

Benzoin Condensation

The Cyanide Connection with Tapioca and Vitamin B₁

Gopalpur Nagendrappa

Benzoin condensation is an important carbon–carbon bond forming reaction. It is achieved by generating an acyl anion equivalent from one aldehyde molecule which adds to a second aldehyde molecule. The reaction is traditionally catalysed by a cyanide ion. Cyanohydrin anion is the first intermediate and is the precursor to the acyl anion equivalent. Cyanohydrins are found in plants as glycosides. A reaction completely analogous to benzoin condensation occurs in our body, which however neither involves cyanohydrin intermediate nor is catalysed by cyanide ion. It is catalysed by the thiazolium moiety of the co-enzyme thiamine pyrophosphate (TPP). This article shows the common links and inclusive chemistry aspects among cyanohydrin formation, naturally occurring cyanohydrins, conversion of cyanohydrins to benzoin/acyloins, the role of vitamin B₁ (thiamine) and the use of thiazolium compounds in benzoin/acyloin condensation.

Introduction

Cyano Group in Natural Products

1. Cyanoglycosides

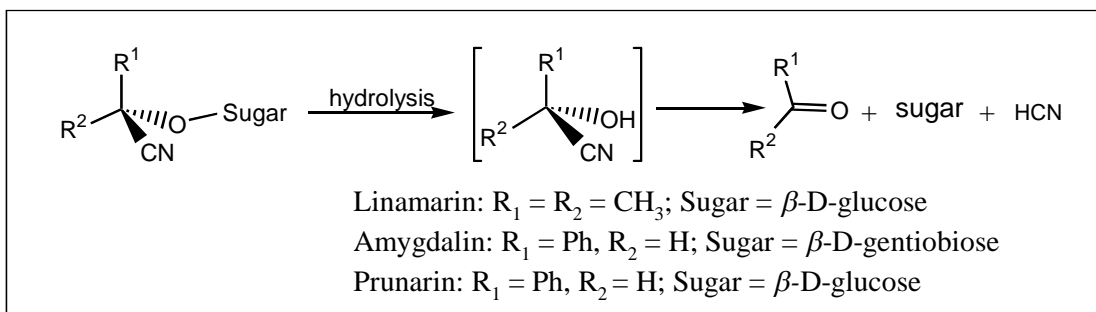
Hydrogen cyanide is a deadly poisonous substance. A variety of plants produce it, though in the hidden form of cyanoglycosides, the sugar derivatives of cyanohydrins. Cyanohydrins are formally the products of HCN addition to ketones or aldehydes, the addition being reversible. Cyanoglycosides hydrolyse enzymatically as well as nonenzymatically in the body to sugar and cyanohydrins, which release hydrogen cyanide, *Scheme 1*. Ingestion of cyanoglycosides through consumption of such plant materials may cause cyanide poisoning if the cyanide concentration in the



G Nagendrappa, retired from Bangalore University, Bangalore, is presently Professor and Head of the Department of Medicinal Chemistry, Sri Ramachandra University, Porur, Chennai. His main work is in the areas of organosilicon chemistry, organic synthesis, reaction mechanism and synthetic methodologies.

Keywords

Benzoin condensation, acyloin condensation, cyanoglycosides, cyanohydrins, vitamin B₁, catalysis, cyanide catalysis, thiazolium salt catalysis, nitrile-containing natural products.



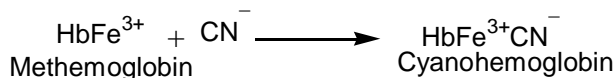
Scheme 1.

body goes beyond the tolerance limit, (see Box 1). This works as a defense mechanism in plants, since high cyanoglycoside content makes such plant parts (seeds, roots, leaves, etc.) bitter. However, we consume many food materials that contain cyanoglycosides.

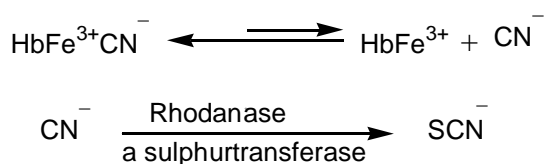
Box 1. Toxicity and Detoxification of Cyanide

Cyanide's Murderous Course: The cyanide inhaled as HCN or consumed as its salts such as NaCN, KCN etc, or released in the body on hydrolysis of cyanogenic glycosides eaten as food, causes poisoning. Orl-hmn $\text{LDL}_0 = 2857 \mu\text{gkg}^{-1}$ for NaCN or KCN. Orl-rat $\text{LD}_{50} = 5 \text{ mgkg}^{-1}$ for KCN, and 6.44 mg kg^{-1} for NaCN.

This is How it Poisons: Cyanide ion binds very strongly to Fe^{3+} of methemoglobin in mitochondria and forms cyanomethemoglobin, which cannot carry oxygen to tissues. The cellular respiration is arrested and the death is imminent.



Detoxification: Small amounts of cyanide present as glycosides in foods we consume is detoxified by the enzyme rhodanase present in liver, erythrocytes, and other tissues by facilitating the conversion of cyanide to thiocyanate. Minor quantities of CN^- are removed by oxidation to cyanate (CNO^-) or combining with cobalamin to form cyanocobalamin (vitamin B_{12}).



Antidote: Nitrite (NO_2^-) functions as antidote for cyanide poisoning. Nitrite is administered either by inhalation or injection, oxygen being given as adjunct along with or after NO_2^- . Giving oxygen alone is not effective.



Roots of cassava (tapioca), an important food crop in many countries of the world, including India, contain acetone cyanohydrin glucoside called linamarin. Tapioca that contains linamarin in excess of 100 mg kg^{-1} of fresh roots is not recommended for food use. Even then, to make it suitable for edible purpose it has to be processed properly to bring down the toxin content to less than 50 mg kg^{-1} , a limit that is considered as acceptable.

A long recognised source of a cyanogenic glucoside is bitter almond, whose bitterness is due to amygdalin, or D-mandelonitrile- α -D-gentiobioside, (*Scheme 1*). Historically, benzaldehyde was first obtained from bitter almonds.

Seeds of apple, peaches, plums, apricots, cherries, etc., contain considerable amounts of amygdalin. Cyanoglycosides are present even in common edible plants such as sorghum, soybeans, lima beans, maize, millet, sweet potatoes, spinach, sugar cane, and bamboo shoots. However, the toxin content in these is low, and is handled by liver and eliminated, (see *Box 1*). Even in the case of apple seeds, seeds of other fruits, and bitter tapioca which have a relatively high cyanoglycoside content, one has to consume huge quantities of them before they could pose toxicity problem.

The name cyanide evokes, in laypersons, a spectre of poisoning and instant death, made famous by authors of detective stories. Indeed, cyanide is one of the most toxic substances. Detoxification of minor amounts of cyanide in the body is brought about by the enzyme rhodanase present in liver, erythrocytes, and other tissues, through its rapid conversion to thiocyanate, (see *Box 1*).

Some insects and mollusks eat plants containing cyanogenic glycosides and accumulate sufficient quantities of these glycosides which serve as defense against their predators.

2. Non-glycosidic Cyano Compounds

Cyano group occurs in natural products not only in cyanohydrin glycosides, but also in non-cyanohydrin form. Some examples are given in *Figure 1*.

Even in the case of apple seeds, seeds of other fruits, and bitter tapioca which have a relatively high cyanoglycoside content, one has to consume huge quantities of them before they could pose toxicity problem.

Detoxification of minor amounts of cyanide in the body is brought about by the enzyme rhodanase present in liver, erythrocytes, and other tissues.



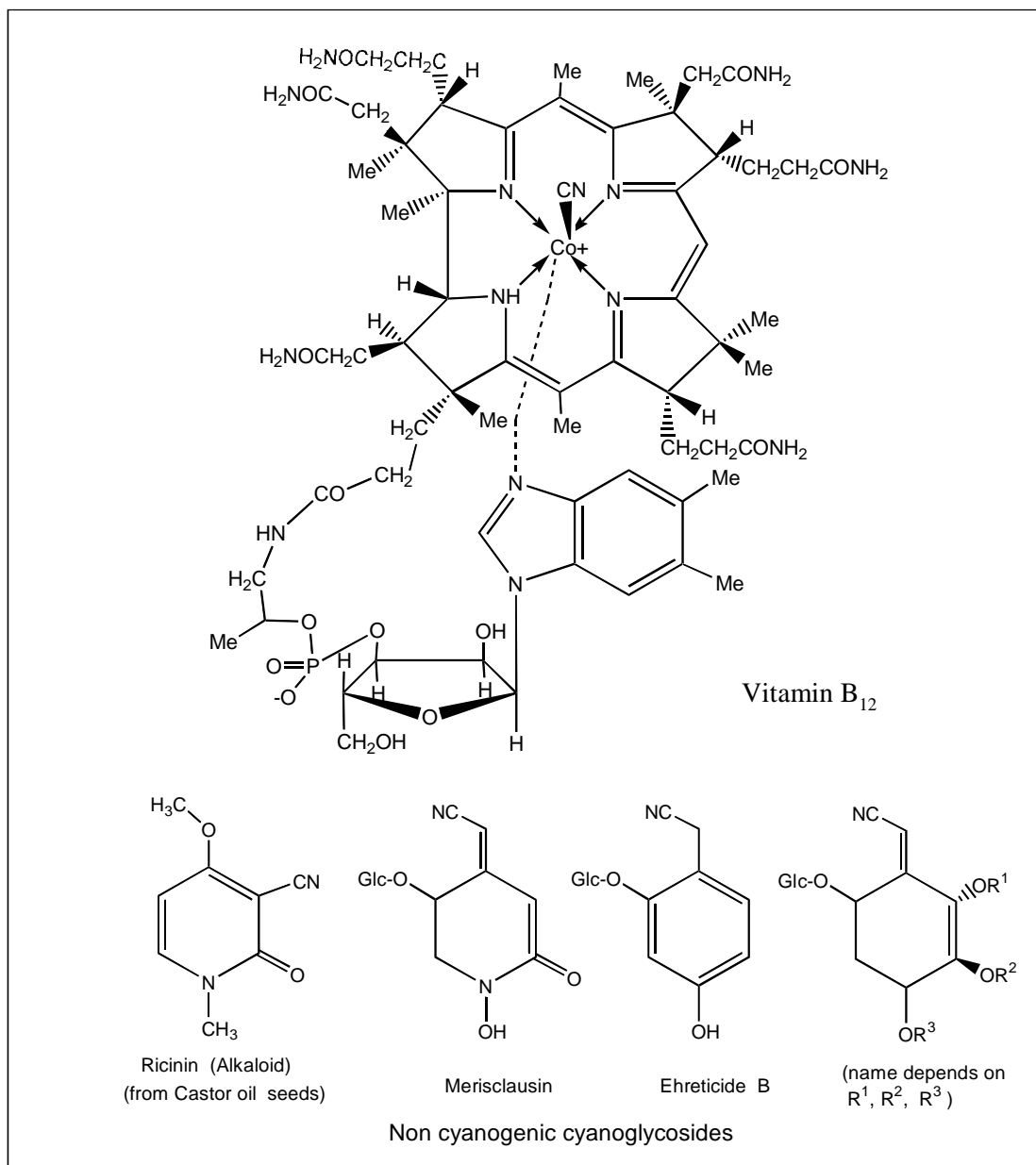
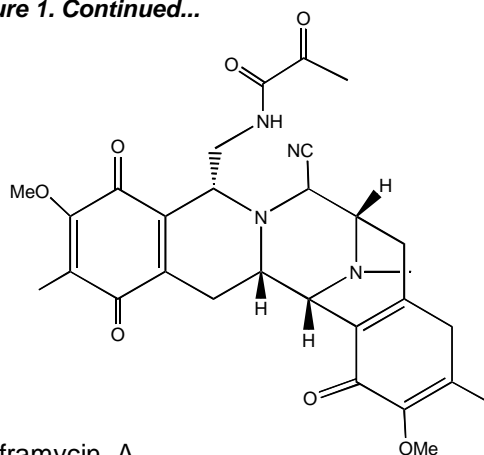


Figure 1.

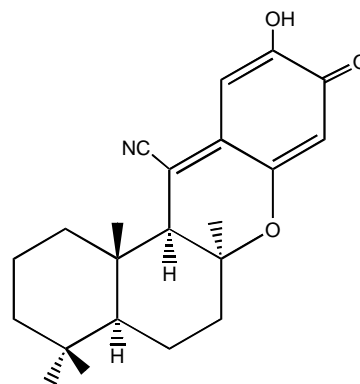
Nitrile-(Cyano Group) Containing Drugs

Though cyanohydrins pose as much toxicity problem as the inorganic cyano compounds, (NaCN, KCN, HCN, Cu(CN)₂, K₃Fe(CN)₆, etc.), the other types of organic nitriles may not be as toxic

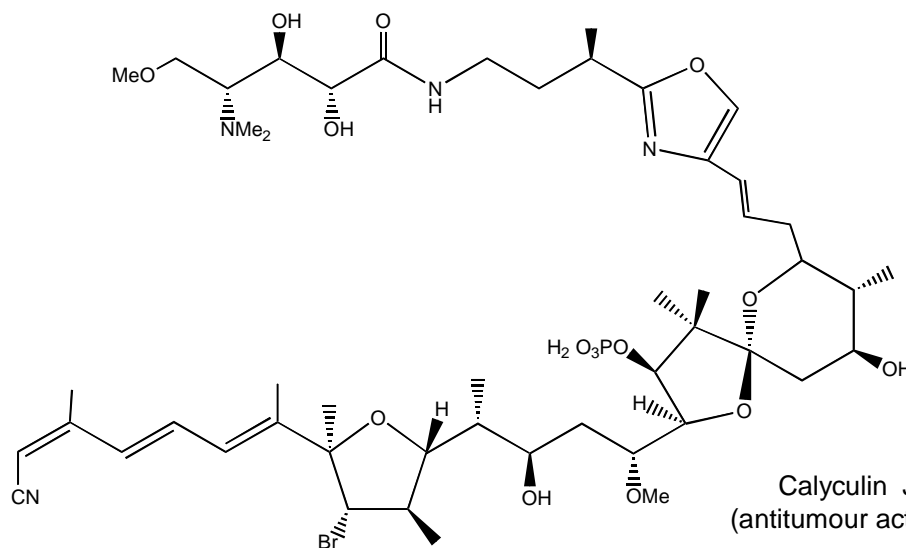
Figure 1. Continued...



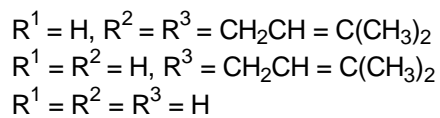
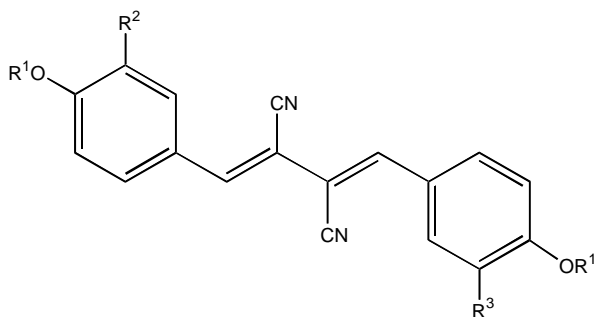
Saframycin A
(antibiotic and antitumor activities)



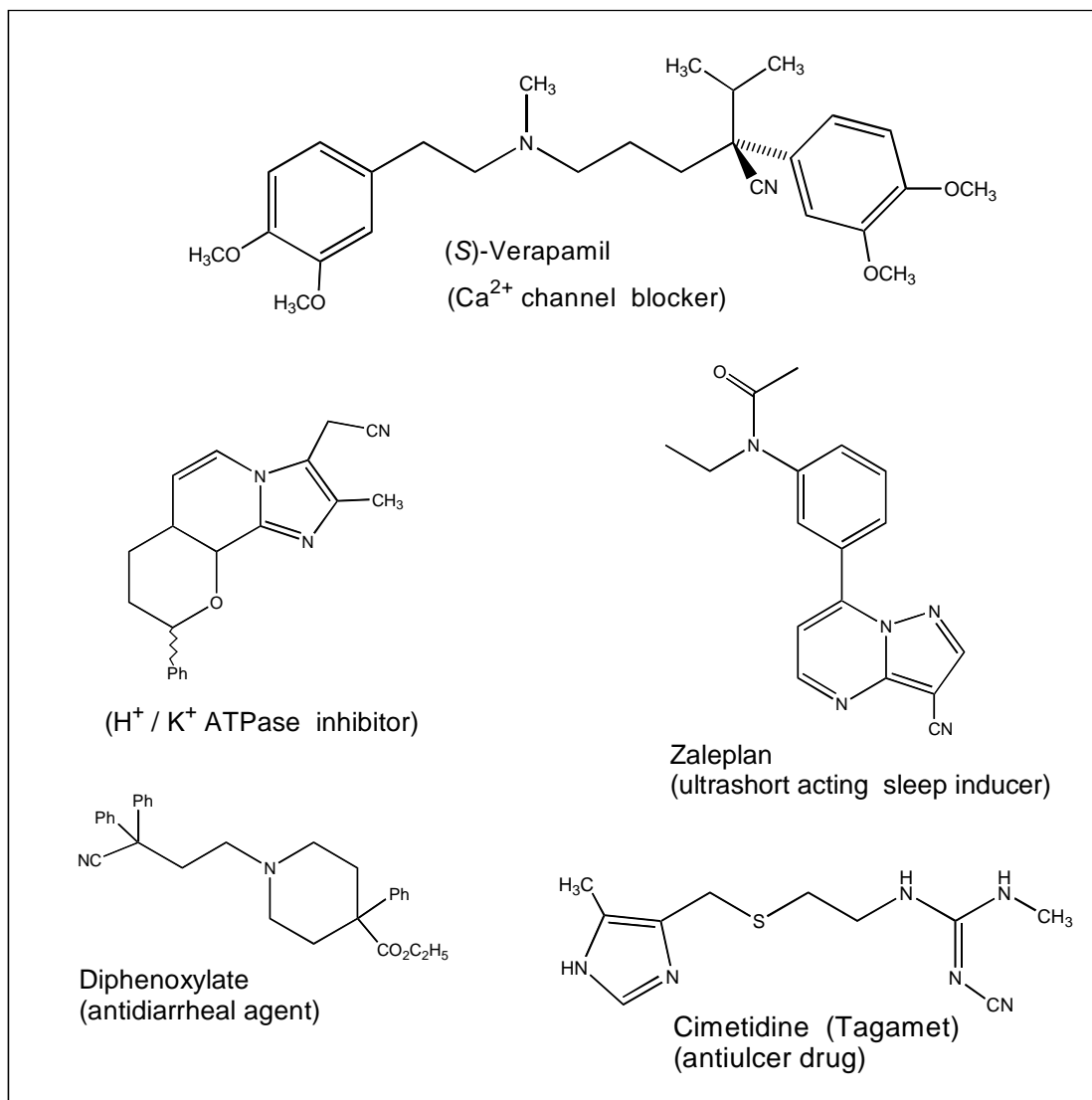
Cyanopuupehenone
(antiviral activity against HIV II)



Calyculin J
(antitumour activity)



Epurpurins

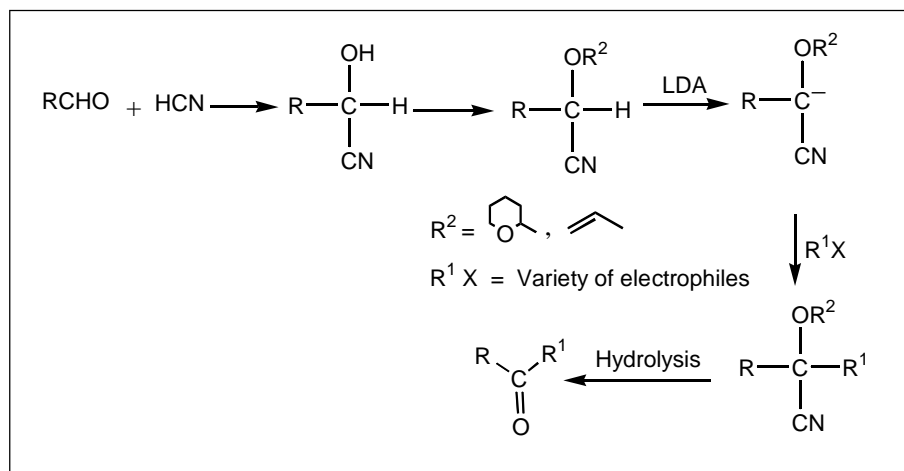
**Figure 2.**

because they do not release the cyanide easily. In fact, a good number of common drug molecules contain cyano group as an important functional group. A few examples are given in *Figure 2*.

Nitrile (Cyano Group): A Versatile Intermediary Functional Group

Synthetic routes of even larger number of drugs employ nitriles as



**Scheme 2.**

intermediates because of their versatility for further useful transformation. The nitrile can be transformed into a variety of other functions such as amine, carboxylic acid, ester, amide, ketone, aldehyde, heterocycle and others. Consequently nitriles have acquired great importance as intermediates in the manufacture of chemicals, including drugs.

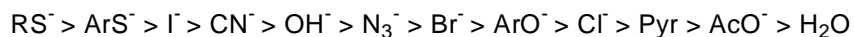
Being a strong electron withdrawing group the cyano group facilitates the formation of α -carbanion and then ensures its stability. This has been exploited in pole reversal (umpolung) of aldehydic carbon from being electrophilic to nucleophilic, as represented in *Scheme 2*.

Cyanide: A Good Nucleophile

Cyano group can be introduced into organic molecules by a variety of methods. Since cyanide is one of the very effective and efficient classic nucleophiles, the most common methods of cyanation exploit this property, such as in (1) the direct displacement of halides, tosylates or similar leaving groups by cyanide, and (2) the addition of cyanide to aldehydes, ketones and their α,β -unsaturated analogues.

Cyanide's high nucleophilic efficiency is due to its easy polarisability and low steric hindrance to its attack. (It is the smallest carbon nucleophile). It is ranked high in the nucleophilicity

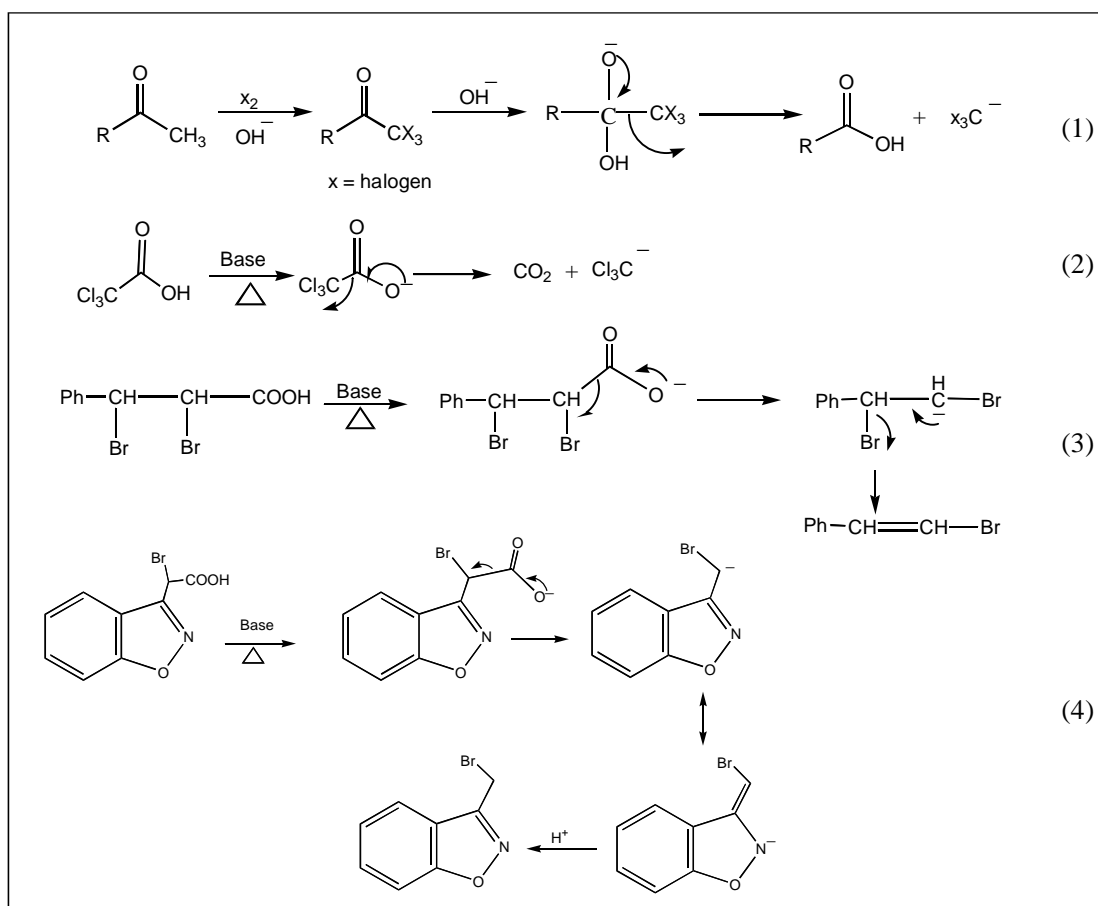
The cyano group facilitates the formation of α -carbanion and then ensures its stability. This has been exploited in pole reversal (umpolung) of aldehydic carbon.

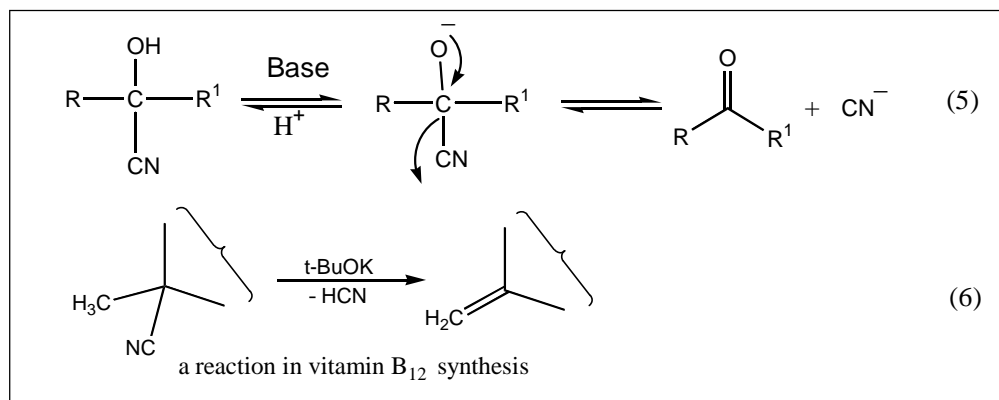
**Figure 3.**

order for $\text{S}_{\text{N}}2$ reactions (in protic solvents), much above OH^- , (Figure 3).

Cyanide as Leaving Group

It is a well-known fact that many good nucleophiles, such as halides, are also good leaving groups. (Of course, all nucleophiles are also leaving groups, in principle, though the two characters do not match in all cases). Carbanions, on the other hand, are good nucleophiles, but are generally not good leaving groups. The exceptions are the groups with carbon bonded to strong electronegative atoms or groups. Some examples are given in Scheme 3.

Scheme 3.



The cyano group attached to an alkoxy carbon departs very easily, which is the reversal of cyanide addition to carbonyl of ketones and aldehydes forming cyanohydrins, (*Scheme 4*). However, only strong bases can eliminate HCN from alkyl nitriles, and this is used in one of the steps of vitamin B₁₂ synthesis.

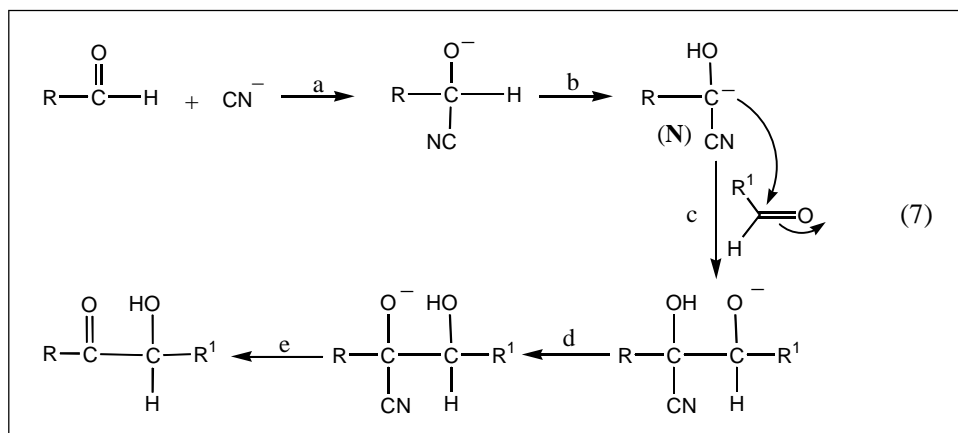
Scheme 4.

Because of this dual character (i.e., easy additions to aldehyde and easy departure from cyanohydrin), cyanide possesses the unique ability to catalyse a useful reaction, the benzoin condensation, in which two aldehyde molecules condense to give a α -hydroxy ketone.

The Benzoin Reaction

Cyanohydrins are the normal end products of nucleophilic addition of NaCN, KCN or HCN to aldehydes or ketones in aqueous alcoholic solution. However, in the case of aldehydes the reaction may proceed further to add a second aldehyde molecule, to produce α -hydroxy ketones, (*Scheme 5*, *Table 1*).

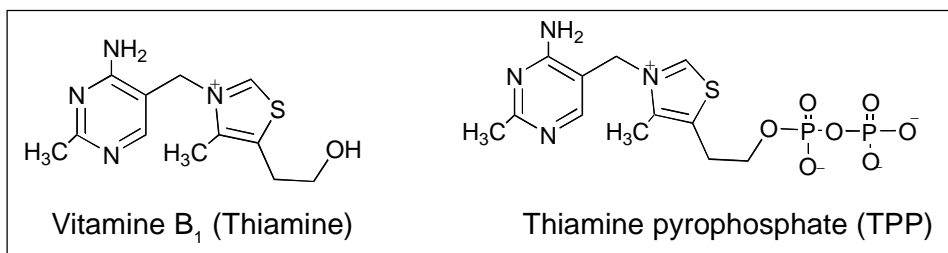
The highlight of the reaction is the fascinating way in which the cyanide ion facilitates and directs it, particularly by transforming the intermediate cyanohydrin adduct to the crucial nucleophilic carbanion species **N**, which then adds to another aldehyde molecule to finally deliver benzoin. The mechanism of this reaction was proposed as early as 1903. Though the correctness of this mechanism was doubted at some stage, but it was finally accepted in 1971. The important steps involved are given in *Scheme 5*.



Scheme 5.

R	R ¹	Yield (%)
		86
		77
		92
		45
		90
		40
		100

Table 1. Some examples of benzoin condensation in Scheme 5.



The uniquely successful role of cyanide ion in catalyzing benzoin reaction is due to its four qualities, namely, (i) high nucleophilic activity, (stage a), (ii) facilitating the α proton transfer, (stage b), (iii) ability to stabilize negative charge in active aldehyde intermediate **N**, (stage c), and (iv) ability to depart finally, (stage e).

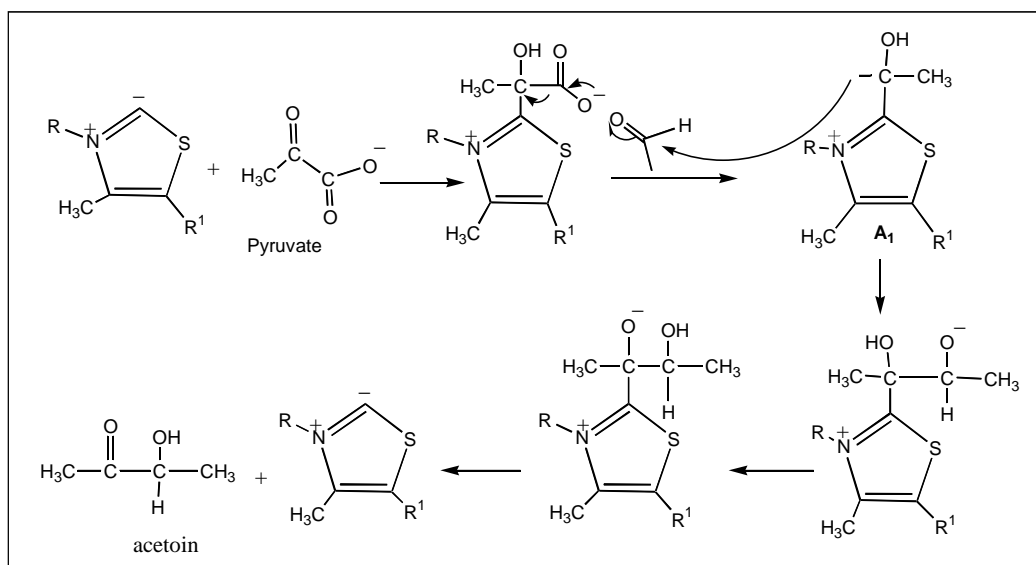
Vitamin B₁ and Thiazolium Salts as Catalysts

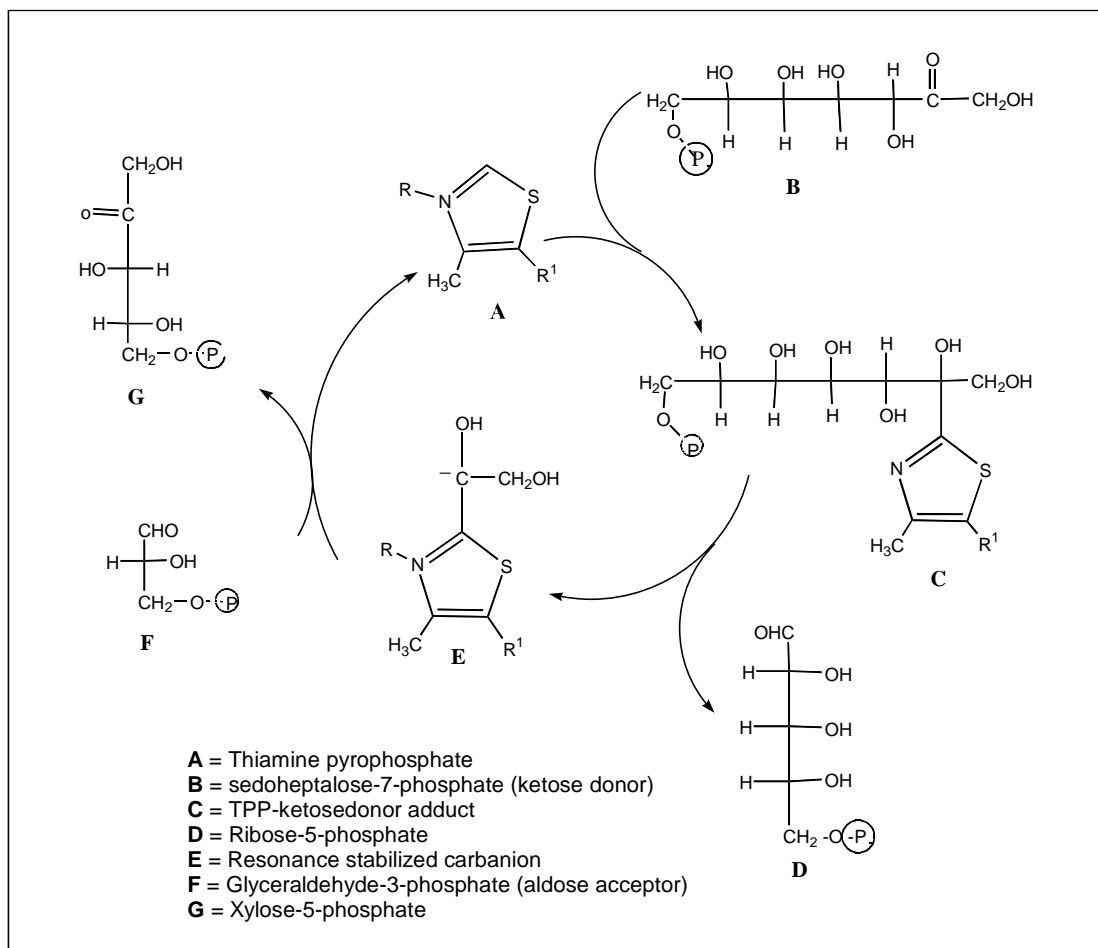
In principle, any chemical entity that incorporates all these four features should be capable of bringing about benzoin condensation. In fact, Nature has been performing this task efficiently in a completely analogous manner using (vitamin B₁)¹ thiamine pyrophosphate, TPP, (*Figure 4*), a coenzyme present in our body, and other living organisms. TPP catalyses several reactions that include decarboxylation of pyruvic acid to acetaldehyde, conversion of pyruvic acid to acetoin, (*Scheme 6*), transfer of 2-carbon

Figure 4.

¹ The preparation of benzoin using thiamine (vitamin B1) as catalyst is one of the experiments being carried out by our I semester MSc. Medicinal Chemistry students. It is a neat reaction, which gives pure, crystalline benzoin in high yield. The preparatory procedure being followed is the one that is given in [7] listed in Suggested Reading. It is highly instructive experiment from the point of chemistry, biochemistry, environmental chemistry, and bio- and organocatalysis.

Scheme 6.



**Scheme 7.**

The key feature of thiazolium moiety in facilitating this reaction so efficiently lies in the fact that the hydrogen on the carbon between sulphur and nitrogen (i.e., the position 2) is acidic.

group from sedoheptalose-phosphate to glyceraldehyde-3-phosphate to produce xylose-5-phosphate (an acyloin reaction), (*Scheme 7*), which involve acyl ion or its equivalent intermediate as in cyanide catalysed benzoin reaction.

The key feature of thiazolium moiety in facilitating this reaction so efficiently lies in the fact that the hydrogen on the carbon between sulphur and nitrogen (i.e. the position 2) is acidic enough to be exchanged with deuterium in D₂O. Removal of this proton by base carries forward the reaction, as depicted in *Schemes 6–8*, in a manner that is completely analogous to the cyanide ion-catalysed one, (*Scheme 5*).

The recognition that thiazolium ion in TPP catalyses these reactions has led to development of improvised thiazolium ion-based catalysts (Figure 5), which are simpler than TPP, yet bring about benzoin condensation effectively (Scheme 8). In fact the thiazolium catalysts show more scope in applicability in that they are able to catalyse the condensation of a wider variety of aldehydes and not only aromatic aldehydes. An added advantage is that they bring about condensation at room temperature and that too without the hazardous risks of environmental pollution posed by cyanide. The replacement of cyanide by the harmless thiazolium salts as catalysts for benzoin condensation is one of the finest examples of Green Chemistry in action.

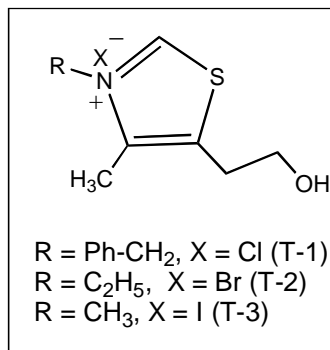
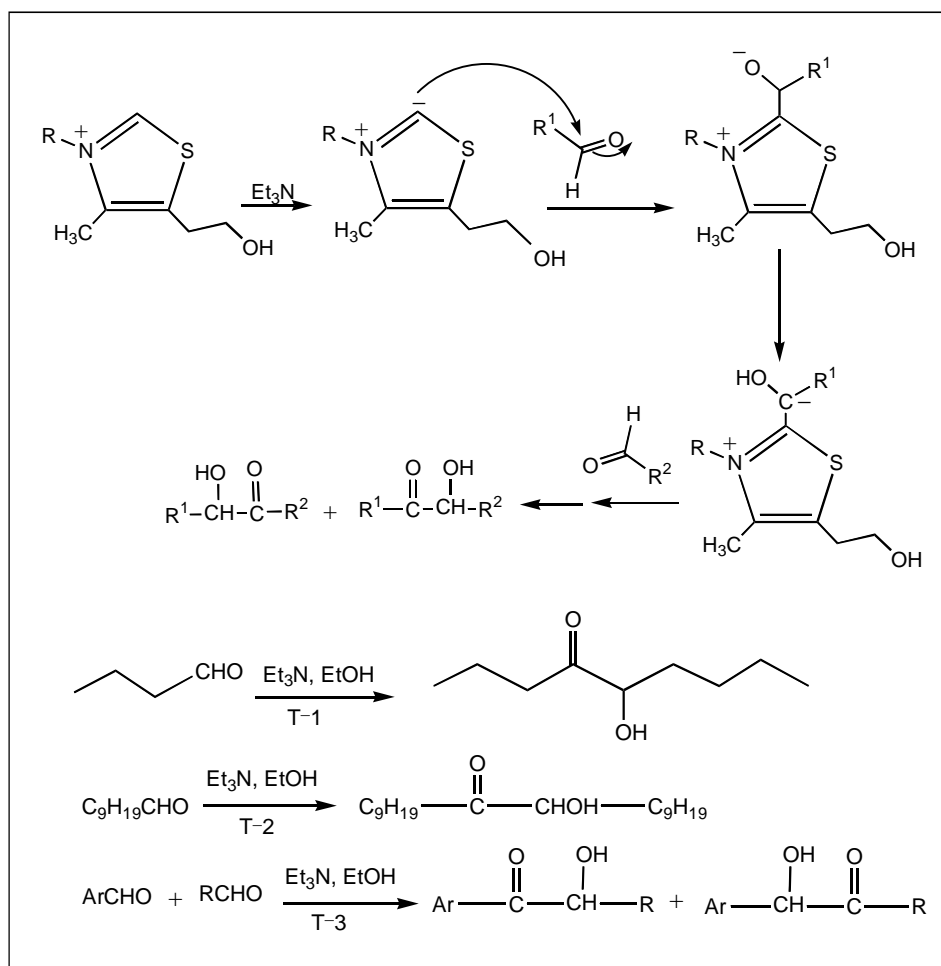


Figure 5.

Scheme 8.



Suggested Reading

- [1] T Laird, in *Comprehensive Organic Chemistry*, (Series Editors: D H R Barton and W D Ollis), Vol.1 (Editor: J F Stoddart), pp.1142–1147, Pergamon Press, Indian Print, 2007.
- [2] G Tennant, in *Comprehensive Organic Chemistry*, (Series Editors: D H R Barton and W D Ollis), Vol.2 (Editor: I O Sutherland), pp.528–550, Pergamon Press, Indian Print, 2007.
- [3] L A Paquette, *Encyclopedia of Reagents for Organic Synthesis*, Vol.6, pp. 4208–4212; Vol.7, pp.4537–4538, John Wiley & Sons, 2005.
- [4] F F Fleming, Nitrile-Containing Natural Products, *Natural Products Report*, Vol.16, pp.597–606, 1999.
- [5] D A Williams and T L Lemke, *Foye's Principles of Medicinal Chemistry*, V Edn., Lippincott Williams & Williams, pp.211, 2002.
- [6] H Stetter and H Kuhlman, *Organic Synthesis*, Coll., Vol.7, pp.95–99, John Wiley, 2005.
- [7] J Werner, *Greener Approaches to Undergraduate Chemistry Experiments*, pp. 14–17, 2002.
- [8] D L Nelson and M M Cox, *Lehninger: Principles of Biochemistry*, IV Edn., W H Freedman & Company, pp.761, 2007.

Address for Correspondence
 G Nagendrappa
 # 13, Basappa Layout
 Gavipuram Extension
 Bangalore 560 019, India.
 Email:
 gnagendrappa@gmail.com

