A Green Approach to Selected Organic Reactions

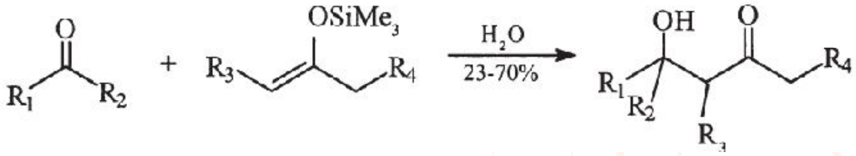
(Student references)

Green Synthesis of Organic compounds

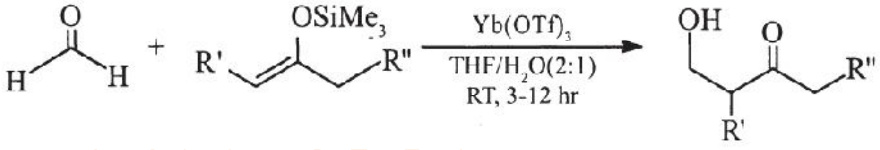
Aldol Condensation

A) Using aqueous media

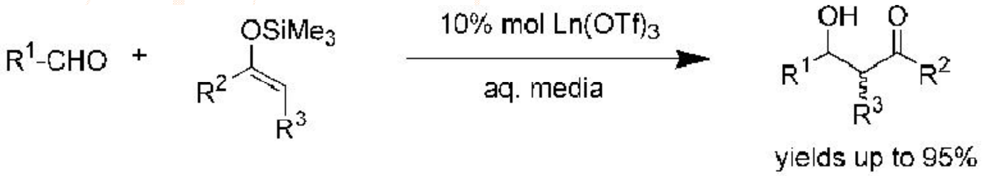
The first green reaction of cross Aldol condensation between silyl enol ethers and aldehydes was reported in water without using acid catalyst. Being a weak Lewis acid, the reactions took long time for completion and the yields are low.



The addition of a stronger Lewis acid such as lanthanide triflate significantly improved the rate and yield (77 —98 %) of the reactions. Metal triflate might soluble the substrate probably through coordination.

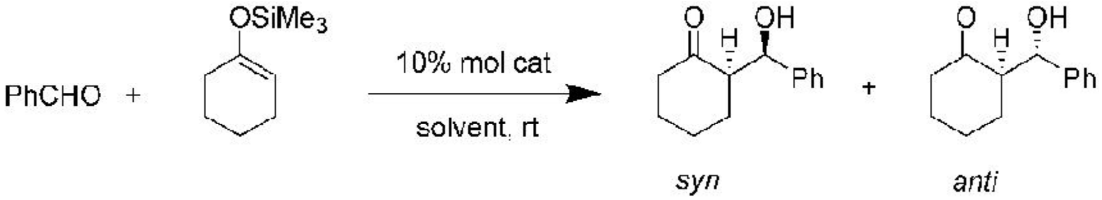


Mukaiyama aldol reaction

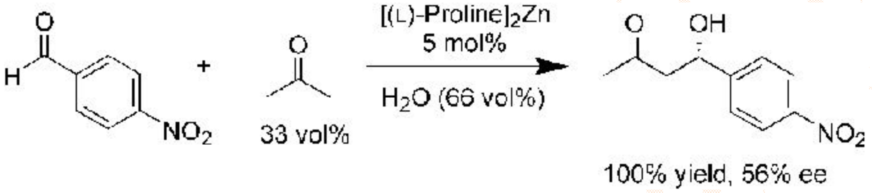


R^1 = H, C_6H_5, C_6H_5-CH_2CH_2, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *o*-HOC_6H_4, CH_3, $CH_2{=}CH$, $ClCH_2$, C_6H_5CO, etc..
Ln = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu

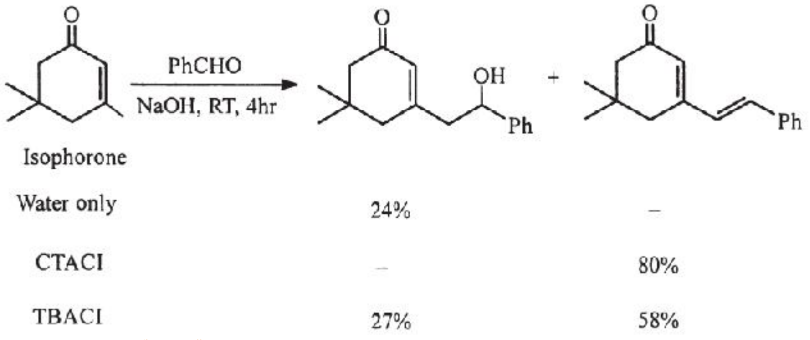
The aldol type reaction between a silyl enol ether and an aldehyde in water at room temperature using various lanthanides triflates is called Mukaiyama aldol reaction. It yields high syn stereoselectivity. The reaction gives low yield without catalyst in water. However, the *addition of surfactant (SDS) in combination with lanthanides triflets as Lewis acid improves the yield to a greater extent.*



In water, Zn—proline catalyst initiates cross Aldol reaction in the absence of strong bases at room temperature.



The vinylogous aldol condensation can be achieved between isophorone and benzaldehyde in water. It producs only vinylogous Aldol adduct but with low conversion. It can be improved in presence of CTACl, or tetrabutylammonium chloride (TBACl).

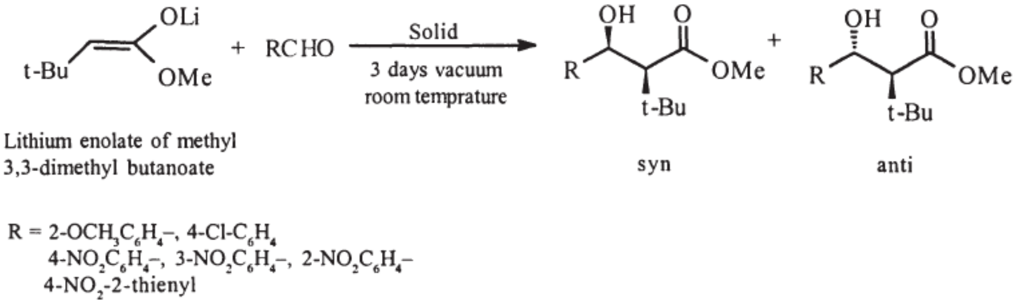


Water only	24%	–
CTACl	–	80%
TBACl	27%	58%

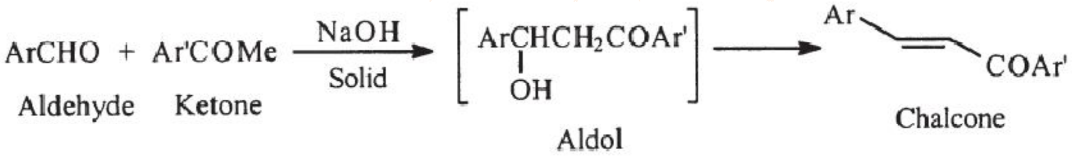
Aldol Condensation

B) Using solid phase

The Aldol condensation is carried out by mixing freshly ground mixture of the lithium enolate of methyl-3,3-dimethylbutanoate with powdered *aromatic aldehyde in vacuum for 3 days at room temperature. It produces 70% yield with stereoselective mixture syn : anti = 8:92 of the products.*



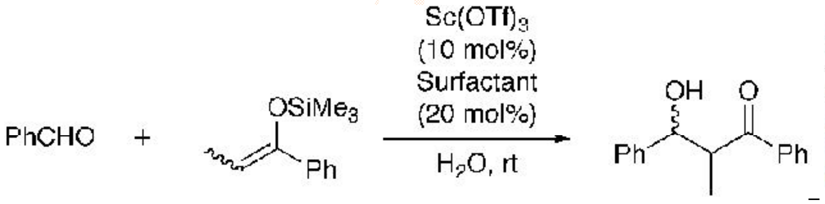
In absence of solvent, an aldehyde, ketone and NaOH are grounded in a pestle and mortar at room temperature for 5 min. The product is chalcone.



Aldol condensation

C) Using surfactant (Micellar catalysis)

A Lewis acid-surfactant-combined catalyst is demonstrated in the Aldol reaction. The idea is to form an emulsion from surfactant in water in which organic compounds can reside.

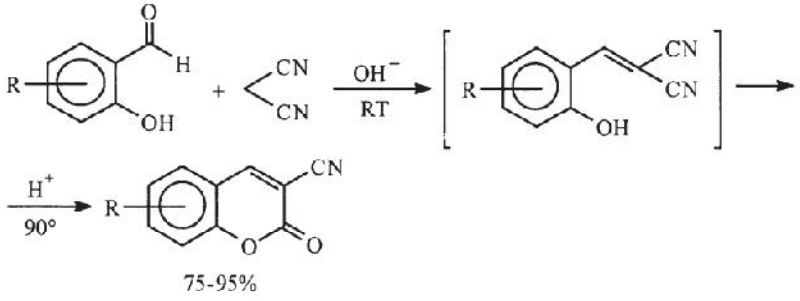


Surfactant	Time (h)	Yield (%)
None	4	3
SDS	4	88
Triton X-100	60	89
CTAB	4	Trace

Knoevenagel Reaction

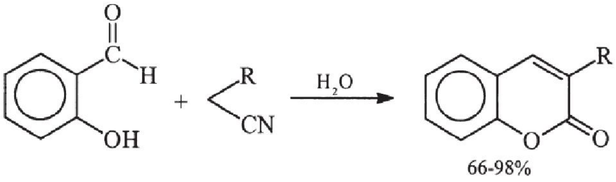
A) Using aqueous media

In water, the Knoevenagel reaction is carried out between aldehydes and acetonitrile. Employing heterogeneous aqueous alkaline medium, various substituted salicylaldehyde react with malononitrile at room temperature to yield a-hydroxybenzylidene malononitriles, which are converted directly to 3-cyanocoumarins by acidification on heating.



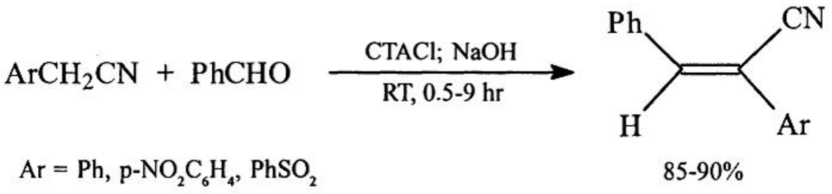
R = H, OH, OMe

Similarly, the use of substituted acetonitriles renders corresponding 3-substituted coumarins with salisaldehyde in 66-98% yields.

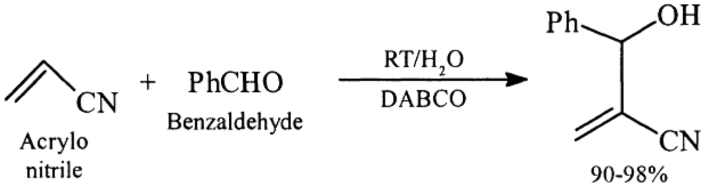


R = CN, CO_2Et, NO_2, Ph, 2-Py

The reaction of benzaldehyde with acetonitrile does not occur in water only but requires the presence of catalytic amount of phase transfer catalyst (PTC) such as CTAC or TBAC to give high yields of the corresponding arylcinnamonitriles.



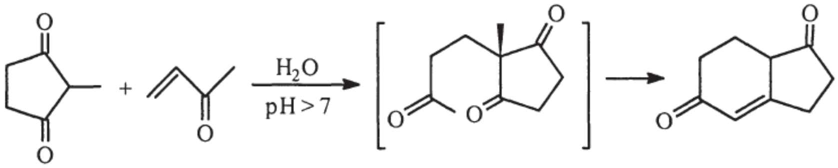
DABCO assisted Knoevenagel-type addition product can be obtained by the reaction of acrylic derivatives in water.



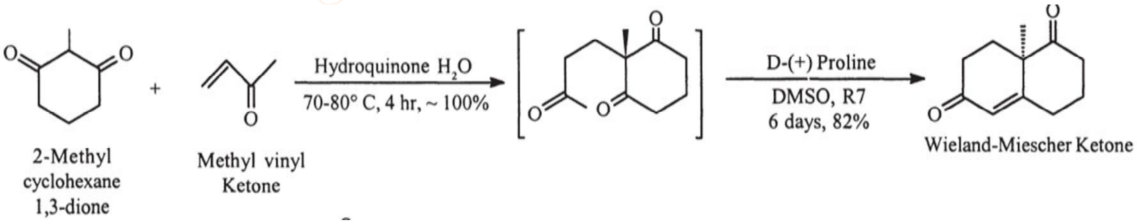
Michael reaction

A) Using aqueous phase

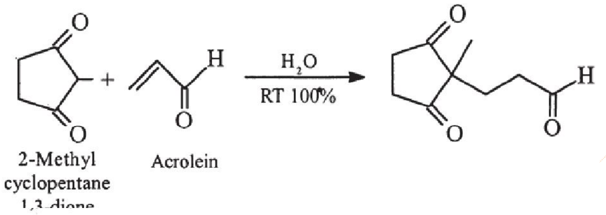
In 1970, the first successful Michael reaction between 2-Methylcyclopentane-1,3-dione and vinyl ketone in aqueous medium without the use of a basic catalyst (pH > 7) was reported. The adduct further cyclises to give a 5-6 fused ring system. Interestingly, the yield was found better in water as compared to methanol as solvent.

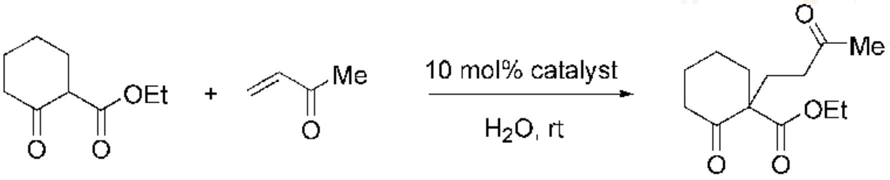


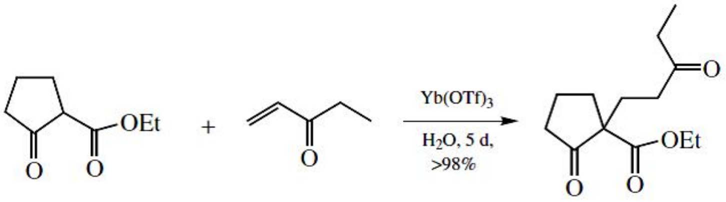
Michael reaction of2-methyl-cyc1ohexane-1,3-dione with vinylketone give optically pure ***Wieland-Miescher ketone****.*



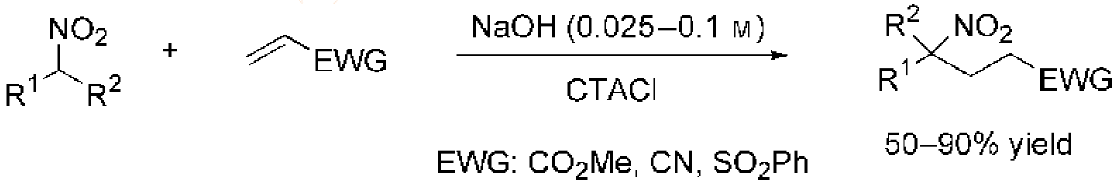
The Michael addition of 2-methyl-cyclopentane 1,3-dione and acrolein in water furnishes an adduct and the rate can be enhanced by the addition of ytterbium triflate [yb(OTf)3] or scandium triflate [Sc(OTf)3].

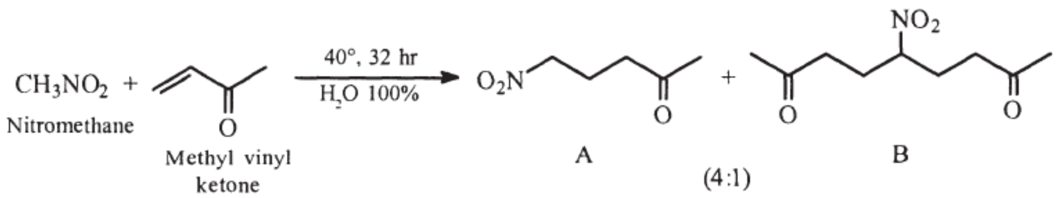




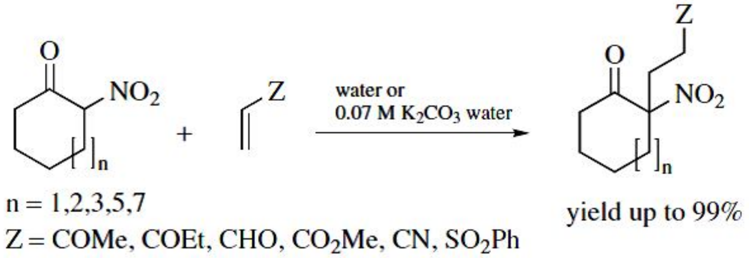


Without using organic solvent, nitroalkanes can be condensed with different electrophilic alkenes in NaOH (0.025–0.1 M), affording Michael adducts with moderate to good yields provided a catalytic amount of cetyltrimethylammonium chloride (CTACl) is employed. The Michael addition of nitro methane to methyl vinyl ketone in water (in absence of a catalyst) gave 4: 1 mixture of adducts. The reaction fails to give products in neat conditions or in solvents like THF, PhMe etc. in the absence of a catalyst.

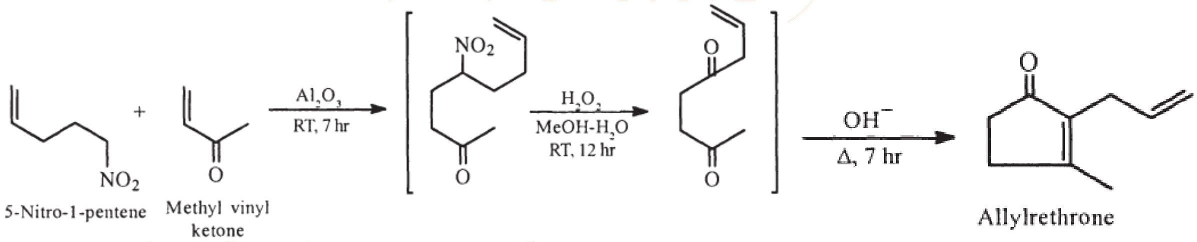




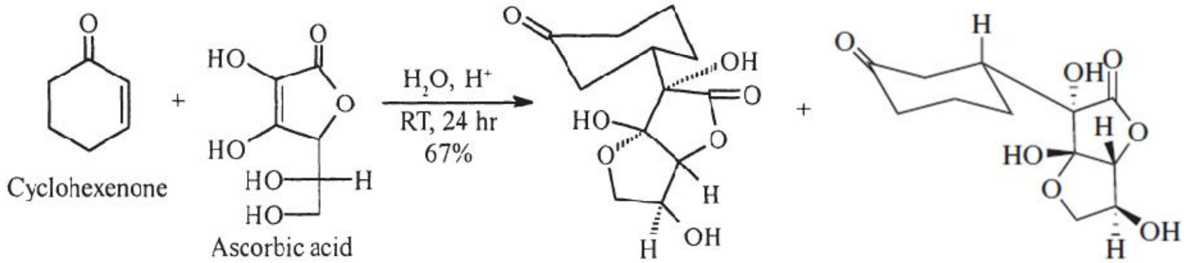
In a very dilute aqueous solution of potassium carbonate, a variety of unsaturated carbonyls gives selective Michael additions with α-nitrocycloalkanones at room temperature without adding catalyst.



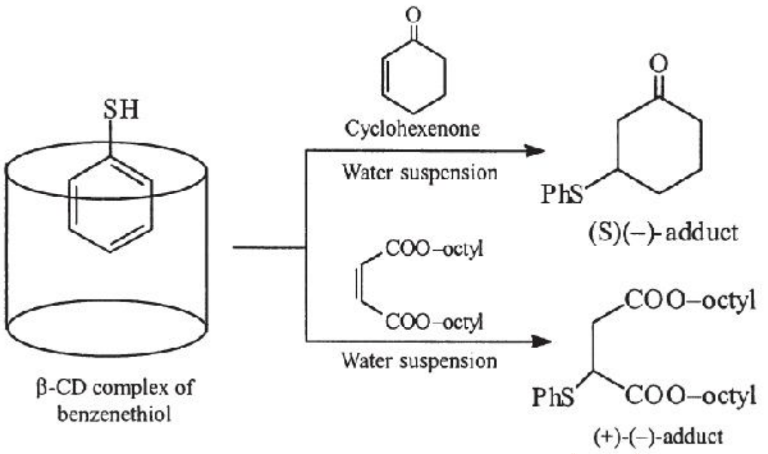
A combination of Michael and intramolecular Aldol condensation is shown below.

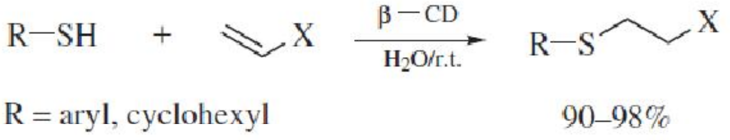


The Michael reaction between cyclohexenone and ascorbic acid offers isomeric adducts in acidic water medium.



β—CD (cyclodextrin) mediated asymmetric Michael addition proceeds enantioselectively.

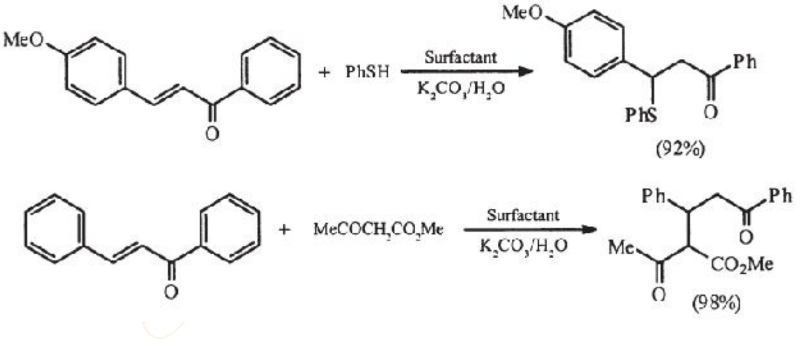




R = aryl, cyclohexyl

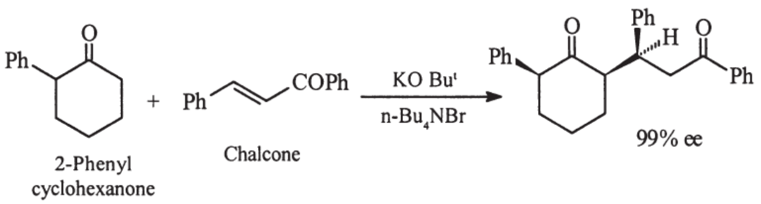
X = CHO, COMe, CN, CO_2Me, $CONH_2$

Surfactant such as hexadecyltrimethylammonium bromide induces the Michael reaction of stirring suspension of powdered chalcone in a little amount of water containing PhSH or methyl acetoacetate or n-Bu2NH . It produces adduct within 2 hr in 98% yield.

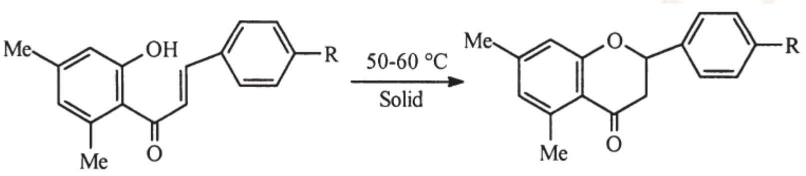


B) Using solid phase

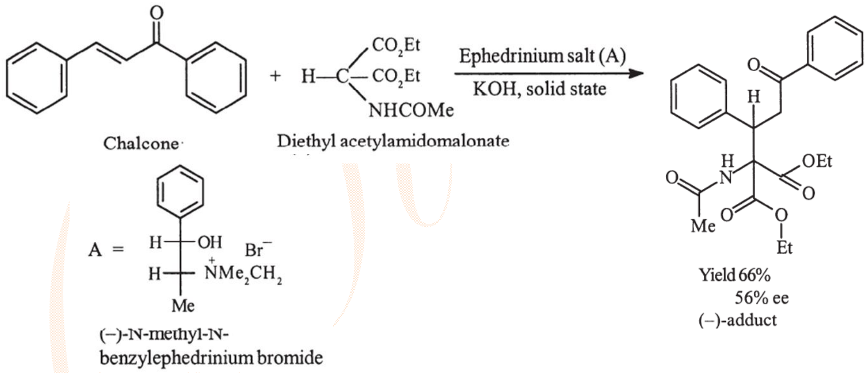
Chalcone forms Michael adduct with 2-phenylcyclohexanone in presence of PTC leading to high distereoselectivity of product.



Chalcones undergo typical intramolcular Michael addition reaction in solid phase to yield flavonones.



Using asymmetric phase transfer catalyst (ephedrinium salts), chalcones forms an Michael adduct with diethyl(acetylamido) malonate in presence of KOH in the solid state.



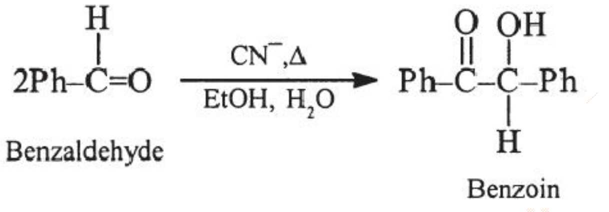
Dieckmann Condensation

Dieckman condensation of diesters can be carried out in solid state in presence of a base (like Na or NaOEt) using high-dilution conditions in order to avoid intermolecular reaction. Using bases like like EtONa, EtOK Bu^tONa or Bu^tOK, the Dieckman condensation of diethyl adipate and pimelate proceed with good yield in absence of the solvent.

Green Synthesis of Organic compounds

Benzoin Condensation

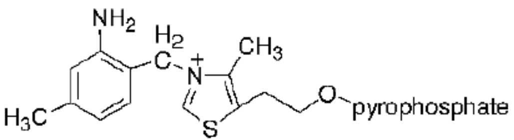
In aqueous ethanolic solution, aromatic aldehydes undergo Benzoin condensation with sodium or potassium cyanide to form benzoins.



$$2\,Ph\text{–}CHO \xrightarrow[EtOH,\ H_2O]{CN^-,\Delta} Ph\text{–}CO\text{–}CH(OH)\text{–}Ph$$

Phase transfer catalyst (PTC) such as quaternary ammonium cyanide strongly catalyses Benzoin condensation of aldehydes. Breslow reported that the Benzoin condensation in aqueous media using inorganic salts (e.g., LiCl) is about 200 times faster than in ethanol without any salt. The addition of γ—cyclodextrin also accelerates the reaction, whereas the addition of β—cyclodextrin inhibits the condensation.

Vitamin B1 or Thiamine; rather thiazolium ylid catalyzes the Benzoin condensation through Green approach. The C-2 hydrogen on the thiazolium ring of thiamine is able to ionize in thiazolium ylide structure which is essentially a 'stabilized carbene'. The precursor of thiamine pyrophosphate 1, the thiazolium ylide 2 is the key to its function as a coenzyme.



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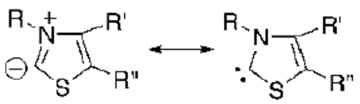

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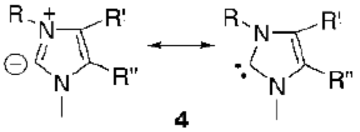

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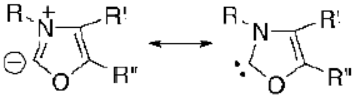

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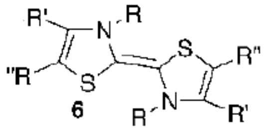

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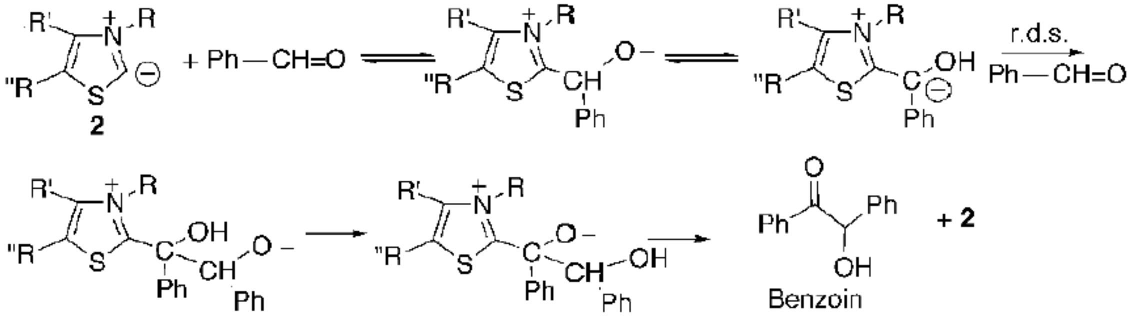
The thiazolium ylide is the intermediate in the action of thiamine pyrophosphate as a coenzyme. It is anlogous to cyanide ion. The mechanism of the thiazolium-catalyzed Benzoin condensation is shown below.

Pathway:



The rate of the cyanide-catalyzed benzoin condensation was 200-fold faster in water than in ethanol. However, the reaction in water could lead to hydrophobic accelerations. The addion of LiCl increases the reaction rate indicating the presence of some acceleration by hydrophobic packing in the transition state for the reaction.

Cannizaro Reaction

The Cannizarro reaction is catalysed by barium hydroxide under heterogenous conditions using sonication giving an yields of 100% after 10 mins. But no reaction is observed in case of using ultrasound.

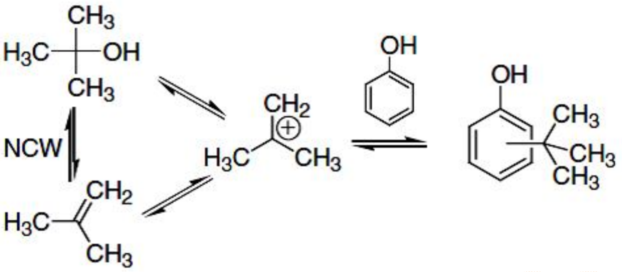
$$C_6H_5CHO \xrightarrow[)))\text{, 10 min}]{Ba(OH)_2\text{, EtOH}} C_6H_5CH_2OH + C_6H_5COOH$$

Green Synthesis of Organic compounds

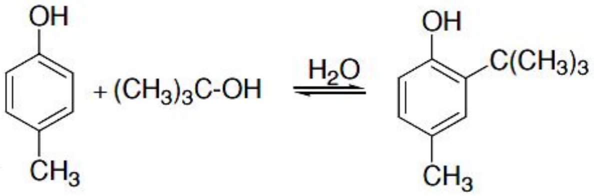
Friedel-Crafts Reaction

Alkylation of phenol

The reaction of phenol with tert-butanol in water at 250, 275, and 300 °C to produce 2-tert-butylphenol and 4-tert-butylphenol via tertiary carbocation in a completely reversible pathway. The reaction is pseudo-first order in phenol as large excess of tert-butanol is present.

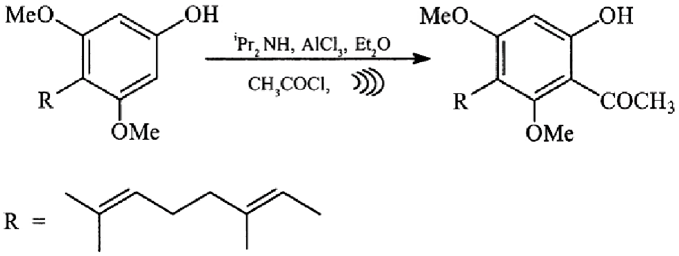


The reaction of p-cresol with tert-butanol occurs in NCW.



[Nearcritical water (NCW) is defined as water that is heated to a temperature range of 200–300 °C where its properties have begun to differ significantly from those of ambient water. NCW is also called as 'high-temperature water', 'hot water', 'subcritical water', and 'near-subcritical water'].

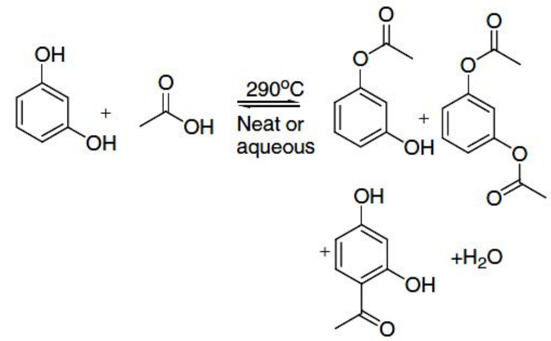
Ultrasound assisted green synthesis facilitates Friedel-Crafts acylation.



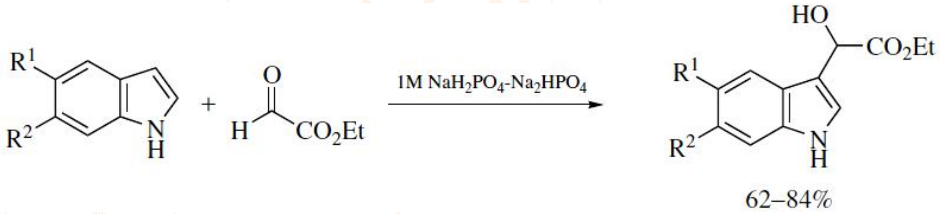
Green Synthesis of Organic compounds

Acylation of phenolics

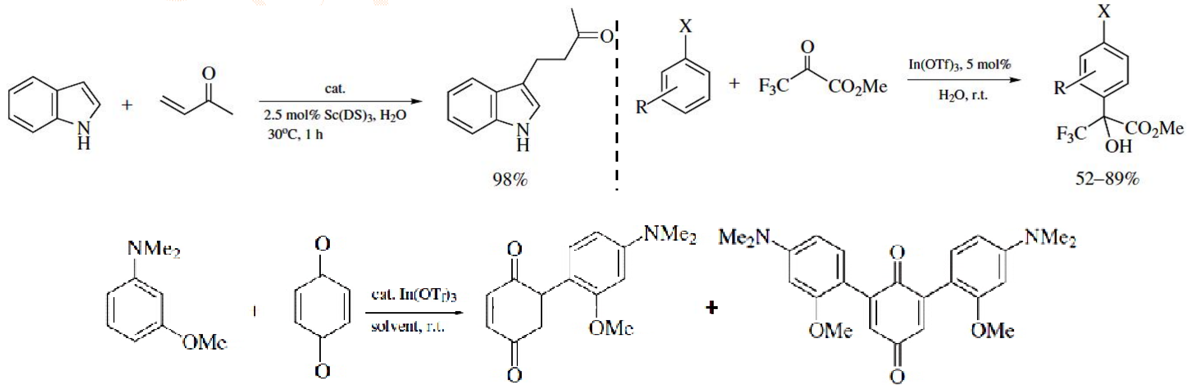
Brown et al. observed that phenol and resorcinol could be successfully acetylated using acetic acid in NCW and in neat acetic acid in the temperature range of 250–300 ◦C without adding catalyst. Like alkylation, the acetylations of phenol and resorcinol are also reversible at high temperatures in the presence of water. Thus, the yield of F/C-acylation is relatively less.



Buffer induced F/C-acylation can be accomplished with indole.



Metal triflets in water have been extensively used to carry out F/C-acylation both for aromatic and heterocyclic moieties.



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