TP de chimie combinatoire basé sur la réaction multicomposant de Biginelli ; une approche de la chimie verte

24ème JIREC

Ambleteuse, 15 mai 2008

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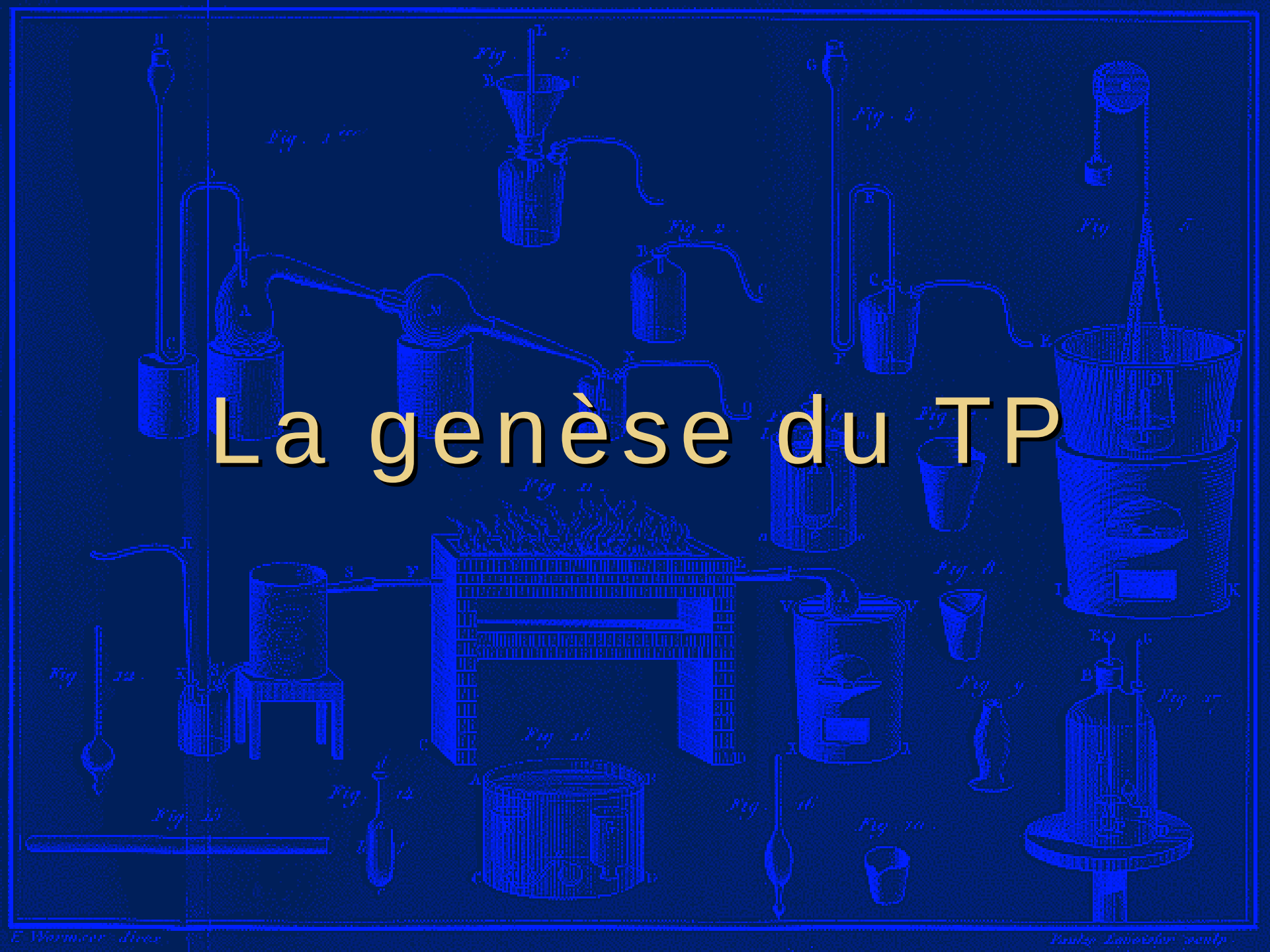


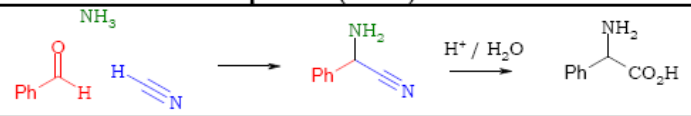
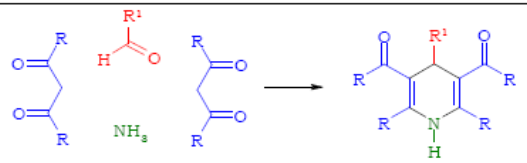
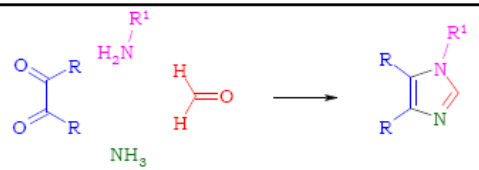
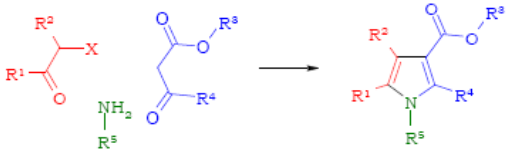
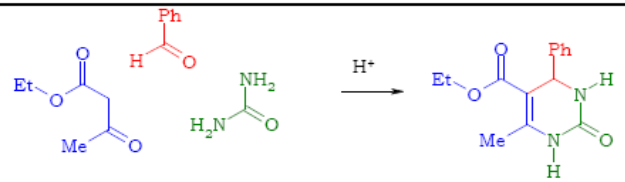
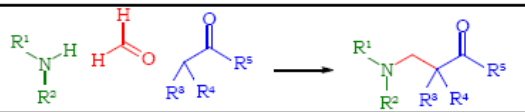
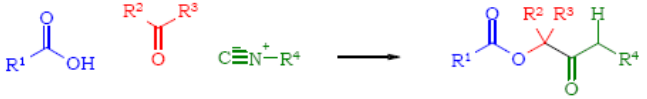
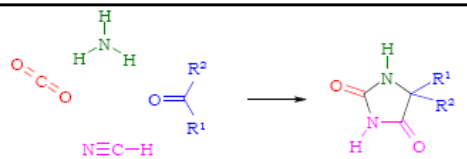
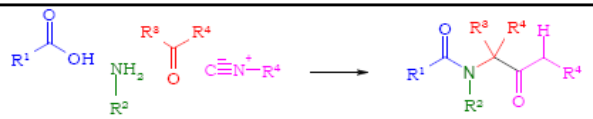
La genèse du TP

Choix du thème : la « réaction chimique idéale »

- La réaction chimique idéale :
  - rendement de 100%, à cinétique rapide
  - s'effectue en une opération,
  - simple à réaliser,
  - partant de réactifs
    - peu coûteux,
    - disponibles,
    - peu toxiques
  - transposable facilement en production
  - et le tout se faisant dans le respect de l'environnement.
- Revenons à la réalité : cette réaction n'existe pas.
- Comment s'en sortir ?
  - chimie enzymatique ?
  - autoorganisation ?
  - réactions domino, cascade et tandem,
  - réactions **R**éactions **M**ulti-**C**omposants (RMC).
    - mettent en jeu au moins 3 réactifs, une étape, « **one pot** ».

- Les « chimistes maudits »
- Adolph **Strecker** (1822-1871), synthèse de l'alanine.
- Arthur **Hantzsch** (1857-1935)
- Karl **Mannich** (1877-1947)
- Pietro **Biginelli** (1860-1937), université de Florence
- Mario **Passerini** (1891-1962), Florence : isonitrile
- Ivar **Ugi**
- Tropanone de **Robinson**

Fig. 1. Exemples de Réactions MultiComposants (RMC)

1838	*Laurent-Gerhardt*	Acides aminés	
1850	*Strecker*	Acides aminés	
1882	*Hantzsch*	Dihydropyridines	
1882	*Radziszewski*	Imidazoles	
1890	*Hantzsch*	Pyrroles	
1891	*Biginelli*	Dihydropyrimidinones	
1912	*Mannich*		
1921	*Passerini*		
1934	*Bucherer-Bergs*	Hydantoïnes	
1959	*Ugi*		

- **Holden M.S. et Crouch D.,** The Biginelli Reaction, *J. Chem. Ed.*, **2001**, *78*, p. 1104.

The Microscale Laboratory

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The Biginelli Reaction

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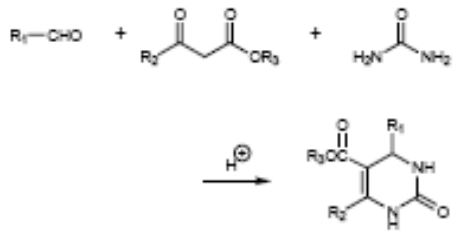
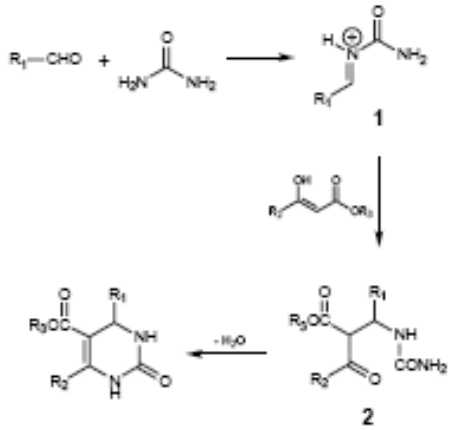
In our laboratory, we often use reactions in which multiple transformations occur (*1*). Such reactions allow students to combine familiar mechanisms to arrive at the overall conversion. A classic example of such a process is the Biginelli reaction, in which an aldehyde, a β-keto ester, and urea are combined in one pot to synthesize a 3,4-dihydropyrimidinone, as shown in eq 1 (*2*).



(1)

Although the mechanism of the Biginelli reaction has been debated for a number of years, most researchers now agree on the following sequence of steps, as proposed by Kappe (*3*), and shown in eq 2. First, a rate-determining protonated imine formation takes place to produce 1; then this species reacts with the enol form of the β-keto ester to form the ureide 2. The final step is the cyclization, with concomitant loss of water. All three steps are processes that are covered in a typical organic sequence; students learn to apply them in sequence to determine the overall mechanism of an apparently complex conversion.

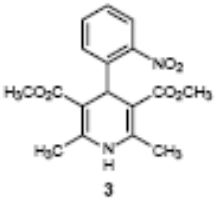


(2)

We have modified the method of Folkers, Harwood, and Johnson (*4*) to develop a Biginelli reaction that works well in a typical laboratory setting. A mixture of benzaldehyde (R_1 = Ph), ethyl acetoacetate (R_2 = Me, R_3 = Et), and urea in ethanol was heated at reflux for 1.5 h. The product precipitated as a pure, white powder. Student yields ranged from 20% to 80%, averaging 58%. The reaction could easily be performed during a single laboratory period and the high melting point and low solubility of the product make it easy to isolate.

It is noteworthy that the Biginelli reaction produces a 3,4-dihydropyrimidinone, an example of a class of compounds exhibiting pharmacological activity. Recently, 4-aryl-dihydropyrimidinones have been recognized as a new class of calcium channel blockers and several biologically active marine alkaloids with the Biginelli product core have been isolated (*5*). Other biological activities have also been noted (*6*).

The identification of Biginelli products as a new class of calcium channel blockers is a subject that is of interest to many students, especially those who are pre-health majors or oriented toward biology. Calcium channel blockers are popular antihypertensives that inhibit the movement and binding of calcium ions, which leads to a relaxation of vascular smooth muscle and reduction of vascular resistance. Nefidipine, 3, exerts a potent vasodilatory effect on both coronary and peripheral vasculatures (*7*). A comparison of the structure of the Biginelli product and of Nefidipine is a good starting point for a discussion of structure-activity relationships.



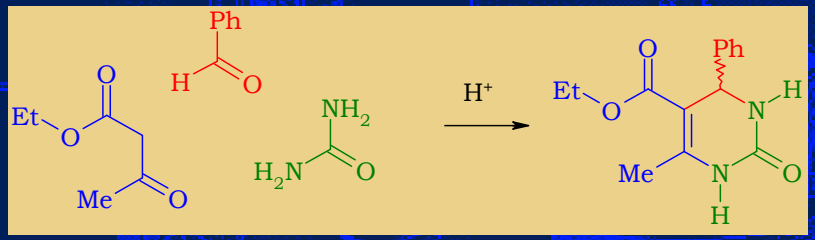
3

The Biginelli Reaction: Procedure

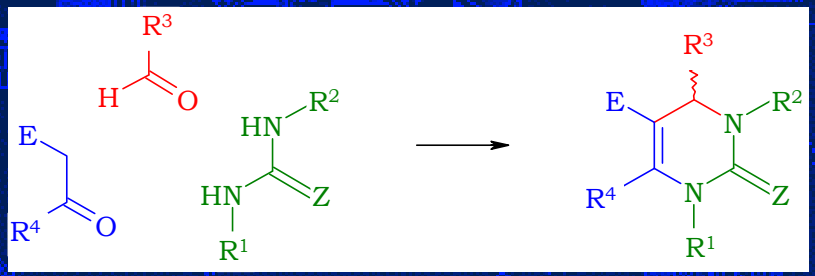
To a 5-mL round-bottomed flask equipped with a spin vane and reflux condenser were added benzaldehyde (127 µL, 133 mg, 1.25 mmol), ethyl acetoacetate (242 µL, 247 mg, 1.90 mmol), urea (75 mg, 1.25 mmol) and 0.5 mL of 95% ethanol. One drop of concentrated HCl was added to the mixture and the system was heated at reflux for 1.5 h. The reaction flask was cooled to 0 °C and the resultant precipitate was collected by filtration (Hirsch funnel) and washed with

Nom de code B-3CR

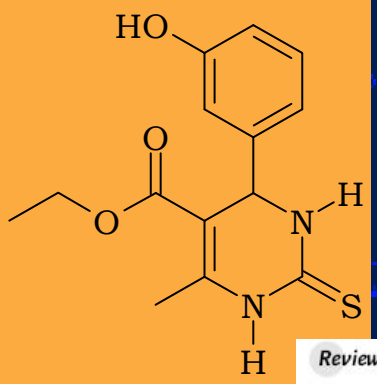
- Formation d'une DiHydroPyriMidinone (DHPM)
  - urée,
  - benzaldéhyde
  - β-cétoester, le 3-oxobutanoate d'éthyle (ou acétoacétate d'éthyle).



- Biginelli généralisée

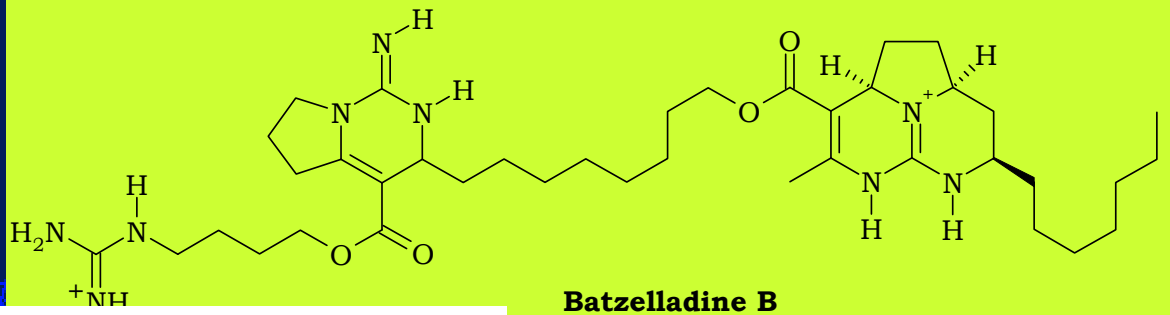


Anticancéreux

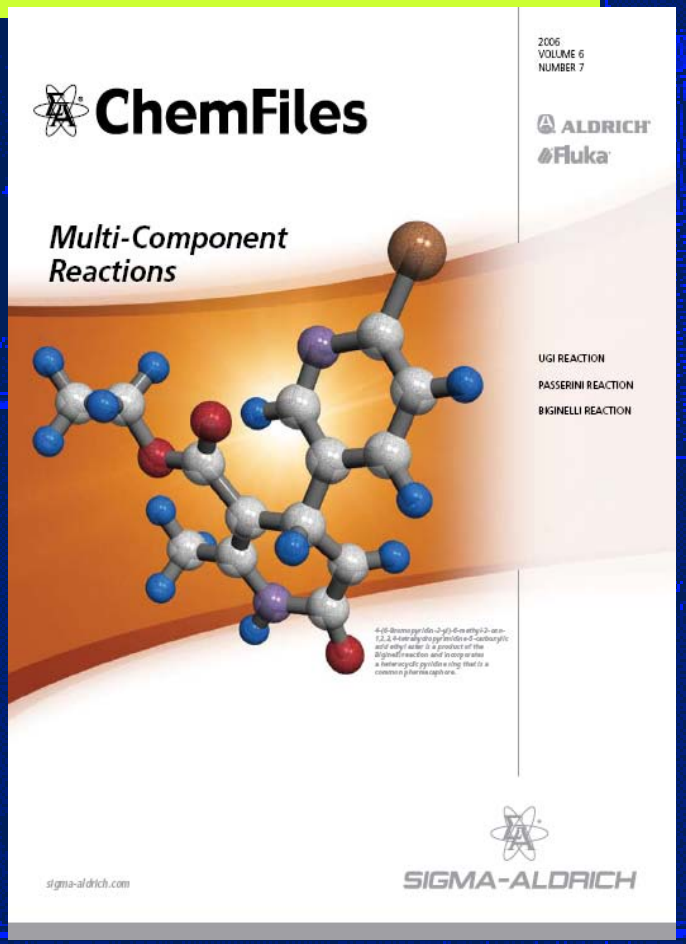


Monastrol

SIDA

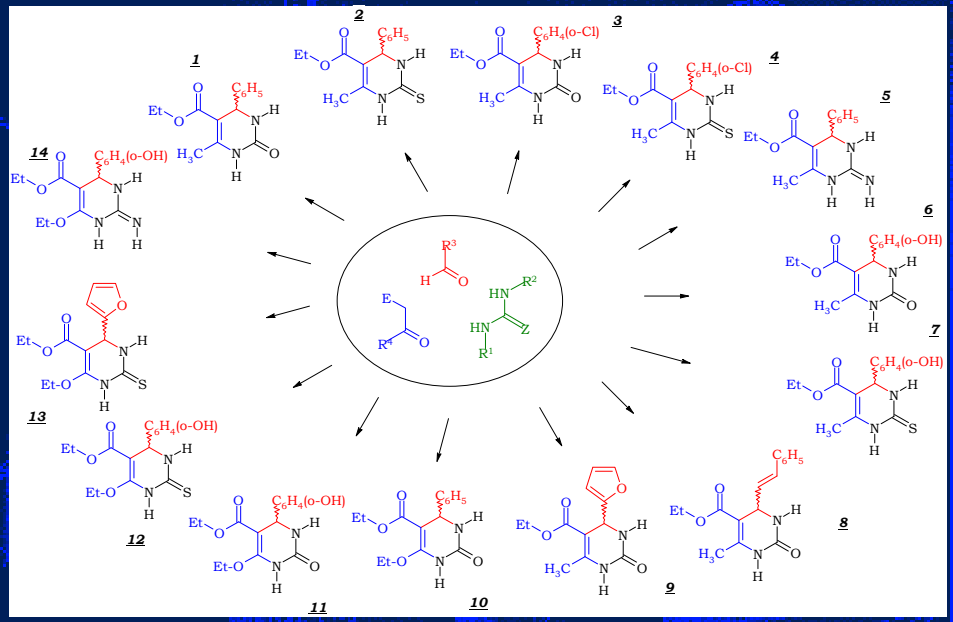


Batzelladine B



Mise en œuvre

- Aspect « chimie combinatoire »
- Activation micro-onde

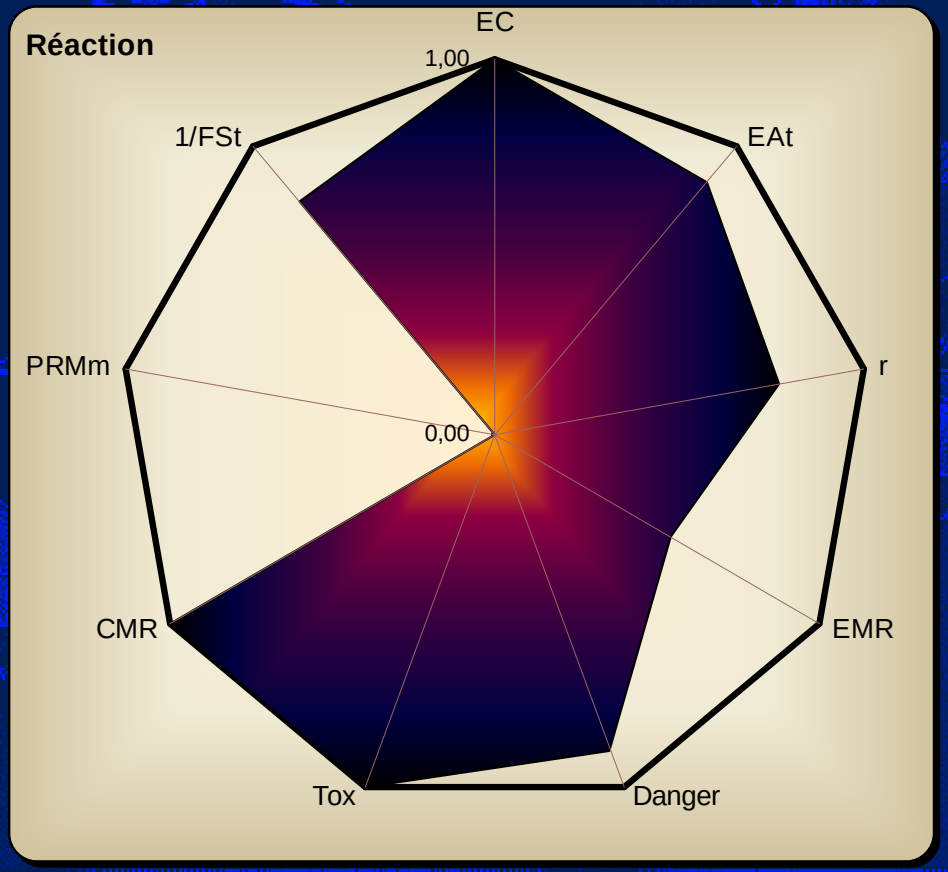


Mise en œuvre

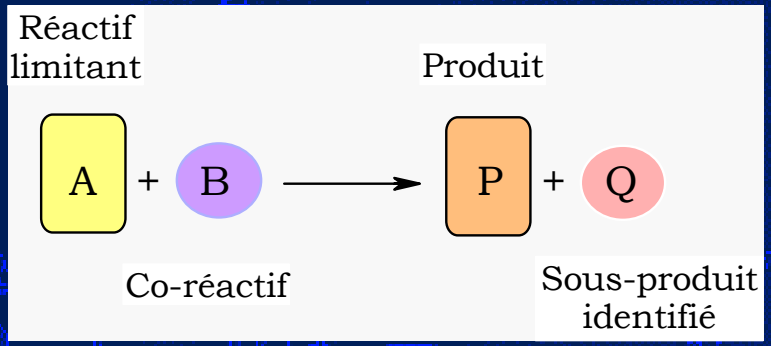
- Micro-chimie

Mise en œuvre

- Ouverture sur la chimie verte



Les paramètres



- ***Économie de carbone, E_C***

$$E_C = \frac{\upsilon_{produit} . n(C)_{produit}}{\sum_i |\upsilon_i| . (n(C)_{réactifs})_i}$$

- ***Économie d'atomes, E_{At}***

$$E_{At} = \frac{\upsilon_{produit} . M_{produit}}{\sum_i |\upsilon_i| . (M_{réactifs})_i}$$

- ***Le facteur environnemental, ou économie de matière, E_m***

$$E_m = \frac{\sum_i (m_{déchets})_i}{m_{produit}}$$

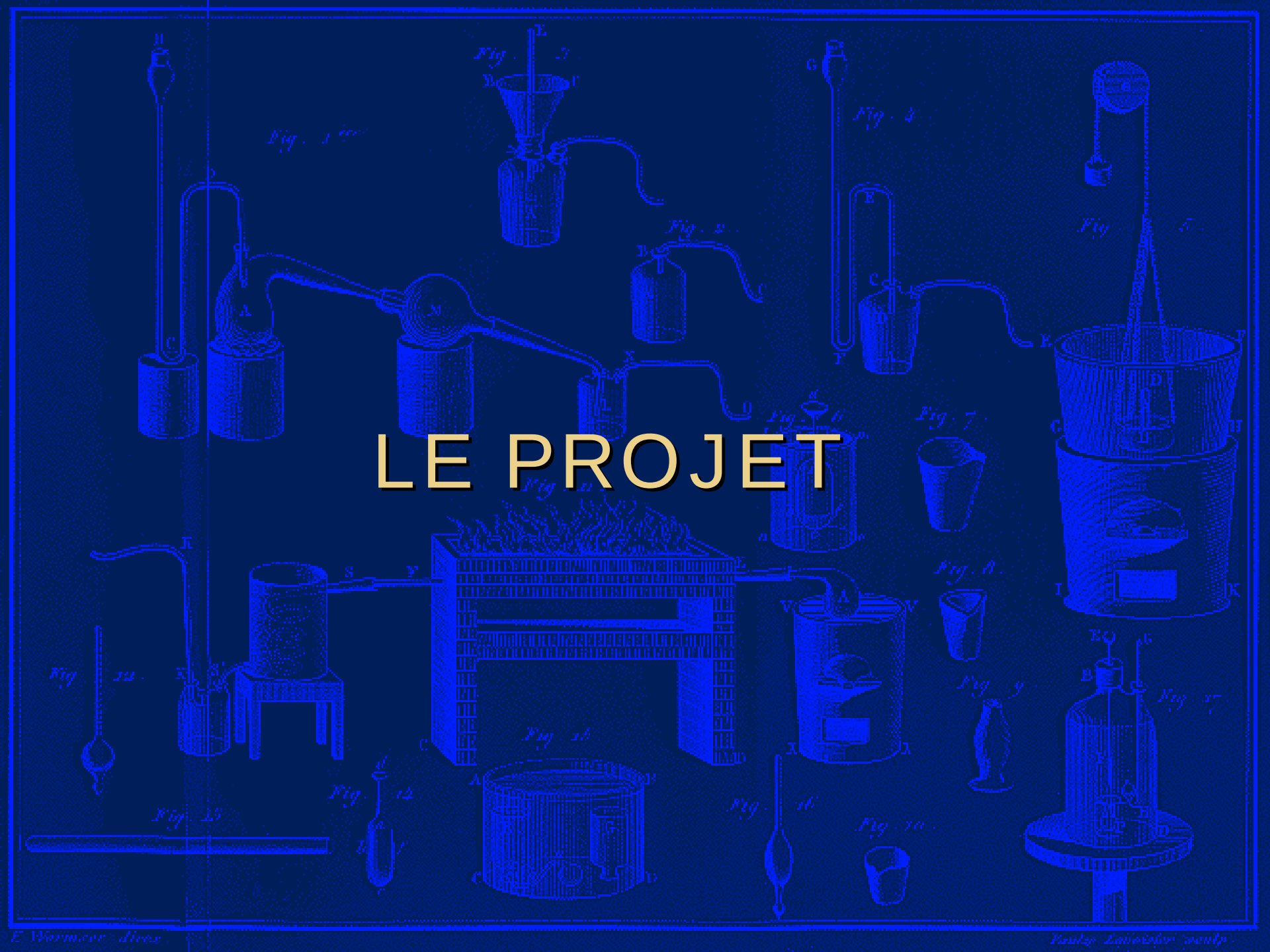
- ***Efficacité Massique de Réaction, EMR***

$$EMR = \frac{m_{produit}}{\sum_i \left(m_{réactifs}\right)_i}$$

- ***Paramètre de Récupération de Matière, PRM***

$$PRM = \frac{m(P)}{m(P) + \frac{\rho . E_{At}}{F_{St}} . \left[m(C) + \sum_i m(S)_i + \sum_i m(S_{PR})_i + \sum_i m(R_{PR})_i \right]}$$

- **J. Andraos**, On the Use of « Green » Metrics un the Undergraduate Organic Chemistry Lecture and Lab to Assess the Mass Efficiency of Organic Reactions, *J. Chem. Ed.*., **2007**, *84*, 1004-1010.
- **J. Andraos,** On Using Tree Analysis to Quantify the Material, Input Energy, and Cost Throughput Efficiencies of Simple and Complex Synthesis Plans and Networks: Towards a Blueprint for Quantitative Total Synthesis and Green Chemistry, *Org. Process Res. Dev.*, **2006**, *10*, p. 212-240.
- **J. Andraos**, Unification of Reaction Metrics for Green Chemistry: Applications to Reaction Analysis, *Org. Process Res. Dev*., **2005**, *9*, 149 -163.



LE PROJET

Le lieu, le public

- ENCPB, Paris
- Etudiants de BTS-Chimiste
- Etudiants de post-BTS de Synthèse Organique

Les différentes phases

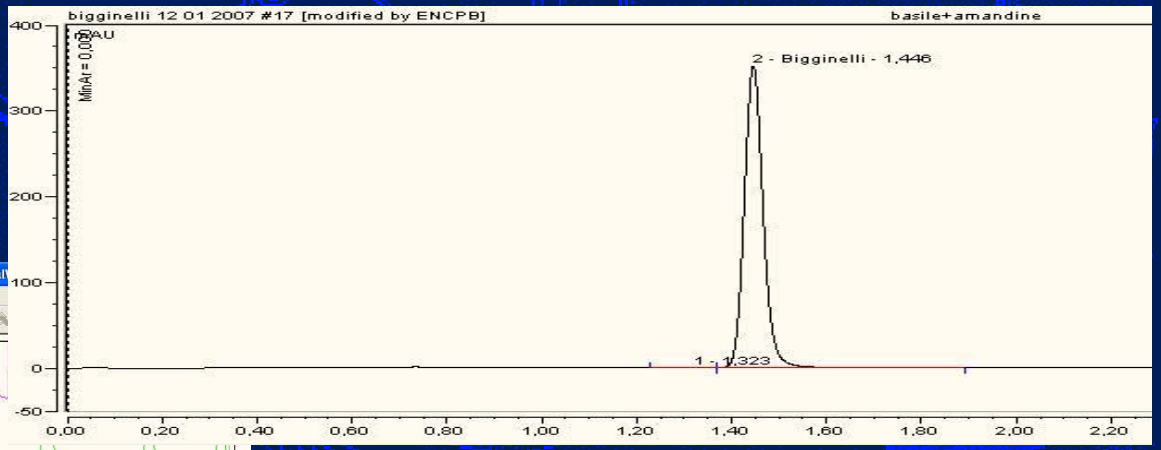
Phase 1

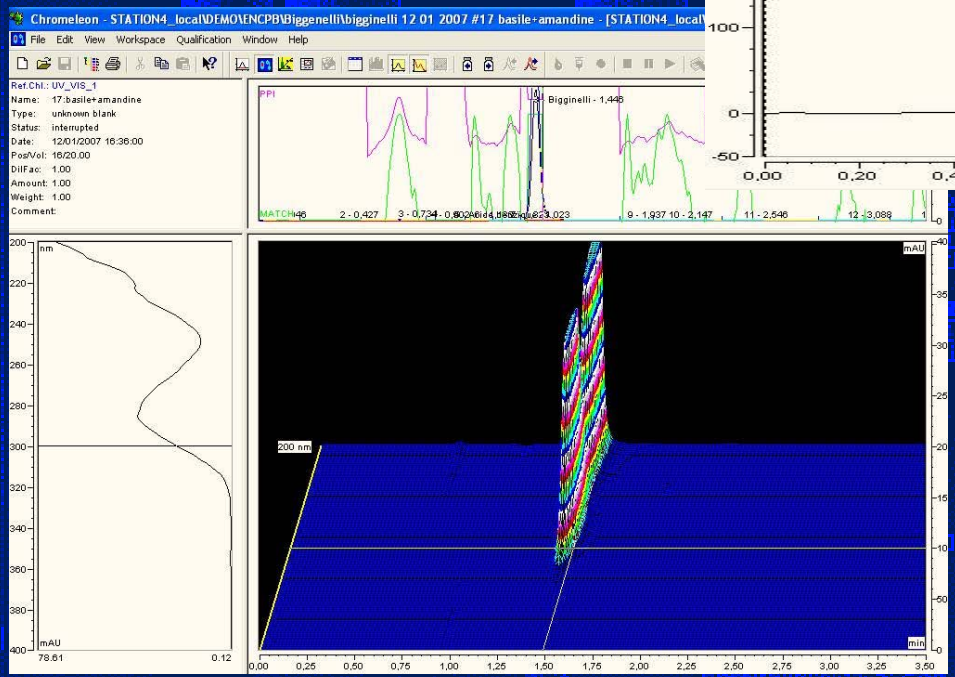
- Séance d'initiation aux techniques
  - Montage classique
  - Activation micro-onde
  - Microchimie

- Organisation de la séance
  - Etudiants en trinômes
  - Essais sur la réaction du JCE avec HCl comme catalyseur
  - Réalisée par deux demi groupes de 15 étudiants (2 x 4h) en 1ère année

Analyse

- Après recristallisation de tous les produits





Phase 2

- Deuxième séance
(un demi groupe de 12, 2ème année, 8h)
  - Sur la même réaction, essai de différents catalyseurs
  - Montage de type « microchimie »

Résultats

Essai n°	1	2	3
Catalyseur	$FeCl_3$ [43]	$ZnCl_2$	$SnCl_2$
Rendement	70%	34%	53%
Photo			
Essai n°	**4**	**5**	**6**
Catalyseur	CuCl	$CuCl_2$	$CoCl_2$
Rendement	50%	80%	20%
Photo			
Essai n°	**7**	**8**	**9**
Catalyseur	$NiCl_2$	$AlCl_3$	$MnCl_2$
Rendement	45%	90%	44%
Photo			

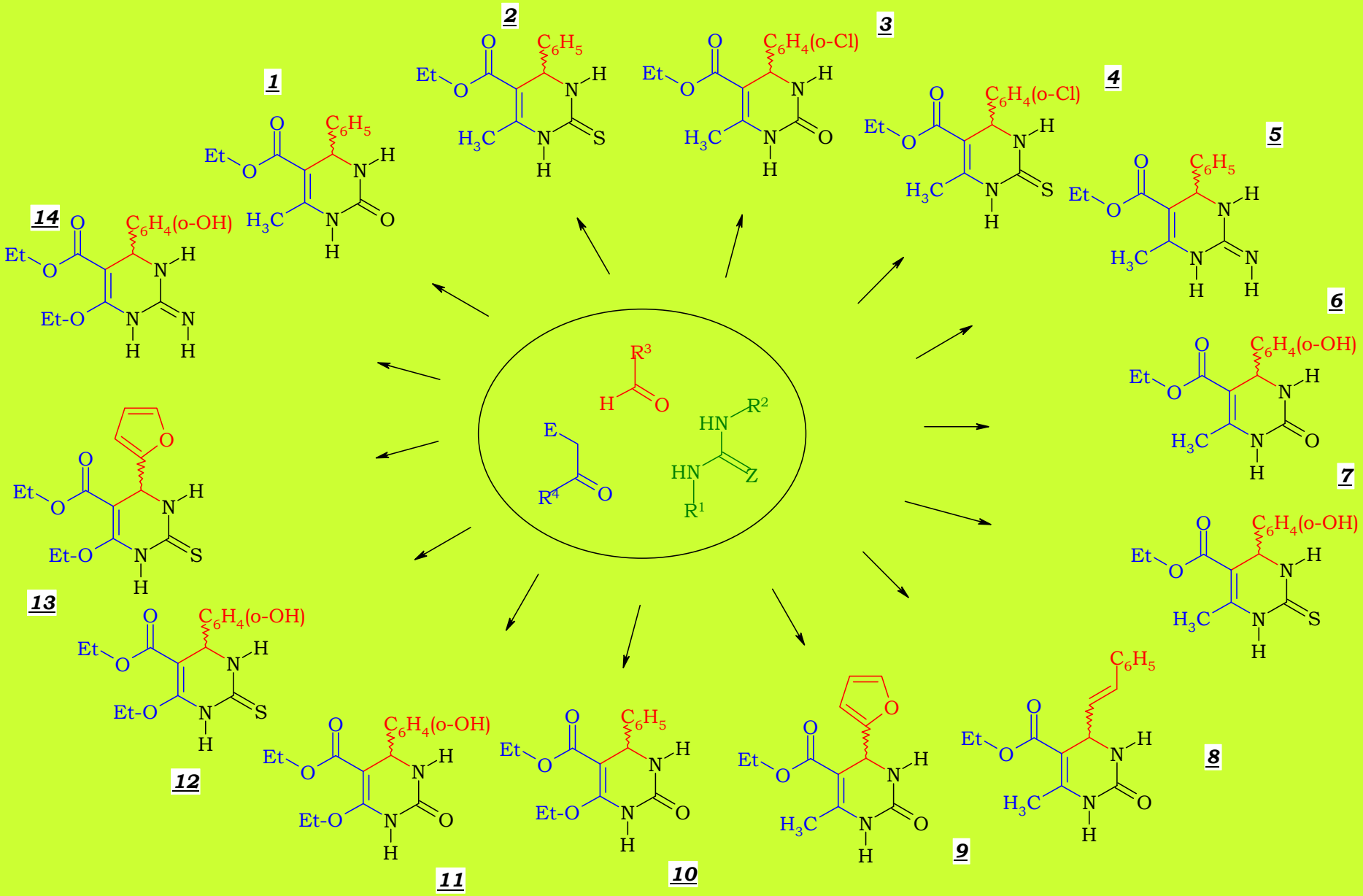
Choix des catalyseurs

- HCl, $FeCl_3$ et $AlCl_3$ donnent de bons rendements
- Utilisation de ces catalyseurs pour la partie chimie combinatoire

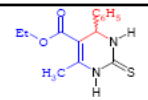
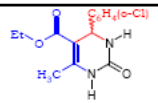
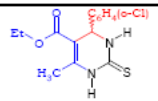
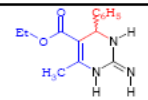
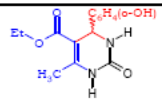
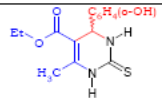
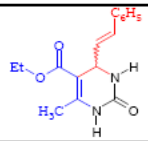
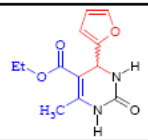
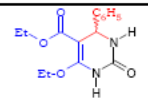
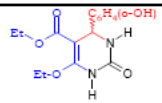
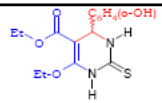
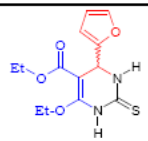
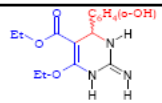
Troisième séance

- Séance de 8h avec deux groupes
  - 12 étudiants en 2ème année de BTS
  - 10 étudiants en post-BTS SO
- Chimie combinatoire
  - Toujours en microchimie avec les étudiants de BTS
  - Sous activation microondes avec les étudiants de SO
- Essais avec les trois catalyseurs pour chaque molécule

Chimie combinatoire



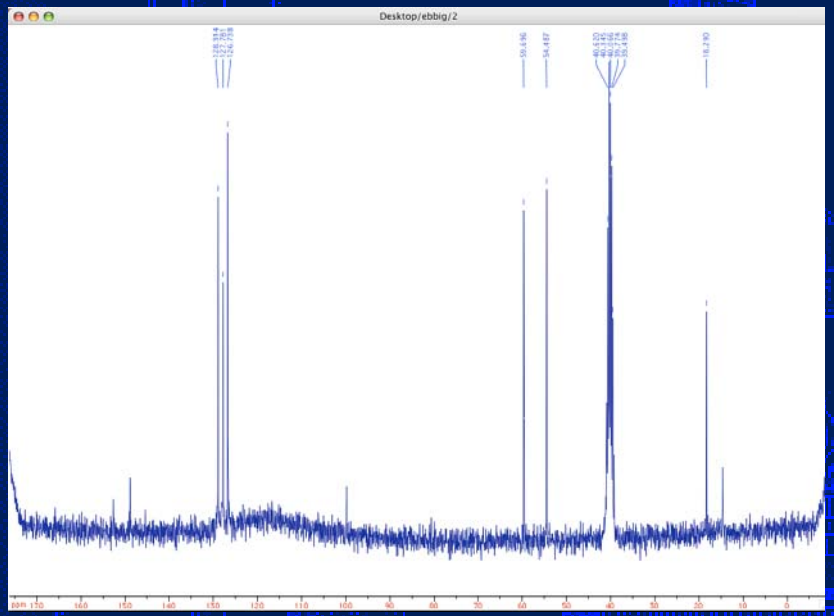
Bilan

Molécule	Molécule	Catalyseur	Produit obtenu	T_{fus} / °C	T_{fus} litt.[41,42]	ρ brut
2		$AlCl_3$	Cristaux blancs	201-204	202-203	85%
3		$AlCl_3$	Cristaux blancs	206	215-218	25%
		HCl	Cristaux blancs	212	215-218	30%
4		HCl	Cristaux violets	-		-
5		HCl, $AlCl_3$	-	-		-
6		HCl, $AlCl_3$	-	-	201-203	-
7		$FeCl_3$	Cristaux beiges	220-225		15%
8		$AlCl_3$	Cristaux blanc crème	235-246	230-232	12%
9		HCl, $AlCl_3$	-	-		-
10		$AlCl_3$	Cristaux blancs	254-320		-
		HCl	Cristaux blancs	242-245		-
11		HCl	Cristaux blancs	220		41%
12		$AlCl_3$	Cristaux blancs	265		26%
		$FeCl_3$	Cristaux blancs	255		11%
13		HCl, $AlCl_3$	-	-		-
14		HCl, $AlCl_3$	-	-		-

Résultats

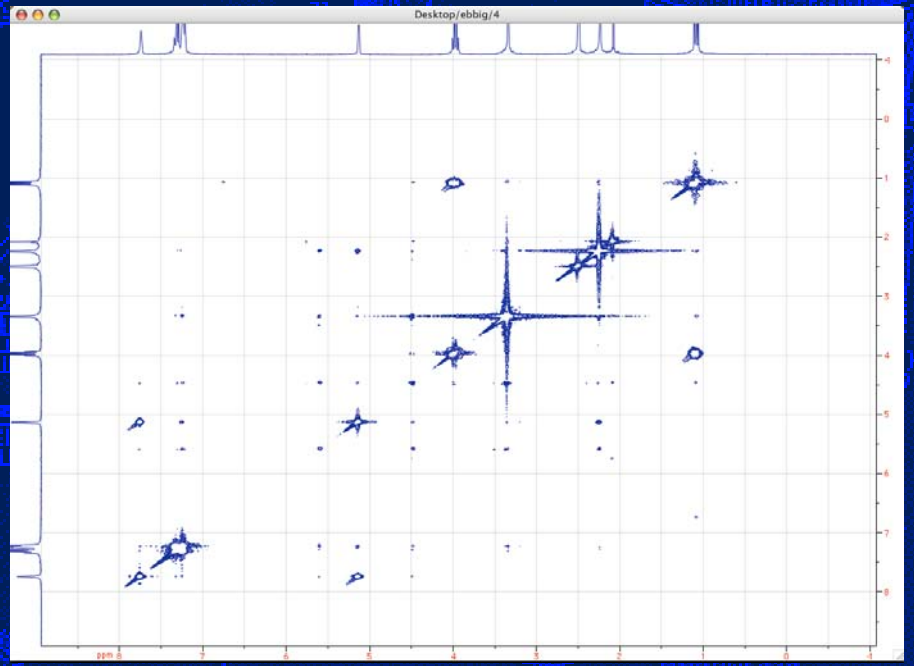
- Une dizaine de molécules obtenues
- Caractérisation difficile
  - Pas de références
  - T_{fus} élevées (si solides…)
- Analyses seulement sur la molécule « classique »
  - Problèmes de solubilité
  - Séparation en LC/MS délicate

Analyse spectrale

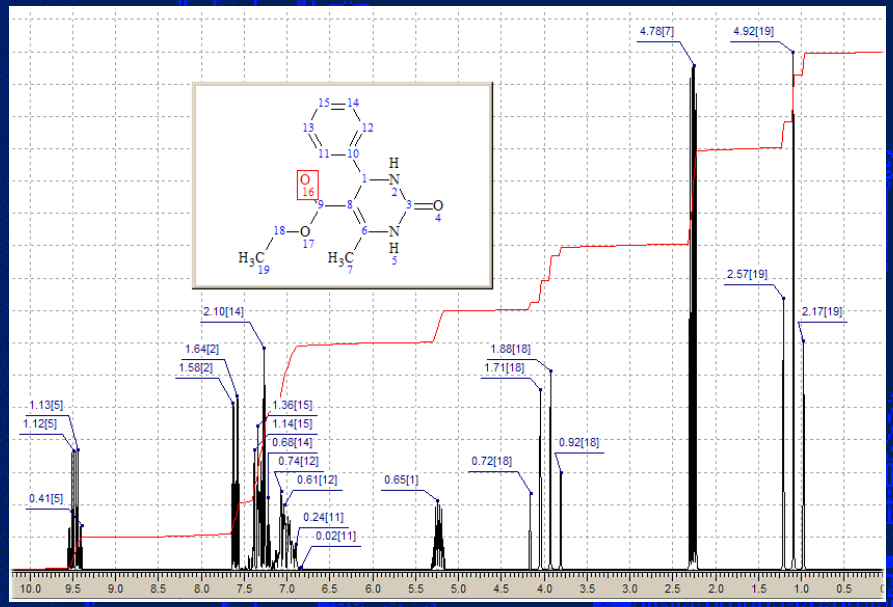


RMN ^{13}C

RMN 2D $^{1}H/^{1}H$

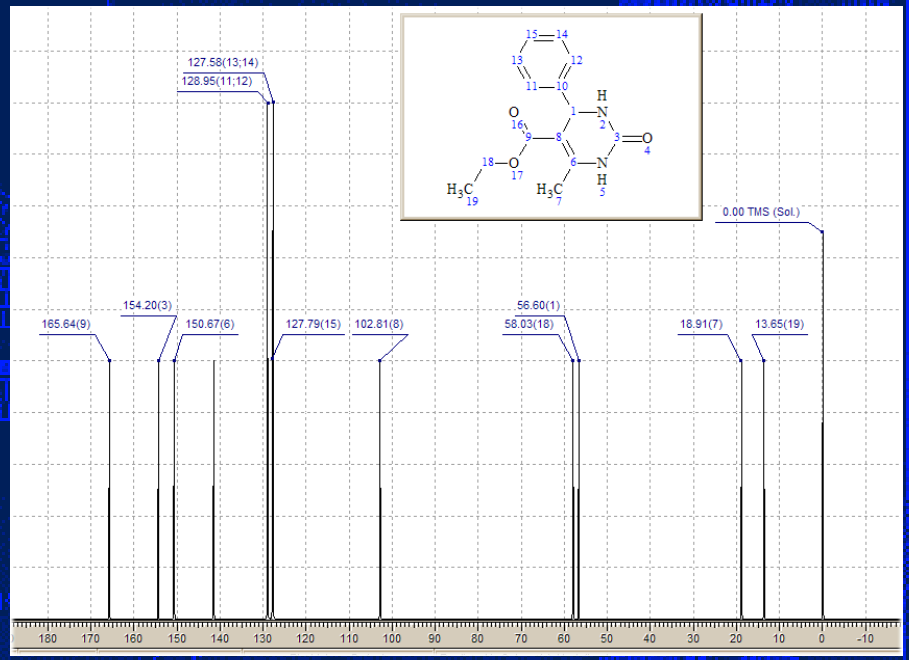


Simulation de spectres RMN



RMN ^{1}H

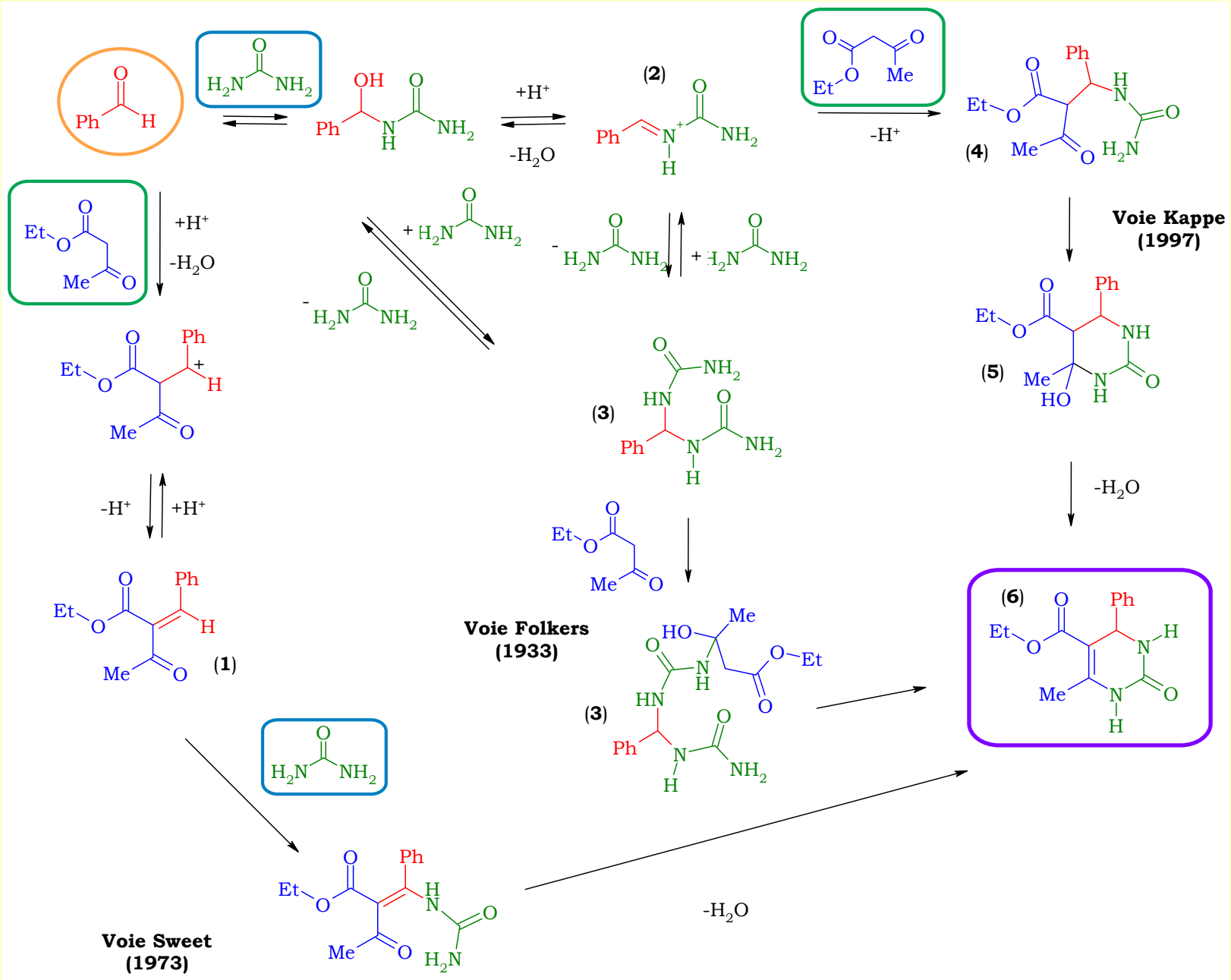
RMN ^{13}C



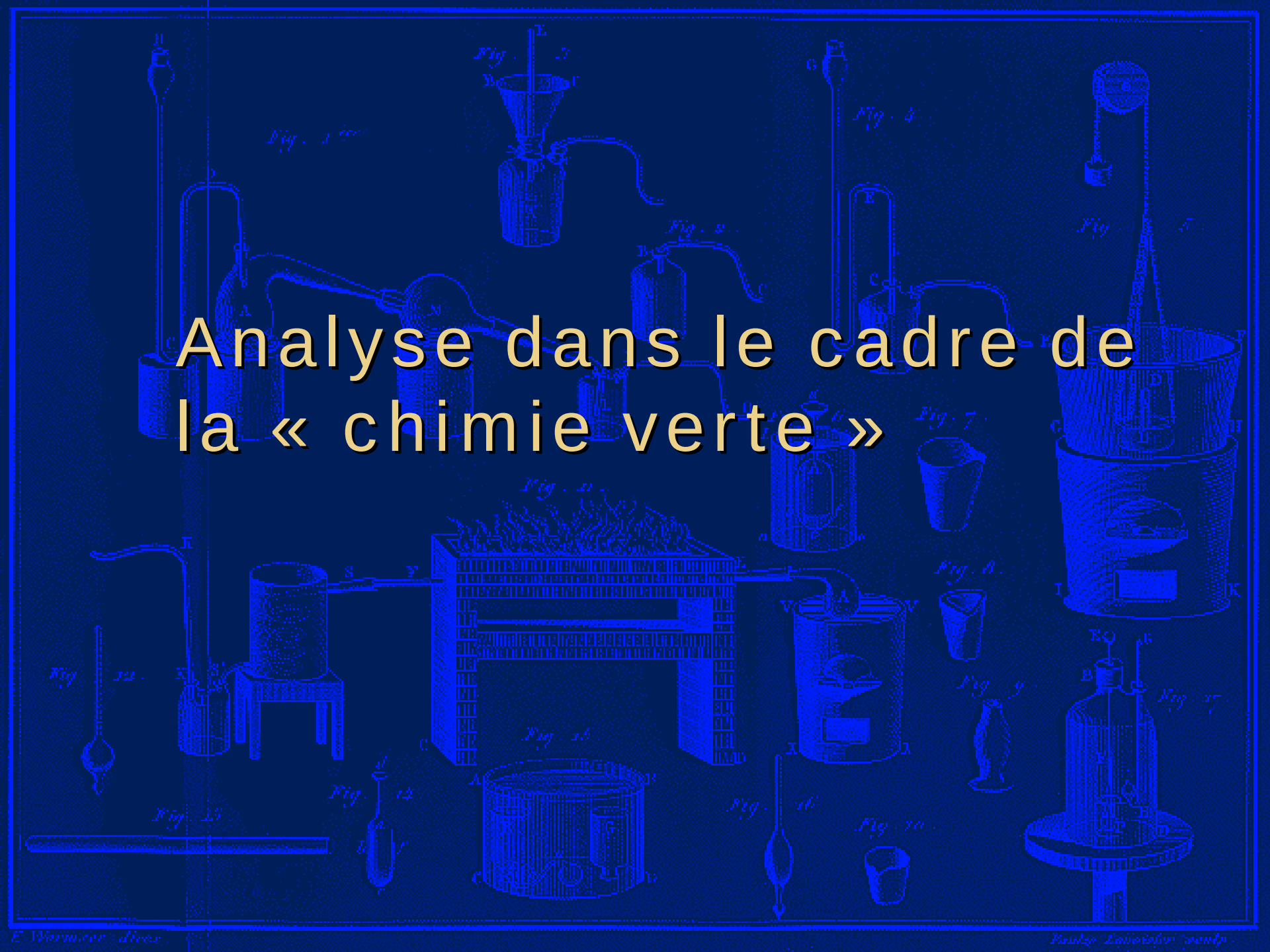
Travail demandé aux étudiants

- Tenue d'un cahier de laboratoire
- Calculs des rendements
- Conclusions sur :
  - les catalyseurs à choisir
  - la difficulté du travail de « recherche »
  - la difficulté des analyses
  - étude mécanistique

Mécanisme de la réaction de Biginelli



Analyse dans le cadre de la « chimie verte »



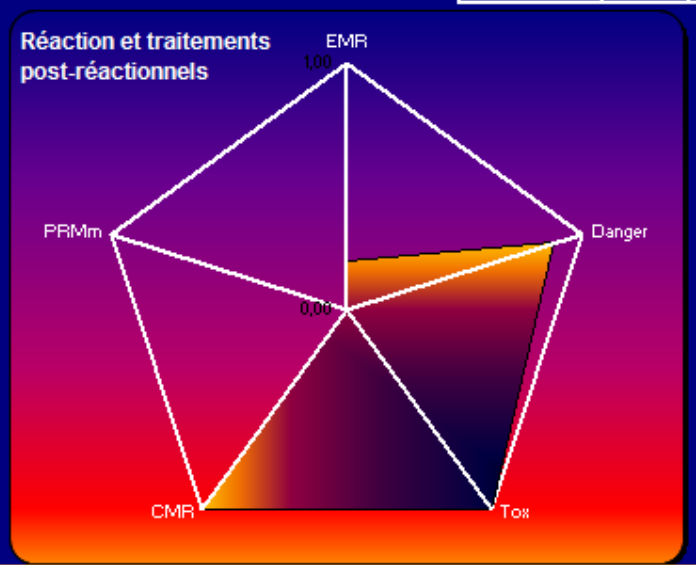
Réaction de Biginelli

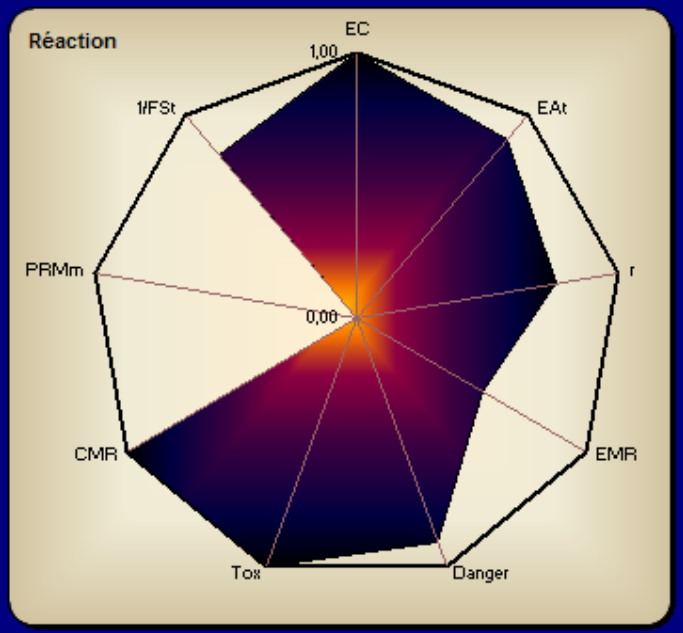
Matière première

Réaction

	Réaction seule	Complet
Masse des déchets		10,26
Facteur Environnemental Molaire		
Facteur Environnemental Massique		
Facteur Stoechiométrique		
$n_{réactif\ max}$ / $n_{réactif}$		
Economie de Carbone	E_C 1,00	
Economie d'Atomes	E_{At} 0,88	
Rendement	ρ 0,77	
Efficacité Massique de Réaction	EMR 0,55	0,20
Coef. Danger	Danger 0,90	0,88
Coef. Tox	Tox 1,00	1,00
Coef. CMR	CMR 1,00	1,00
PRM_m	PRM_m 0,00	0,00
Inverse du Facteur Stoechiométrique	$1/F_{St}$ 0,81	
$n_{réactif\ min}$ / $n_{réactif\ max}$	$1/F_{St,n}$ 0,66	
BILAN	76	62

chimie-verte_biginelli.xls





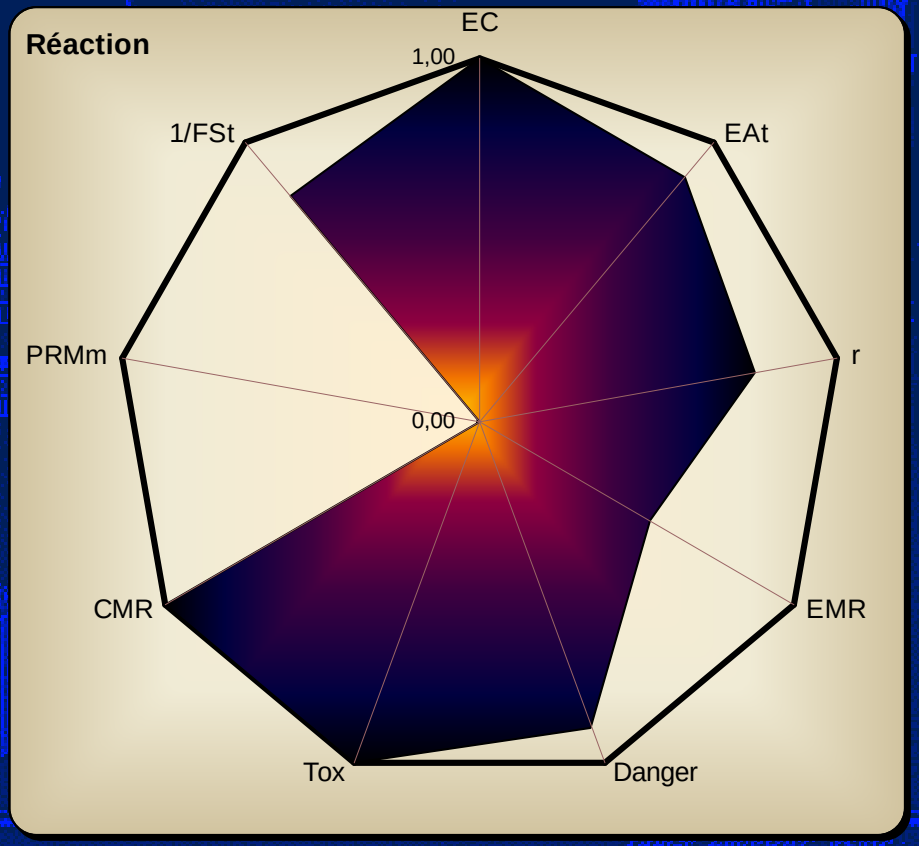
	Coef. Danger	Coef. Tox	Coef. CMR
	2,3	2,47	2,47
	0,7	0,75	0,75
	1,27	1,37	1,37
		0	0
	4,26	4,59	4,59

	Coef. Danger	Coef. Tox	Coef. CMR
	0,55	0,59	0,59
	0	0	0
	0,55	0,59	0,59

	Coef. Danger	Coef. Tox	Coef. CMR
	3,56	3,56	

Comment améliorer ce TP ?

- Assurer un recyclage
  - Des solvants ?
  - Envisager un travail sur support solide par activation micro-onde



Bilan très positif et enrichissant