طرح درس مباحث نوین فوق لیسانس

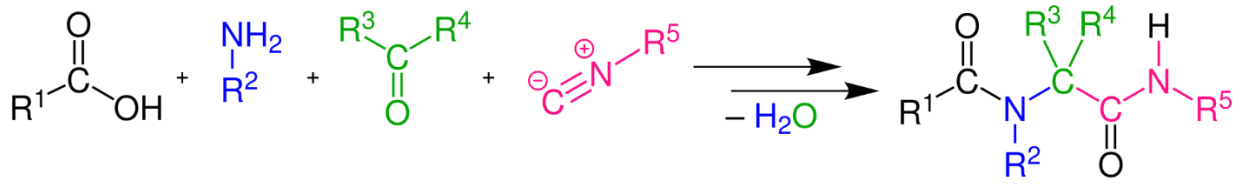
کتاب مرجع:

کتاب واکنش های چند جزیی (multicomponent reactions) ترجمه اینجانب داود حبیبی

هر هفته در شروع کلاس، واکنش جدیدی مطرح و در باره آن در طی ۱۶ جلسه ترم، بحث می شود.
مثلا به واکنش های زیر در جلسه اول دقت فرمایید:

Ugi Reaction

The Ugi reaction is a multi-component reaction in organic chemistry involving a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid to form a bis-amide. The reaction is named after Ivar Karl Ugi, who first reported this reaction in 1959.

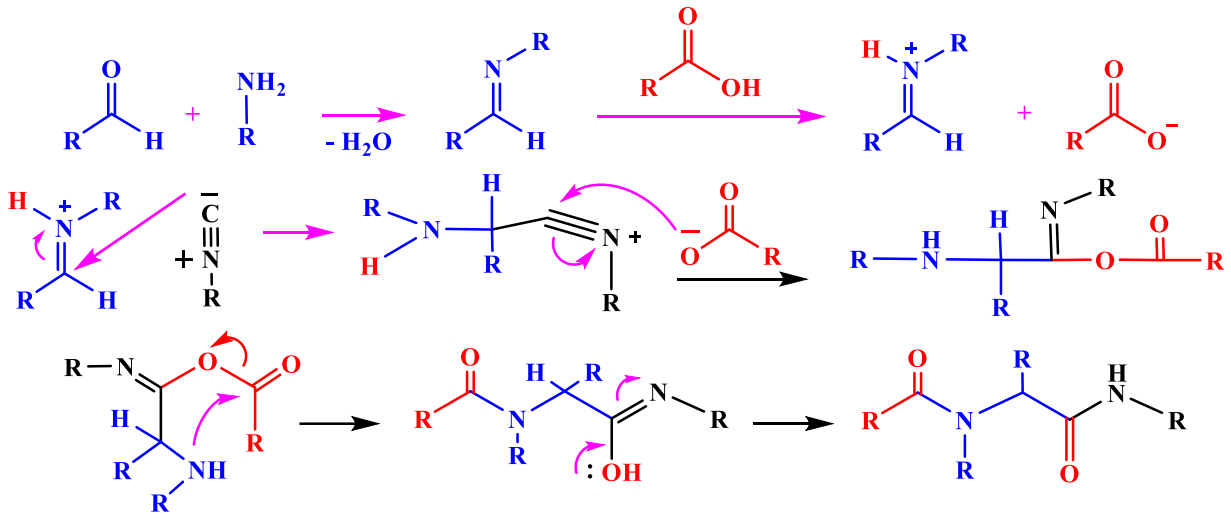


The Ugi reaction is exothermic and usually complete within minutes of adding the isocyanide. High concentration (0.5-2.0 M) of reactants gives the highest yields. Polar, aprotic solvents, like DMF, work well. However, methanol and ethanol have also been used successfully. This uncatalyzed reaction has an inherent high atom economy as only a molecule of water is lost, and the chemical yield in general is high. Several reviews have been published.

Due to the reaction products being potential protein mimetics there have been many attempts to development an enantioselective Ugi reaction, the first successful report of which was in 2018.

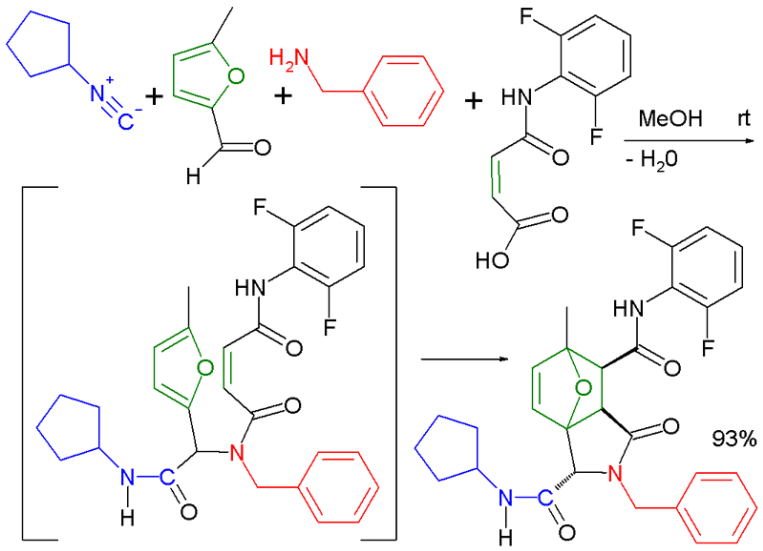
Mechanism of the Ugi Reaction

The mechanism is believed to involve a prior formation of an imine by condensation of the amine with the aldehyde, followed by addition of the carboxylic acid oxygen and the imino carbon across the isocyanide carbon; the resulting acylated isoamide rearranges by acyl transfer to generate the final product.



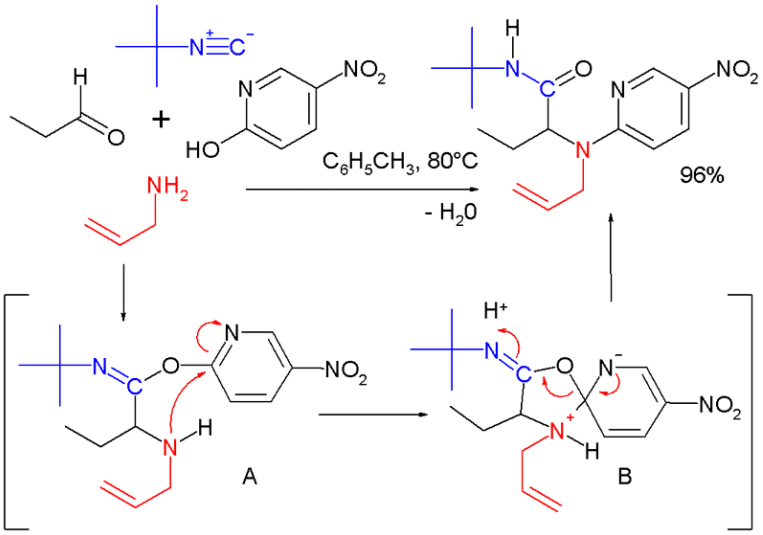
Combination of reaction components

The usage of bifunctional reaction components greatly increases the diversity of possible reaction products. Likewise, several combinations lead to structurally interesting products. The Ugi reaction has been applied in combination with an intramolecular Diels-Alder reaction in an extended multistep reaction.



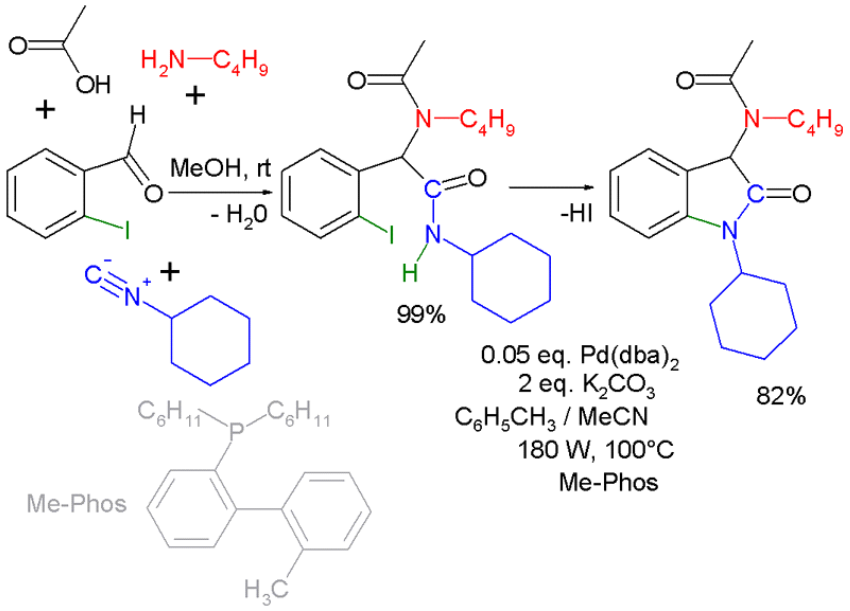
Ugi–Diels–Alder reaction

A reaction is the Ugi–Smiles reaction with the carboxylic acid component replaced by a phenol. In this reaction the Mumm rearrangement in the final step is replaced by the Smiles rearrangement.



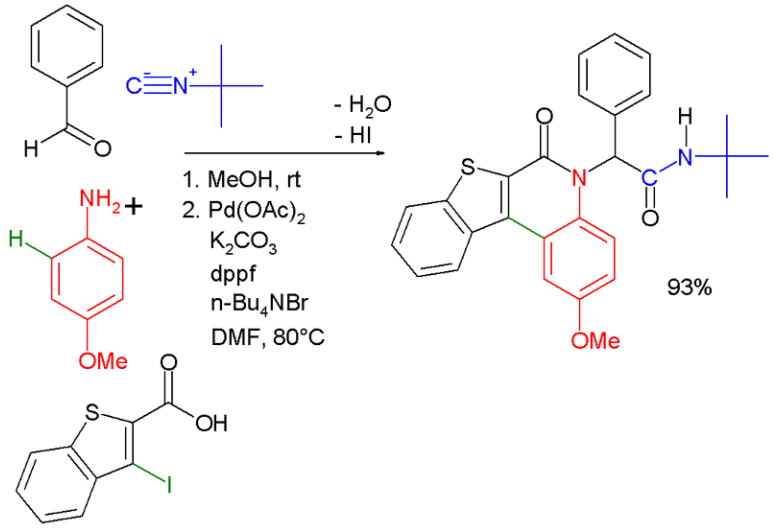
Ugi–Smiles reaction

Another combination (with separate workup of the Ugi intermediate) is one with the Buchwald–Hartwig reaction.



Ugi Buchwald–Hartwig reaction

In the Ugi–Heck reaction a Heck aryl-aryl coupling takes place in a second step.

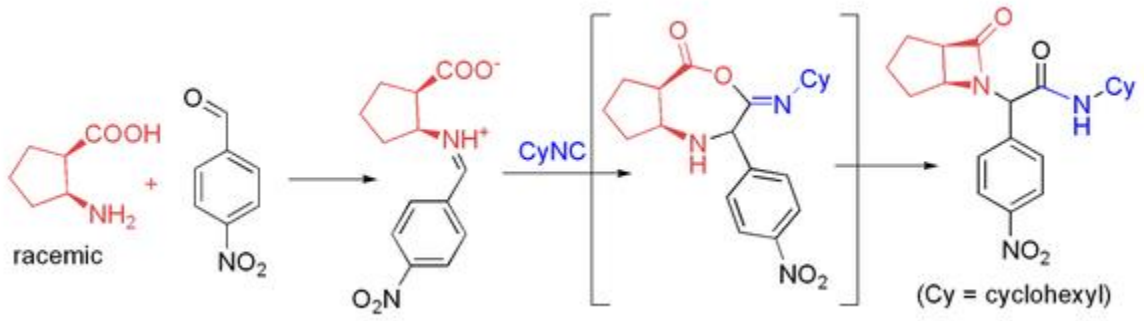


The Ugi-Heck reaction

Combination of amine and carboxylic acid

Several groups have used β-amino acids in the Ugi reaction to prepare β-lactams. This approach relies on acyl transfer in the Mumm rearrangement to form the four-membered ring. The reaction proceeds in moderate yield at room

temperature in methanol with formaldehyde or a variety of aryl aldehydes. For example, *p*-nitrobenzaldehyde reacts to form the β-lactam shown in 71% yield as a 4:1 diastereomeric mixture:



Combination of carbonyl compound and carboxylic acid

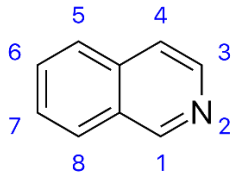
Zhang *et al.* have combined aldehydes with carboxylic acids and used the Ugi reaction to create lactams of various sizes. Short *et al.* have prepared γ-lactams from keto-acids on solid-support.

Chemical libraries

The Ugi reaction is one of the first reactions to be exploited explicitly to develop chemical libraries. These chemical libraries are sets of compounds that can be tested repeatedly. Using the principles of combinatorial chemistry, the Ugi reaction offers the possibility to synthesize a great number of compounds in one reaction, by the reaction of various ketones (or aldehydes), amines, isocyanides and carboxylic acids. These libraries can then be tested with enzymes or living organisms to find new active pharmaceutical substances. One drawback is the lack of chemical diversity of the products. Using the Ugi reaction in combination with other reactions enlarges the chemical diversity of possible products.

Examples of Ugi reaction combinations:

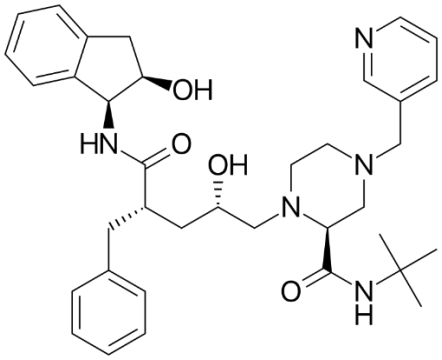
Isoquinolines from Ugi and Heck reactions.



Isoquinoline

Pharmaceutical industry

Crixivan (trade name for indinavir) can be prepared using the Ugi reaction.



indinavir

Indinavir is a protease inhibitor used as a component of highly active anti-retroviral therapy to treat HIV/AIDS. It is soluble white powder administered orally in combination with other antiviral drugs. The drug prevents protease from functioning normally. Consequently, HIV viruses cannot reproduce, causing a decrease in the viral load. Commercially sold indinavir is indinavir anhydrous, which is indinavir with an additional amine in the hydroxy-ethylene backbone. This enhances its solubility and oral bioavailability, making it easier for users to intake. It was synthetically produced for the purpose of inhibiting the protease in the HIV virus.

Currently, it is not recommended for use in HIV/AIDS treatment due to its side effects. Furthermore, it is controversial for many reasons starting from its

development to its usage. It was patented in 1991 and approved for medical use in 1996.

Indivanir does not cure HIV/AIDS, but it can extend the length of a person's life for several years by slowing the progression of the disease. The type that is widely used and created by Merck is indinavir sulfate. The pills are created from sulfate salts and are sold in dosages of 100, 200, 333, and 400 mg of indinavir. It is normally used as one of the three drugs in a triple-combination therapy for the HIV virus.

Commercially available capsules should be stored at 15-30 °C. It should be kept in a tight container so that it is kept away from moisture. Therefore, it is advised that users should keep the pills in the manufacturer-provided bottle and do not remove the desiccant.

Indinavir wears off quickly after dosing. Unboosted indinavir requires a very precise dosing of 400 mg every eight hours to thwart HIV from forming drug-resistant mutations, including resistances to other protease inhibitors. Boosted indinavir requires two 400-mg indinavir capsules with 1 to 2 100-mg ritonavir capsules twice a day. In both cases, the drugs must be taken with plenty of water one or two hours after a meal. It is recommended that users drink at least 1.5 liters a day when intaking the drug. Drug users must significantly increase their water intake due to indinavir's low solubility that can cause it to crystallize. There are restrictions on what sorts of food may be eaten concurrently with the unboosted indinavir treatment. Furthermore, it is no longer recommended to use in the United States for initial treatments due to pill burden and risk of kidney stones.

Many people were skeptical of being too hopeful with indinavir due to previous events that occurred with AZT. Viral resistance to the drug leads to the drug becoming useless since the virus evolves to have cells that can resist the protease inhibitor. In order to avoid this as much as possible, it is important for users to

consistently take the exact amount of the drug at the allocated times. This fear of viral resistance caused a lot of users to be wary of the drug.

The most common side effects of indinavir include:

Gastrointestinal disturbances (abdominal pain, diarrhea, nausea, vomiting).

General malaise and fatigue.

Nephrolithiasis/urolithiasis (the formation of kidney stones), which sometimes may lead to more severe condition including kidney failure.

Metabolic alterations including hyperlipidemia (cholesterol or triglyceride elevations) and hyperglycemia.

Alterations in body shape (lipodystrophy), colloquially known as "Crix belly".

Increased levels of Bilirubin, causing skin and white parts of the eyes to turn yellow.

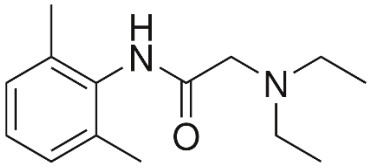
Inhibits urinary nitrous oxide production and may inhibit nitric oxide production.

Renal abnormalities, sterile leukocyturia, and reduced creatinine clearance.

Impairs endothelial function in healthy HIV-negative men and may accelerate atherosclerotic disease.

Indinavir is a white crystalline powder. It is very soluble in water and methanol. Each capsule contains sulfate salt in addition to anhydrous lactose and magnesium stearate. The capsule shell is made of gelatin and titanium dioxide. Its melting point or its temperature of decomposition is 150-153 °C at which it starts to emit toxic vapors such as nitrogen oxides and sulfur oxides. The drug fits inside the protease, stopping it from functioning normally. As a result, structural proteins, resulting from polypeptide products of gag and gag-pol genes, that are necessary for the HIV virions cannot form. Eventually, the viral load decreases because of the lack of reproduction.

Additionally, many of the *caine*-type anesthetics are synthesized using this reaction. Examples include lidocaine and bupivacaine.



lidocaine

Lidocaine, also known as lignocaine and sold under the brand name Xylocaine among others, is a local anesthetic of the amino amide type. It is also used to treat ventricular tachycardia. When used for local anaesthesia or in nerve blocks, lidocaine typically begins working within several minutes and lasts for half an hour to three hours. Lidocaine mixtures may also be applied directly to the skin or mucous membranes to numb the area. It is often used mixed with a small amount of adrenaline (epinephrine) to prolong its local effects and to decrease bleeding.

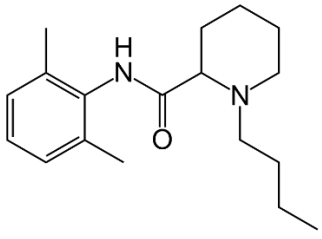
If injected intravenously, it may cause cerebral effects such as confusion, changes in vision, numbness, tingling, and vomiting. It can cause low blood pressure and an irregular heart rate. There are concerns that injecting it into a joint can cause problems with the cartilage. It appears to be generally safe for use in pregnancy. A lower dose may be required in those with liver problems. It is generally safe to use in those allergic to tetracaine or benzocaine. Lidocaine is an antiarrhythmic medication of the class Ib type. This means it works by blocking sodium channels and thus decreasing the rate of contractions of the heart. When injected near nerves, the nerves cannot conduct signals to or from the brain.

Lidocaine was discovered in 1946 and went on sale in 1948. It is on the World Health Organization's List of Essential Medicines. It is available as a generic medication. In 2019, it was the 219th most prescribed medication in the United States, with more than 2 million prescriptions.

Bupivacaine, marketed under the brand name Marcaine among others, is a medication used to decrease feeling in a specific area. In nerve blocks, it is injected around a nerve that supplies the area, or into the spinal canal's epidural space. It is available mixed with a small amount of epinephrine to increase the duration of its action. It typically begins working within 15 minutes and lasts for 2 to 8 hours.

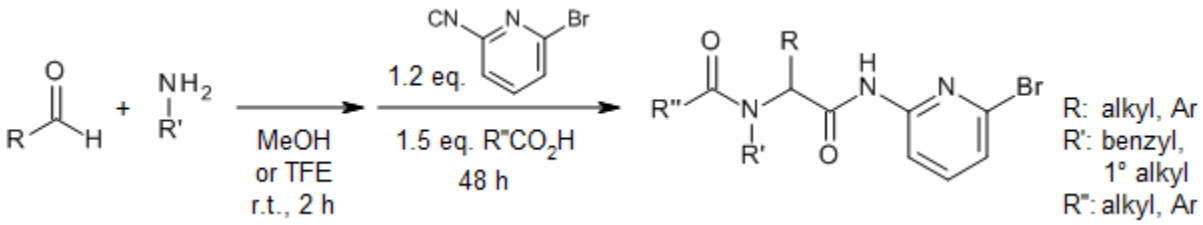
Possible side effects include sleepiness, muscle twitching, ringing in the ears, changes in vision, low blood pressure, and an irregular heart rate. Concerns exist that injecting it into a joint can cause problems with the cartilage. Concentrated bupivacaine is not recommended for epidural freezing. Epidural freezing may also increase the length of labor. It is a local anaesthetic of the amide group.

Bupivacaine was discovered in 1957. It is on the World Health Organization's List of Essential Medicines. Bupivacaine is available as a generic medication. An implantable formulation of bupivacaine (Xaracoll) was approved for medical use in the United States in August 2020.

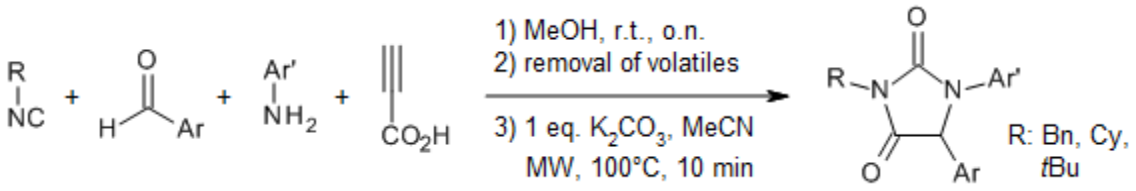


Bupivacaine

Recent Literature



G. van der Heiden, *Org. Lett.*, 2016, *18*, 984-987.



Z.-G. Xu, *Synlett*, 2018, *29*, 2199-2202.