

Thirty Years of Continued Cooperation with the AvH: What is the Outcome? From Classical Synthesis to Green Chemistry

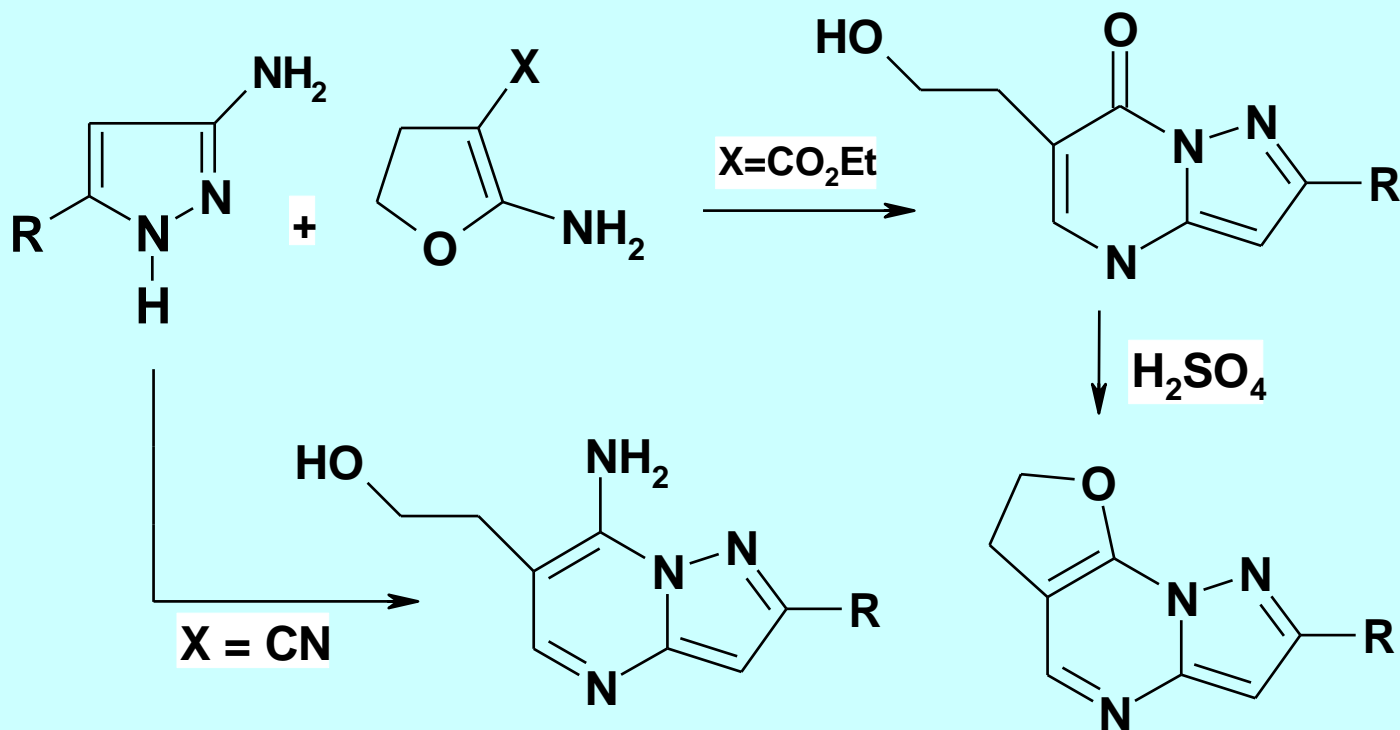
BY

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Introduction

It is now exactly thirty years since I got my first AvH fellowship with Prof. H. Wamoff of Bonn University. I did investigate during this fellowship the reactivity of heterocyclic enaminoesters and enaminnitriles with aminopyrazoles. The results of this work are summarised below.

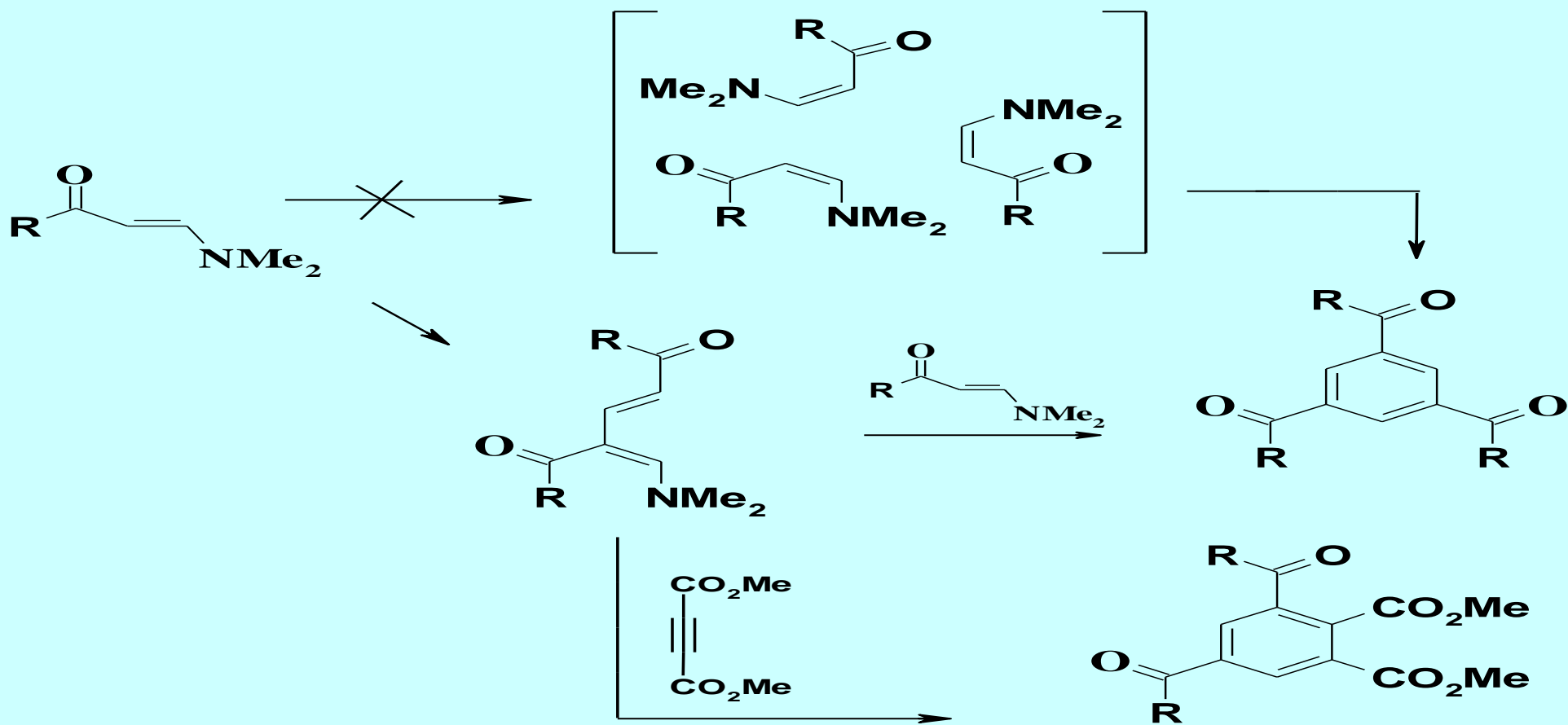


M. H. Elnagdi and H. Womhoff, (1981) J. Heterocyclic. Chem., 18, 1287-1292.

By the end of my stay I spent two months visiting Kaiser's Lawtern with M. Regitz during this fellowship I could learn interpretation of ^{13}C NMR spectroscopy of complex organic compounds .

I got the AvH support several times in my carrier latest time was in Halle with E. Fanghanel (2001) where we could solve via inspection of analytical data a mystery of the chemistry of enaminones. We noted that heating these in AcOH produces product of condensation of three molecules of the enaminones with elimination of three molecules of Me_2N , we came to conclude formation of triaroylbenzen (see below).

When reaction was conducted in presence of dimethyl acetylenedicarboxylate other product was obtained indicating the acetylene was incorporated proving that the reaction is not 2+2+2 cycloaddition but instep condensations



Abdel-Khalik, Mervat Mohammed; Elnagdi, Mohamed Hilmy. Synthetic Communications (2002), 32(2), 159-164.

Shortly after return from Halle I started my Green Chemistry Programme with participation of Egyptian, Kuwaiti, Saudi and German scientists.

Green Chemistry

Introduction

The economic prosperity of the world demands that we continue to have a robust chemical industry. In this age of environmental consciousness, however, we can no longer afford to allow the type of industry that has been characteristic of past practices to continue operating it as it has always been. There is a real need to develop an environmentally benign or "green" technology. Chemists must not only create new products but also design the chemical syntheses in such a way that their environmental ramifications are considered carefully.

Beginning with the first earth day in 1970, scientists and general public began to understand that the earth is a closed system in which consumption of resources and indiscriminate disposal of waste material are certain to bring about profound long lasting effects on the world wide environment. Over the past decade, interest has begun to grow in an initiative known as “green chemistry”.

Green Chemistry may be defined as the invention, design and application of chemical products and processes to reduce or eliminate the use and generation of hazardous substances. Practitioners of green chemistry strive to protect the environment, both by cleaning up toxic waste sites and by inventing new chemical methods that do not pollute or minimize the consumption of energy and natural resources.

Guidelines of green chemistry technologies are summarized in the twelve principles of green chemistry as taken from:

P. T. Anastas, J.C. Warner, "Green Chemistry: Theory and practical, New York, Oxford University Press, 1998".

- **It is better to prevent waste than to treat or clean it up after it is formed.**
- **Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.**
- **Wherever possible, synthetic methodologies should be designed to use and generate substances that possess little or not toxicity to human health and environment.**
- **Chemical products should be designed to preserve the function efficiently while reducing waste.**

- **The use of auxiliary substances (solvent, separation agents, etc...) should be avoided whenever possible and innocuous substances should be used.**
- **Energy requirements should be recognized for their environmental and economic impact and should be minimized. Synthetic methods should be conducted at ambient temperatures and pressure.**
- **A raw material or feedstock should be renewable rather than depleting technically and economically whenever it is practicable.**
- **Unnecessary privatization (blocking groups, protection, deportation, temporary modification of physical/ chemical process) should be avoided whenever possible.**

- **Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.**
- **Chemical products should be designed so that at the end of their function, they do not persist in the environment and break down into innocuous degradation products.**
- **Analytical methodologies need to be further developed to allow for real-time, to monitor and control prior to the formation of hazardous materials.**
- **Substances and the form of a substance used in chemical process should be chosen to minimize the chemical accidents including, releases, explosions and fire. These principles can be explained in Fig. 1.**

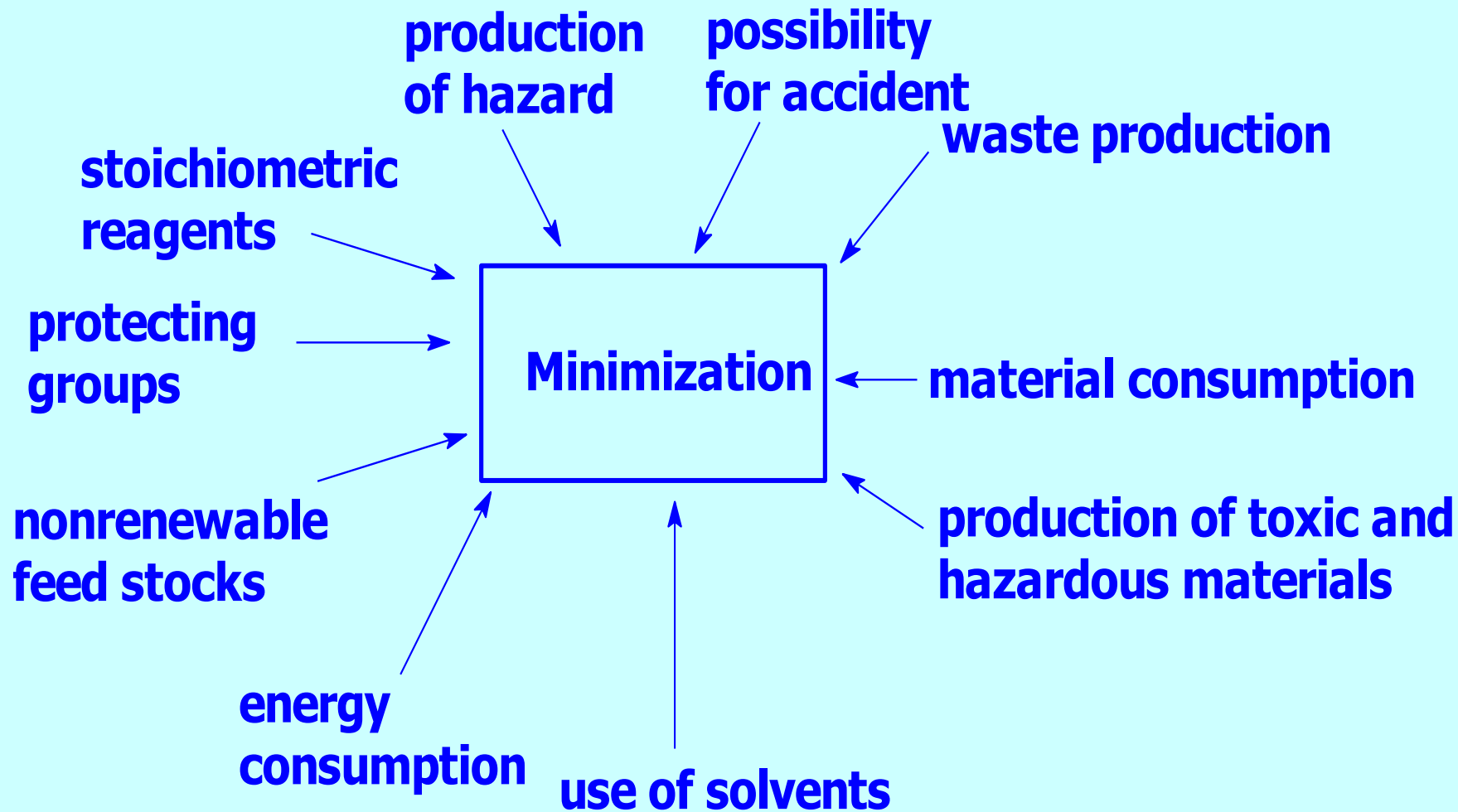
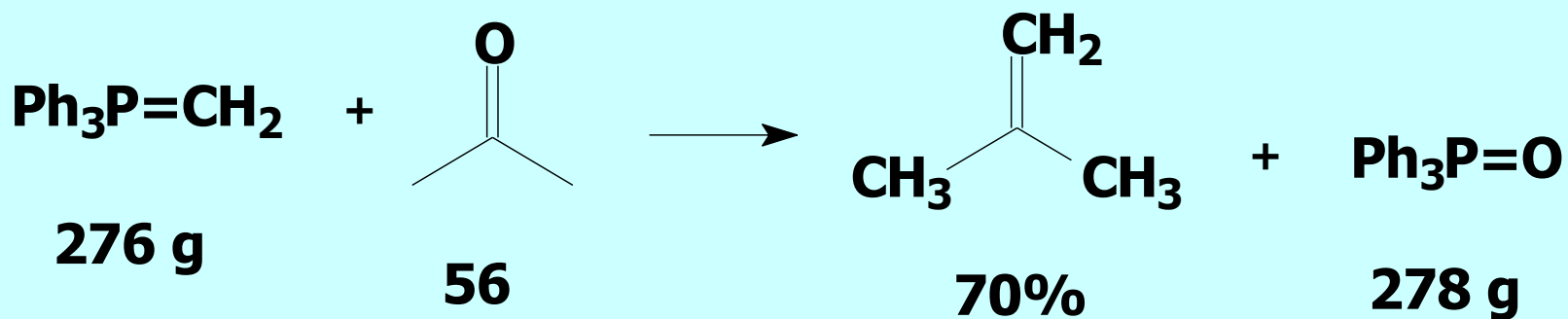


Figure 1

In the light of this new Directions chemists started looking around them in the following directions:

A) For minimizing waste production, chemists developed the term atom economy. For example, consider the following Wittig reaction:



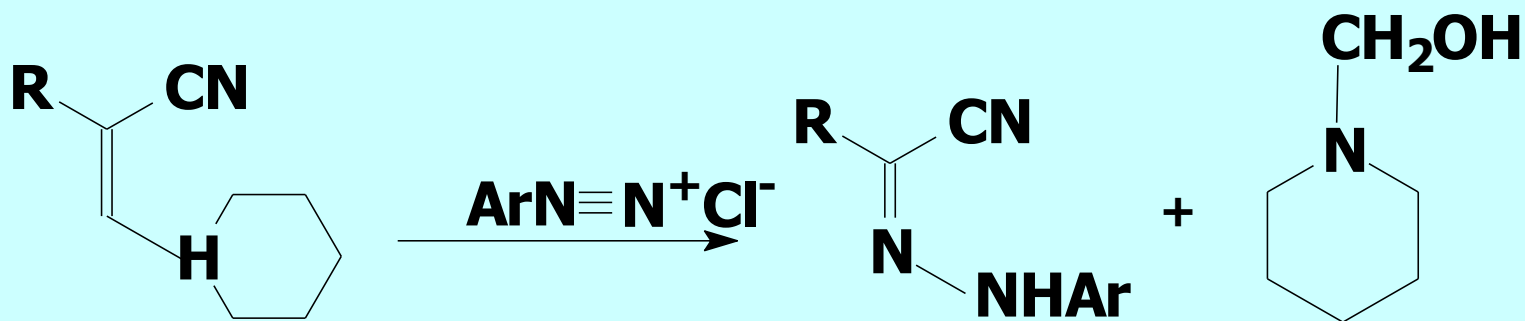
Atom economy:

$$\frac{\text{Weight of useful product}}{\text{Weight of}} = \frac{39.2}{332}$$

This reaction produces more waste than the product.

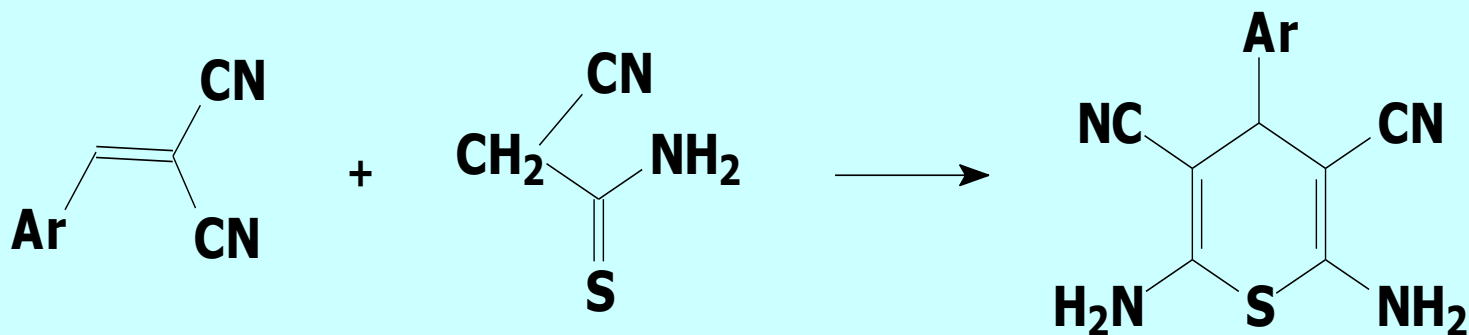
Atom non-economical reactions:

- 1) Wittig's reaction.
- 2) Friedel craft acylations.
- 3) Condensation reactions in which large molecules are eliminated. For example, the Japp Klingmann reaction reported recently by us.

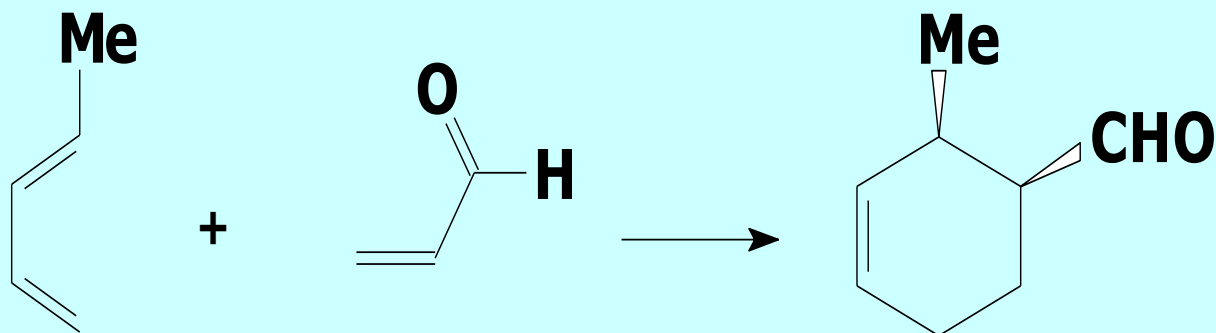


Atom economic process:

1) Addition reactions. E.g.



2) Precyclic reactions. E.g.

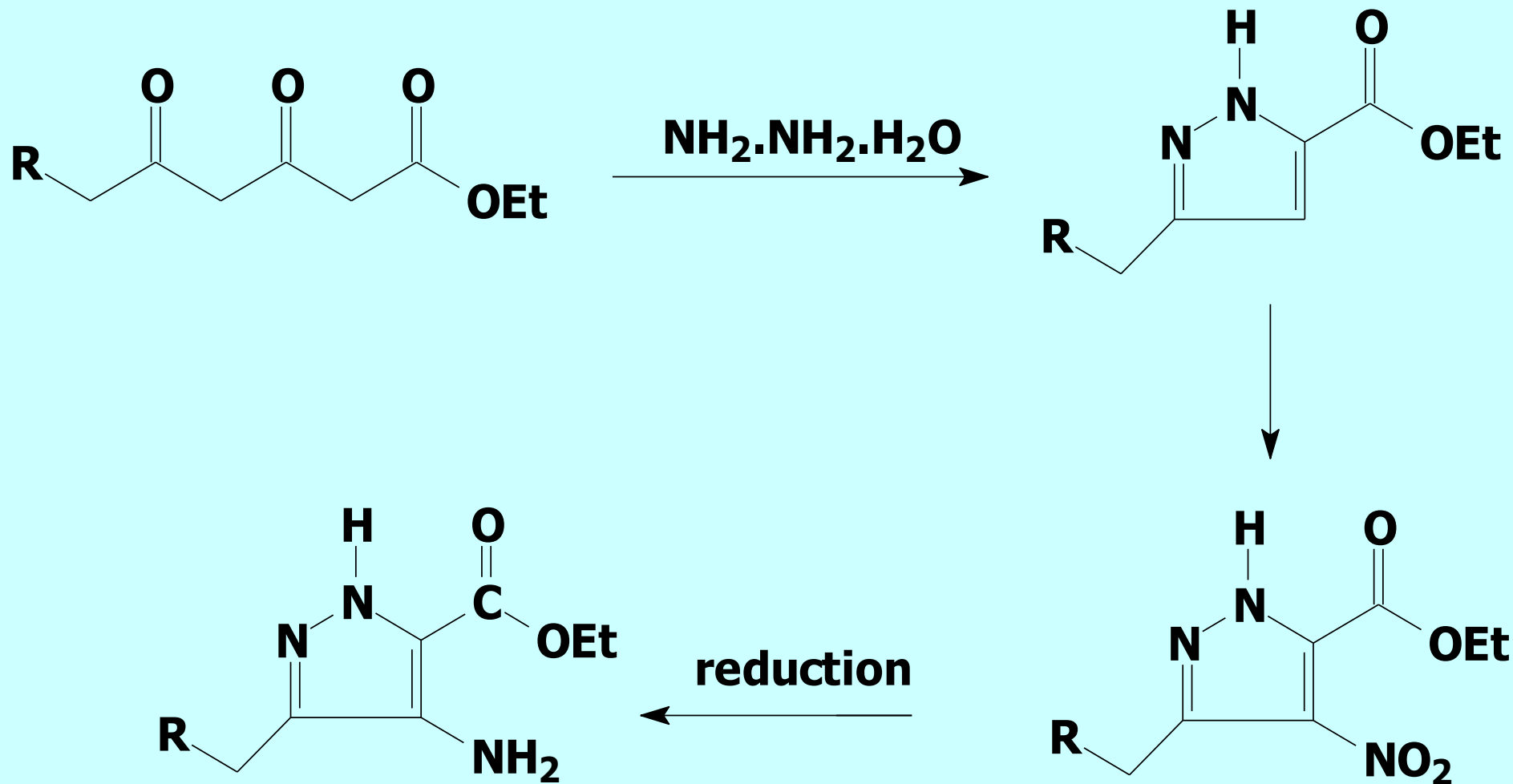


Thus there is now effort directed to develop useful addition and precyclic reactions especially in the absence of solvent and utilizing ecologically friendly catalysts.

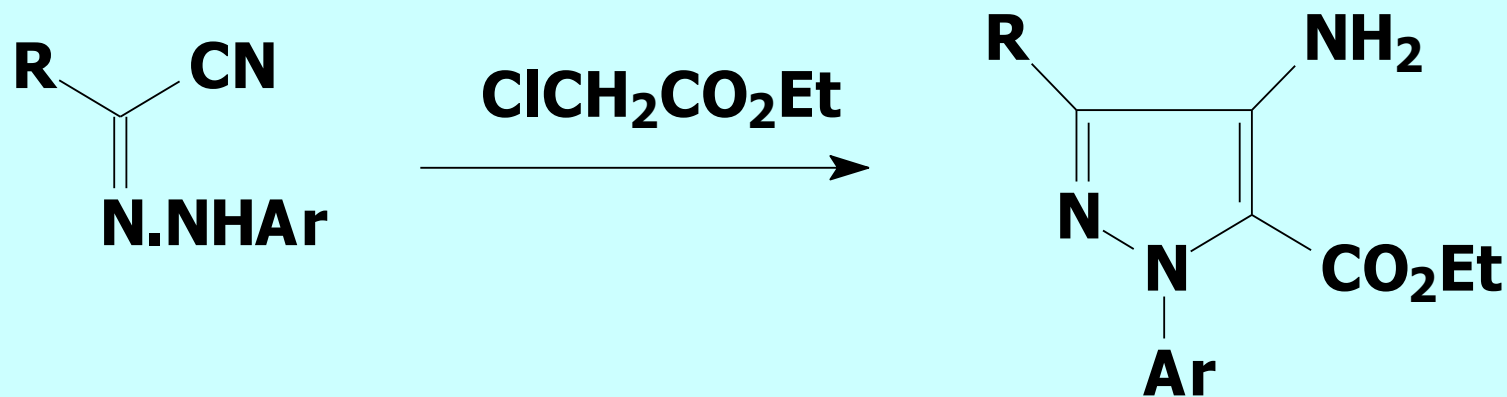
B) Get rid of toxic and hazardous reagents

- There is now effort to replace phosgene, HCN, H₂SO₄/HNO₃ in plenty of industrial processes.
- An example from our recent work is trials to the synthesis of pyrazol-4-amine-5-carboxylic acid derivatives used as precursors for the synthesis of pharmaceuticals, e.g. Viagra and allopurinol *via* a new route avoiding nitration step.

Industrial synthesis used now.



A new methodology developed in Kuwait (S. Makhseed and M. H. Elnagdi).

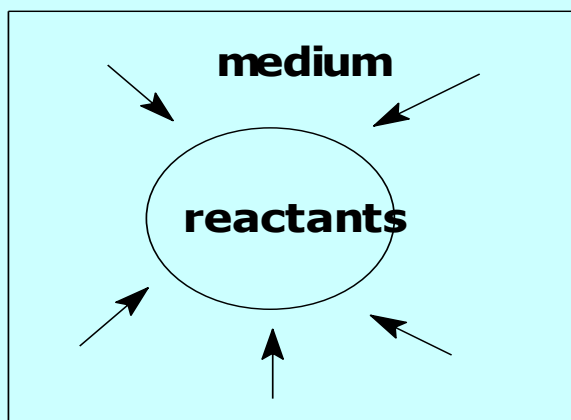


Al-Mousawi, Saleh M.; Moustafa, Moustafa Sherief; Elnagdi, Mohamed Hilmy. *Heterocycles* (2008),

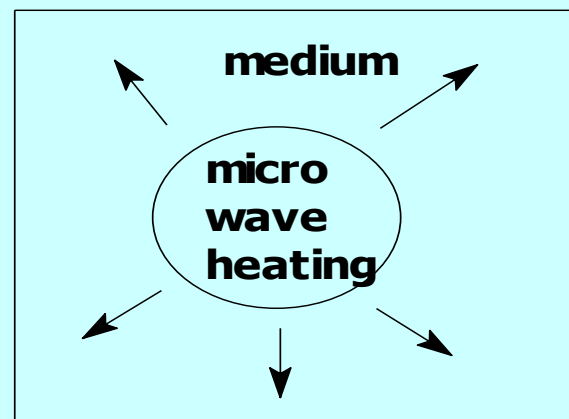
Use of alternate energy sources

- There is tremendous interest now for using:
 - a) Electrical energy
 - b) Sunlight
 - c) Microwaves
 - d) Ultrasound
- In 2002 I started with Dr. Balkis Al-Saleh in Kuwait and with Dr. M. Abdel Khalek in Cairo, trials to utilize microwaves as energy source. Although, every one suspected our failure, I think we not only succeeded but also could attract plenty of colleagues to try this technique.

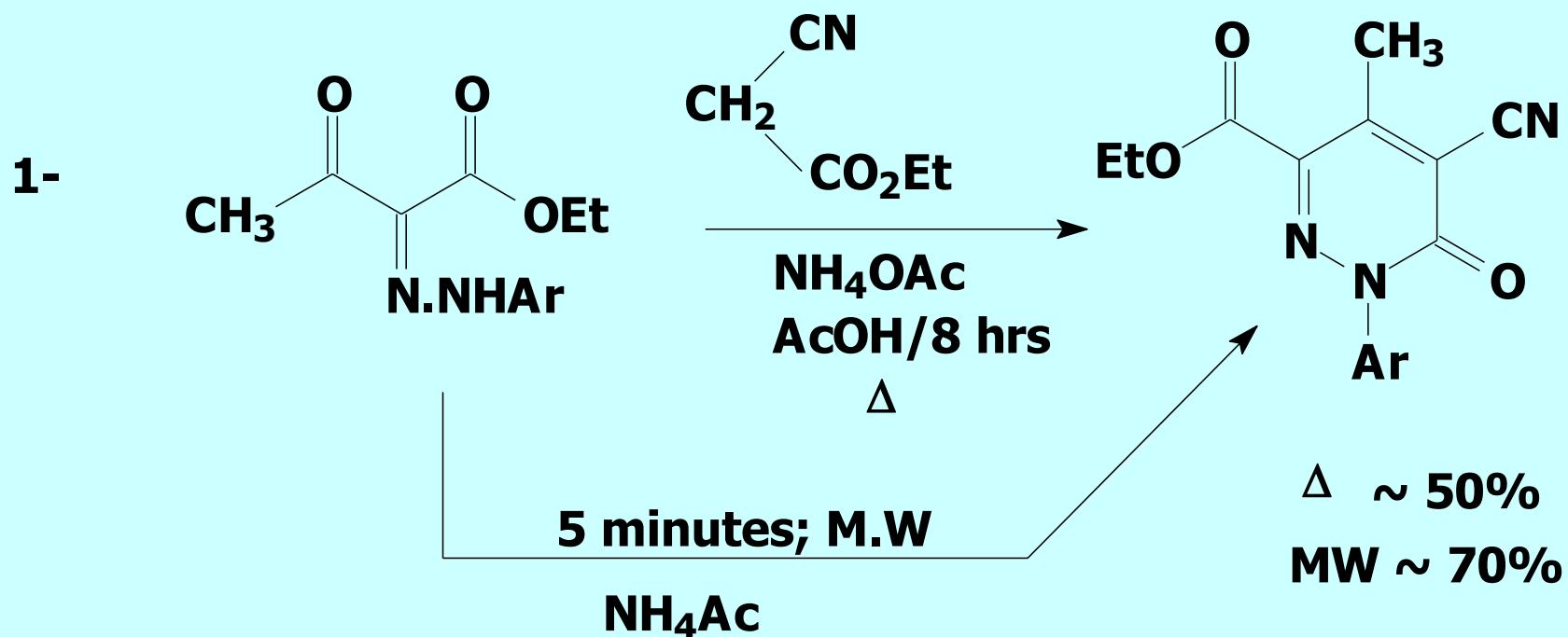
- I think I need not repeat this since everyone is aware of the fact that polar molecules absorb microwaves and convert it into heat energy which would enable in attaining energy of transition
- states for reactions by directly absorbing energy. Hot spots are formed and their energy is then dissipated in the medium.



**conventional
heating**

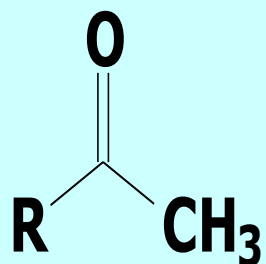


We started looking into our old chemistry to see how well it could proceed in microwaves. Here are some examples:

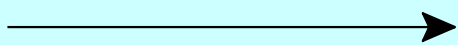


**Balkis AL-Saleh, Noha M. Helmy, Morsy Ahmed EL-Asery and Mohamed Hilmy Elnagdi,
J. Heterocycl. Chem, 43, 1575, 2006.**

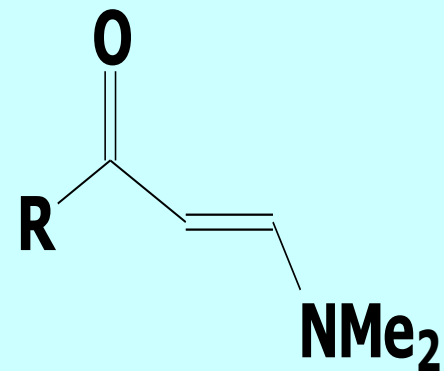
2-



Δ /5 hrs; no
solution



DMF DMA



Δ ~ 50%

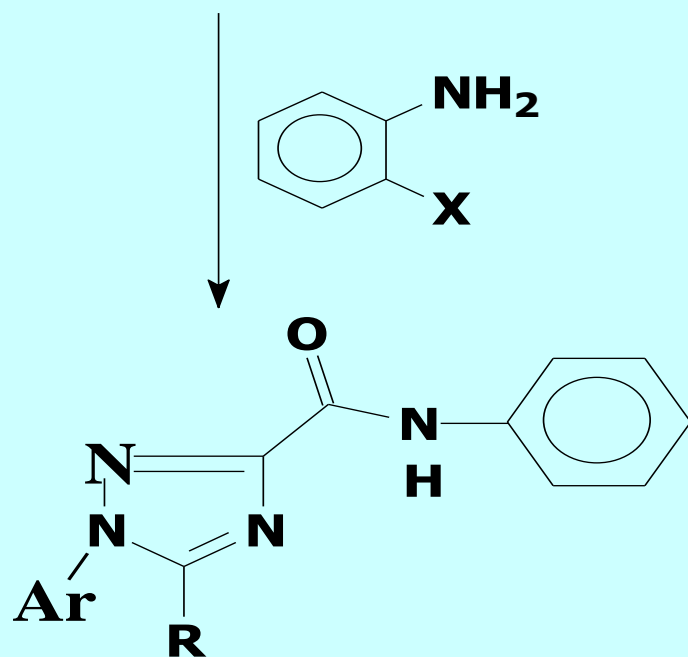
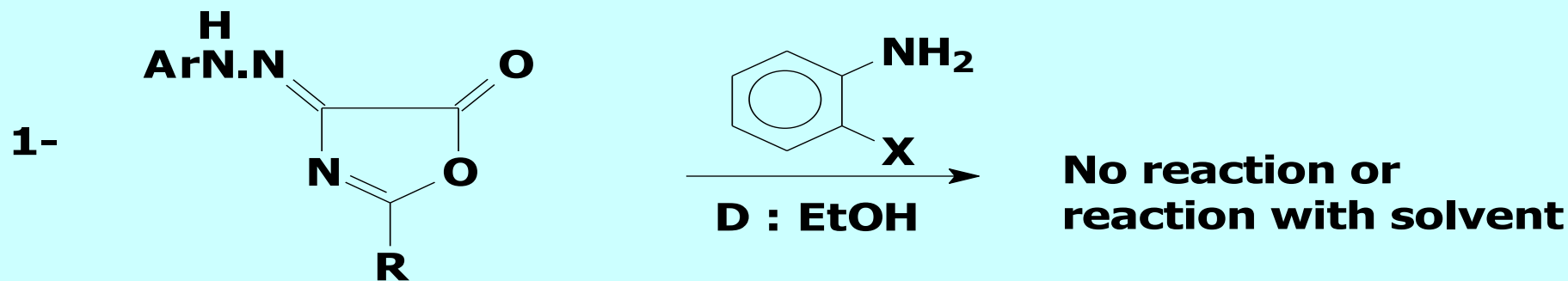
MW ~ 65%

5 minutes; M.W

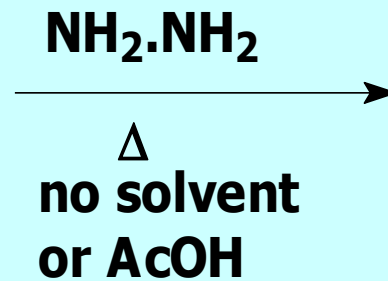
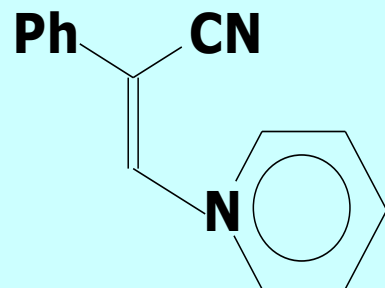
no solvent

M. H. Elnagdi et al.

Then, we started to look into new chemistry. We found that some reactions that do not proceed thermally can proceed very nicely by microwaves in reasonable time and yields.

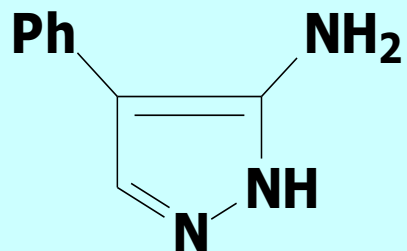


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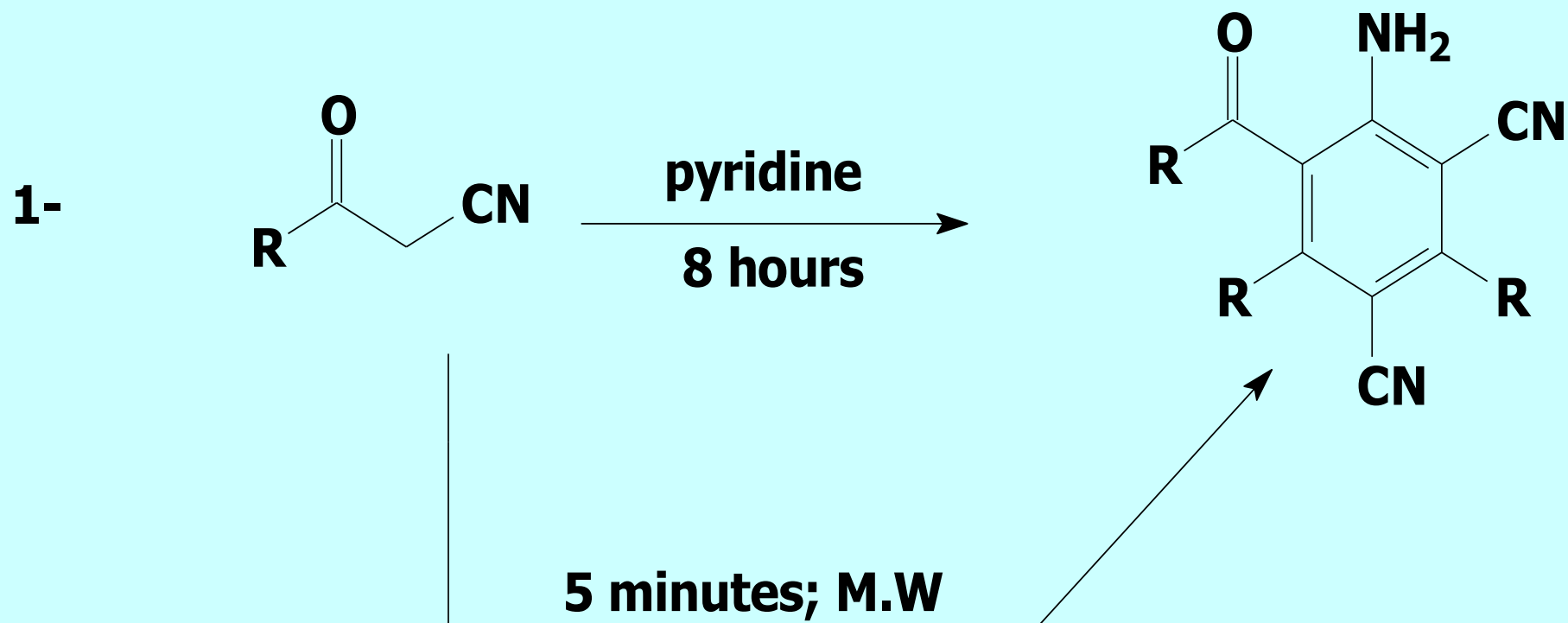


No reaction

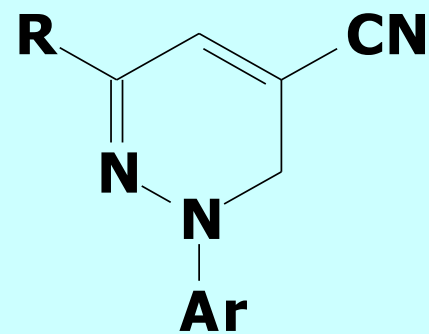
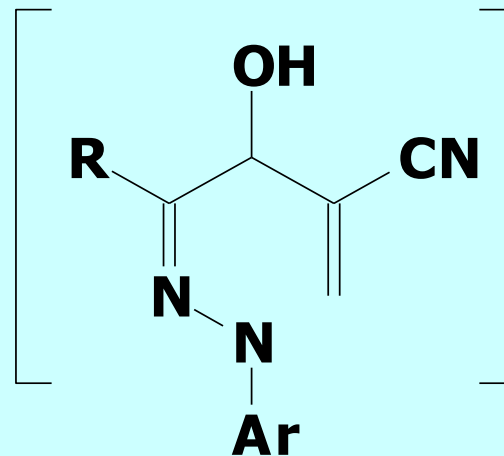
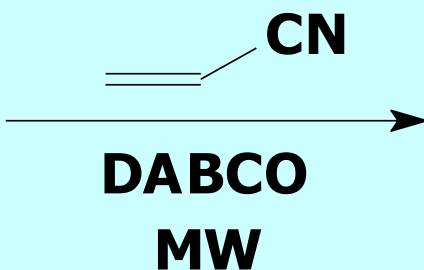
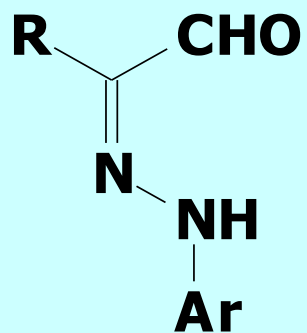
$\text{NH}_2\cdot\text{NH}_2\cdot\text{H}_2\text{O}$
MW 2.0 minutes
AcOH drops



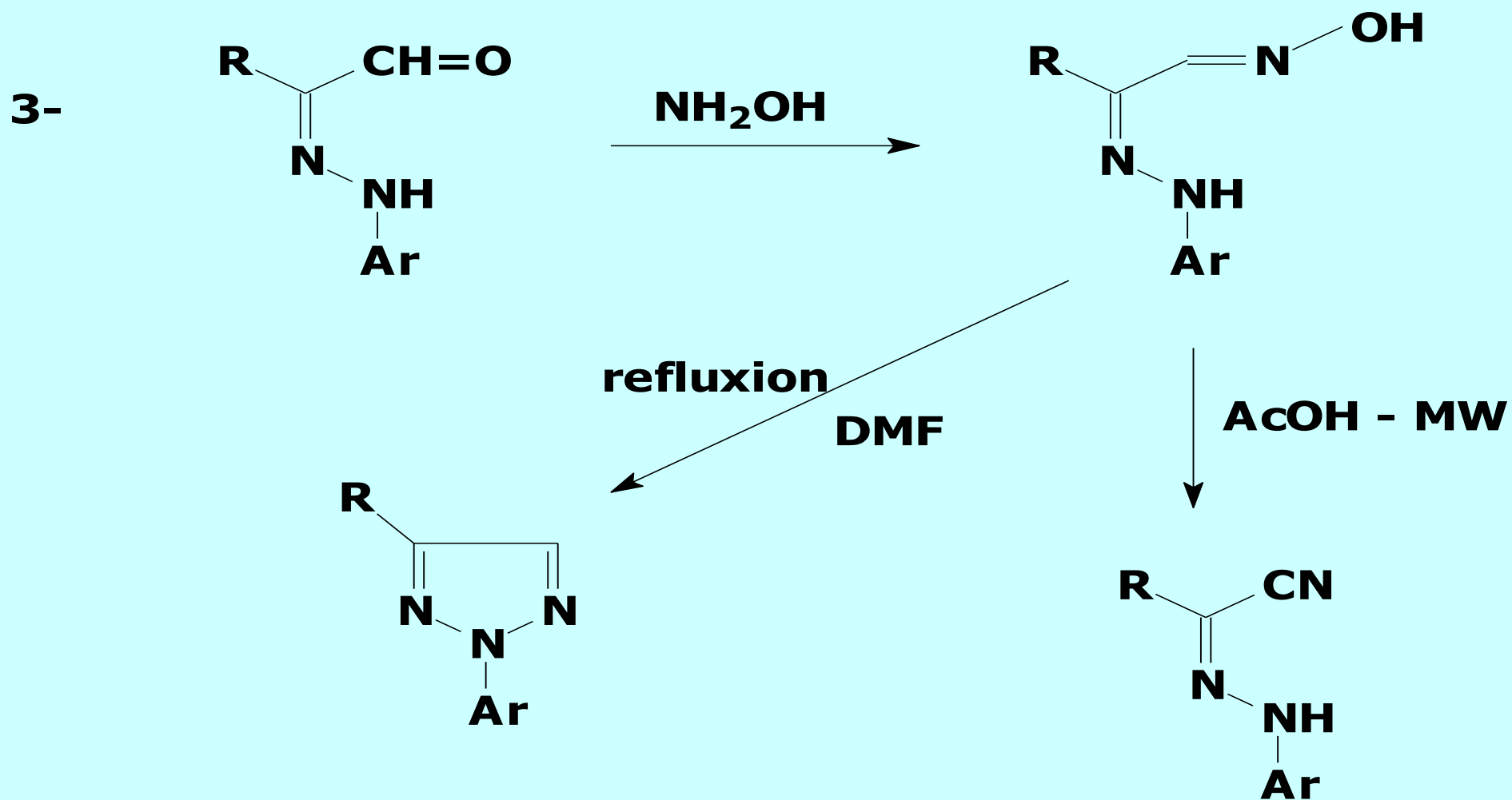
We are now cooperating with Prof. Al-Awadi in utilizing microwaves as energy source for pyrolytic reactions. In the last few months, lot of progress has been achieved.



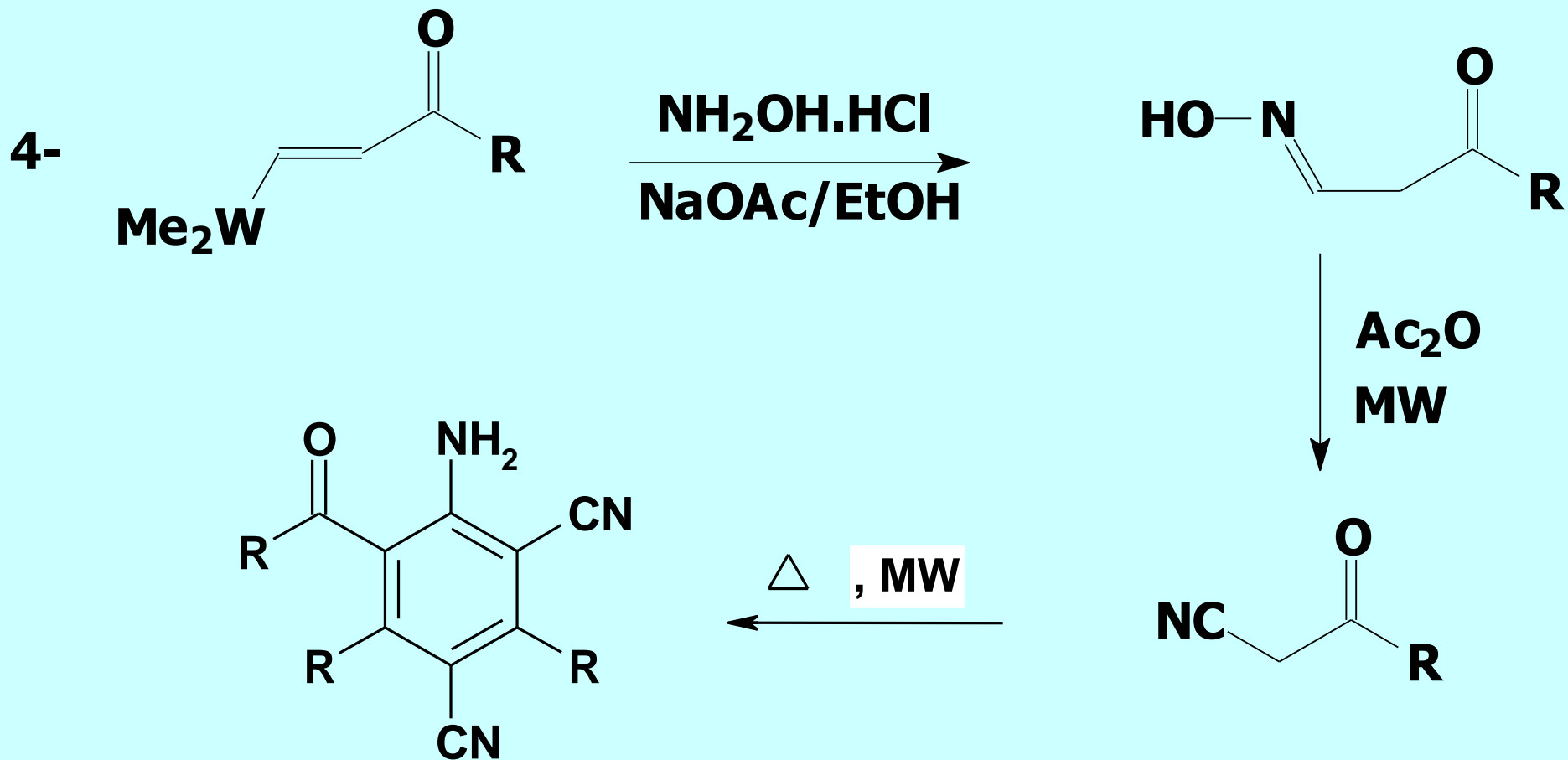
2-



Al-Awadi, Nouria A.; Ibrahim, Maher R.; Abdelhamid, Ismail A.; Elnagdi, Mohamed H. *Tetrahedron* (2008), 64(35), 8202-8205.

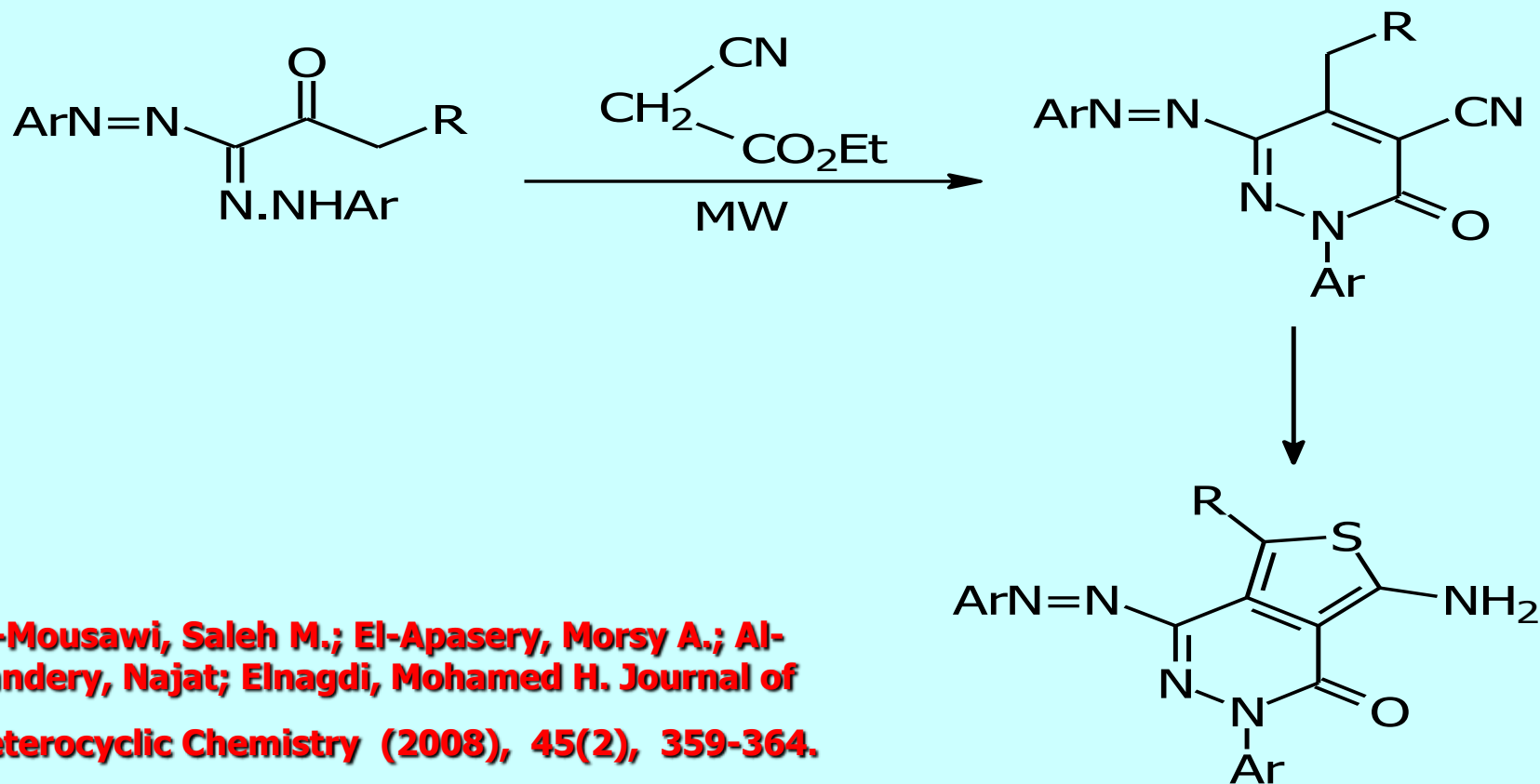


El-Dusouqui, Osman M. E.; Abdelkhalik, Mervat M.; Al-Awadi, Nouria A.; Dib, Hicham H.; George, Boby J.; Elnagdi, Mohammed H. Journal of Chemical Research (2006), (5), 295-302.



Al-Awadi, Nouria A.; Abdelkhalik, Mervat M.; Abdelhamid, Ismail A.; Elnagdi, Mohamed H.. *Synlett* (2007), (19), 2979-2982.

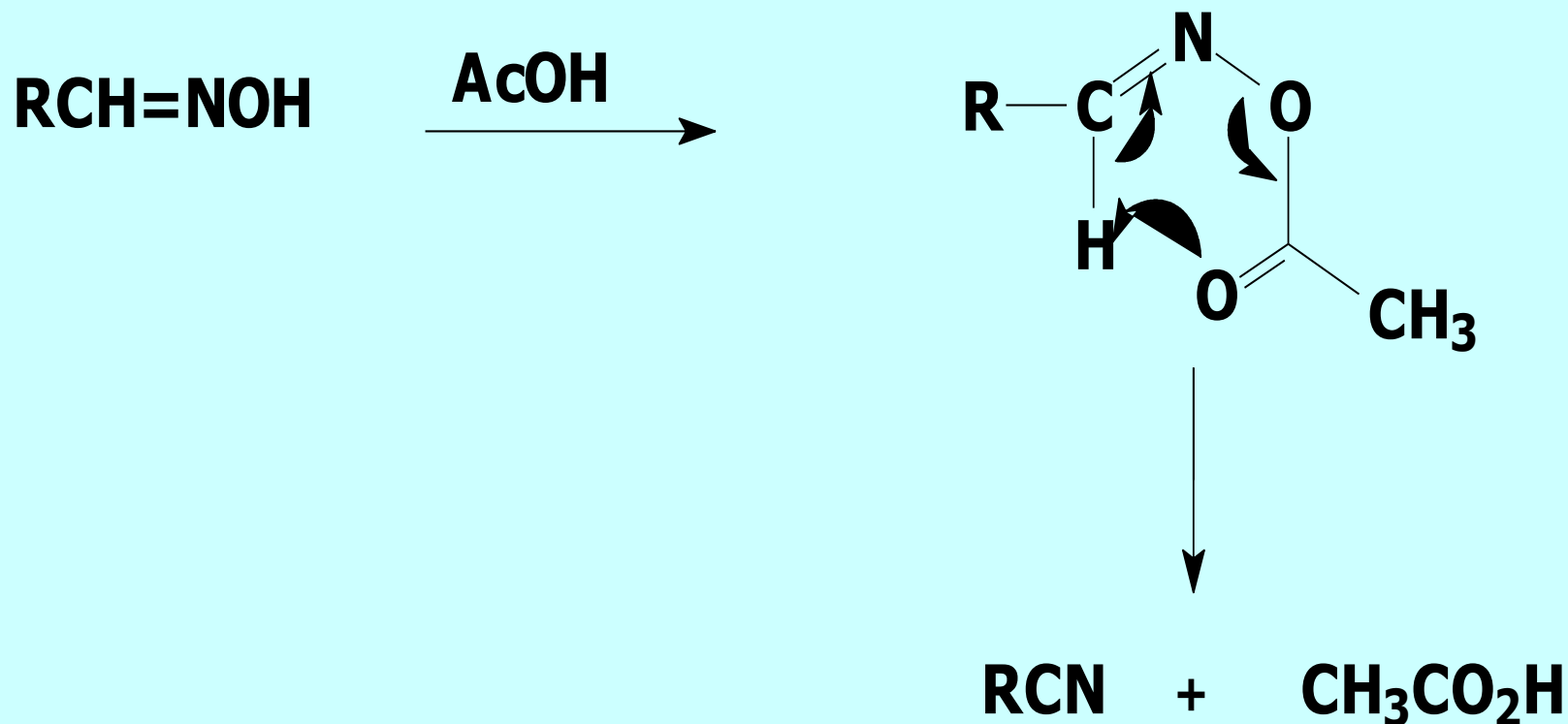
Arylazopyridazinones were synthesized by utilizing MW



Al-Mousawi, Saleh M.; El-Asasery, Morsy A.; Al-Kandery, Najat; Elnagdi, Mohamed H. Journal of Heterocyclic Chemistry (2008), 45(2), 359-364.

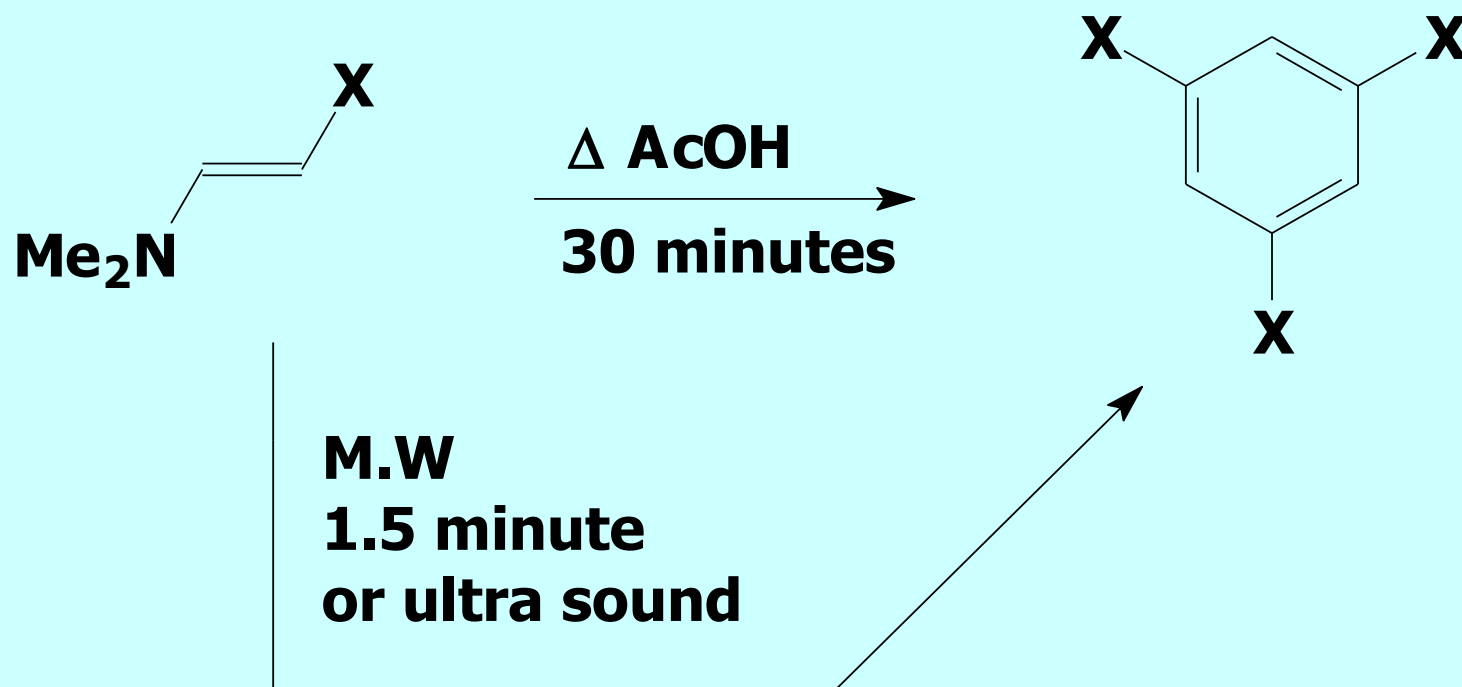
Structure elucidated
by X-ray

General pyrolytic reaction of Al-Awadi et al

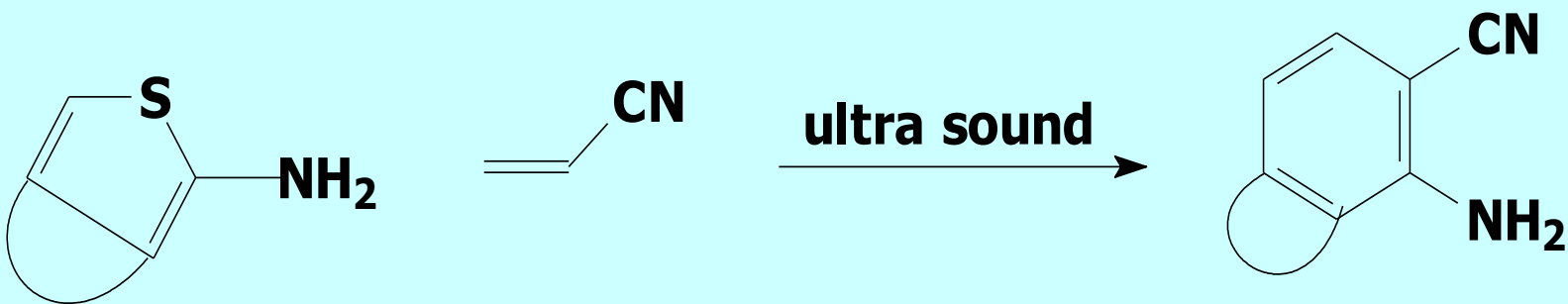


Utility of Ultrasound as Energy Source

In Saudi Arabia, we have done the following with Dr. Kh. Al-Zaidi:

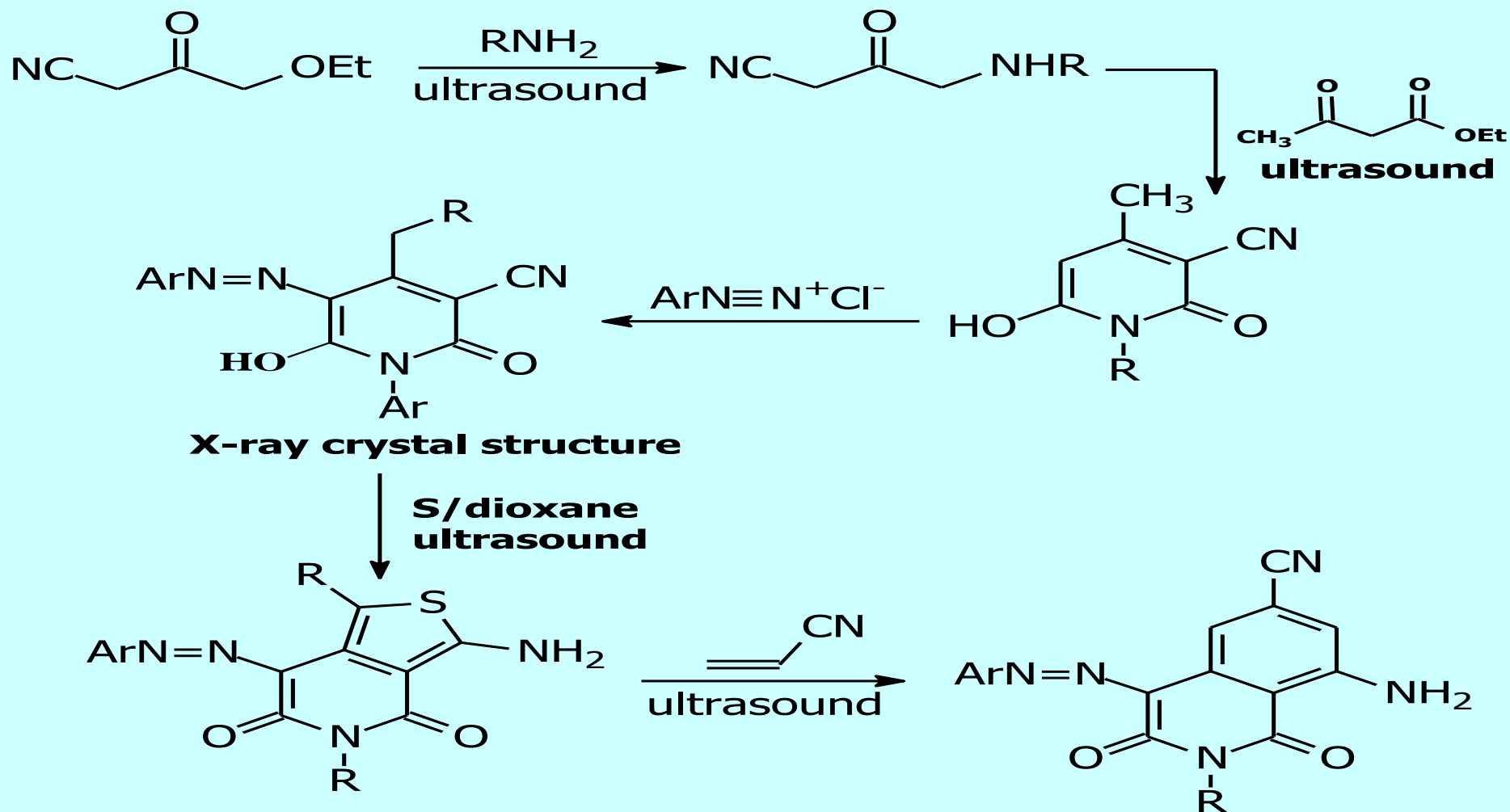


- Ultrasound is around for long time as energy which is used in military and medicine.
- Ultrasound can produce about chemical transformation through cavitations which is equivalent in a way of applying pressure and that is why all reactions in which two or more molecules are unified in transition state like all precyclic reactions and addition reactions are assisted by sonfication. We looked into our old cycloaddition chemistry and it proceeded quite effectively on sonfication at room temperature in stead of reflux in solvent.



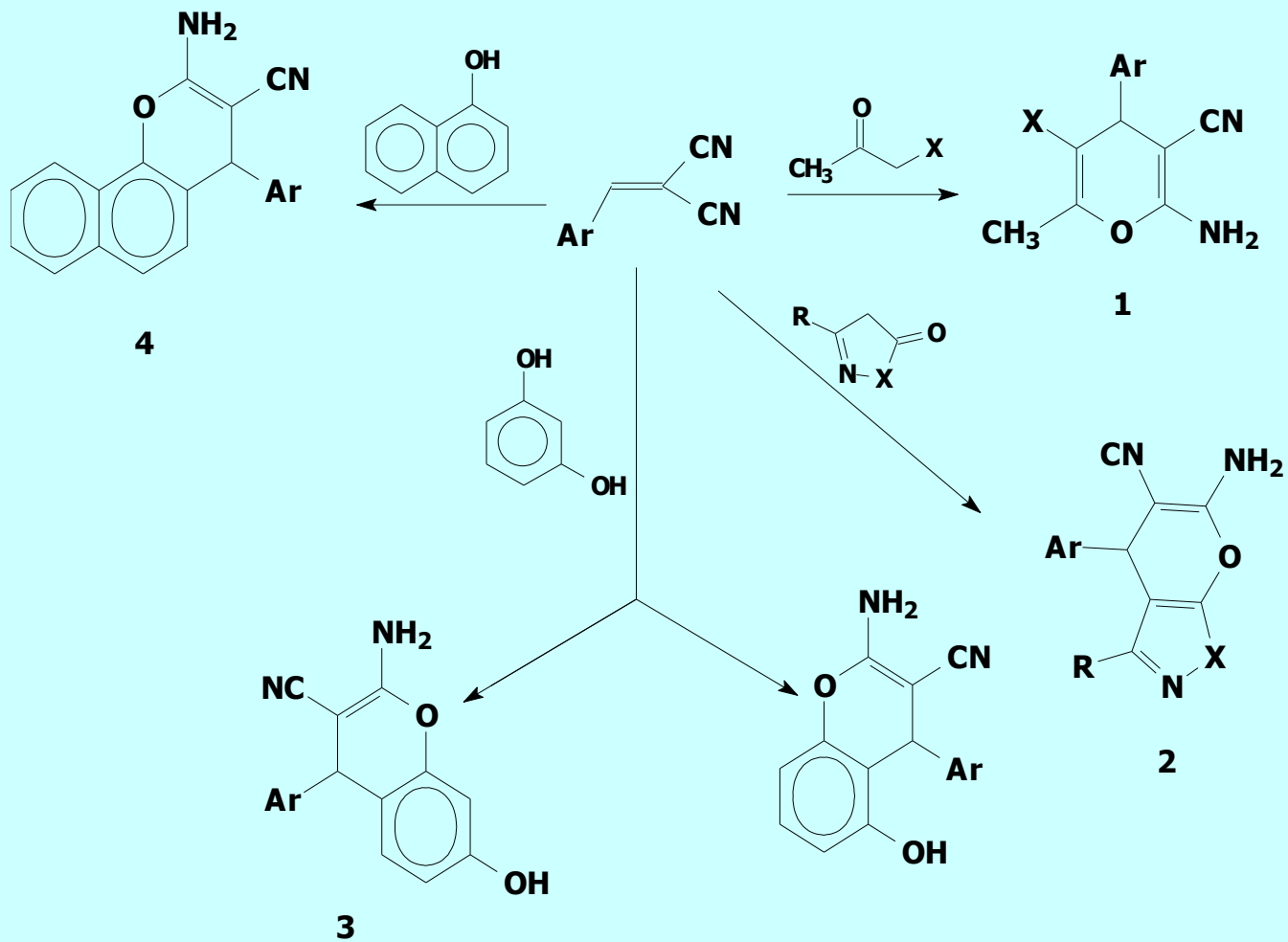
Ultrasound as source of needed energy for reaction

Recently, we reported the following with Dr. Kh. Azaidi

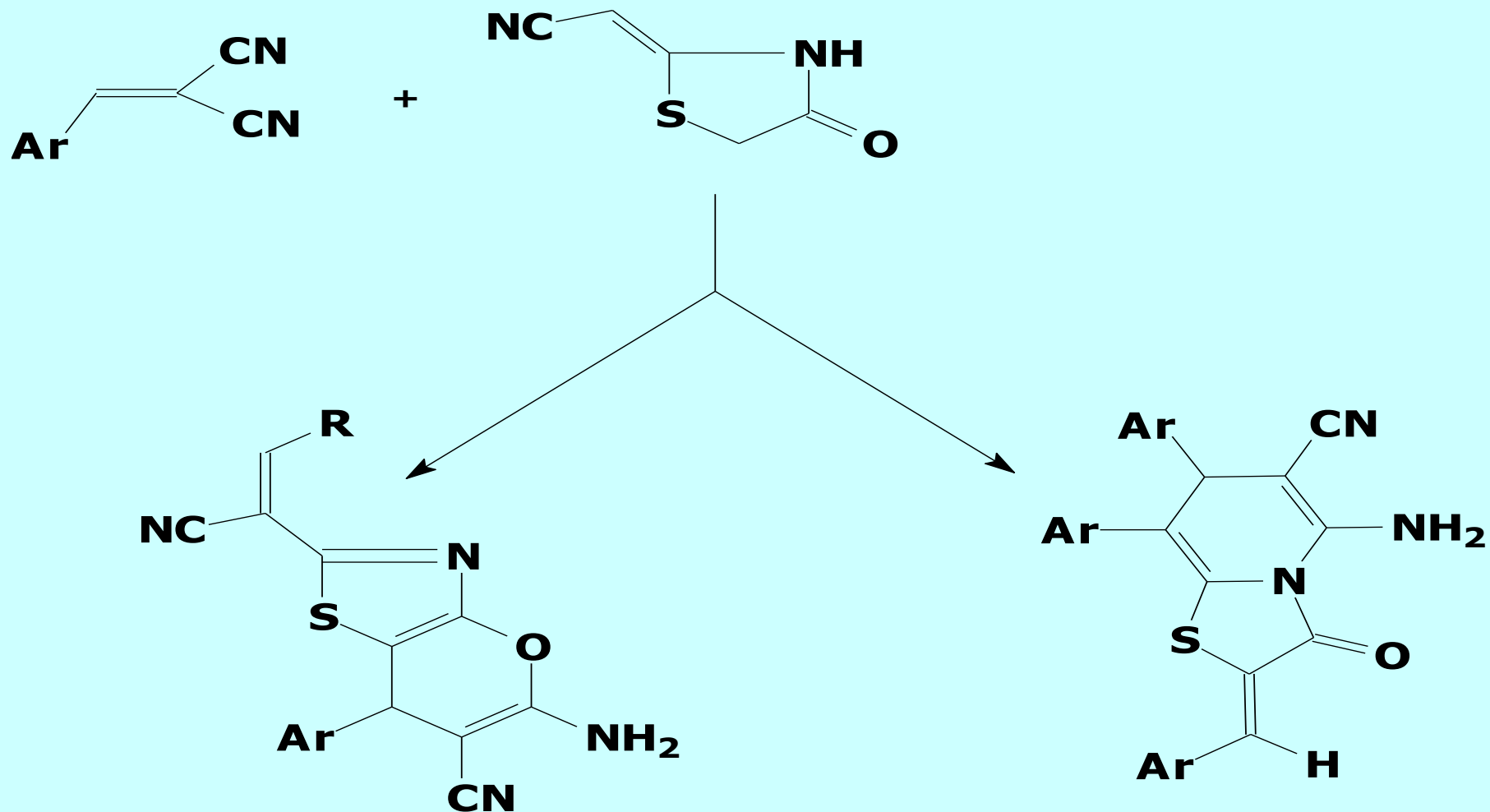


Al-Mousawi, Saleh Mohamed; Abdelhamid, Ismail Abdelshafy; Moustafa, Moustafa Sherief. ARKIVOC (Gainesville, FL, United States) (2007), (1), 213-221.

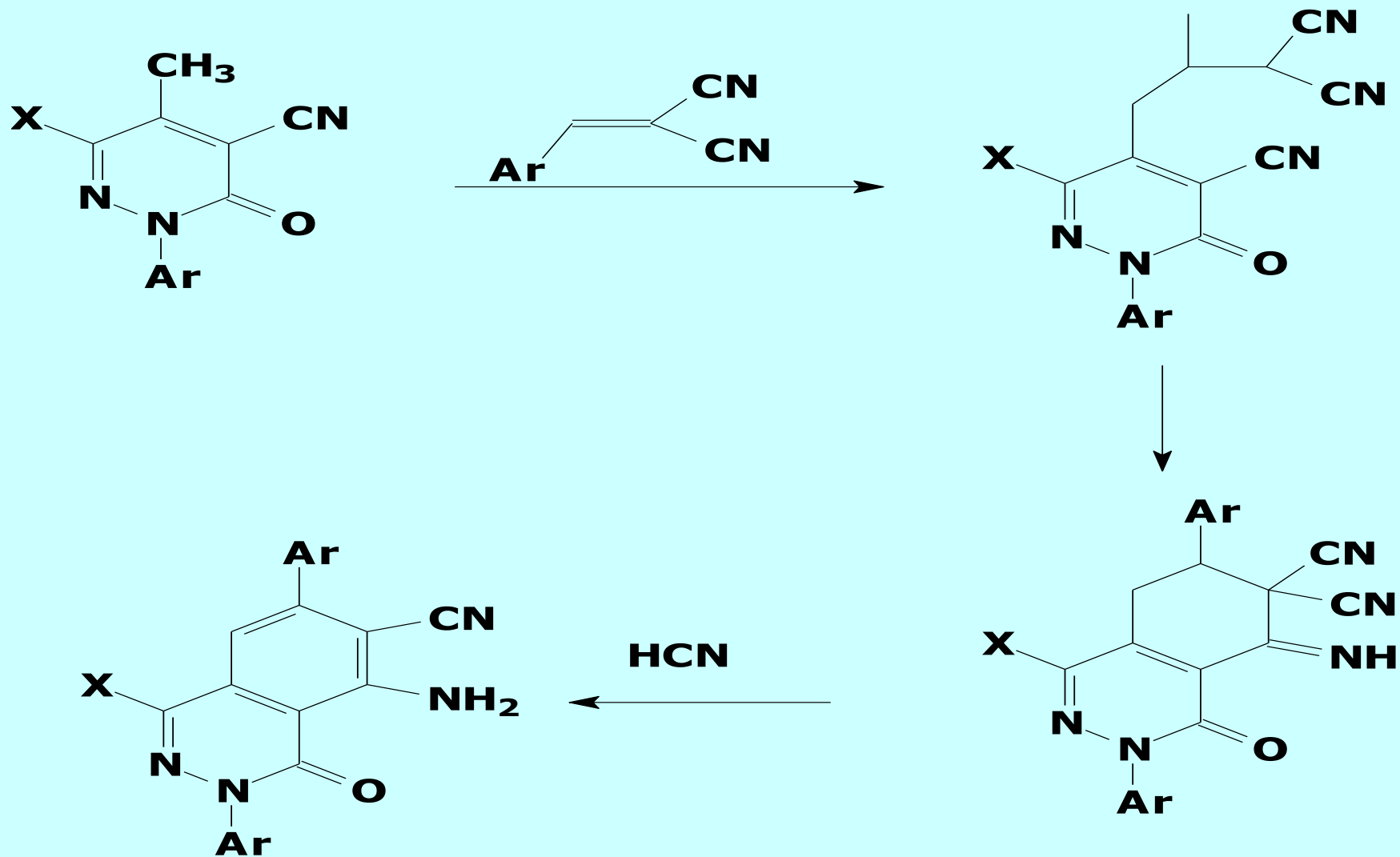
- Ecofriendly heterogeneous catalysis for Michael additions: old chemistry and a new insight.
- During the period 1976-1989, we have investigated reactivity of arylidene malononitriles toward a variety of active methylenes forming a diversity of heterocycles. Several of which proved biologically active and brought tremendous interest. We did our reactions in solvents, e.g. EtOH or pyridine and in the presence of piperidine as catalyst. We have now looked again into this chemistry taking green chemical consideration into account.



	water	water/pip	water/chitozane	EtOH/pip	EtOH/chitozane
1; X=CO ₂ Et	23.47	44.7	42.5	67	58.86
1; X=COCH ₃	No reaction	31	26	64	58



**Al-Matar, Hamad M.; Khalil, Khaled D.; Meier, Herbert; Kolshorn, Heinz; Elnagdi, Mohamed H..
 ARKIVOC (Gainesville, FL, United States) (2008), (16), 288-301.**

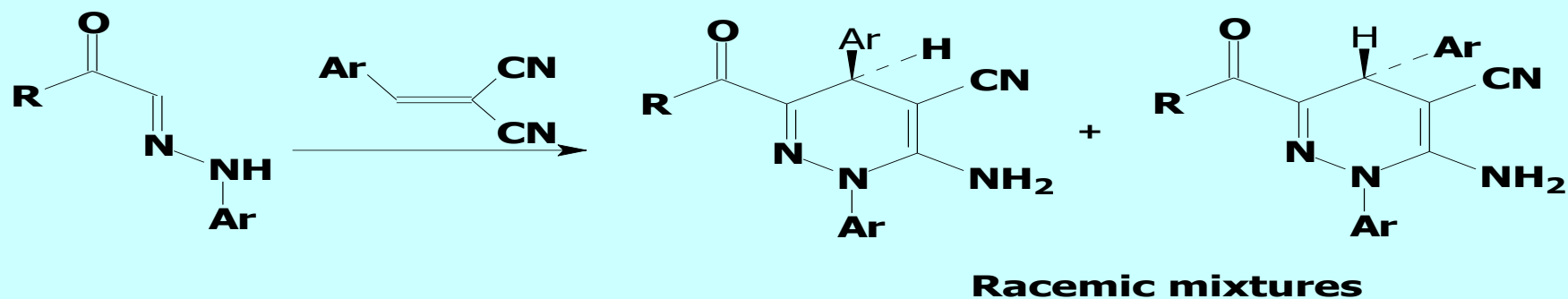


Saleh M. Al-Mousawi, Morsy A. El-Asery, Najat Al-Kandery, and Mohamed H. Elnagdi. *J. Heterocyclic Chem.*, 45, 359 (2008).

Biotransformations in Organic Synthesis:

Why Biotransformations are attractive?

Organic reactions in which a chiral center is produced like in the Michael addition we recently conducted, produces racemates as transition state is enantiomers.



➤ To prepare a chiral product, transition states leading to products should be diastomeric. This can be achieved *via*:

- 1) use of chiral auxiliary
- 2) use of chiral catalyst
- 3) use of chiral solvent.

Synthesized chiral catalysis are expensive while enzyme, or less expensive whole organisms are less. Moreover, using naturally occurring material looks eco-friendly. We thus desired to invade this area.

DEFINITION OF BIOTRANSFORMATIONS

- Biotransformations: The use of living organisms (named biocatalysts) to perform chemical transformations on organic compounds which are not their natural host.

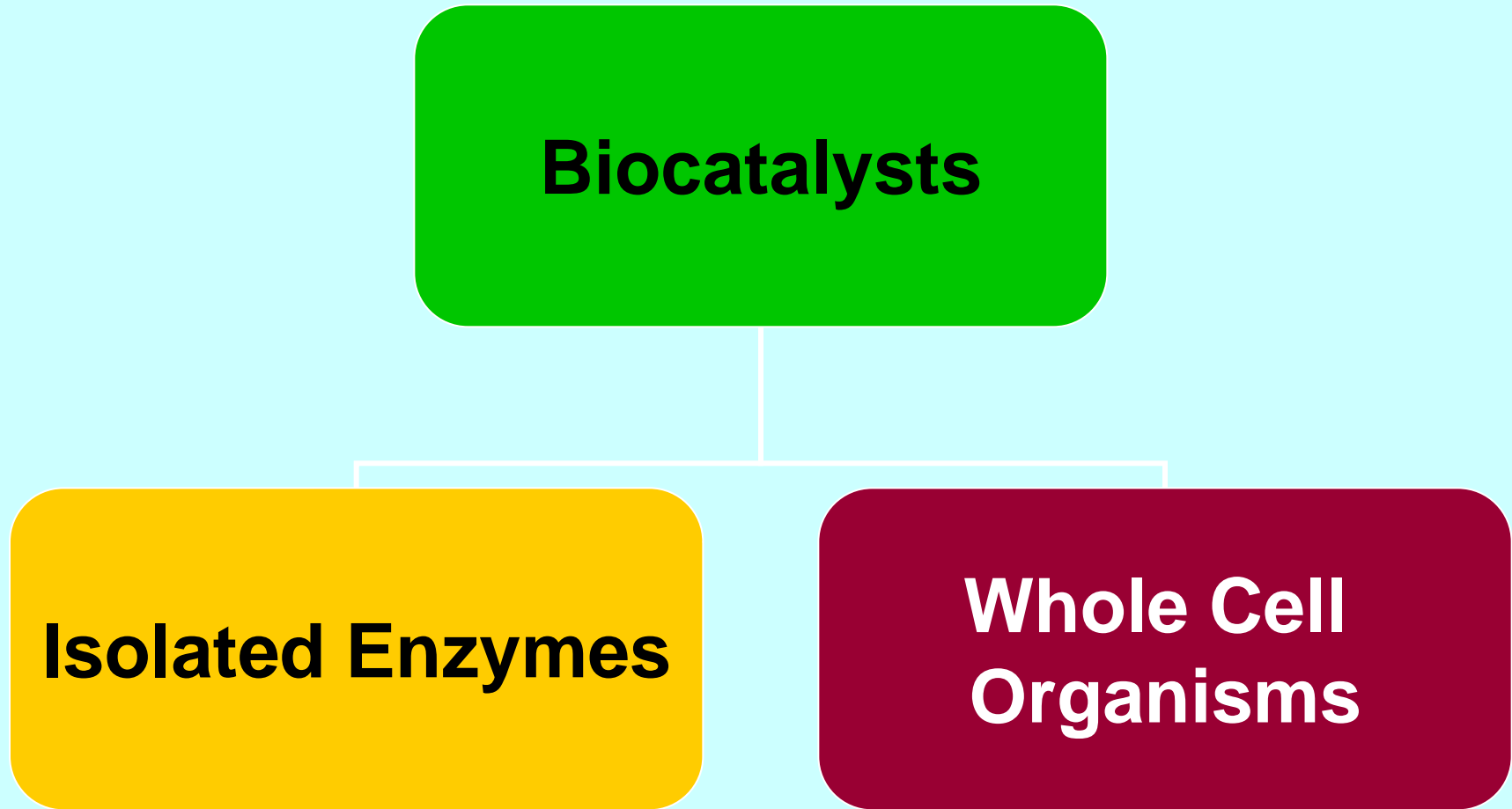
BIOCATALYSTS: ADVANTAGES

- Enzymes are very efficient catalysts
- Enzymes are environmentally acceptable
- Enzymes act under mild conditions
- Enzymes are not bound to their natural role
- Enzymes display 3 major types of selectivities
 - Chemoselectivity & Regioselectivity
 - Enantioselectivity

BIOCATALYSTS: DISADVANTAGES

- Enzymes require narrow operation parameters
- Enzymes display their highest catalytic activity in water
- Enzymes are prone to inhibition phenomena

BIOCATALYSTS: CLASSIFICATION



ISOLATED ENZYMES

- Advantages
 - Simple Apparatus
 - Simple Procedure
 - Better Productivity

- Disadvantages
 - Co-factor Recycling Necessary

WHOLE CELL ORGANISMS

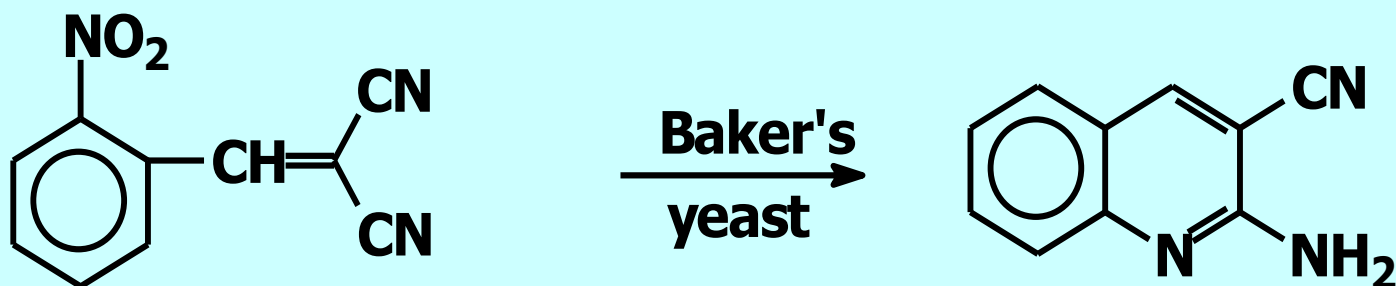
- Advantages

- High Enzymes Activity
- No Co-factor recycling necessary

- Disadvantages

- Side Reactions Possible
- Work Up Requires Extraction

Al-Mousawi and Elnagdi are now investigating the utility of biocatalysts in synthesis. A synthesis of aminoquinoline could be developed utilizing Baker's yeast as biological reducing catalyst.



Acknowledgements

The continual support of the AvH foundation over the last thirty years is highly acknowledgment. The green chemistry work was financed mainly by university of Kuwait, Research Administration through eleven-research project. Partial support was also received from L'Oreal Paris and the International Organisation for Chemistry Development
I thank Prof. Dr. H. Meier (University of Mains) for help in solving plenty of structural problems.

Thank s to my colleuges and co-workers especially:

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Prof. Dr. N. Al-Awadi

Dr S. Al-Mousawi

Prof. Mervat M Abdelkhalik

Mr. Moustaf Sherif

American University in Cairo

Prof. Dr. D. H. Felita

National Research Center (Cairo)

Ass. Prof. M. H. El-Asery

Cairo University

Prof. Dr. E. A. Hafez

Dr. I. Abdelshafi

Dr. K. El-Desouky

Mr. H. Fakhrey

Thank You