

*In the Name of God*



Razi University

**Faculty of Chemistry**  
**Department of Organic Chemistry**

**M.Sc.Thesis**

**Title:**

**Synthesis of alkyl nitriles & Quinolines**

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**By:**

**Parisa Mehrdadi-nejad**

**March 2013**



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*Dedicated to:*

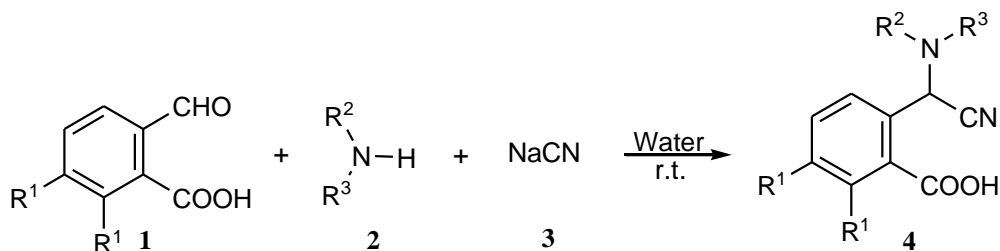
*My dear parents*

*&*

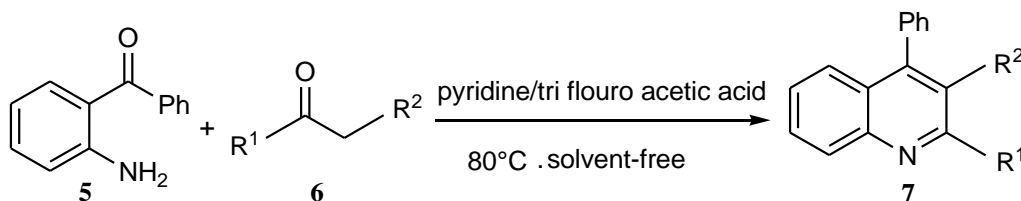
*My dear husband*

## Abstract

In this research we have developed synthesis of some new  $\alpha$ -benzoic acid  $\alpha$ -aminonitriles via a three-component condensation reaction of 2-formylbenzoic acids **1**, secondary amines **2**, and sodium cyanide **3** in water at room temperature without any activation or catalyst. This reaction led to the construction of one carbon–carbon bonds and one carbon–nitrogen bonds.



Furthermore a reaction between 2-aminoaryl ketones **5**, methylene ketones **6** has been developed for a highly efficient preparation of poly-substituted quinolines derivatives **7** via Friedlander annulations under solvent-free conditions. This reaction was carried out at  $80^\circ\text{C}$ .



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# **Chapter 1**

## **Introduction**

# **Part A**

**Synthesis of some  $\alpha$ -benzoic acid  $\alpha$ -aminonitrile derivatives *via* the Strecker reaction in aqueous media**

### 1.1.1. Green chemistry

Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. Whereas environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source. In 1990 the pollution prevention act was passed in the United States. This act helped create a modus operandi for dealing with pollution in an original and innovative way. It aims to avoid problems before they happen [1].

As a chemical philosophy, green chemistry applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. While green chemistry seems to focus on industrial applications, it does apply to any chemistry choice. Click chemistry is often cited as a style of chemical synthesis that is consistent with the goals of green chemistry. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice. It is distinct from environmental chemistry which focuses on chemical phenomena in the environment.

In 2005 *Noyori* identified three key developments in green chemistry: use of supercritical carbon dioxide as green solvent, aqueous hydrogen peroxide for clean oxidations and the use of hydrogen in asymmetric synthesis examples of applied green chemistry are supercritical water oxidation, on water reactions, and dry media reactions [2].

Bioengineering is also seen as a promising technique for achieving green chemistry goals. A number of important process chemicals can be synthesized in engineered organisms, such as shikimate, a Tamiflu precursor which is fermented by Roche in bacteria [3].

### 1.1.2. Clean chemical synthesis in green chemistry

Green or sustainable chemistry has now attained the status of a major scientific discipline and the studies in this area have led to the development of cleaner and relatively benign chemical processes with many new technologies being developed each year. Among them, much effort has been devoted to the use of non traditional solvents for chemical synthesis.

Water is commonly considered as a benign solvent in view of its non-toxicity and abundant natural occurrence, yet in the semiconductor industry, untreated wastewater contaminated with trace amounts of metals is a serious environmental problem. However, the use and release of “clean water” will have the least impact to the environment, and this article discusses the main advantages of using water as a reaction medium to develop cleaner chemical processes.

The use of water as solvent features many benefits such as improving reactivities and selectivities, simplifying the work up procedures, enabling the recycling of the catalyst and allowing mild reaction conditions and protecting-group free synthesis in addition to being benign itself. In addition, exploring organic chemistry in water can lead to uncommon reactivities and selectivities complementing the organic chemist’s synthetic toolbox in organic solvents. Studying chemistry in water also allows insight to be gained into nature's way of chemical synthesis [4].

### 1.1.3. Water

Water is the solvent in which numerous biochemical organic reactions (and inorganic reactions) take place. All these reactions affecting the living system have inevitably occurred in an aqueous medium. On the other hand, modern organic chemistry has been developed almost on the basis that organic reactions are often to be carried out in organic solvents. It is only within the last two decades or so that people have again focused their attention on carrying out organic reactions in water. This development is in large part due to the study by *Breslow* on the Diels-Alder reactions [5]. Water is the cheapest solvent available on earth, using water as a solvent can make many chemical processes more economical Safety. Many organic solvents are flammable, potentially explosive, mutagenic, and/or carcinogenic. Water, on the other hand, is none of this synthetic



efficiency. In many organic syntheses, it may be possible to eliminate the need for the protection and deprotection of functional groups, and save many synthetic steps. Water-soluble substrates can be used directly. This will be especially useful in carbohydrate and protein chemistry. Simple operation in large industrial processes, isolation of the organic products can be performed by simple phase-separation. It is also easier to control the reaction temperature, since water has the largest heat capacities of all substances. Environmental benefits it may alleviate the problem of pollution by organic solvents since water can be recycled readily and is benign when released into the environment (when no harmful residue is present). Potential for new synthetic methodologies compared to reactions in organic solvents, the use of water as a reaction solvent has been explored much less in organic chemistry. There are many opportunities to develop novel synthetic methodologies that have not been discovered before [6].

#### **1.1.3.1. Solvent of water**

Water is a very good solvent for many substances, which is of fundamental importance in nature. The solubility of a chemical substance is dependent upon the temperature. The solubility of gases such as oxygen, nitrogen, and carbon dioxide in water usually decreases with a rise in temperature. However, there are some gases whose solubility increases with an increase in temperature. An example of such is helium. Similarly, there is variation in the relation between the solubility of solids in water and the temperature. For example, the solubility of  $\text{AgNO}_3$  rapidly increases with an increase in temperature, but for  $\text{NaCl}$  there is only a slight increase in solubility with a rise in temperature. On the other hand, when temperature increases there is a decrease in solubility for  $\text{Li}_2\text{CO}_3$  [7]. The influence of the temperature on the solubility of substances is dictated by the heat of solution of the substance, which is the heat emitted or absorbed during the dissolution of one mole of a substance in one liter of water. Metal ions in aqueous solution exist as complexes with water. The solubility of organic compounds in water depends primarily on their polarity and their ability to form hydrogen bonds with water [8].

Water is a good solvent due to its polarity. Substances that will mix well and dissolve in water (e.g. salts) are known as hydrophilic "water-loving" substances, while those that do not mix well with water (e.g. fats and oils), are known as hydrophobic

"water-fearing" substances. If a substance has properties that do not allow it to overcome these strong intermolecular forces, the molecules are "pushed out" from the water and do not dissolve. Contrary to the common misconception, water and hydrophobic substances do not "repel", and the hydration of a hydrophobic surface is energetically, but not entropically, favorable [9].

When an ionic or polar compound enters water, it is surrounded by water molecules (Hydration). The relatively small size of water molecules typically allows many water molecules to surround one molecule of solute. The partially negative dipole ends of the water are attracted to positively charged components of the solute, and vice versa for the positive dipole ends.

In general, ionic and polar substances such as acids, alcohols, and salts are relatively soluble in water, and non-polar substances such as fats and oils are not. Non-polar molecules stay together in water because it is energetically more favorable for the water molecules to hydrogen bond to each other than to engage in vanderwaals interactions with non-polar molecules [10].

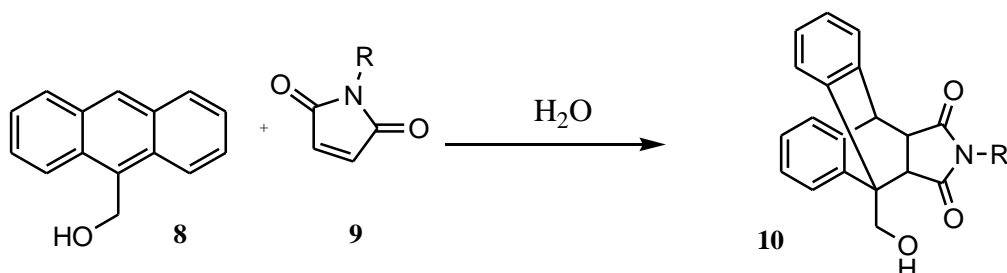
An example of an ionic solute is table salt; the sodium chloride, NaCl, separates into Na<sup>+</sup> cations and Cl<sup>-</sup> anions, each being surrounded by water molecules. The ions are then easily transported away from their crystalline lattice into solution. An example of a non ionic solute is table sugar. The water dipoles make hydrogen bonds with the polar regions of the sugar molecule (OH groups) and allow it to be carried away into solution [11].

### **1.1.3.2. Organic reactions in water**

#### **1.1.3.2.1. Diels-Alder reaction in water**

Diels Alder reactions are very important tools in carbon-carbon bond formation. Much study has been done on the mechanisms and reaction rates of this reaction [12]. Exciting work focuses on the rate acceleration of these reactions due to the hydrophobic effect in water. A Diels-Alder reaction in water with anthracene-9-methanol (**8**) and N-methyl maleimide (**9**). This reaction demonstrates how a greener solvent can be used not only because it is more environmentally benign but also because it improves other aspects of there action [13].

This reaction is highly atom economic and uses green solvent, water. Separation of the product is easy and green because it precipitates out of the reaction solution upon cooling. The Diels-Alder reaction is an important carbon-carbon bond forming operation [14]. It is a common component of the undergraduate organic lecture curriculum [15] (Scheme 1.1.1).

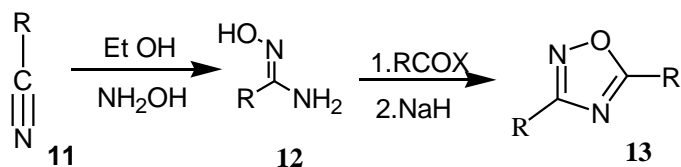


Scheme 1.1.1: Diels-Alder reactions in Water

### 1.1.3.2.2. Synthesis of 1,2,4-oxadiazoles in water

A simple and efficient process has been developed for the Synthesis of 1, 2, 4-oxadiazoles (**13**) in good yields through the reaction of amidoximes with anhydrides under catalyst-free conditions in water.

Several methods have been reported for the synthesis of 1, 2, 4-oxadiazoles. In general, the two most common routes are: (i) 1, 3-dipolar cycloaddition of nitriles to nitrile oxides; (ii) cyclization of amidoxime derivatives. In the second method, 1, 2, 4-oxadiazoles are prepared in two steps by O-acylation of an amidoxime, which can be easily prepared by the reaction of nitriles (**11**) with hydroxylamine (**12**), with an activated carboxylic acid derivative, typically an active acyl chloride, followed by cyclodehydration. New Synthesis of 1, 2, 4-triazoles and 1, 2, 4-oxadiazoles [16] (Scheme 1.1.2).

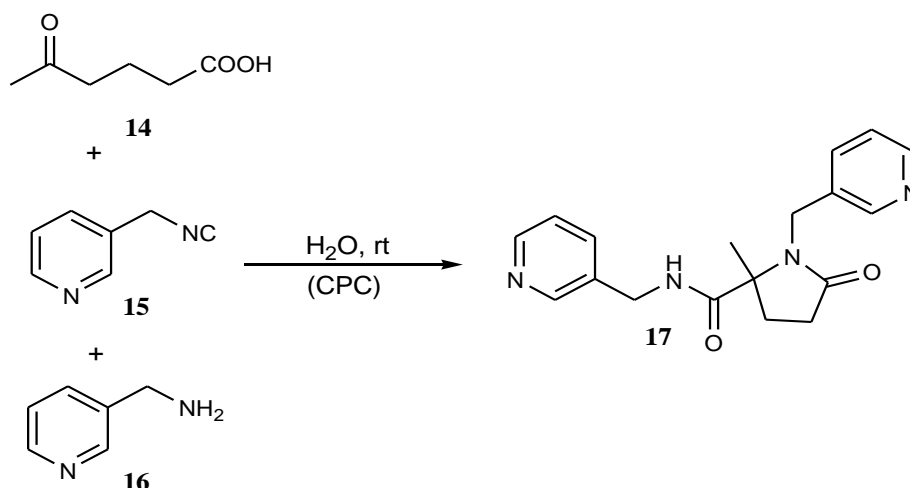


Scheme 1.1.2: Synthesis of 1, 2, 4-oxadiazoles in water

### 1.1.3.2.3. IMCRs in water

IMCRs of Ugi type are mostly performed in protic alcoholic solvents. Two groups concurrently reported IMCRs in water. Mironov noted the advantage of performing MCRs in water with the addition of small amounts of phase transfer catalysts (PTCs). Thus, the reaction of levulinic acid (**14**), isocyanides (**15**), and primary amines (**16**) nicely gives the

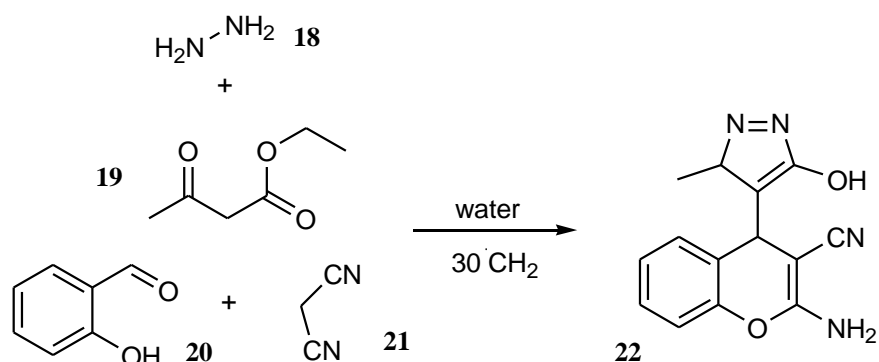
corresponding  $\gamma$ -lactams (**17**) in good yield. Cetylpyridinium chloride (CPC) (0.1 M) or bovine serum albumin was used as phase transfer catalyst. Advantageously, mostly the pure products precipitated during the reaction. Thus, simple filtering of the solutions afforded products of very pure quality and in good yields [17] (Scheme 1.1.3).



Scheme 1.1.3: U-MCRs of lactams performed in water

#### 1.1.3.2.4. Synthesis of chromenes in water

*Kumaravel et al* they reported actively engaged in developing multi-component reaction protocols in water. They reported for the first time a catalyst-free four-component reaction for a combinatorial synthesis of novel highly functionalised 4-pyrazolyl-4*H*-chromene (**22**) frameworks in water at ambient temperature [18] (Scheme 1.1.4).



Scheme 1.1.4: Synthesis of chromenes in water

#### 1.1.3.2.5. Synthesis of tetraketones in water