

# Organic Synthesis under Solvent-free Condition. An Environmentally Benign Procedure – I

*Gopalpur Nagendrappa*



The author is a Professor of Organic Chemistry at Bangalore University, Bangalore. His main area of research is organosilicon chemistry with particular attention to developing new synthetic procedures and reagents, and studying the reaction mechanisms.

Though it is a common practice to run the organic reactions in solvent media, the chemists' concern to minimize the environmental pollution caused by solvents and also their academic interest in solid-solid reactions have led them in recent times to develop methodologies for solvent-free reactions with considerable success.

## The Function of a Solvent

A general assumption with regard to organic reactions is that they are performed in a solvent medium. The rationale behind this concept is simple. That is, the reactants can interact effectively if they are in a homogeneous solution, which facilitates the stirring, shaking or other ways of agitation, whereby the reactant molecules come together rapidly and continuously. Moreover, uniform heating or cooling of the mixture, if needed, can be carried out in a solution relatively easily. However, the role of a solvent in the context of an organic reaction is much more complex than merely providing a homogeneous setting for a large number of collisions of the reactants to take place. A solvent has the power to enhance or reduce the speed of a reaction, at times enormously. Changing of solvent of a reaction can influence the rate of that reaction, and it can be powerful enough to change the reaction course itself. This may manifest in altered yields and ratios of the products. Thus a solvent could be deeply and inseparably associated with the process of an organic reaction through the solvation of the reactants, products, transition-state or other intervening species. Such intimate interactions between the solvent and the reaction partners are due to many factors that include electrostatic, steric and conformational effects, among others. In spite of such a strong involvement, the solvent does not normally become part of the

### Keywords

Solvents-free reactions, eco-friendly reactions, solid-solid reactions.



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product, except in the case of solvolysis reactions, and is recovered unchanged after the reaction is over. Even then, one may not envisage or plan to perform a reaction in the absence of a solvent.

### Which Liquid can act as a Solvent?

In principle, any liquid can be used as a solvent. However, the number of commonly used solvents is severely restricted. They include a few hydrocarbons, chlorinated hydrocarbons, a few ethers, esters, alcohols, amide derivatives, sulphoxides, etc. Liquid ammonia,  $CS_2$ , and of course water, are also frequently used as medium to carry out synthesis. The suitability of a solvent for a reaction depends on many factors. An experienced investigator selects a solvent for a new reaction based on its physical and chemical properties. At times the liquid reactant itself would serve as solvent. In any case, a solvent is usually considered to be an inevitable component of a reaction. A reaction under solvent-free condition or in solid state (not to be confused with Merrifield solid-phase synthesis!) was generally thought to be not quite feasible, or at least not quite efficient, though several solid state organic reactions have been known for a long time. However, as described in [1,2], the chemists' concern for developing environment-friendly synthetic procedures has made them turn their attention to minimize or circumvent the use of solvents that are a major cause of pollution. This has led, in recent times, to vigorous research activity and reinvestigation of known reactions to achieve organic synthesis under solvent-free condition.

### Advantages of Solvent-free Reactions

A solvent-free or solid state reaction may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina or other matrices.

A solvent-free or solid state reaction may be carried out using the reactants alone or incorporating them in clays, zeolites, silica, alumina or other matrices. Thermal process or irradiation with UV, microwave or ultrasound can be employed to bring about the reaction. Solvent-free reactions obviously reduce pollution, and bring down handling costs due to simplification of experimental procedure, work up technique and saving in labour. These would be especially important during industrial production.

Often, the products of solid state reactions turn out to be different from those obtained in solution phase reactions. This is because of specific spatial orientation or packing of the reacting molecules in the crystalline state. This is true not only of the crystals of single compounds, but also of co-crystallized solids of two or even more reactant molecules. The host-guest interaction complexes obtained by simply mixing the components intimately also adopt ordered structure. The orientational requirements of the substrate molecules in the crystalline state have provided excellent opportunities to achieve high degree of stereoselectivity in the products. This has made it possible to synthesize chiral molecules from prochiral ones either by complexation with chiral hosts or formation of intermediates with chiral partners.

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### Experimental Method

If two or more substrates are involved in the reaction, they are thoroughly ground together in a glass mortar or cocrystallized, and allowed to stay at room temperature or transferred to a suitable apparatus and heated carefully in an oil bath or exposed to appropriate radiation until the reaction is complete. More sophisticated reaction procedures are also adopted, if necessary. The progress of the reaction can be monitored by TLC. In some cases, a small quantity of water or a catalyst may be added. If it is a single-compound reaction, it is subjected to heat or radiation directly. Care is to be taken to collect the volatile products, if they are produced.

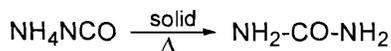
In this article illustrative examples representing a number of organic syntheses performed under both thermal and photochemical conditions are described.

### Thermal Solid State Reactions – Classic Examples

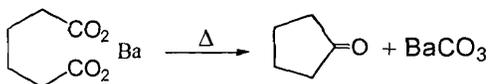
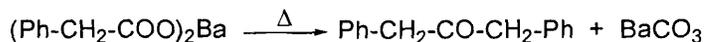
Solid state reactions are not really a new concept. Many of them can be found in undergraduate text books. In fact, the historically significant first organic synthesis of urea by Wöhler achieved in 1828 belongs to this class.



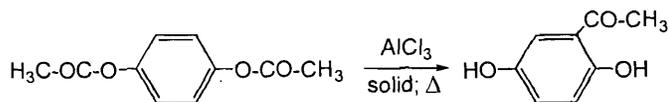
Historically significant organic synthesis achieved by Wöhler in 1828 belongs to the class of solid state reaction.



Pyrolytic distillation of barium or calcium salts of carboxylic acids to prepare ketones is even now a commonly used procedure.



Certain Friedel-Crafts reactions or the related Fries reaction are carried out in the absence of solvent.

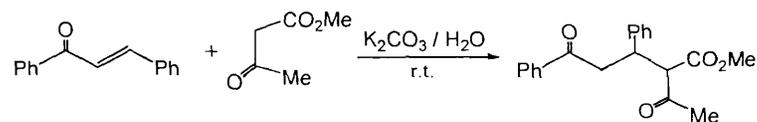
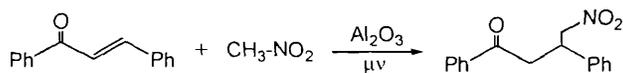


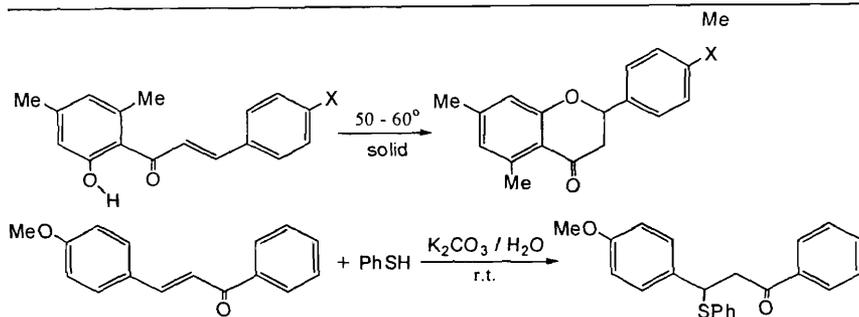
However, the following examples focus on the reactions studied in recent times with the specific purpose of conducting them under solvent-free condition. In some reactions water may have been used, but as it is harmless to the environment, such reactions are also included. It should be noted that all these reactions were conventionally being performed in organic solvent media.

### Michael Addition

The addition of a nucleophile to a carbon-carbon double bond with a strong electron-withdrawing group at the vinylic position is known as Michael addition.

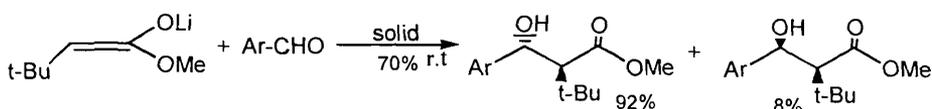
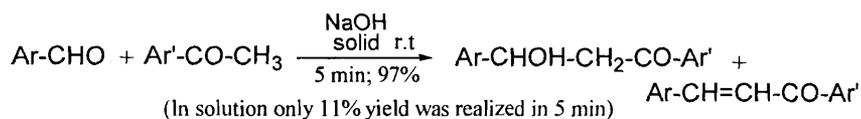
Michael addition is a reaction of a nucleophile with an  $\alpha, \beta$ -unsaturated ketone or aldehyde.



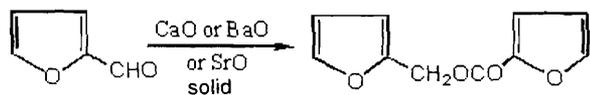


## Aldol Reaction

The addition of an enol or enolate ion of an aldehyde or a ketone to the carbonyl group of an aldehyde or a ketone is aldol addition, or aldol condensation, if water is eliminated in a subsequent step to produce  $\alpha, \beta$ -unsaturated aldehyde or ketone. Many variations of this reaction are known and are called by different names.



## Tishchenko Reaction



## Robinson Annulation

A tandem reaction comprising a Michael addition step followed by an aldol condensation to produce a cyclic compound is Robinson annulation. A number of such reactions have been successfully carried out under solvent-free condition.

The incorporation of (S)-proline in the reaction produces a chiral intermediate that ultimately yields a high percentage of

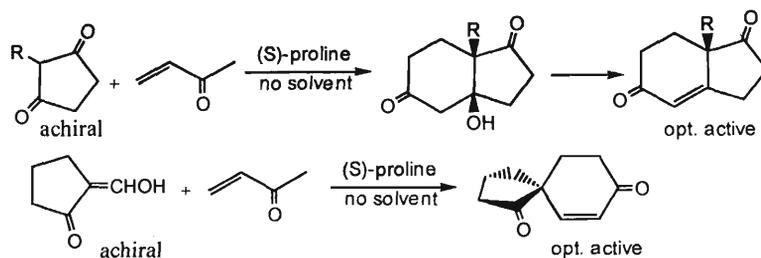
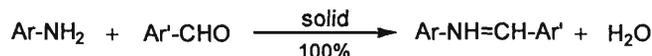
Aldol condensation is an important reaction of aldehydes and ketones in forming carbon-carbon bonds.

**Box 1. Robinson, Sir Robert (1886-1975)**

Sir Robert Robinson was one of the top most organic chemists of the twentieth century. His contribution to synthetic organic chemistry during the first half of the century is monumental. He isolated and solved the structures of many natural products that included anthocyanins (plant pigments), alkaloids, terpenes and steroids. The synthetic methods he developed were widely adopted for the synthesis of many natural products, particularly in the areas of steroids and alkaloids, which also led to commercial production of certain drugs (for example, anti-malarials). In addition, he founded the electronic theory of resonance in 1926, just when quantum chemistry was taking birth.

Robinson was born in 1886 in Bufford, Derbyshire, England. After doing his early schooling in Leeds, he obtained PhD/DSc (1910) under the guidance of W H Perkin, Jr., from the University of Manchester. He taught and researched at the universities of New South Wales, Sydney, Australia (1912-15), Liverpool (1915-21), St. Andrews (1921-22), Manchester (1922-28), London (1928-30) and Oxford (1930-55). He was knighted in 1939. He was a recipient of many prizes and medals, and was awarded the Nobel Prize in 1947 for his work on alkaloids. He was president of Royal Society during 1945-50 and the British Association for the Advancement of Science in 1955.

one enantiomer.

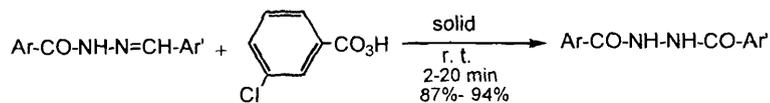
**Condensation of Amines with Carbonyl Compounds****1. Schiff's bases/Azomethines****Box 2.**

Robinson annulation (also written as annelation) is a reaction sequence consisting of a Michael addition of a cycloalkanone  $\alpha$ -carbanion to methyl vinyl ketone or its derivative, followed by aldol condensation of the resulting product. The final product of annulation will have a 2-cyclohexenone system fused to the starting alkanone. The method has found extensive application in organic synthesis, especially in the areas of steroid, terpene and alkaloid chemistry to construct six membered ring systems. Many variations in the structure of reactants and the reaction conditions have been developed in order to achieve the desired results in terms of product structure and yield.

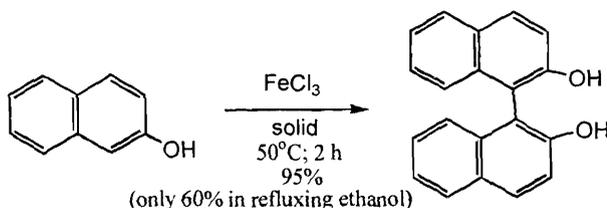


Binaphthol has played an important role in asymmetric synthesis that led to 2001 chemistry Nobel Prize.

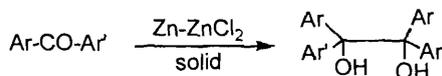
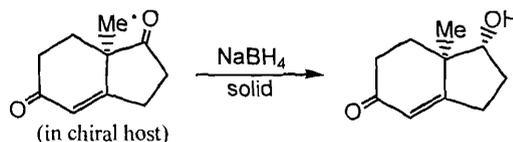
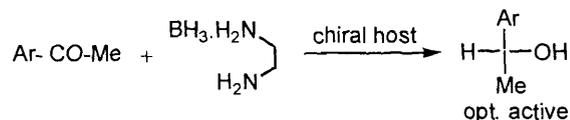
### Oxidation of Imines



### Oxidative Coupling

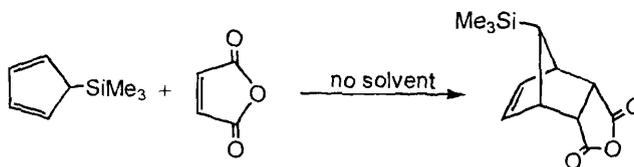
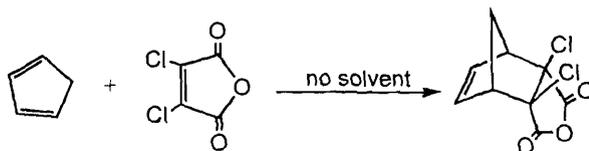


### Reductions



### Pericyclic Reactions

1. Diels–Alder reactions quite easily occur in the absence of solvents. Just mixing the reactive dienes and dienophiles is enough to bring about a number of these [4+2] addition.



Pericyclic reactions are concerted inter- or intra-molecular reactions involving a cyclic transition state formed by the reorganization of  $4n+2$  electrons. The rules governing such reactions are called Woodward–Hoffmann rules.

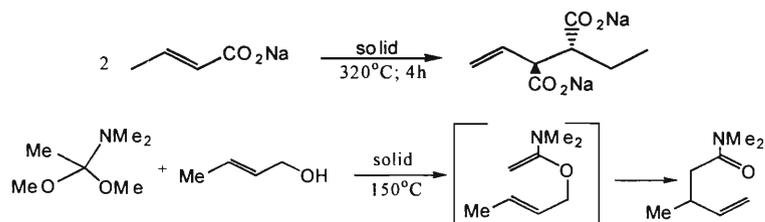
## Box 3. Chiral Host

Chemical reactions are facilitated by the interaction of molecules present in the reaction medium, and the inputs like temperature, pressure, etc. A vast majority of reactions take place through formation of unions between molecules. Selective binding between molecules resulting from geometric complementarity in which shape and size are as important as the noncovalent forces that stabilize the complex, is a phenomenon of molecular recognition.

The molecule having precise shape into which the substrate molecule neatly fits is called the host, and the substrate is called the guest. The combined entity is called the host-guest complex, or inclusion complex. The contours of the host and the guest molecules may be regular or irregular, but they should fit into each other perfectly. A lock and key system, an electrical plug and socket, or the standard cone and socket joints of glass apparatus are a few examples of 'right fit'. Enzymes are the best known biological hosts, which enhance the reactivity of biosubstrates through shape selective binding.

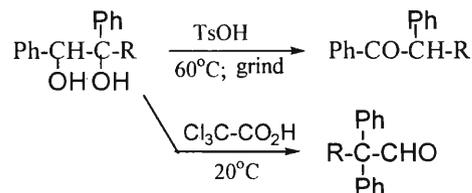
The guest molecule in an inclusion complex attains a specific orientation. Exploiting this property a predetermined orientation of the guest molecule can be achieved by anchoring it to a suitable chiral or optically active host. A chiral host is also capable of binding selectively with one of the enantiomers of a racemic mixture. Thus a racemic mixture can be resolved and the guest enantiomer subjected to a desired reaction. This has led to much progress in enantioselective organic synthesis.

## 2. Related ene-reactions or sigmatropic rearrangements also occur under neat conditions.



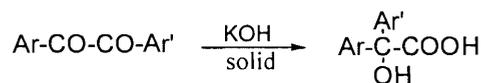
## Rearrangement Reactions

### 1. Pinacol-Pinacolone

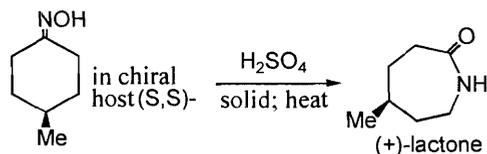


An achiral oxime in a chiral host is arranged in a chiral form, and on rearrangement gives one enantiomeric lactone.

## 2. Benzilic Acid



## 3. Beckmann



An inclusion complex of a prochiral guest oxime in a chiral host will have the guest molecule arranged in a chiral form and when the rearrangement occurs, an excess of one enantiomeric lactone is formed.

The foregoing short discussion shows that a variety of organic reactions, which are traditionally conducted in solvent media, can be carried out more profitably in the absence of solvents. The organic chemist will certainly continue his endeavor to bring more and more reactions into the fold of the solvent-free synthetic methodology. As mentioned already, the solvent-free reactions can be run not only at various temperatures, but also by exposing the reactants to ultraviolet or visible radiation. In the next part of the article, the photochemical reactions carried out under solvent-free conditions are described.

## Suggested Reading

- [1] G Nagendrappa, *Resonance*, Vol.7, No.1, pp.64-77, 2002.
- [2] G R Desiraju, *Organic Solid State Chemistry*, Elsevier, 1987.
- [3] V Ramamurthy (Editor), *Photochemistry in Organized and Constrained Media*, VCH, Weinheim, 1991.
- [4] K Tanaka and F Toda, *Chem. Rev.*, Vol. 200, pp. 1025-1074, 2000.
- [5] D Rajagopal, R Narayanan and S Swaminathan, *Proc. Indian Acad. Sci. (Chem. Sci.)*, Vol. 113, pp. 197-213, 2001.
- [6] N S Isaacs, *Physical Organic Chemistry*, Longman (ELBS), pp.171-209, 1990.
- [7] G Rothenberg, A P Downie, C L Raston and J L Scott, *Understanding Solid-Solid Organic Reactions*, *J. Amer. Chem. Soc.*, Vol. 123, pp. 8701-8708, 2001.

Address for Correspondence  
Gopalpur Nagendrappa  
Department of Chemistry  
Bangalore University  
(Central College Campus)  
Bangalore 560001, India.