INSTRUCTIONS FOR STUDENTS

Background and Theory

Multicomponent reactions (MCRs) are one-pot procedures in which almost all atoms of three or more reagents are combined, in order to afford only one product. Usually, water is the solo byproduct from MCRs. This procedure is distinguished from classical linear synthesis. MCRs have several advantages when compared to classical procedures, especially considering atom economy and purification procedures. Different levels of complexity and high structural diversity from structurally simple starting materials may be attained from MCR procedures. MCRs have attractive features such as being converged, operational simplicity, atom economy, structural diversity and complexities of compounds. Ideally, such reactions end with an irreversible new chemical bond, therefore favoring the product formation, decreasing reaction time and increasing the reaction’s selectivity. For these aforementioned reasons, MCRs are emerging as superior tools for the synthesis of biologically active compounds and never-ending libraries of such derivatives. Some examples of well-known MCRs (Scheme 1) are

**Scheme 1S. Examples of widely explored multicomponent reactions (MCRs)**
the Biginelli, Mannich and Hantzsch reactions; there is also a class of isocyanide-based MCRs such as Passerini and Ugi.

In 1891 (and revisited in 1893) Pietro Biginelli published his pioneering findings on the three-component reaction that is known as the Biginelli reaction. This three-component one-pot reaction leads to the synthesis of 3,4-dihydropyrimidin-2(1H)-one or –thione (DHPM) typically by mixing an aldehyde (1), an 1,3-dicarbonyl derivative (2), and urea (or thiourea) (3) under catalyzed conditions (see Scheme 2). The Biginelli reaction is quite a versatile MCR as it can be performed with several variations in the three components, affording therefore an infinity of DHPMs. To improve yields, reaction times and selectivities and to minimize reagent excesses and by-product formation (from side reactions) it is necessary to understand the mechanism of the Biginelli reaction.

![Scheme 2S. The classical Biginelli reaction with three common tested reagents i.e. benzaldehyde, ethyl acetoacetate and urea](image)

During the 1930s, Folkers and Johnson proposed that structures shown in Scheme 3 could be involved in the mechanism. Compound 5 was the result from intermolecular condensation of benzaldehyde 1 and two equivalents of urea 3. Another compound involved is enamine 6, formed by the condensation of 2 and 3, while compound 7 is known as the Knoevenagel adduct, formed from the condensation of 1 and 2. A more detailed mechanistic interpretation for the Biginelli reaction was later proposed by Sweet and Fissekis, known as the Knoevenagel reaction pathway. Their mechanism is based on the formation of a carbenium ion (Scheme 3).

Later, Kappe reinvestigated the Biginelli intermediates using NMR techniques and monitored the standard reaction of benzaldehyde 1 and ethyl acetoacetate 2 in MeOD/HCl. No evidence was found that related products of the two reagents at room temperature, but in the same study the formation of bisureide 5 (see the iminium mechanism pathway in Scheme 3) was detected.

More recently, direct infusion electrospray ionization mass spectrometry (ESI-MS) has been incorporated in the set of major techniques for mechanistic studies of organic and inorganic reactions. Owing to its outstanding ability to detect ionic or ionized intermediates directly from reaction solutions and due to the gentle transfer into the gas phase, with high sensitivity and speed, ESI-MS(ESI) has provided continuous snapshots of the ionic composition of reaction solutions, allowing on-line MS monitoring and characterization of the intercepted intermediates. It was possible therefore to monitor the mechanistic pathways for the Biginelli reaction and to analyze the influence of different catalysts. Based on these previously published works, and knowing that Scheme 3 may be used as the basis for discussion of the mechanism, it is possible to explore the catalyst’s influence over the reaction pathway of the Biginelli reaction, to discuss with the audience the preferred reaction pathway and how to influence the selection of one mechanism over another based on the catalyst choice.

![Scheme 3S. The accepted mechanisms (via iminium, enamine, and Knoevenagel) for the Biginelli reaction](image)
Experimental

Chemicals
CAS Number 62-56-6 - Thiourea
CAS Number: 100-83-4 - 3-hydroxybenzaldehyde
CAS Number: 141-97-9 - Ethyl acetoacetate

Hazards
Thiourea is very hazardous if ingested. Hazardous in the case of skin contact (irritant), of eye contact (irritant), of inhalation. Slightly hazardous in the case of skin contact (permeator). Severe over-exposure can result in death. When manipulating ethyl acetoacetate, contact with skin, eyes and clothing must be avoided. If contact takes place, wash hands. Also, wash hands after the product manipulation. In the case of vapor formation use a respirator with an approved filter; it is recommended that experiments be performed in a well-ventilated fume hood. All reagents are irritants, so nitrile-type protective gloves must be put on when handling these compounds. It is necessary to take care in handling liquid nitrogen because it may cause severe cold burns in contact with skin. When operating vacuum pumps care is also necessary. Ethanol is flammable and toxic if swallowed. The Bronsted acids cause burns and are irritating to the respiratory system. The Lewis acids are toxic by ingestion or inhalation. Appropriate safety goggles, gloves, and laboratory coats should be worn during all the experimental time period.

SPECTRAL DATA

Monastrol: Light yellow solid. Melting point 180-181 °C (literature9 180-183 °C) and Rf 0.24 (hexane/AcOEt 7:3).

INSTRUCTOR NOTES

In order to verify the knowledge acquired during the experimental classes, the following questions are proposed:

1 - What is the role of catalysis? And for the Biginelli reaction?
Answer: Catalysis is very useful to diminish reaction times, and to improve yields, selectivities, turnover numbers and frequency. Considering the Biginelli MCR, catalysis plays a major role in improving yields, diminishes reaction times, avoids reagent waste and
helps to select one reaction pathway. We strongly suggest the reading of reference 25 cited in the main text.

2 - How can you select one mechanistic pathway for the Biginelli reaction?
Answer: The paths can be directed from the proportions of the reagents used or through the use of a catalyst, which is decisive in the formation of the key intermediates for each of the three possible mechanisms. It is interesting to note that catalysts (Bronsted or Lewis acids) have already been described which may select one among the three possible mechanisms.

3 - Why are MCRs so important?
Answer: MCRs are extremely important for easy and direct access to libraries of bioactive compounds through one-pot procedures which are found in line with green principles and more eco-friendly approaches. Moreover, MCRs allow the generation of several derivatives which may have their biological potential tested, aiming at structure-active relationship studies.

REFERENCES