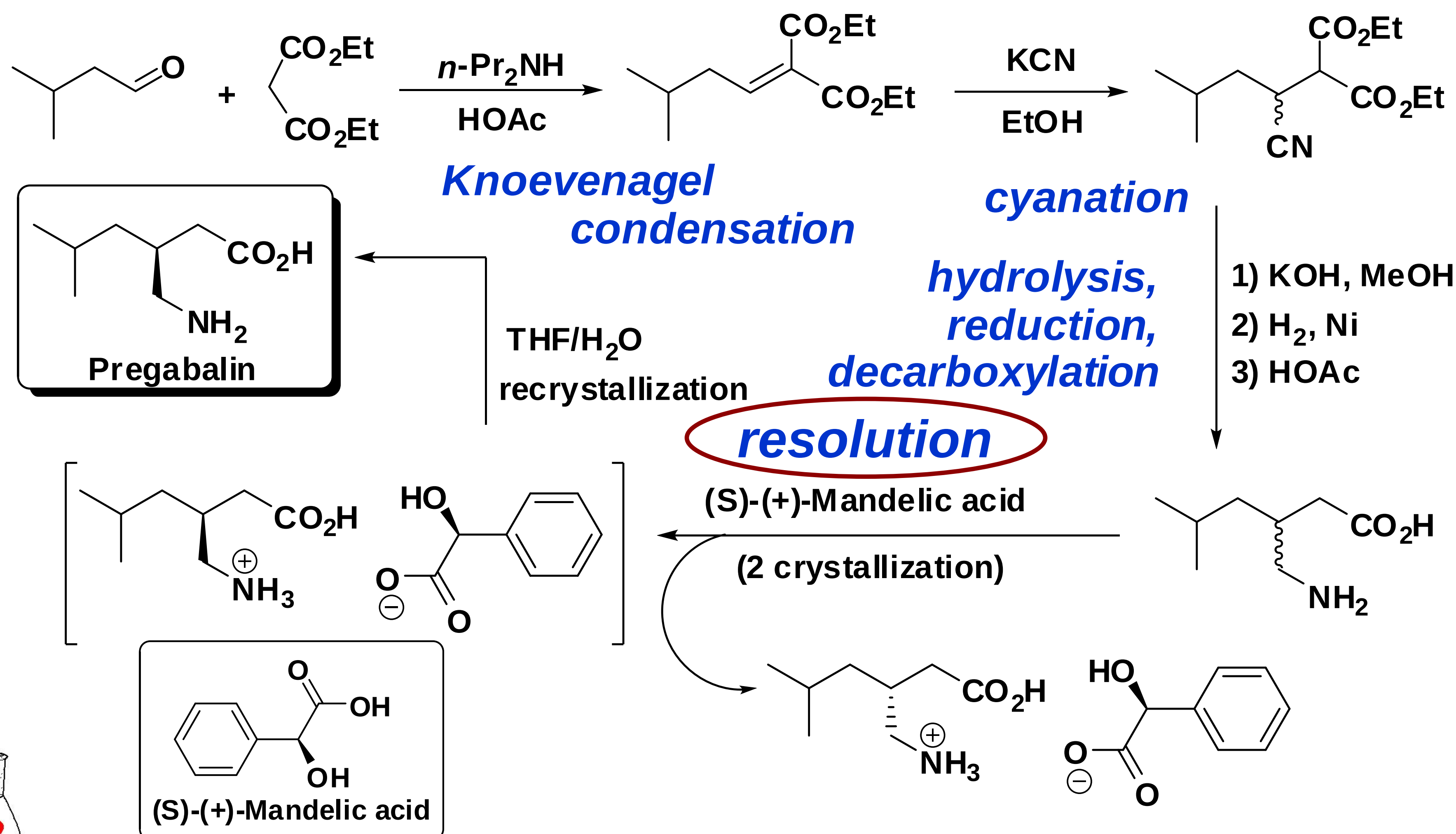
● Chemoenzymatic Process *(2006→)*



Using commercially available Lipolase to resolve rac-2-carboxyethyl-3-cyano-5-methylhexanoic acid ethyl ester

C. A. Martinez, et. al. *Organic Process Research & Development* **2008**, *12*, 392–398

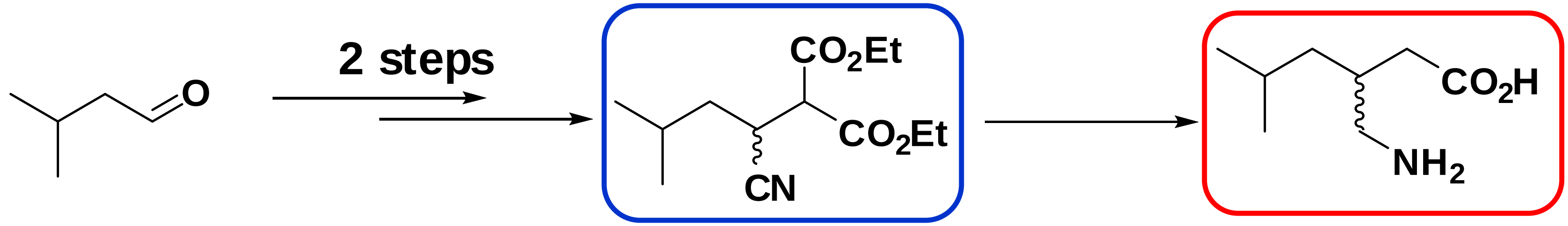
Pregabalin Manufacturing Process *(Launch Process)*



苦杏仁酸

Org. Process Res. Dev. ***1997****, 1, 26,*

Problems

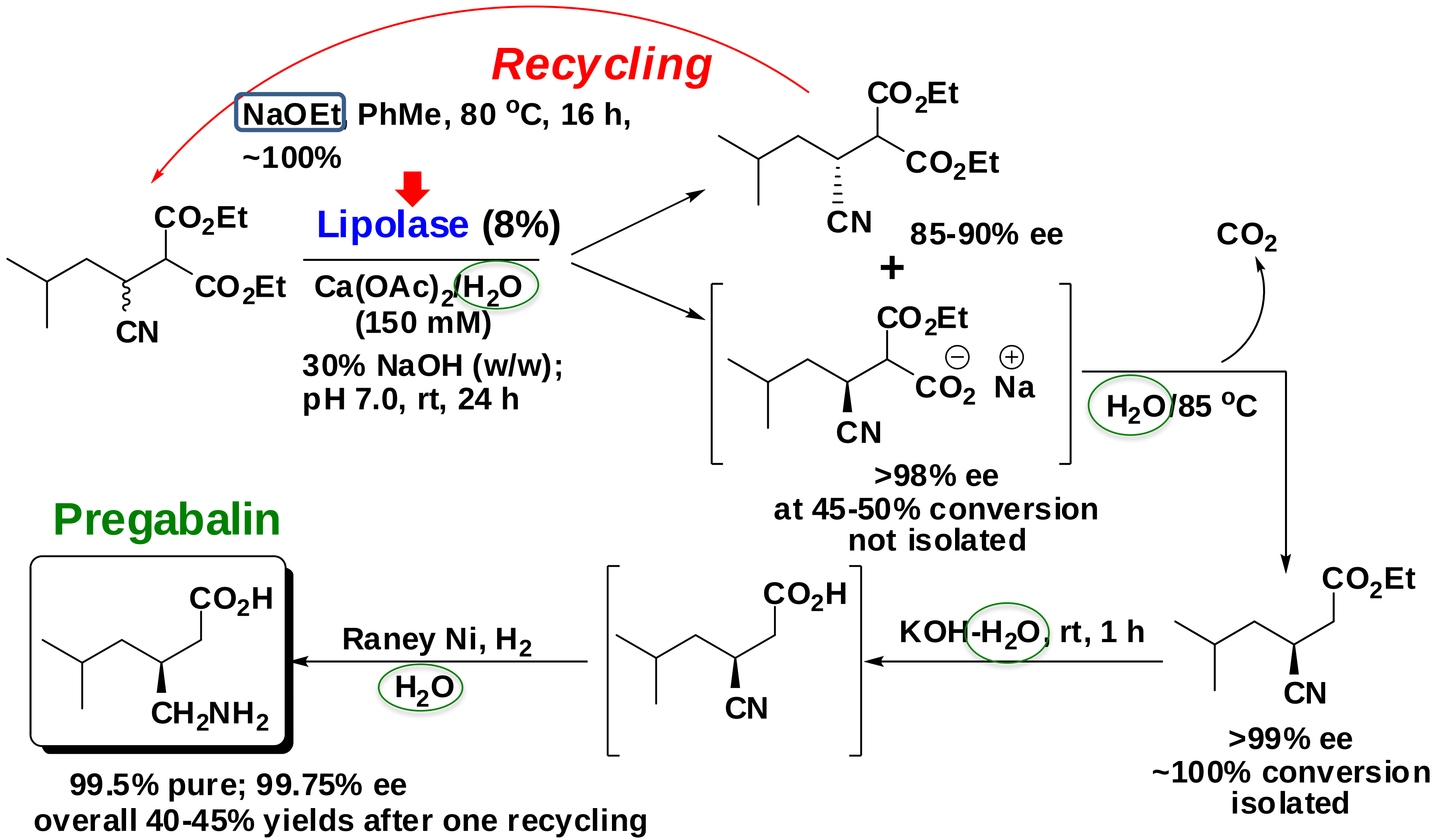


- *Atom economy: ~40%*
- *Using extremely toxic potasium* cyanide

Any synthetic solution??

- Classical resolution
  - *Requires stoichiometric mandelic acid*
- *Undesired enantiomer difficult to recycle*
  - *75% of everything becomes waste*
- *Overall low yield, low throughput, and high cost*

Solution – Chemoenzymatic resolution



Organic Process Research & Development **2008,** *12, 392*

Environmental benefits

The IChemE Award for Excellence in Green Chemistry and Engineering (2006)

- Biocatalytic with low (~0.5%) protein loading,
- Resolution at first step (wrong enantiomer can be recycled),
- Higher yields (40–45% after one recycle),
- Substantial reductions of waste streams,
  (the *E factor* decreased from 86 to 17 to 8)
- All reactions performed exclusively in water!
- Organic solvents (IPA, toluene) used for drying and cleaning only.

Between 2007 and 2020 the new synthesis will eliminate:

- 185,000 tonnes of solvent (water, THF, MeOH, EtOH, IPA), **> 90 % reduction**
- 4800 tonnes of *(S)*-mandelic acid, **100 % reduction**
- 2000 tonnes of Raney Ni catalyst, **90 % reduction**
- 15,000 tonnes of starting material (***CNDE***), **> 50 % reduction**
- Solvent and Energy savings are the equivalent to saving 413,550 tonnes of CO_2 emissions

Equivalent to taking 69,000 US cars off the road for a year!

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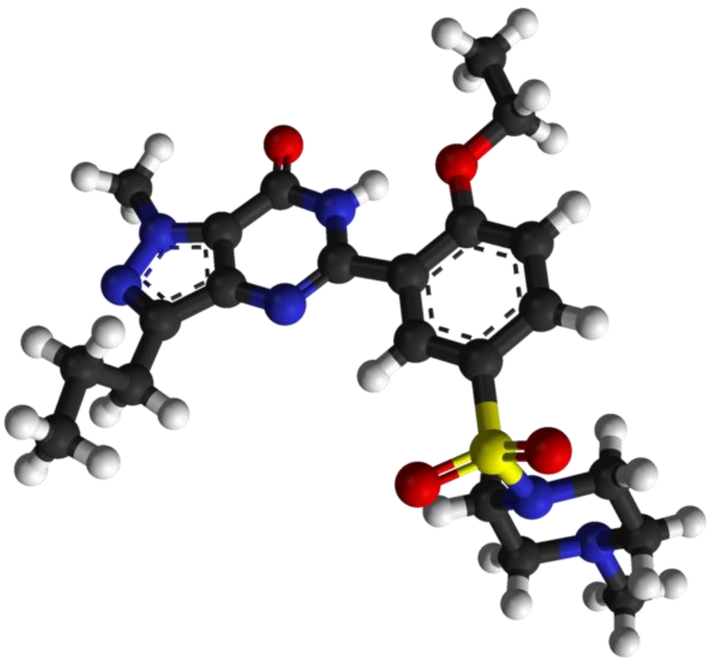
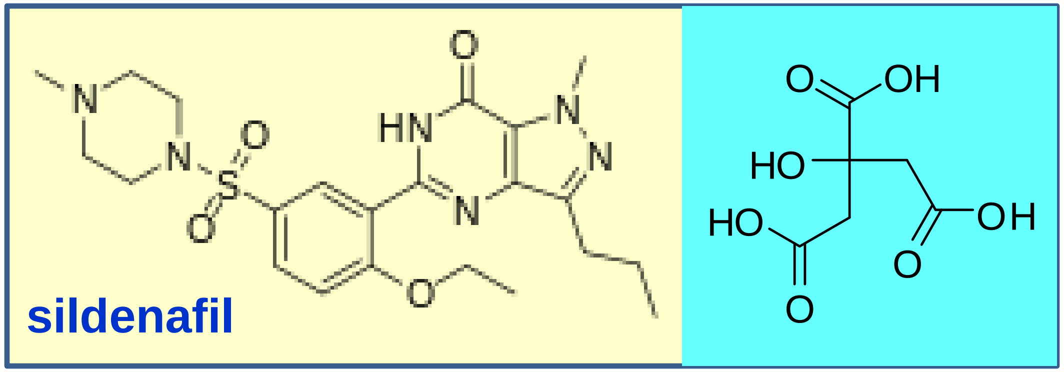
Case 2. 實例2

Sildenafil Citrate

The Active pharmaceutical ingredient (API) in the PDE_5 Inhibitor Viagra™



What is Sildenafil Citrate?



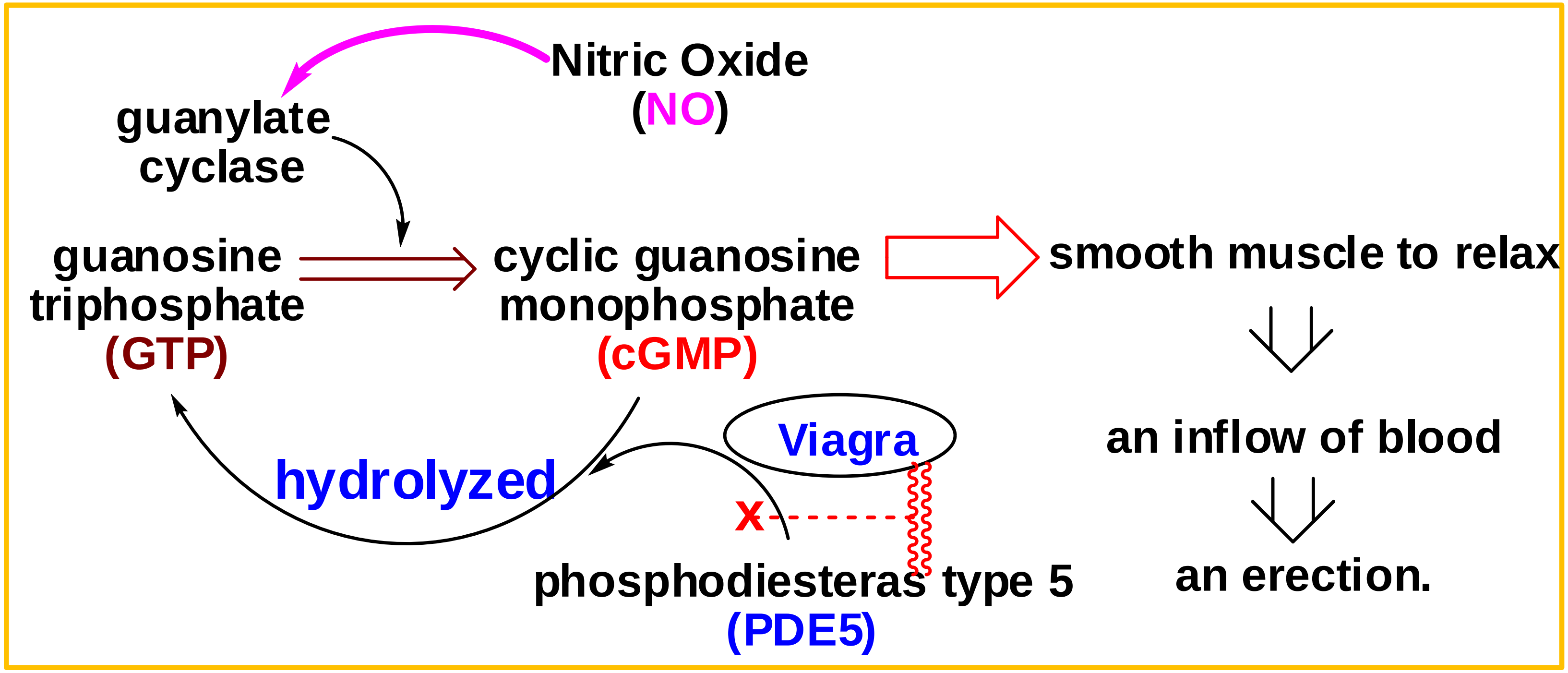
- ✓ Sildenafil was synthesized at Pfizer's research facility at Sandwich, Kent, in England.
- ✓ It was initially studied for use in treating hypertension (高血壓) and angina pectoris (心絞痛).
- ✓ It was approved by the US FDA on 27 March 1998 for use in treating erectile dysfunction (勃起機能障礙) under trade name Viagra™.

- ✓ In June 2005, it was approved by FDA for treatment of pulmonary arterial hypertension (肺動[靜]脈高血壓), marketed as Revatio®.
- ✓ It has been shown to be useful for the prevention and treatment of high-altitude pulmonary edema (肺水腫) associated with altitude sickness such as that suffered by mountain climbers.

- ✓ Viagra™ is actually a citrate salt and water-soluble, obtained simply by reacting sildenafil, a base, with citric acid (100% efficient).
- ✓ In 2003 Pfizer received the UK IchemE Crystal Faraday Award for designing the green sildenafil process.

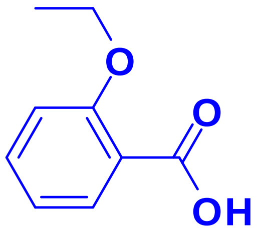
- ✓ Sildenafil is a potent and highly selective inhibitor of PDE5 (phosphodiesterase type 5), acting as a molecular impostors (冒名頂替者) of cGMP.

- ✓ **How sildenafil acts in the body.**

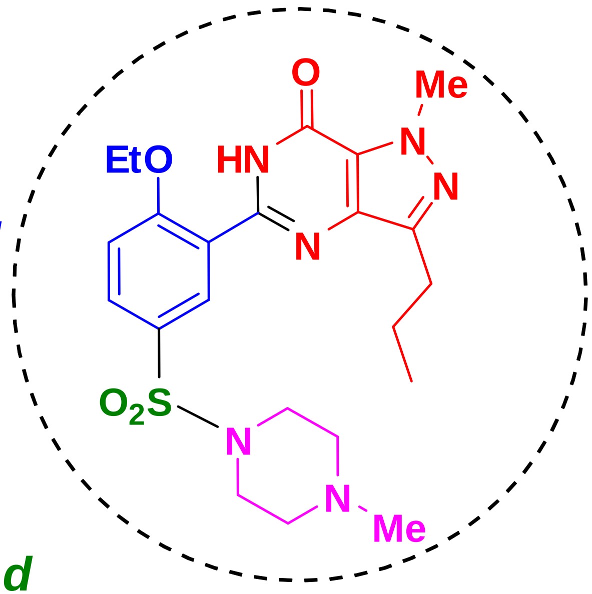


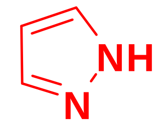
* Sildenafil works by inhibiting the enzyme PDE5 by occupying its active site. This means that cGMP is not hydrolysed as fast and this allows the smooth muscle to relax.

Chemical Synthesis of Sildenafil

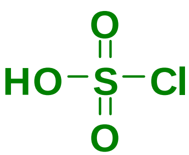


2-ethoxybenzoic acid

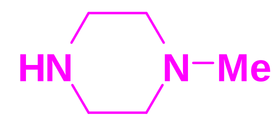




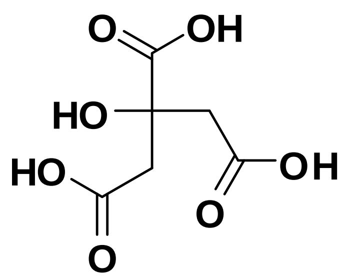
pyrazole-derivative



chlorosulfuric acid

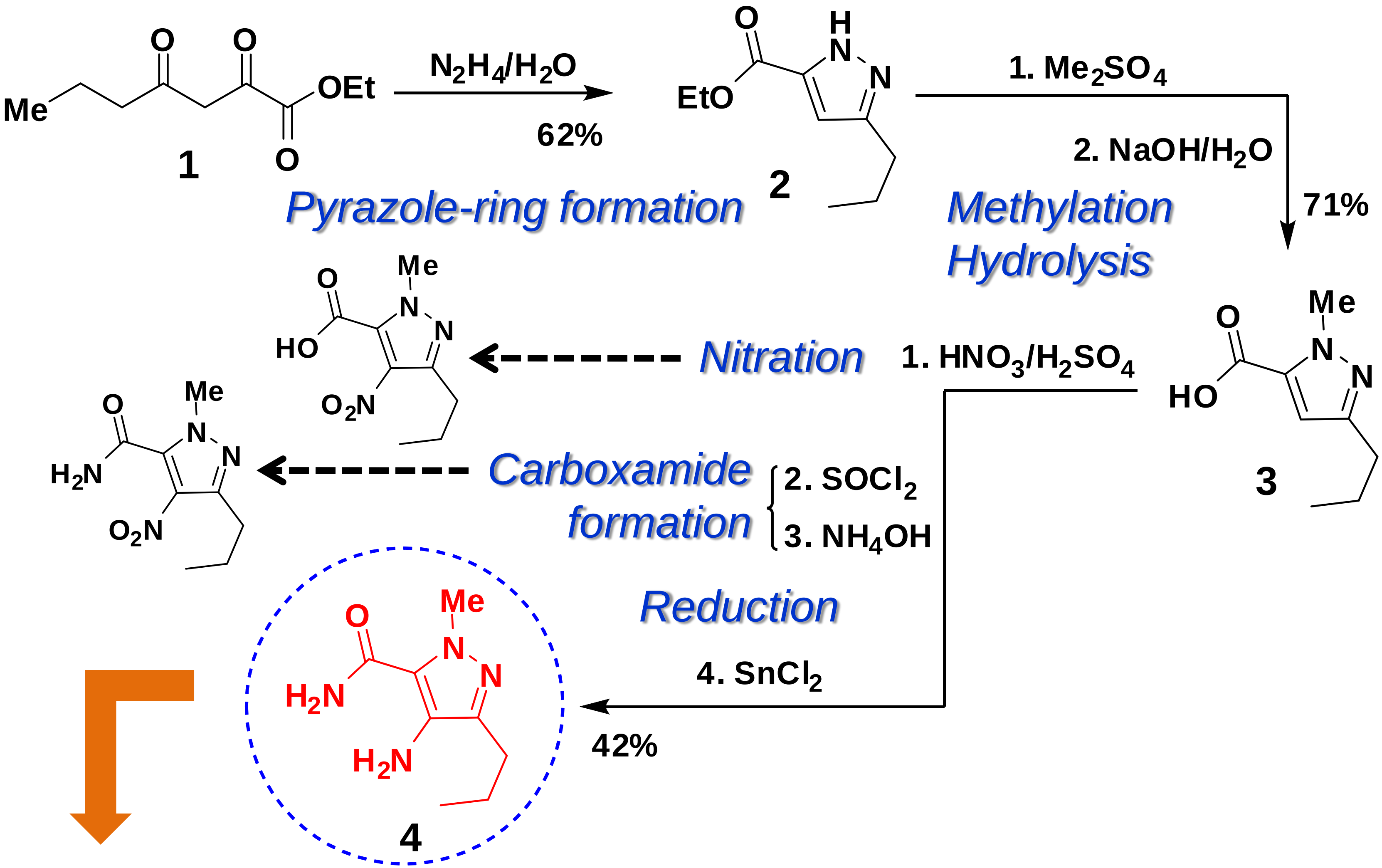


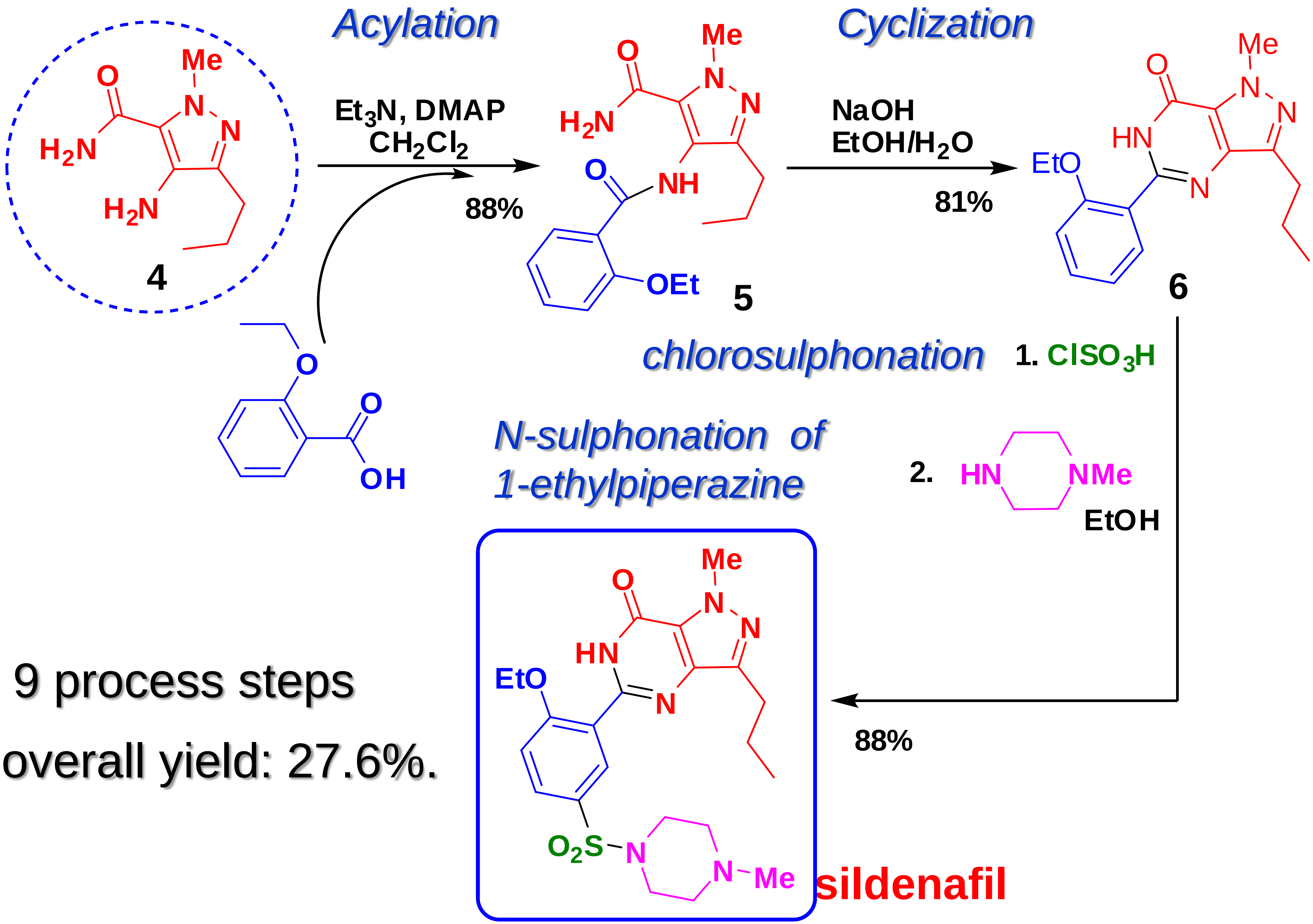
1-methylpiperazine



Chemical Synthesis – original, basic (academic)

Bioorganic & Medicinal Chemistry Letters, **1996**, *6*, 1819-1824.





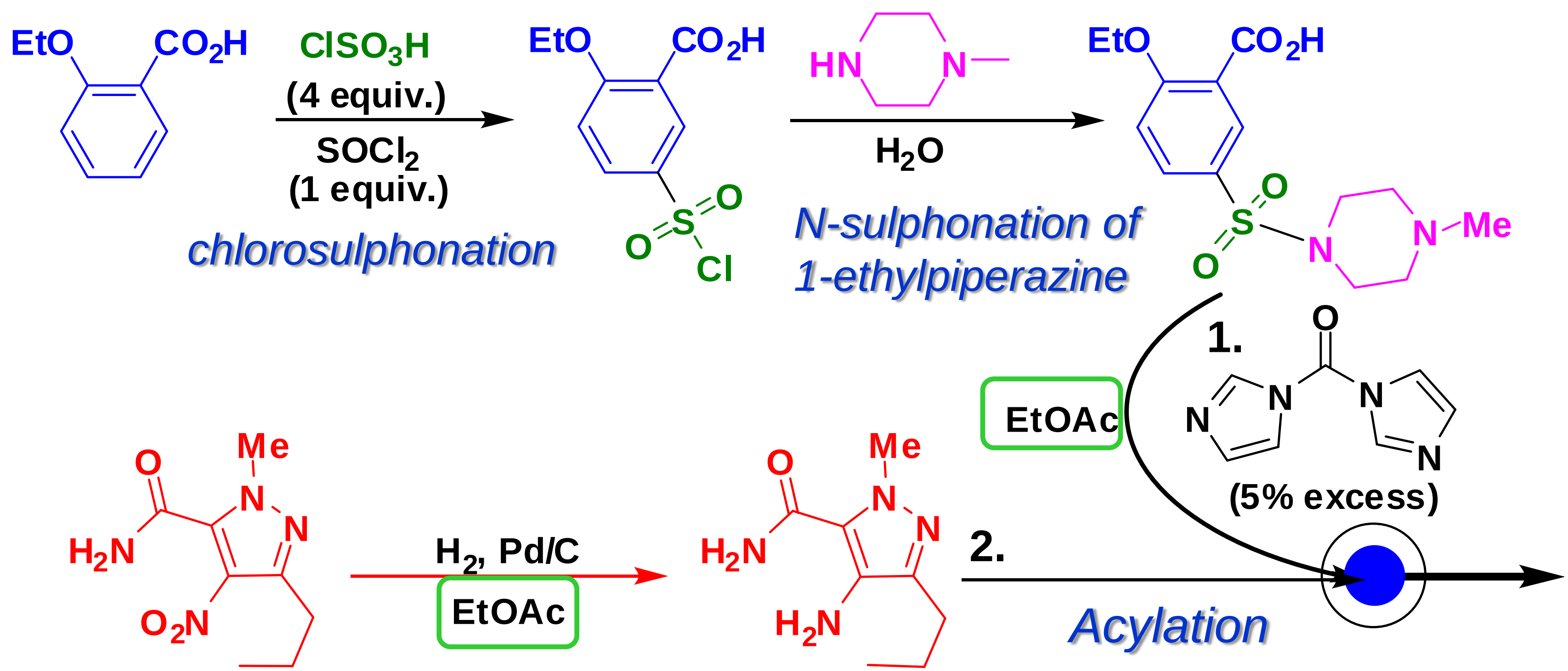
9 process steps

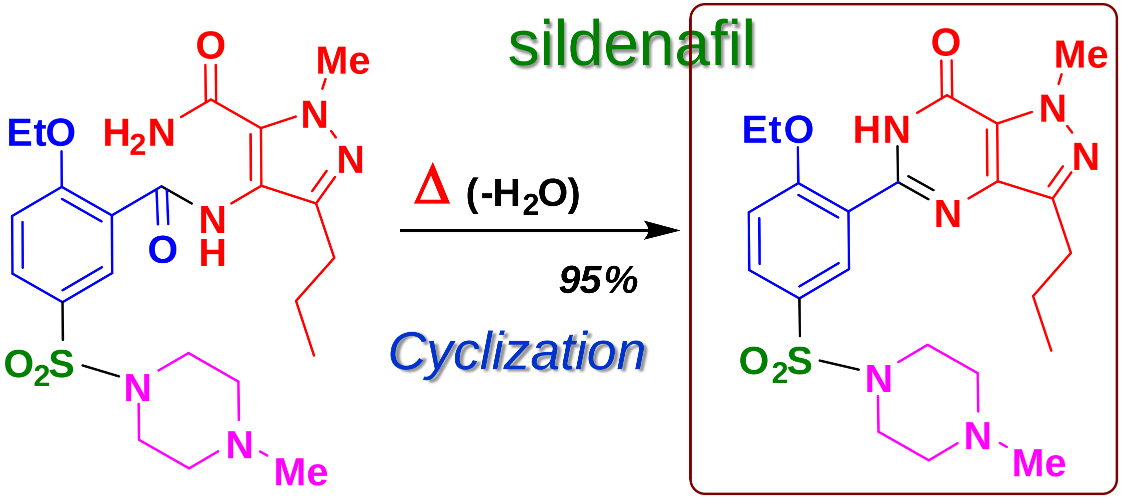
overall yield: 27.6%.

Chemical Synthesis – Patent, Manufacturing Process (Industry)

P. J. Dunn *Organic Process Research & Development* **2005**, *9*, 88-97
P. J. Dunn, S. Galvin and K. Hettenbach *Green Chem.*, **2004**, *6*, 43–48.

The United Kingdom Award for Green Chemical Technology ("Best Process" category). -- 2003





(1) under neutral conditions: heated with or without a solvent or a dehydrating agent; or

(2) under acidic conditions: a protic or Lewis acid with or without a solvent.

EtOAc

overall yield 51.7%

Significant achievements:

(i) a convergent, efficient synthetic route

(ii) 8 process steps, no extractive work-up in any step

(iii) implementing efficient solvent recovery early in the product's commercial lifetime.

- a convergent ***vs.*** a linear synthetic route.
- overall yield 51.7% ***vs.*** 27.6%.
- In a typical production year Pfizer (worldwide) produces 300 tons of organic waste in the preparation of sildenafil citrate. ***vs.*** 4300 tons.

↓

- The overall environmental impact is low with ***E* = ~6**. (industry average 25 ~100).

- The last three key steps of the reaction make use of only one solvent (EtOAc).

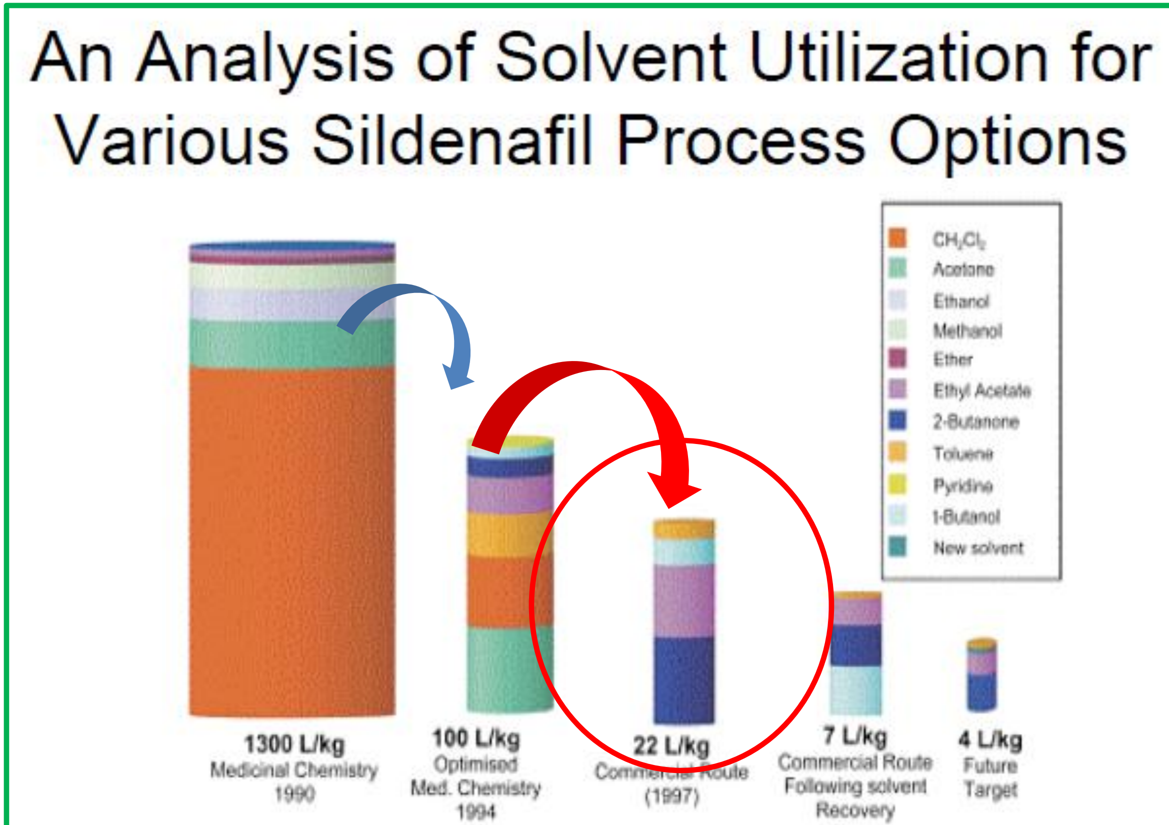


Fig. 1 The amount of organic waste produced by the sildenafil citrate processes at various time points.

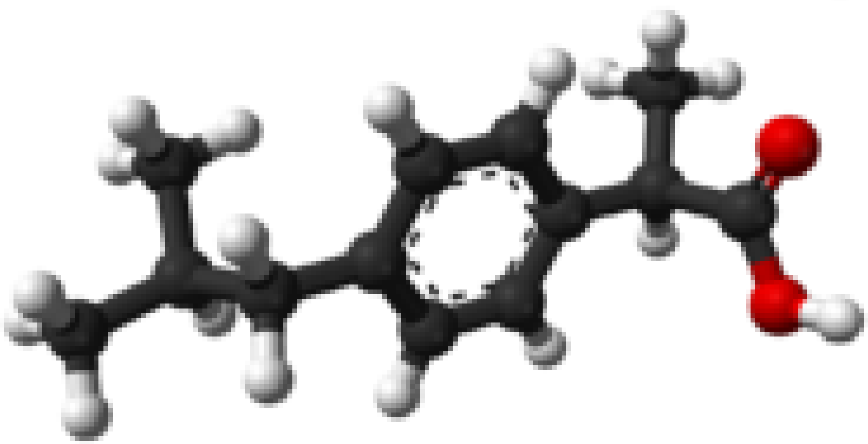
Green Chem. **2004**, *6*, 43–48

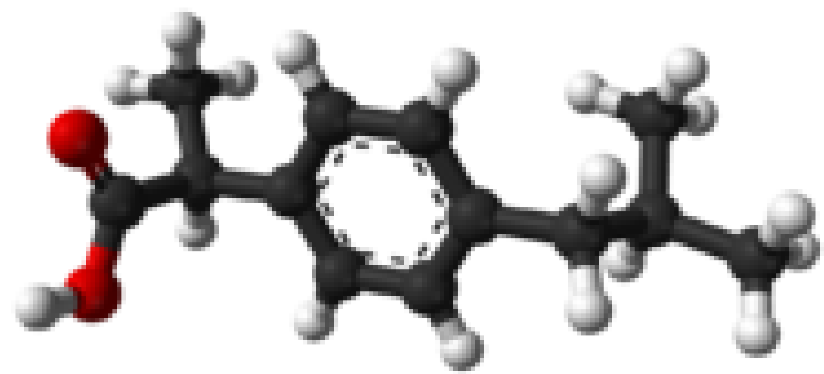
讚

In a typical production year Pfizer (worldwide) eliminates 3900 tons of aqueous waste.

Case 3. 實例3

Ibuprofen

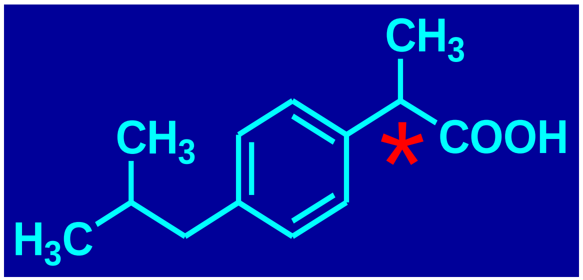


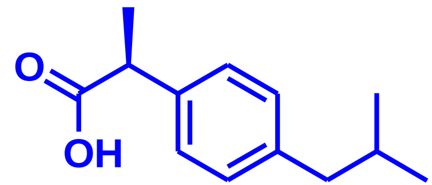


US Presidential Green Chemistry Challenge Awards:

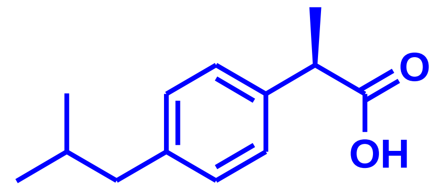
Greener Synthetic Pathways Award **1997**

What is ibuprofen?





(S)-ibuprofen



(R)-ibuprofen

(S)-2-(4-isobutylphenyl)propanoic acid, (S)-ibuprofen, is active form both *in vitro* and *in vivo*.

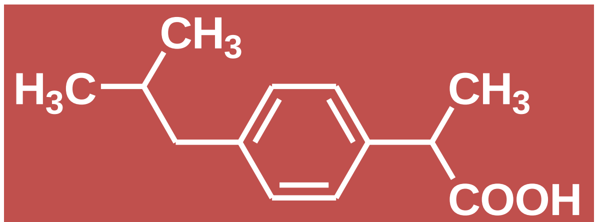
(S)-ibuprofen ← (R)-ibuprofen

2-arylpropionyl-CoA epimerase (isomerase)

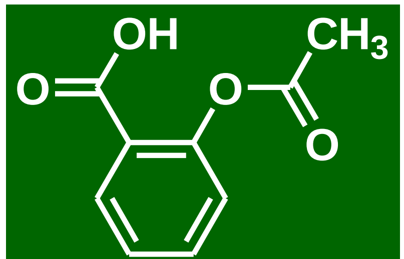
↓

marketed as racemic mixtures.

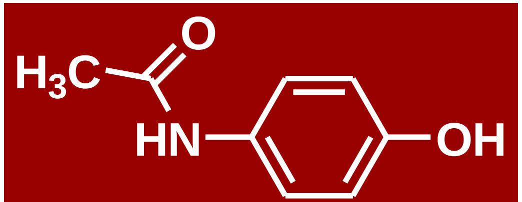
- One of core non-steroidal anti-inflammatory medicines (非類固醇消炎藥) in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system ---- *Over-the-Counter (不需處方可出售的) medicine.* [others: aspirin, paracetamol (acetaminophen)]



ibuprofen



aspirin



acetaminophen

- Discovered by S. Adams, with J. Nicholson, A. R. M. Dunlop, J. B. Wilson & C. Burrows (Boots Company), and was patented in 1961. Dr. Adams initially tested the drug on a hangover（宿醉）.

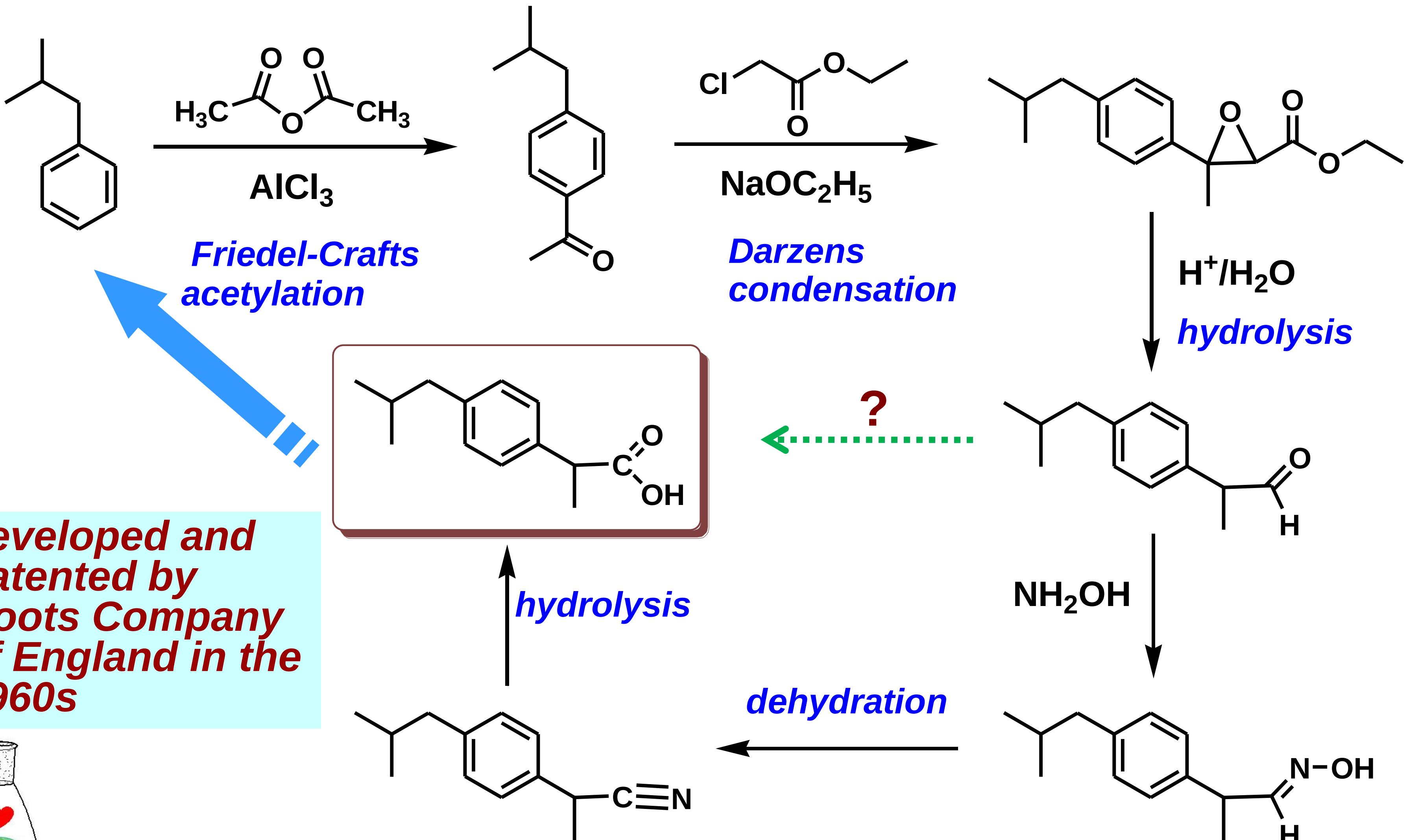
- It was launched in 1969 as a medication for the treatment of rheumatoid arthritis [風濕性關節炎] in the UK and in 1974 in the USA.
- The Boots Group was awarded ***Queen's Award for Technical Achievement*** for the development of ibuprofen in 1987.
- 具解熱、消炎和鎮痛的作用，可治療發燒、疼痛和發炎。
- 減輕關節炎(arthritis) ，原發型痛經(primary dysmenorrhea) ，發燒 (fever)，等症狀；作為止痛劑（analgesic)；具抑制血小板凝集效應（antiplatelet effect）。
- Active ingredient in “Motrin”, “Advil”, Medipren”.…，“炎熱消”（水液），“普服芬”（錠劑), 宜痛炎錠, 伊普®鎮痛, ….

Synthesis

- The industrial synthesis was developed and patented by Boots Company of England in 1961. ***--- brown synthesis***
- A new greener industrial synthesis was developed and implemented by the BHC Company (now BASF Corporation) in 1991. ***--- green synthesis***
- BHC won Presidential Green Chemistry Challenge Awards (USA) **---- Greener Synthetic Pathways Award in 1997.**

BHC = Boots + Hoechst Celanese

Boots synthesis of ibuprofen
--- brown synthesis

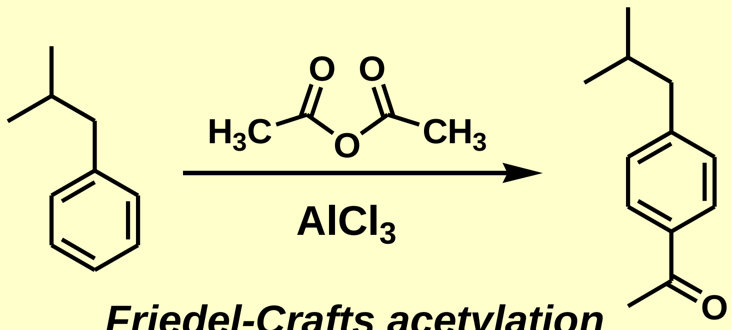


developed and patented by Boots Company of England in the 1960s

	Reagent		Used in ibuprofen		Unused in ibuprofen	
	Formula	Mw	Formula	Mw	Formula	Mw
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3	24	$C_2H_3O_3$	75
2	$C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
	C_2H_5ONa	68		0	C_2H_5ONa	68
3	H_3O	19		0	H_3O	19
4	NH_3O	33		0	NH_3O	33
6	H_4O_2	36	HO_2	33	H	3
	Total		**Ibuprofen**		**Waste products**	
	$C_{20}H_{42}NO_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5
	▸ = (206)/(514.5) x 100 = **40%**					

Table 1. Atom economy in the Boots' synthesis of ibuprofen

Problems with Boots synthesis of ibuprofen

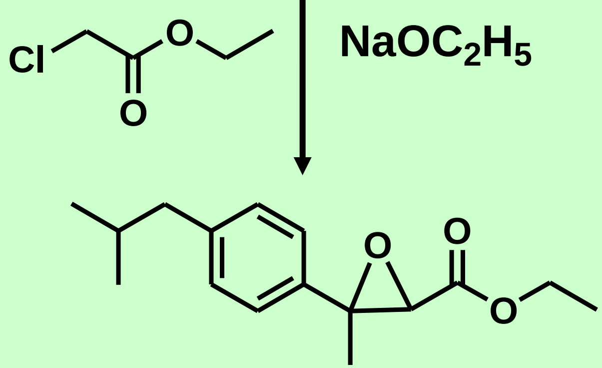


Friedel-Crafts acetylation

HCl AcOH Al

atom economy = 74.5%

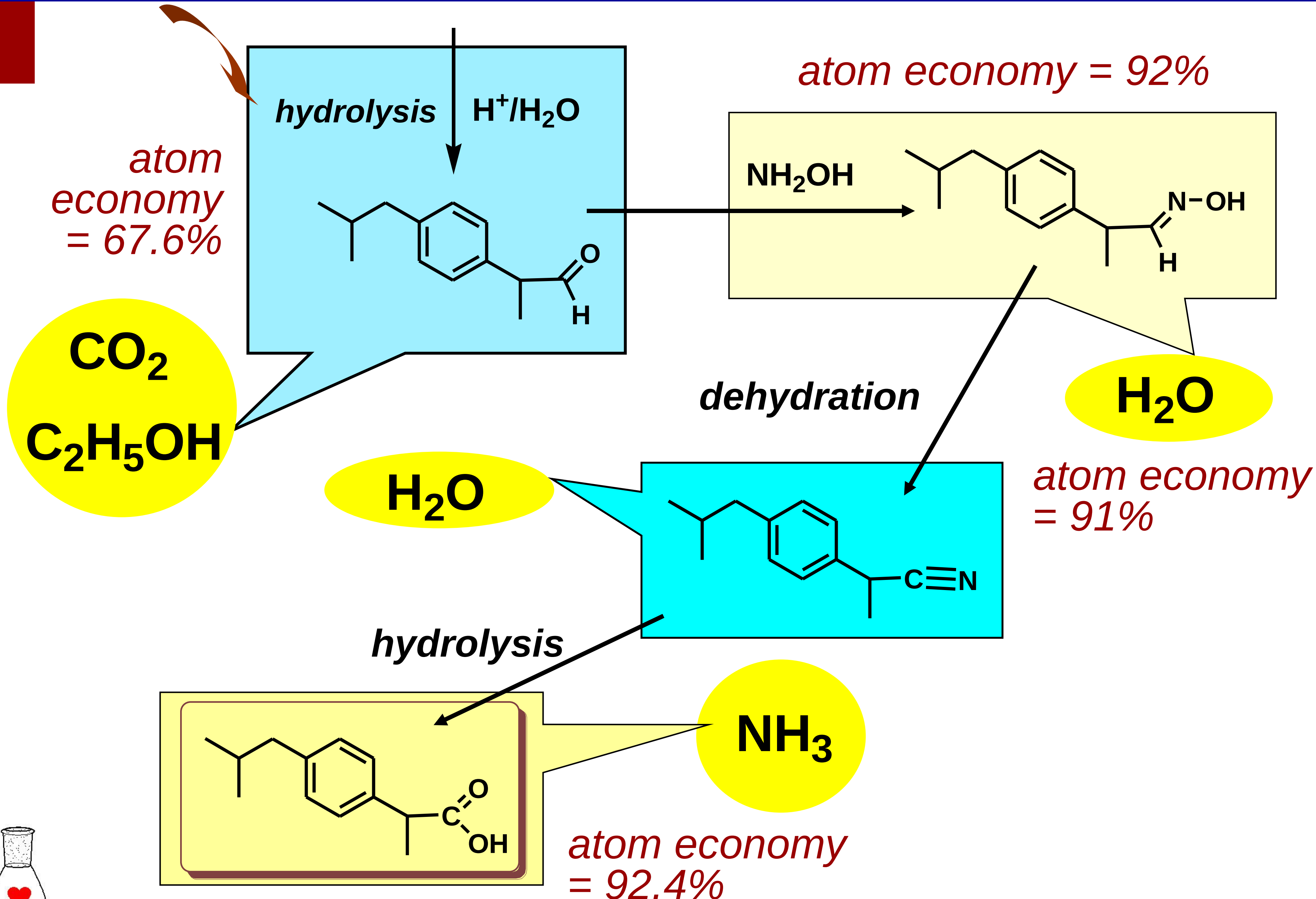
aluminium trichloride, **$AlCl_3$**, is not a true catalyst. it is changed into a hydrated form, $Al(OH)_3/H_2O$, that has to be disposed of – usually in landfill sites.



Darzens condensation

NaCl C_2H_5OH

atom economy = 71.6%


hydrolysis
H+/H2O
atom economy = 67.6%
CO2
C2H5OH
NH2OH
atom economy = 92%
N−OH
H
O
H
dehydration
H2O
atom economy = 91%
H2O
C≡N
hydrolysis
NH3
C
O
OH
atom economy = 92.4%

- 6 steps!

  If 90% yield for each step, then overall yield is 53%.
- atom economy is 40%!

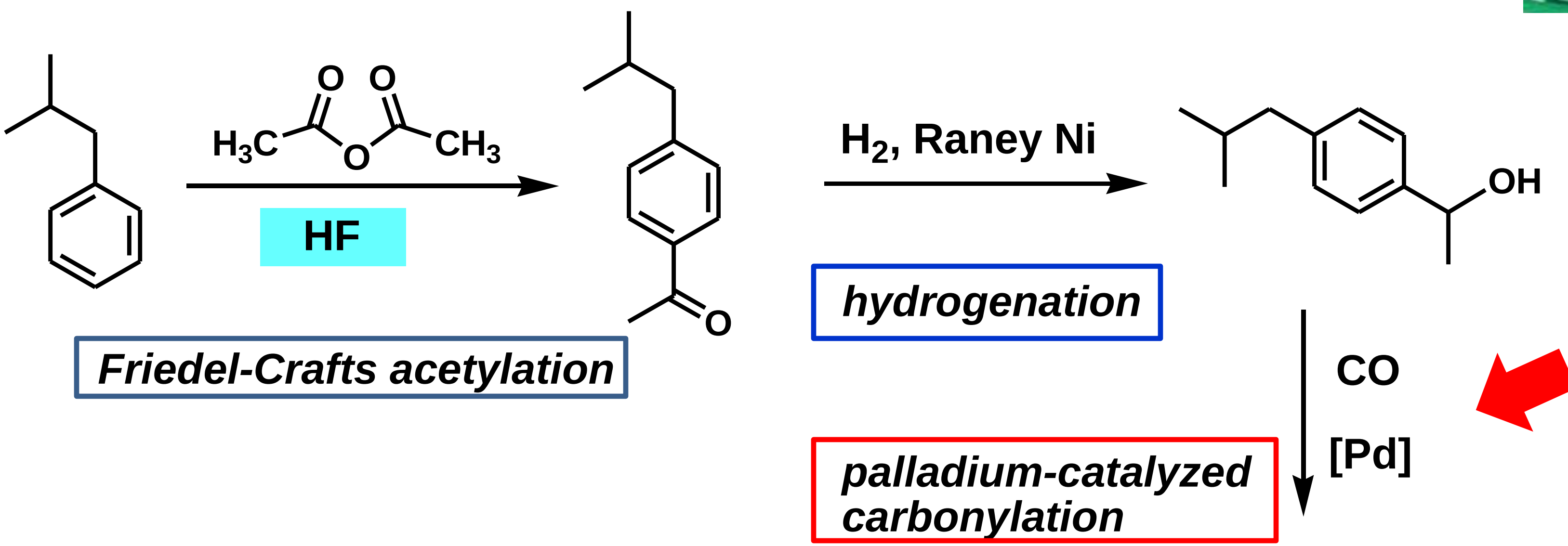
  thus every 1 kg of ibuprofen produced is accompanied with more than 1.5 kg of waste.
- UK market for ibuprofen is about 3,000,000 kg per year!
  - *about 4,500,000 kg of waste are produced.*
  - *a typical tablet contains 200 mg of ibuprofen, then 15,000,000,000 (1.5×10^{10}) tablets are produced.*

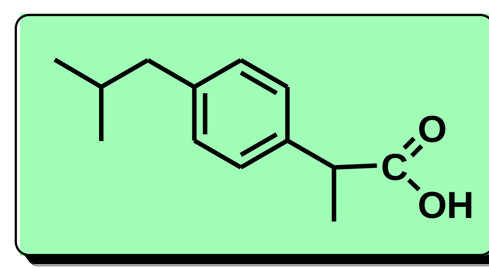
World population on November 2010 is estimated by the United States Census Bureau to be 6.884 billion (0.7×10^{10}).

BHC synthesis of ibuprofen --- green synthesis

(USA) Presidential Green Chemistry Challenge Awards

Greener Synthetic Pathways Award in 1997





developed and implemented by the BHC Company in 1991

	Reagent		Used in ibuprofen		Unused in ibuprofen	
	Formula	**Mw**	**Formula**	**Mw**	**Formula**	**Mw**
1	$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
	$C_4H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
2	H_2	2	H_2	2		0
3	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
atom economy = (206)/(266) x 100 = **77.4%**						

Table 2. Atom economy in the BHC synthesis of ibuprofen

Economic and Environmental Advantages of BHC Synthesis

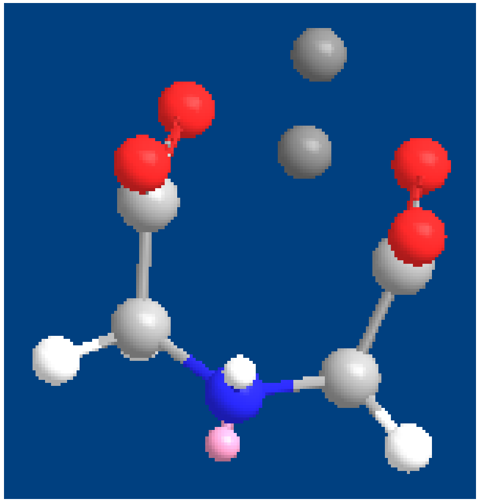
- Greater overall yield (three steps *vs.* six steps)
- Greater atom economy (77% *vs.* 40%; uses less feedstocks)
- Fewer auxiliary substances (products and solvents separation agents)
- **Less waste:** greater atom economy, catalytic *vs.* stoichiometric reagents, recovery of byproducts and reagents, recycling, and reuse, lower disposal costs.

The BHC ibuprofen process is an innovative, efficient technology that has revolutionized bulk pharmaceutical manufacturing. ☺

Case 4.

實例4

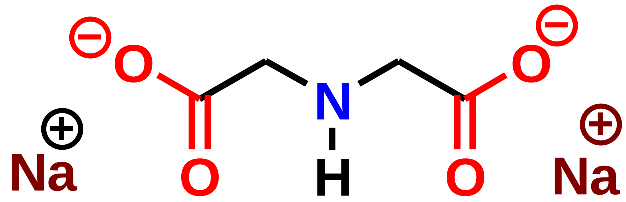
Disodium iminodiacetate (DSIDA)



US Presidential Green Chemistry Challenge Awards:

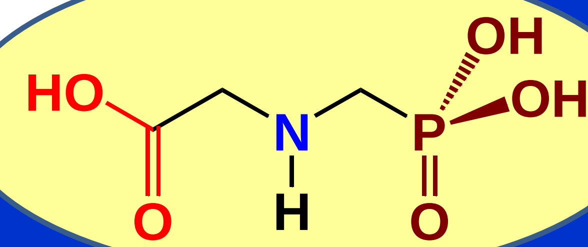
Greener Synthetic Pathways Award **1996**

What is Disodium iminodiacetate (DSIDA)?



sodium 2,2'-azanediyldiacetate
disodium 2-[(2-oxido-2-xoethyl)amino]acetate

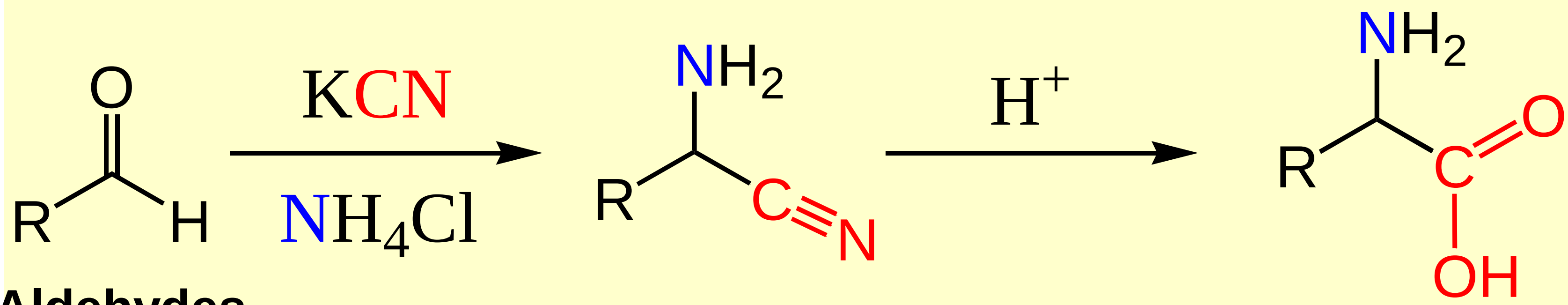
a key intermediate in the production of Monsanto's Roundup® herbicide



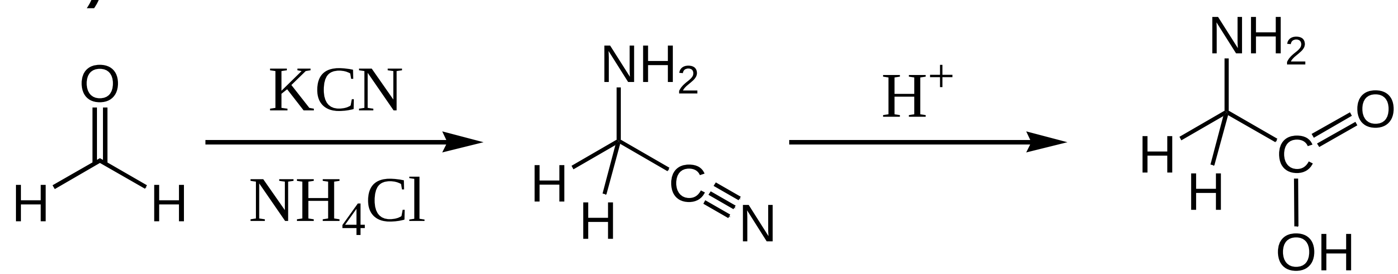
Glyphosate: *N*-(phosphonomethyl)glycine in the form of its isopropylamine salt (41%)

Roundup® agricultural herbicides are the flagship of Monsanto's agricultural chemicals business.

Strecker amino acid synthesis



Aldehydes
(or Ketones)

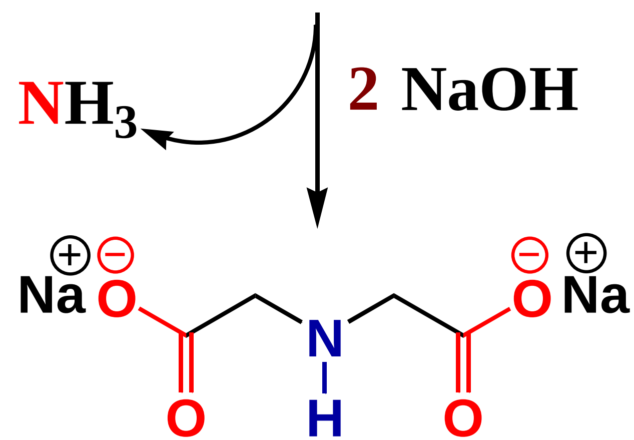


glycine

2-aminoacetic acid

Traditionally, the Strecker process has been used to manufacture DSIDA. It requires formaldehyde, ammonia, hydrogen cyanide, and hydrochloric acid.

The Strecker process for synthesizing DSIDA



disodium iminodiacetate

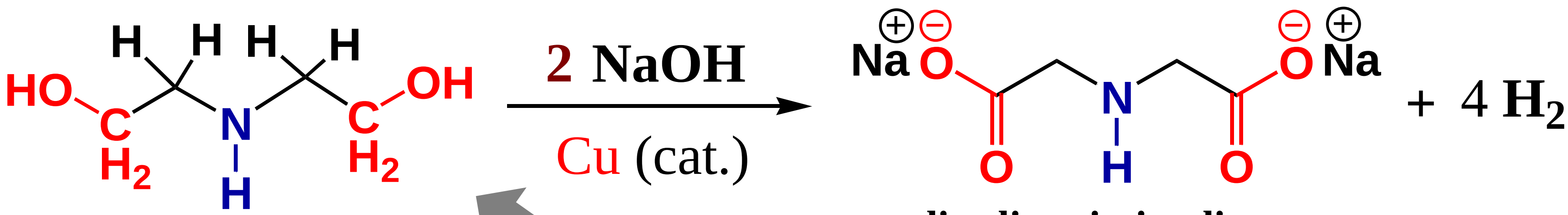
hydrogen cyanide:
extremely toxic;
requires special handling

exothermic reaction
generating potentially unstable intermediates.

waste: *1 kg for every 7 kg of product.*

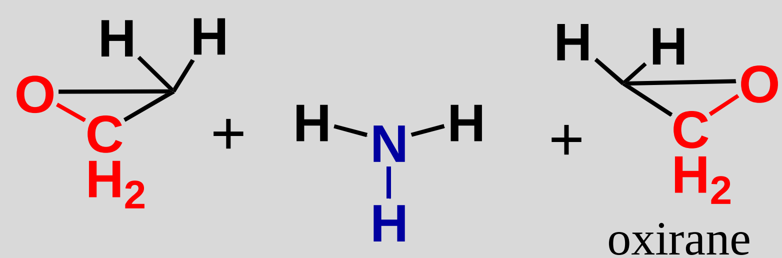
Green process for synthesizing DSIDA

copper-catalyzed dehydrogenation of diethanolamine



diethanolamine
2,2'-azanediyldiethanol

disodium iminodiacetate



oxirane
ethylene oxide

Greener Synthetic Pathways Award
1996

- *the dehydrogenation reaction is endothermic;*
  avoid the use of cyanide and formaldehyde;
- *fewer process steps, higher overall yield;*
  no purification or waste cut is necessary;
- *recover catalyst by filtration, ready for subsequent use in the manufacture of* Roundup*;*
- *This catalysis technology is applicable in the production of other amino acids and*
- *becomes a general method for conversion of primary alcohols to carboxylic acid salts.*

1. Prevent Waste
2. Increase Atom Economy
3. Design Less Hazardous Chemical Syntheses
4. Design Safer Chemicals
9. Use Catalysts

Conclusion

Process chemistry is more than just scale-up

[製程化學並非僅止於量產規模]

Safe　安全

Cost effective　成本效率

Enviromentally friendly　環境友善

Timely development　適時發展

Green chemistry & engineering

offers a system approach to innovating

a healthy business and

sustainable future!

"The chemical industry plays a key role in sustaining the world economy and underpinning future technologies, yet is under unprecedented pressure from the effects of globalization and change in many of its traditional markets."

［化學工業在永續世界經濟和奠立未來的技術上扮演著關鍵的角色，但也承受著來自全球化和很多傳統市場變化的衝擊所帶來的前所未有壓力。］

"Against this background, what will be needed for the industry to embrace efforts to make it "greener"?"

［在這種情況下，工業界致力於成為"更綠色"的努力中，會需要些什麼？］

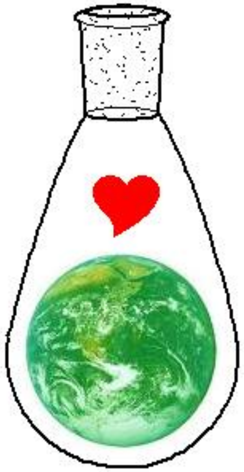
Green Chemistry: Science and Politics of Change,
M. Poliakoff, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas,
Science, **2002**, 297, 807 – 810.

The best way to predict the future is to create it!

預測未來的最佳方法是創建它！

- - *Peter Drucker* an Austrian-born American management consultant, educator, and author.

感謝您的聆聽



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Appendix

12 More Principles of Green Chemistry*

12 Principles of Green Engineering**

9 Principles of Green Engineering ***

(The Sandestin Declaration of Green Engineering Principles)

Some suggested readings

* *Winterton N, Green Chemistry 2001, G73*

Anastas, P.T., and Zimmerman, J.B., *Design through the Twelve Principles of Green Engineering, Env. Sci. and Tech., 37, 5, 94A-101A,* ***2003**.*

***as developed by more than 65 engineers and scientists at the Green Engineering: Defining the Principles Conference, held in Sandestin, Florida in May of 2003.

Twelve more principles of green chemistry

(Winterton N, Green Chemistry 2001, G73)

1. **Identify and quantify byproducts**
   鑑定並定量所有的副產物
2. **Report conversions, selectivities and productivities**
   記錄所有的轉換率、選擇性和產量
3. **Establish full mass balance for process**
   建立製程中完整的質量平衡
4. **Measure catalyst and solvent losses in air and aqueous effluent**
   測量空氣和水的流出物中催化劑和溶劑的耗損量
5. **Investigate basic thermochemistry**
   查悉基本熱化學
6. **Anticipate heat and mass transfer limitations**
   預估傳熱與傳質的限制
7. **Consult a chemical or process engineer**
   諮詢化學或製程工程師

Twelve more principles of green chemistry

8. Consider effect of overall process on choice of chemistry

考量整個製程對選擇化學的影響

[化學反應和方法的選擇要依據整體製程]

9. Help develop and apply sustainability measures

協助開發和應用永續發展的措施

10. Quantify and minimize use of utilities

量化並減少使用通用性器材（水、電、煤氣等）

11. Recognize where safety and waste minimization are incompatible

認知安全和廢棄物減化在（製程中）何處會是不相容的

[不能兼顧的]

12. Monitor, report and minimize laboratory waste emitted.

監控、記錄和減少實驗室的廢棄物排放

12 Principles of Green Engineering**

1. Inherent Rather Than Circumstantial
2. Prevention Instead of Treatment
3. Design for Separation
4. Maximize Efficiency
5. Output-Pulled Versus Input-Pushed
6. Conserve Complexity
7. Durability Rather Than Immortality
8. Meet Need, Minimize Excess
9. Minimize Material Diversity
10. Integrate Material and Energy Flows
11. Design for Commercial "Afterlife"
12. Renewable Rather Than Depleting

9 Principles of Green Engineering***

1. Engineer processes and products holistically, use systems analysis, and integrate environmental impact assessment tools.
2. Conserve and improve natural ecosystems while protecting human health and well-being.
3. Use life-cycle thinking in all engineering activities.
4. Ensure that all material and energy inputs and outputs are as inherently safe and benign as possible.
5. Minimize depletion of natural resources.
6. Strive to prevent waste.
7. Develop and apply engineering solutions, while being cognizant of local geography, aspirations, and cultures.

9 Principles of Green Engineering*

8. Create engineering solutions beyond current or dominant technologies; improve, innovate, and invent (technologies) to achieve sustainability.

9. Actively engage communities and stakeholders in development of engineering solutions.

***** *The preliminary principles are intended for engineers to use as a guidance in the design or redesign of products and processes within the constraints dictated by business, government and society such as cost, safety, performance and environmental impact.*

Some suggested readings

Green Chemistry in the Pharmaceutical Industry P. J. Dunn, *et .al. Eds.;* Wiley-VCH, 2010.

Dunn, P. J. *Pharmaceutical Process Development;* J. A. Blacker and Williams, M. T., Eds.; Royal Society of Chemistry: London, 2011; Chapter 6.

P. J. Dunn, *The importance of Green Chemistry in Process Research and Development,* Chem. Soc. Rev., **2012**, ***41***, 1452–1461.

P. J. Dunn, S. Galvin and K. Hettenbach, *The development of an environmentally benign synthesis of sildenafil citrate (Viagra™) and its assessment by Green Chemistry metrics*. Green Chem. **2004**, *6*, 43–48.

P. J. Dunn, *Synthesis of Commercial Phosphodiesterase(V) Inhibitors*. Organic Process Research & Development **2005**, *9*, 88-97

J. M. Fortunak, *Current and future impact of green chemistry on the pharmaceutical industry,* Future Med. Chem. **2009**, *1*, 571-575.

P. T. Anastas and M. M. Kirchhoff, *Origins, Current Status, and Future Challenges of Green Chemistry,* Acc. Chem. Res. **2002**, *35*, 686-694.

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吳丁凱 (supporter)

& 我

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