

2.1 How to study a named reaction

Every named reaction in this unit is examined in the same four parts: what bond is made or broken, the reagents and conditions, the mechanism in words, and where the reaction earns its keep in synthesis, especially of drugs. A reaction that forms a carbon-carbon or carbon-heteroatom bond under mild, predictable conditions survives in textbooks because process chemists can trust it at scale.

2.2 Ugi reaction

The **Ugi reaction** is a four component condensation: a carboxylic acid, an aldehyde (or ketone), an amine and an isocyanide combine in one pot to give a dipeptide like product, an alpha-(acylamino)amide, with water as the only byproduct.

Mechanism in words: the amine and aldehyde first condense to an imine. The carboxylic acid protonates the imine, and the isocyanide carbon, which is both nucleophilic and electrophilic, adds to the iminium carbon, giving a nitrilium ion. The carboxylate traps the nitrilium ion, and the resulting imidate undergoes the key irreversible step, the **Mumm rearrangement**, an acyl transfer from oxygen to the neighbouring nitrogen, which fixes the final amide skeleton.

Scope and applications: all four components can be varied independently, so one reaction generates a whole library of products, which made the Ugi reaction a foundation of combinatorial and medicinal chemistry. It builds peptidomimetic scaffolds and heterocycle precursors, and Ugi products can be cyclised in second steps to imidazoles, benzodiazepines and other drug nuclei met in Unit 4. Limitations: the need for an isocyanide (unpleasant, sometimes unstable) and modest stereocontrol at the new centre.

Ugi four component reaction, step by step

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amine + aldehyde -> imine + water
imine + carboxylic acid -> iminium carboxylate pair
isocyanide carbon adds to the iminium carbon -> nitrilium ion
carboxylate traps the nitrilium ion -> imidate intermediate
Mumm rearrangement (O to N acyl transfer) -> dipeptide like product
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2.3 Brook rearrangement

The **Brook rearrangement** is the migration of a silyl group from carbon to an adjacent oxygen: an alpha-silyl alkoxide rearranges so that silicon ends on oxygen and the negative charge ends on carbon. The driving force is the great strength of the silicon-oxygen bond compared with the silicon-carbon bond. The migration is intramolecular, passes through a three membered cyclic transition state, and usually proceeds with retention of configuration at silicon and at carbon.

The **retro-Brook** rearrangement runs the other way when a carbanion is better stabilised than the alkoxide. Synthetically, the Brook rearrangement converts an acylsilane addition product into a protected cyanohydrin equivalent: addition of a nucleophile to an acylsilane, Brook rearrangement and alkylation turns the carbonyl carbon into a nucleophile, an umpolung (polarity inversion) device that reappears in the retrosynthesis logic of Unit 5.

2.4 Ullmann coupling reactions

The classical **Ullmann reaction** couples two aryl halides with copper metal at high temperature to give a biaryl. In its modern, far more useful form, copper catalysis couples an aryl halide with a nucleophile: phenols give diaryl ethers (Ullmann ether synthesis), amines and amides give N-aryl products (the Goldberg coupling), and thiols give diaryl sulfides.

Conditions and mechanism: copper(I) salts or copper metal with a ligand (diamines, amino acids and phenanthrolines are common) in a polar solvent with a base such as potassium carbonate or cesium carbonate, typically at 80 to 110 degrees C in the modern version. The mechanism is discussed in terms of oxidative addition of the aryl halide to copper(I), coordination of the nucleophile, and reductive elimination from a copper(III) intermediate, though radical pathways operate in some systems; for examination purposes the copper(I)/copper(III) cycle is the expected account.

Scope and applications: aryl chlorides are sluggish unless activated; bromides and iodides are standard. Diaryl ether and N-aryl units appear throughout drug chemistry (the diaryl ether of thyroid hormones and of several kinase inhibitors, N-aryl amides and sulfonamides), and Ullmann conditions are often cheaper than palladium catalysis at process scale, which keeps the reaction industrially important.

2.5 Dieckmann reaction

The **Dieckmann reaction** (Dieckmann condensation) is the intramolecular Claisen condensation of a diester: a base removes an alpha proton from one ester group, the enolate attacks the other ester carbonyl inside the same molecule, and a cyclic beta-keto ester results after work up.

Key points: it works best for five and six membered rings, giving 2-carbalkoxycyclopentanones and cyclohexanones from adipate and pimelate esters; a full equivalent of base is needed because the product beta-keto ester (pKa about 11) is deprotonated and pulls the equilibrium forward, and the alkoxide base should match the ester alkoxy group to avoid transesterification. One ester group must carry an alpha hydrogen. Hydrolysis and decarboxylation then deliver the cyclic ketone itself, making Dieckmann a standard ring closing step (see also Unit 5). Crossed Dieckmann reactions are useful only when one partner has no alpha hydrogen or geometry strongly favours one pairing.

2.6 Doebner-Miller reaction

The **Doebner-Miller reaction** synthesises quinolines from an aniline and two molecules of an alpha,beta-unsaturated carbonyl compound (or a mixture of aldehydes that forms one in situ), under acidic, oxidising conditions.

Mechanism in words: the aniline first adds conjugately (Michael addition) to the enal or enone; the resulting secondary amine condenses with a second molecule of the carbonyl compound to an imine; acid catalysed cyclisation onto the aromatic ring closes the second ring, and oxidation (by nitrobenzene, arsenic acid or the excess carbonyl compound in classical conditions) aromatises the dihydroquinoline to the quinoline. It belongs to the same family as the Skraup synthesis (aniline, glycerol, oxidant) and is compared with the Combes synthesis in Unit 4: Doebner-Miller builds the ring from an enone side chain, Combes from a 1,3-diketone.

Applications: 2-methyl and 2,4-disubstituted quinolines and, by varying the aniline, ring substituted quinolines, the nucleus of antimalarial and antibacterial drugs (Unit 4).

2.7 Sandmeyer reaction

The **Sandmeyer reaction** replaces the diazonium group of an arenediazonium salt with chlorine, bromine or cyanide using copper(I) salts (CuCl, CuBr, CuCN) as catalysts.

Mechanism in words: the reaction is radical, not ionic. Copper(I) transfers one electron to the diazonium ion, nitrogen is lost and an aryl radical forms; the radical then takes the halogen or cyano ligand from the copper(II) species formed in the first step, giving the product and regenerating copper(I). This explains why Sandmeyer conditions succeed where direct ionic substitution on the ring would fail.

Scope and applications: arenediazonium salts are made from anilines with sodium nitrite and acid at 0 to 5 degrees C, so the Sandmeyer reaction converts the amino group, itself installed by nitration and reduction, into Cl, Br or CN at a defined position. The nitrile product hydrolyses to benzoic acids, so the sequence NH₂ to N₂⁺ to CN to COOH is a standard way to put a carboxyl group where direct methods cannot. Related replacements need no copper: water gives phenols, ethanol or hypophosphorous acid removes the group entirely (deamination), and potassium iodide alone gives aryl iodides. Fluoride is installed by the Balz-Schiemann reaction (diazonium tetrafluoroborate, heat). Aryl halides and nitriles made this way feed cross coupling chemistry such as the Suzuki reaction below.

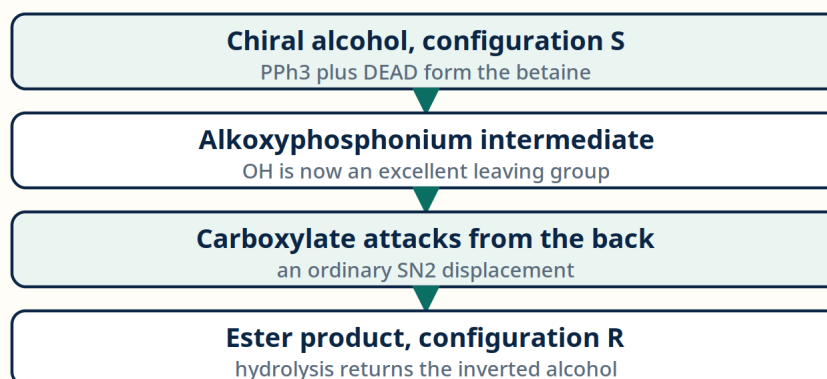
2.8 Mitsunobu reaction

The **Mitsunobu reaction** converts an alcohol into an ester, ether, amine or other substitution product **with inversion of configuration**, under remarkably mild and nearly neutral conditions. The reagent pair is triphenylphosphine and diethyl azodicarboxylate (DEAD, Unit 3), with the incoming nucleophile present as a weak acid (pronucleophile of pK_a below about 13: carboxylic acids, phenols, phthalimide, hydrazoic acid, sulfonamides).

Mechanism in words: triphenylphosphine adds to DEAD to give a betaine, which deprotonates the pronucleophile. The alcohol then displaces on phosphorus, forming an alkoxyphosphonium ion: the poor leaving group OH has been converted into an excellent one, triphenylphosphine oxide in waiting. The nucleophile anion attacks the carbon from the back in a clean S_N2 step, so the configuration inverts, and triphenylphosphine oxide precipitates as the thermodynamic sink of the whole process.

Scope and applications: primary and secondary alcohols react; tertiary alcohols fail because the S_N2 step is blocked. Its great synthetic value is stereochemical: a secondary alcohol of the wrong configuration for a target is inverted while being functionalised, a standard correction in carbohydrate, nucleoside and macrolide synthesis and in medicinal chemistry routes to chiral ethers and amines (phthalimide product, then hydrolysis, gives the inverted amine by the Gabriel logic). The drawbacks are stoichiometric triphenylphosphine oxide and hydrazine byproducts, which complicate purification and process scale use.

Mitsunobu Reaction: Inversion Step by Step



Stoichiometric waste: triphenylphosphine oxide and the reduced hydrazine ester.

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Figure: The Mitsunobu sequence. The key step is an ordinary SN2 displacement, which is why the configuration inverts.

2.9 Mannich reaction

The **Mannich reaction** joins three components: a compound with an acidic alpha hydrogen (usually a ketone), formaldehyde and ammonia or a primary or secondary amine, to give a beta-amino carbonyl compound, a **Mannich base**.

Mechanism in words: formaldehyde and the amine condense to an iminium ion (with dimethylamine, the preformed Eschenmoser salt is the same species bottled). The enol or enolate form of the carbonyl compound attacks the iminium carbon as a nucleophile, exactly as in an aldol reaction but with C=N in place of C=O. Acidic or basic conditions both work, matching the enol or enolate pathway.

Applications: Mannich bases are versatile intermediates: quaternisation and Hofmann elimination of the amino group reveals an alpha,beta-unsaturated carbonyl, making the Mannich reaction a controlled equivalent of direct alpha-methylenation. The classic target example is Robinson's tropinone synthesis, in which a double Mannich reaction builds the bicyclic alkaloid skeleton in one step, and Mannich bases themselves occur in drug structures and as intermediates toward analgesics and other amines. Phenols undergo ortho aminomethylation by the same reaction.

2.10 Vilsmeier-Haack reaction

The **Vilsmeier-Haack reaction** formylates electron rich aromatic and heteroaromatic rings. The reagent is made from dimethylformamide and phosphorus oxychloride (or oxalyl chloride): DMF attacks the chlorinating agent and chloride displaces to give the chloroiminium salt, **the Vilsmeier reagent**, $[\text{Cl}-\text{CH}=\text{N}^+(\text{CH}_3)_2] \text{Cl}^-$, a compact electrophile.

Mechanism in words: the aromatic ring attacks the iminium carbon in an ordinary electrophilic aromatic substitution; the sigma complex loses its proton to give an aryl iminium salt, and aqueous work up hydrolyses the iminium to the aldehyde. Formylation therefore appears at the most electron rich free position, para to a dialkylamino group on benzene rings, and at the alpha position of pyrroles and indoles.

Scope and applications: the ring must be activated: dialkyl anilines, phenol ethers and, above all, heteroaromatics such as pyrrole, indole, furan and thiophene react well; plain benzene and deactivated rings do not. Indole-3-carbaldehydes and pyrrole-2-carbaldehydes made this way are standard building blocks for drug synthesis, and the reaction also converts ketones to beta-chloroacraldehydes (the Vilsmeier-Haack-Arnold variant used for pyridine and quinoline ring construction).

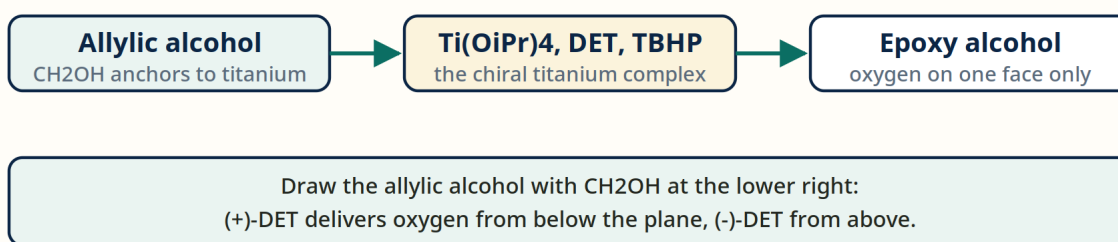
2.11 Sharpless asymmetric epoxidation

The **Sharpless asymmetric epoxidation** converts an allylic alcohol into an epoxy alcohol with high enantioselectivity, using tert-butyl hydroperoxide (TBHP) as oxidant, titanium tetraisopropoxide as catalyst and a diethyl tartrate (DET) ester as the chiral ligand.

Mechanism in words: titanium binds the tartrate, the hydroperoxide and the allylic alcohol in one chiral complex; the alcohol group is essential because it anchors the substrate to the metal. Oxygen is delivered from the bound peroxide to one face of the double bond, selected by the tartrate. The mnemonic: draw the allylic alcohol with the CH₂OH group at the lower right and the double bond horizontal; (+)-diethyl tartrate delivers oxygen from below the plane and (-)-diethyl tartrate from above. The drawing rule and the reagent must always be quoted together.

Scope and applications: only allylic alcohols react, but predictably, and the epoxy alcohol products open regioselectively to diols, amino alcohols and other three carbon units. The reaction is a landmark of asymmetric synthesis, used for intermediates toward beta blockers, statins and many chiral building blocks; with a racemic allylic alcohol, one enantiomer is epoxidised much faster, giving a kinetic resolution.

Sharpless Asymmetric Epoxidation



Only allylic alcohols react, but they react with predictable stereochemistry.

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Figure: Sharpless epoxidation and its mnemonic. The tartrate enantiomer selects the face that receives the oxygen.

2.12 Baeyer-Villiger oxidation

The **Baeyer-Villiger oxidation** converts a ketone into an ester, or a cyclic ketone into a lactone, by inserting one oxygen atom next to the carbonyl. The oxidant is a peracid (m-chloroperbenzoic acid, MCPBA, is standard; peracetic acid, trifluoroperacetic acid and hydrogen peroxide systems are also used).

Mechanism in words: the peracid adds to the carbonyl carbon, giving the tetrahedral **Criegee intermediate**. In the slow step, the group anti-periplanar to the O-O bond migrates from carbon to the outer oxygen as the weak O-O bond breaks and the carboxylate leaves; the migrating group keeps its configuration because it moves with its bonding pair and never becomes free. Migration aptitude follows the ability to support partial positive charge: tertiary alkyl > secondary alkyl and phenyl > primary alkyl > methyl, and electron rich aryl groups migrate faster than electron poor ones.

Applications: ring expansion of cyclic ketones to lactones (cyclohexanone to epsilon-caprolactone, the monomer of a biodegradable polyester), synthesis of esters from aryl methyl ketones where the aryl group migrates, and the Dakin oxidation of hydroxy aryl ketones noted in Unit 1. In medicinal chemistry it is a clean way to place an ester oxygen inside a carbon skeleton and a standard step in steroid and macrolide intermediate synthesis.

2.13 Shapiro reaction

The **Shapiro reaction** converts a ketone into an alkene by way of its tosylhydrazone. Treatment of the tosylhydrazone with two equivalents of an alkyl lithium (usually butyllithium) gives a vinyl lithium, which is protonated on work up to the alkene or trapped with other electrophiles.

Mechanism in words: the first equivalent of base removes the sulfonamide N-H proton; the second removes a proton from the carbon alpha to the C=N bond, on the less hindered side where possible. The resulting dianion expels the sulfinate group and nitrogen to leave a vinyl anion equivalent, the vinyl lithium, with the double bond between the carbonyl carbon and the deprotonated alpha carbon. The regiochemistry is therefore set by which alpha proton is removed, and the less substituted alkene is typically formed, a useful contrast with acid catalysed dehydration, which favours the more substituted alkene through the E1 pathway.

Comparison and applications: the Bamford-Stevens reaction (tosylhydrazone with base and heat) passes through a diazo compound and a carbene, giving more rearrangement; the Shapiro conditions are colder, anionic and cleaner. The great value of the Shapiro reaction is the vinyl lithium itself: quenching with carbon dioxide gives alpha,beta-unsaturated acids, with aldehydes gives allylic alcohols, and with other electrophiles gives substituted alkenes of defined geometry, making it a carbonyl to vinyl anion umpolung used in complex molecule synthesis.

2.14 Suzuki reaction

The **Suzuki reaction** (Suzuki-Miyaura coupling) joins an aryl or vinyl halide (or triflate) to an organoboron partner, an aryl or vinyl boronic acid or ester, under palladium catalysis with a base, forming a new carbon-carbon bond. It is the most widely used cross coupling in medicinal chemistry.

The catalytic cycle in words: palladium(0) **oxidatively adds** into the carbon-halogen bond, giving a palladium(II) complex and raising the metal oxidation state by two. The base activates the boronic acid to a boronate, which **transmetalates**: the organic group moves from boron to palladium, displacing the halide. The two organic groups on palladium then **reductively eliminate**, forming the C-C bond and returning palladium(0) to the cycle. The geometry at a vinyl partner is retained, so defined alkene geometry survives the coupling.

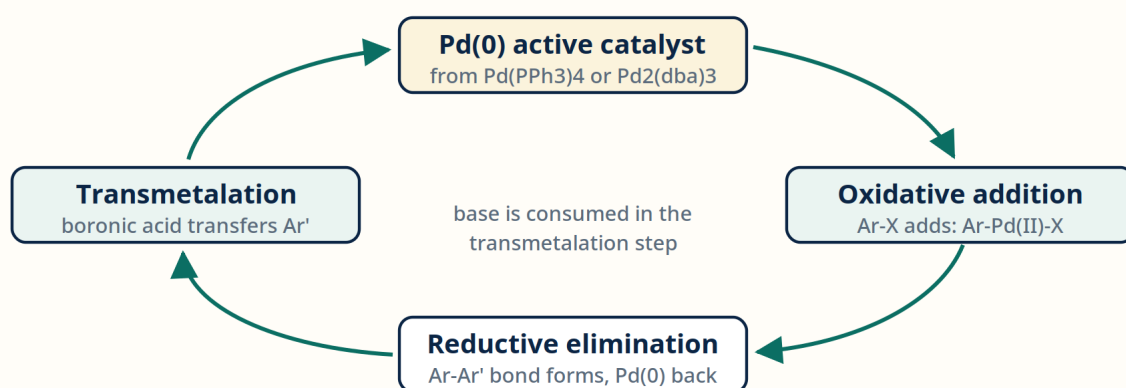
Suzuki catalytic cycle

Pd(0) catalyst

- | | |
|--|--------------------------------|
| -> oxidative addition of Ar-X | : Ar-Pd(II)-X |
| -> base activates Ar'-B(OH) ₂ | : boronate formed |
| -> transmetalation | : Ar-Pd(II)-Ar' |
| -> reductive elimination | : Ar-Ar' product + Pd(0) again |

Scope and applications: the reaction tolerates most functional groups, the boronic acids are stable, storable and low in toxicity, and conditions are mild (aqueous base, 60 to 100 degrees C). Biaryl products are everywhere in drug chemistry: the biphenyl unit of losartan and the other sartans, and countless kinase inhibitor and agrochemical intermediates, are assembled by Suzuki coupling. Limitations to note: protodeboronation of electron poor or heteroaryl boronic acids, homocoupling of either partner as a side reaction, and the need to remove residual palladium from pharmaceutical products to strict limits.

Suzuki Coupling: The Catalytic Cycle



One turn joins one aryl halide to one boronic acid: the biphenyl bond of losartan is made this way.

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Figure: The Suzuki catalytic cycle. Three steps repeat until the aryl halide is consumed.

2.15 Ozonolysis

Ozonolysis cleaves carbon-carbon double bonds with ozone. Ozone adds across the alkene to give a primary ozonide (molozonide), which rearranges to the more stable ozonide; work up then converts the ozonide into carbonyl products.

Work up decides the products: a reductive work up (zinc and water, dimethyl sulfide or triphenylphosphine) gives aldehydes and ketones, preserving aldehydes as aldehydes; an oxidative work up (hydrogen peroxide) carries aldehydes on to carboxylic acids. Alkynes cleave to carboxylic acids.

Applications: the classical use is structural determination: locating a double bond in an unknown alkene by identifying the two carbonyl fragments, a method that belongs to the era before routine spectroscopy and is still examined for that logic. Synthetically, ozonolysis converts cyclic alkenes into dicarbonyl compounds (cyclohexene gives hexanedial) for ring opening strategies in retrosynthesis (Unit 5), and converts terminal alkenes into one carbon shorter aldehydes. Ozonides are explosive and are not isolated in process work; modern practice uses flow reactors or in situ quenching, a safety point worth stating in any examination answer.

2.16 Michael addition reaction

The **Michael addition** is the conjugate (1,4) addition of a nucleophile, the **Michael donor**, to an α,β -unsaturated carbonyl or similar activated alkene, the **Michael acceptor**. Donors are stabilised carbanions: malonic and acetoacetic esters, nitro compounds, thiols, amines and enolates generally. Acceptors carry electron withdrawing groups: enones, enals, acrylates, acrylonitrile and nitroalkenes.

Mechanism in words: the nucleophile attacks the beta carbon, not the carbonyl carbon, because the resulting negative charge lands on oxygen as an enolate, the most stable anion available. Protonation of the enolate at carbon completes the addition and the carbonyl survives intact. The competition with direct 1,2 addition is decided by the nucleophile: soft, stabilised nucleophiles and cuprates favour 1,4 addition; hard organolithiums and Grignard reagents favour 1,2 addition to the carbonyl.

Applications: the Michael addition is the reliable way to build a 1,5-dicarbonyl pattern and therefore sits inside the Robinson annulation (Michael addition of a ketone enolate to methyl vinyl ketone, then intramolecular aldol) that constructs steroid and terpene ring systems. Thiol Michael additions are used to attach linker units in antibody-drug conjugate chemistry, and aza-Michael additions of amines appear in

many alkaloid and drug routes. In retrosynthesis (Unit 5) a 1,5-difunctional relationship is the signal to disconnect by a Michael reaction.

2.17 Fischer indole synthesis

The **Fischer indole synthesis** (present in the KBH syllabus copy of this unit) converts a phenylhydrazone of an aldehyde or ketone into an indole on heating with an acid catalyst such as zinc chloride, polyphosphoric acid or a Lewis acid.

Mechanism in words: the phenylhydrazone tautomerises to its ene-hydrazine form; this undergoes a [3,3]-sigmatropic rearrangement that sets two new bonds on the ring; the resulting diamine cyclises onto the imine carbon, and ammonia is lost to aromatise the five membered ring. With an unsymmetrical ketone, two regioisomeric indoles can form; the more substituted side usually dominates under thermodynamic acid conditions.

Applications: indole is one of the most common nuclei in drugs (the triptans, indomethacin and many alkaloids), and the Fischer synthesis remains a first choice route because phenylhydrazines and carbonyl compounds are cheap and varied.

2.18 Multi-component reactions in outline

The KBH syllabus copy groups several named condensations as **multi-component synthesis**, in which three or more reactants assemble in one pot with most atoms retained in the product. The Ugi reaction of section 2.2 is the four component member. The others named there, in outline:

- **Biginelli reaction:** an aldehyde, urea and a beta-keto ester condense under acid catalysis to a dihydropyrimidinone (DHPM), a calcium channel and mitotic spindle (monastrol) pharmacophore, through an iminium ion, enol addition and cyclodehydration.
- **Hantzsch reaction:** two molecules of a beta-keto ester, an aldehyde and ammonia give a dihydropyridine, the synthesis of the nifedipine family of calcium channel blockers, whose dihydropyridine ring is the drug itself.
- **Passerini reaction:** a carboxylic acid, an aldehyde and an isocyanide give an alpha-(acyloxy)amide in one step, the three component relative of the Ugi reaction.
- **Strecker synthesis:** an aldehyde, ammonia and hydrogen cyanide give an alpha-aminonitrile, hydrolysed to an alpha-amino acid; the first amino acid synthesis.
- **Bucherer-Bergs reaction:** a ketone with potassium cyanide and ammonium carbonate gives a hydantoin; the classical synthesis of the phenytoin ring system.

Their shared medicinal chemistry value is speed of diversity: many analogues from one reaction by varying each input, which is why they anchor screening library synthesis.

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