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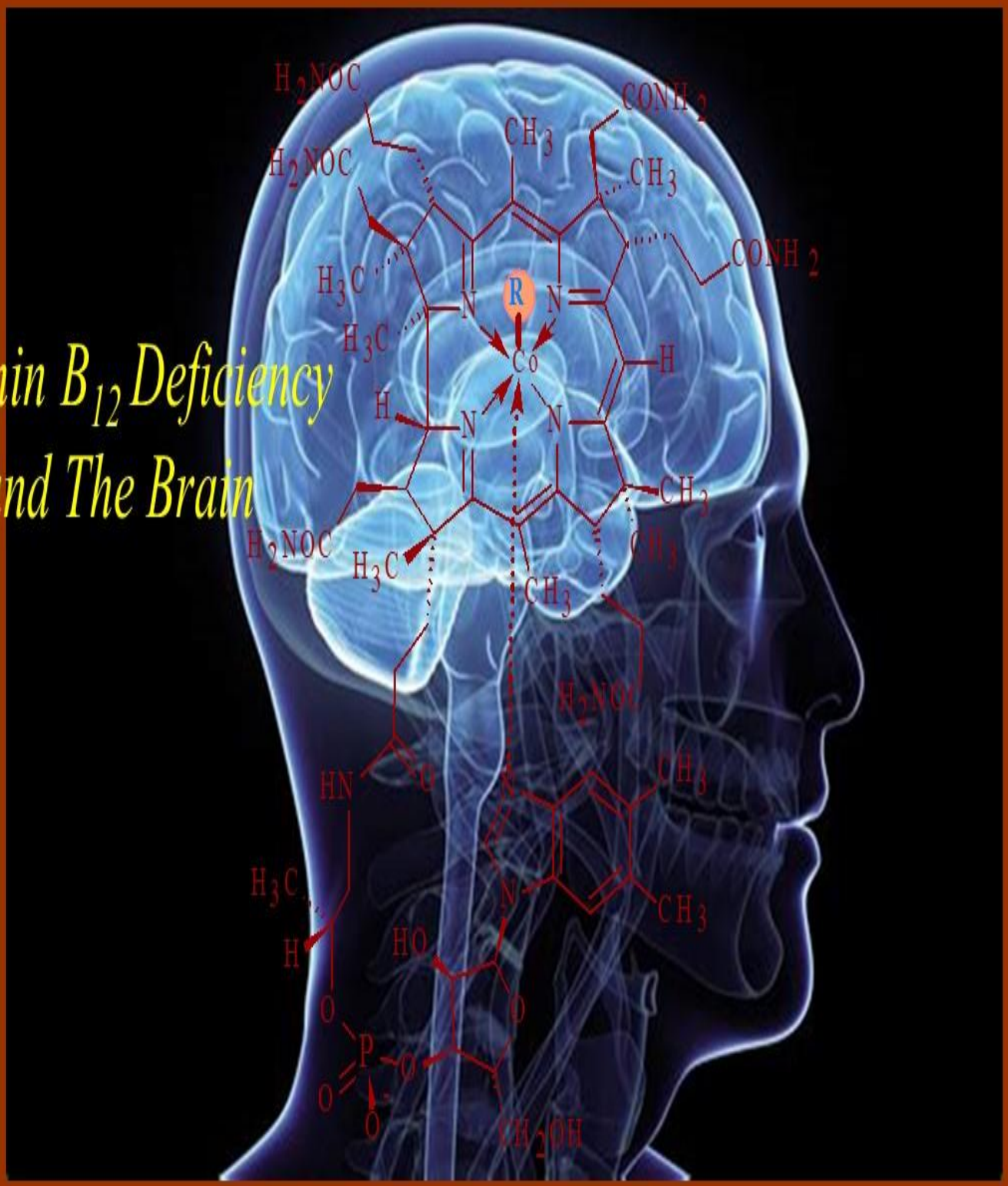
Vitamin B_{12} Deficiency and The Brain



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Vitamin B_{12} Deficiency and The Brain

Atef S. Iskander

Vitamin B_{12} deficiency manifests itself by many neurological abnormalities. The function of coenzyme B_{12}, as a carrier of methyl group, is necessary for the methylation processes in brain, *i.e.* the methylation of proteins in nerve tissue, genes, or homocysteine. This article focuses on some aspects of the relationship between brain function and vitamin B_{12} deficiency.

Keywords: Vitamin B_{12} deficiency, coenzyme B_{12}, methionine synthase, neurological abnormalities.

1. Introduction

Ever since the isolation of a red crystalline compound from liver, which had the therapeutic activity of liver concentrations in the treatment of pernicious anemia, as marked by Folkers and Smith's pioneer work in 1948, the ambiguous role of this substance, known as vitamin B_{12} or cyanocobalamin (CNCbl), in cells is still not fully known. Although, it is known that it acts as a coenzyme for various metabolic functions, including fat and carbohydrate metabolism, protein synthesis, its necessary for growth, cell replication, hematopoiesis, and nucleoprotein and myelin synthesis, the understanding of its mechanism of action with multifarious complex cellular functions is still not clear. This article focuses on the impact of vitamin B_{12} deficiency on brain function, but firstly, it is necessary to introduce briefly general considerations on vitamin B_{12}.

2. Coenzyme B_{12}

Cyanocobalamin (CN-Cbl) is a water-soluble vitamin, which its structural framework consists of a central cobalt atom surrounded equatorially by a corrin ring and axially coordinated on the lower *α-face* by 5,6-dimethylbenzimidazole base and on the upper *β-face* by cyanide group (CN^-). The CN^- group in the axial site can be readily replaced by hydroxyl (OH), aquo (H_2O), nitro (NO), methyl (CH_3), or adenosyl groups, which allow them to participate in various metabolic functions (Figure 1). Interestingly, cobalamin B_{12} (Cbl) can form a cobalt-carbon σ-bond, which marked it as a unique biomolecule that found in living systems possessing such Co-C bond.

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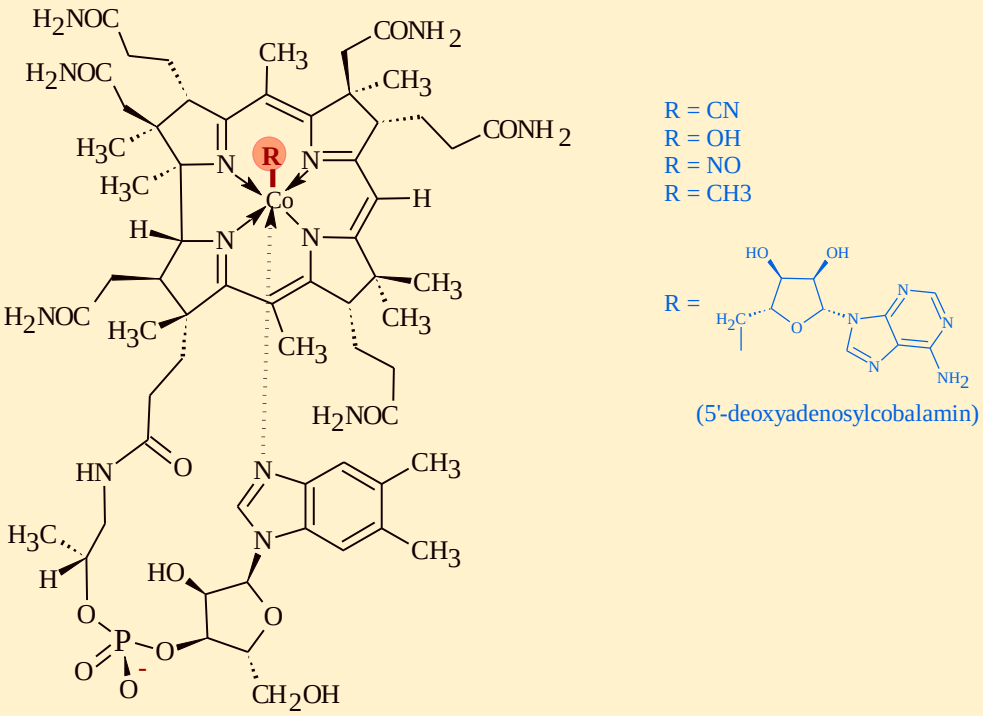

Figure 1. Cobalamin structures.

CN-Cbl is biologically inactive, but it can be converted *in vivo* into an active form "coenzyme B_{12}" in order to participate in enzymatic reaction. In fact, enzymes, that undergo chemically difficult reactions or not possessing a catalytic capacity, may resort to an additional device. Hence, using cofactors of potentially high energy can transform the bound substrates into highly reactive intermediates, especially radicals, which may undergo the enzymatic reaction selectivity by preventing undesired reactions rather than by facilitating the target ones, *i.e.* serving as negative catalysis.[1]

Alongside numerous bacterial enzymes, there are two essential enzymes in mammals, methionine synthase and L-methylmalonyl-CoA mutase, that require vitamin B_{12} derivatives, namely, methyl-cobalamin (MeCbl) and adendosylcobalamin (AdoCbl), respectively, as organometallic cofactors. They are produced and activated in two different cellular compartments: MeCbl in the cytosol, and AdoCbl in the mitochondria. MeCbl-dependent methionine synthase transfers a methyl group from methyltetra-hydrofolate to homocysteine to generate methionine and tetrahydrofolate via the heterolytic fission of the C-Co bond[2] (Scheme 1), whereas AdoCbl-dependent L-methylmalonyl-CoA mutase catalyzes the isomerization of L-methylmalonyl-CoA to succinyl-CoA through the homolytic fission of the C-Co bond[3] (Scheme 2). A lack of Ado-Cbl in the later process leads to the hydrolysis of methylmalonyl-CoA to methylmalonic acid, which subsequently eliminated in the urine.

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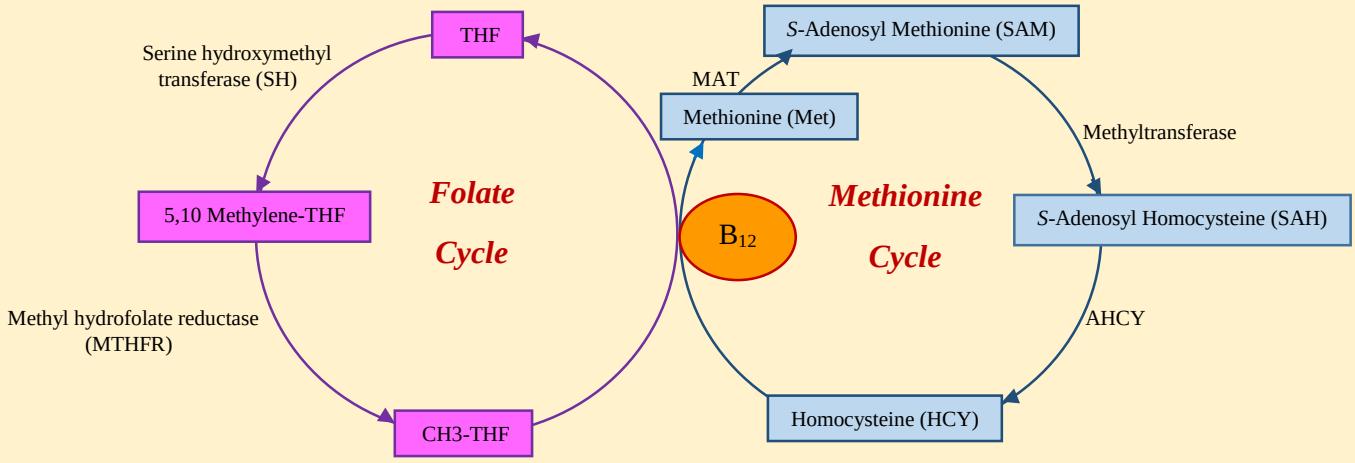
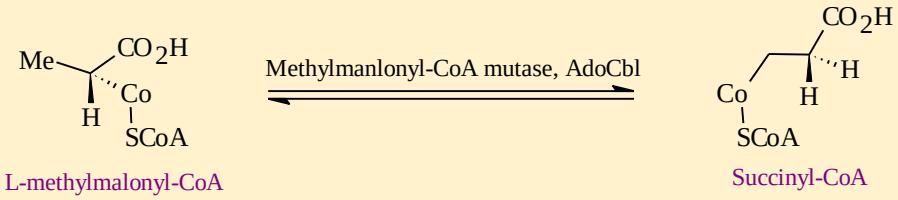


Scheme 1. The methylation cycle. MAT: methionine adenosyltransferase; AHCY: adenosylhomocysteinase.

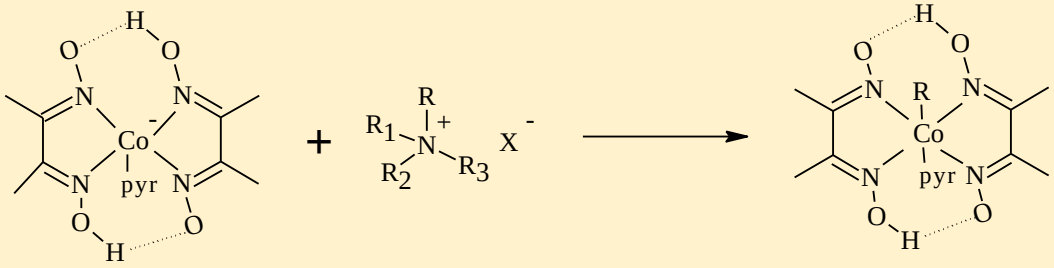


Scheme 2. AdoCbl-dependent enzyme reaction.

3. The Cobalt Atom

The cobalt atom is the core of coenzyme B_{12} (Cbl) molecule. The cobalt ion in Cbl exists, mainly, in three oxidation states: +1 (B_{12S}); +2 (B_{12r}); or +3 (B_{12a}) that influences the coordination environment and the redox properties. Intrinsically, the lowest cobalt oxidation state, Cob(I)alamin (B_{12S}), which also referred to as "*Supernucleophile*", has broad reactivity properties. Its nucleophilic strength is estimated to be ca. 10 on the Swain-Scott scale[4] and can be existed at pH > 9.9 in inert atmosphere[5]. These features make Cbl(I) the most powerful nucleophile known. Therefore, the strength of Co-CH_3 bond; its resistance against Brønsted acids and the high nucleophilicity (and nucleofugicity) of Co(I) corrins are reactivities essential in the methylation process. Using model systems, it was investigated coenzyme B_{12}'s possible role in the methyl transfer from nitrogen to cobalt, wherein a range of quaternary

ammonium salts were reacted with cobaloxime (I), [Co(I)(dmgH)$_2$pyr], which resulted in the corresponding Co-alkylated products (Scheme 3).[6]



Scheme 3. Transfer of alkyl groups from quaternary ammonium salts to Co(I)[dmgH]$_2$pyr.

The highly reactive radical Cob(II)alamin (B_{12r}) intermediate is formed by the homolytic cleavage of the C-Co bond of coenzyme B_{12} as in the case of AdoCbl-dependent L-methylmalonyl-CoA mutase.

The cobalt atom of coenzyme B_{12} can never be far from the action in any B_{12}-dependent biological process and it is necessary to determine its role either as a "conductor" of the action or as a "spectator" of protein-mediated events.[7] If it is a spectator, then the motive of cobalt in B_{12} is to act as a carrier of the initiator, e.g. the methyl or the adenosyl group.

From a chemical point of view, the cobalt ion, in a general sense, is not a true catalyst in the hydrolysis reaction since it must be regenerated. Its role is more of a promoter of the hydrolytic reaction. In fact, the cobalt ion plays a dual role in such reactions, *i.e.*, the first is an orientation or template effect, while the second is a concentration (of the nucleophile) effect at the active site.

4. Nervous System

Methionine is the precursor of the universal methyl donor *S*-adenosylmethionine (SAM), which is involved in different epigenomic regulatory mechanisms, especially in brain development. The function of coenzyme B_{12} is linked to the folate, vitamin B_9, due to their complementary roles in the folate (through its trapping in the form of methyltetrahydrofolate) and methionine cycles (Scheme 1).[8] The efficient functioning of the folate cycle is also necessary for the synthesis and regeneration of tetrahydrobiopterin, an essential cofactor for the enzymes that convert amino acids to both monoamine neurotransmitters (serotonin, melatonin, dopamine, noradrenaline, adrenaline) and nitric oxide.[9,10] Although the function of betaine-homocysteine *S*-methyltransferase is a methyl donor to homocysteine, which catalyzes the transfer of a methyl group from trimethylglycine and hydrogen ion from homo-

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cysteine to generate methionine and dimethylglycine, its role cannot compete with coenzyme B_{12} to the brain function. The importance of coenzyme B_{12} to brain function is manifested in the form of neurological symptoms such as those observed in Alzheimer's disease and senile dementia.[11] The coenzyme B_{12} has the unique ability to provoke the regeneration of nerves because it facilitates the methylation, the process that creates and maintains nerves and brain chemicals. A lack of coenzyme B_{12} results in nerves lose their insulation and begin to deteriorate (a process known as demyelination).

The evidences with folic acid show that gene methylation prevents overproduction of the amyloid-forming proteins.[12] In fact, folic acid is linked with coenzyme B_{12} in the methylation cycle, thus, the neurological abnormalities caused by the deficiency of any of them are the same.[13] Evidences showed that congenital deficiency of methylenetetrahydrofolate reductase (MTHFR) interferes with folic acid metabolism and causes hyperhomocysteinemia and decreased blood levels of methionine and SAM.[14] While congenital deficiency of methionine adenosyl transferase with hypermethioninemia causes demyelination in the brain.[15]

5. Conclusion

Brain tissue depends mainly on methionine synthase in which coenzyme B_{12} play a crucial role in maintaining the methylation processes. Methylation of homocysteine would remove its toxic effects. Methylation of proteins in nerve tissue may prevent their aggregation. Besides, methylation of genes may suppress synthesis of the amyloidogenic proteins.

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Snapshots of some topics of interest of recent notable advances in chemistry

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Managing Director / Founder

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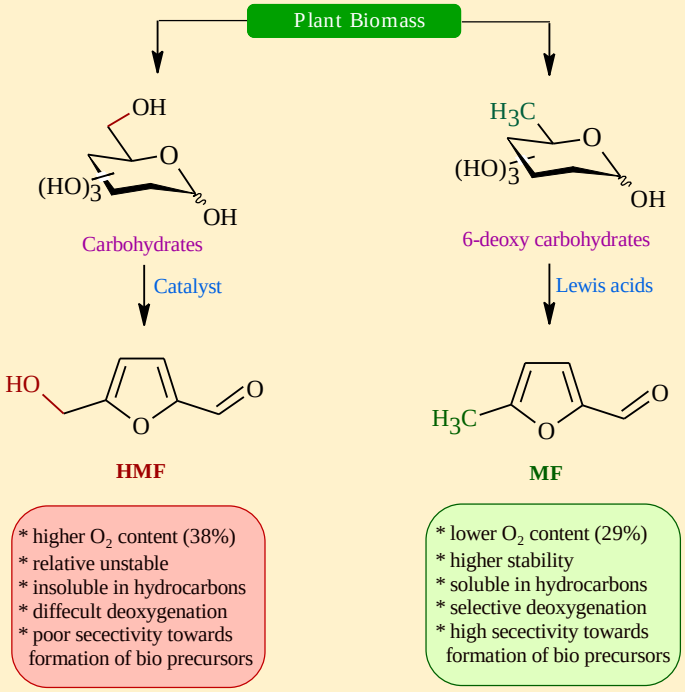
5-Methylfurfural as a Reliable Renewable Platform for Biofuels Production

5-Methylfurfural considered as a competitive chemical platform for biofuel development. This promising biofuel candidate is prepared from renewable feedstocks by the Lewis-acid-catalyzed dehydration of 6-deoxy sugars. The synthetic procedure and the features of 5-methylfurfural in comparison with its analogue 5-(hydroxymethyl) furfural are highlighted.

The utilization of 5-(hydroxymethyl)furfural (HMF) in biofuels development is limited owing to its high oxygen content, relative chemical stability, and insolubility in hydrocarbons. Searching for an alternative, Ananikov and co-worker reported that 5-methylfurfural is a promising platform for biofuels development, taking advantage of its availability and advantages (Scheme 1).



Scheme 1. Conversion of plant biomass into HMF and MF, as well as a comparison between their utilization for biofuels development.

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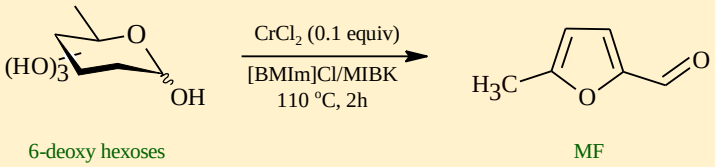
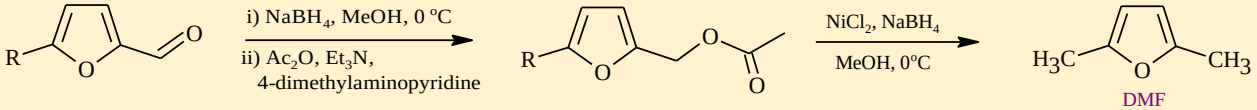
The conversion of L-rhamnose (6-deoxy-L-mannopyranose) as a model synthesis of 6-deoxy sugar, which is abundant in plants, into MF was achieved using chromium chloride ($CrCl_2$) as a catalyst in a biphasic 1-butyl-3-methylimidazolium chloride/methyl isobutyl ketone ([MBIm]Cl/MIBK) system to afford MF in 61% yield (Scheme 2).



6-deoxy hexoses MF

Scheme 2. Conversion of 6-deoxy hexoses.

The liquid biofuel 2,5-dimethylfuran (DMF), which its combustion properties and physical features is comparable to gasoline was obtained from 5-methylfurfural acetate (MFAc) through Ni-mediated transfer hydrogenation under mild conditions (Scheme 3).



MF; R = CH_3
HMF; R = CH_2OH

96% MFAc; R = CH_3
93% BAcMF; R = CH_2OAc

DMF

95%
67%

Scheme 3. Synthesis of DMF.

The synthetic utilities of MF and HMF in benzoin and aldol condensation reactions to afford long-chain alkane precursors demonstrated the potency of MF.

The demonstrated results revealed the high potential of MF as a bio-based platform for biofuels development.

Review

K. I. Galkin, V. P. Ananikv, *ChemSusChem*, **2019**, *12*, 185-189.

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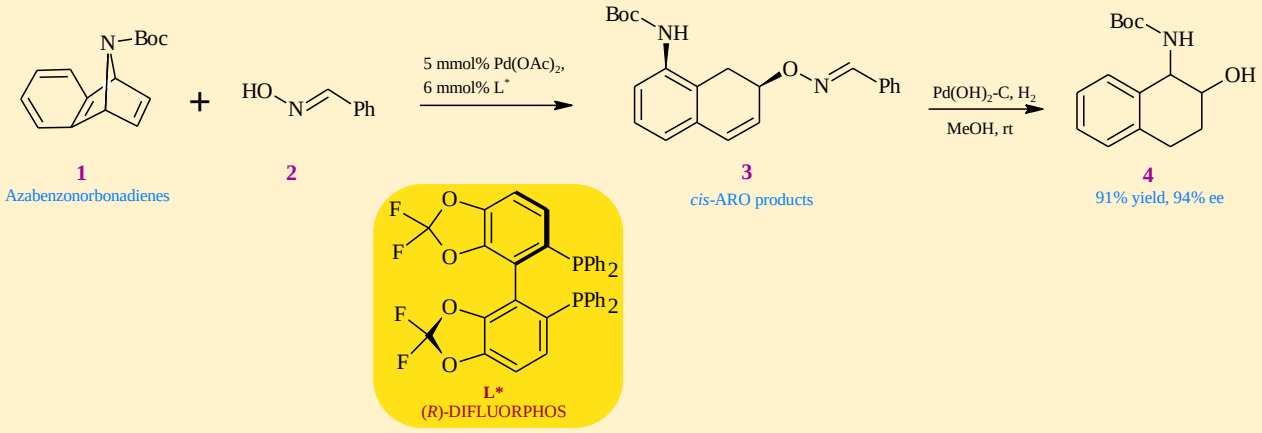
Asymmetric Ring-Opening Reactions of Aza/Oxabicyclic Alkenes with Oximes

Reaction of aza/oxabicyclic alkenes with aromatic oximes under co-catalytic system of palladium and zinc resulted in *cis*-stereoselective asymmetric ring-opening products.

The development of an effective method for asymmetric ring-opening (ARO) reaction of bicyclic alkenes presents an interesting field in organic synthesis. In this regard, Fan and co-workers reported a direct synthetic route for asymmetric ring-opening reaction of aza/oxabicyclic alkenes **1** with various oximes **2** as nucleophiles in the presence of $Pd(OAc)_2$ as catalyst, $Zn(OTf)_2$ as a co-catalyst, and (*R*)-DIFLUORPHOS as the chiral ligand (L^*) in DCE solvent. The reaction afforded the corresponding *cis*-stereoselective asymmetric ring-opening products **3** in moderate to high yields with excellent enantioselectivities (Scheme).



Scheme ARO reaction of aza/oxabicyclic alkene **1** with oxime **2**, and the synthetic application of *cis*-ARO products **3**.

Oximes with substituents at *ortho* and *meta* positions were found to promote the ARO reaction in good to high yields and enantioselectivities as compared to the *para*-substituted oximes (probably owing to the steric hindrance).

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The method provided a route for the preparation of tert-butyl((1*R*, 2*S*)-2-hydroxyl-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate **4**, as well as (1*R*-2*S*)-1,2,3,4-tetrahydronaphthalen-1,2-diol derivatives with high enantioselectivities.

The procedure showed broad substrate scope, functional group tolerance with high enantioselectivity.

Review

G. Shen, R. Khan, F. Yang, Y. Yang, D. Pu, Y. Gao, Y. Zhan, Y. Luo, B. Fan, *Asian J. Org. Chem.*, **2019**, *8*, 97-102.

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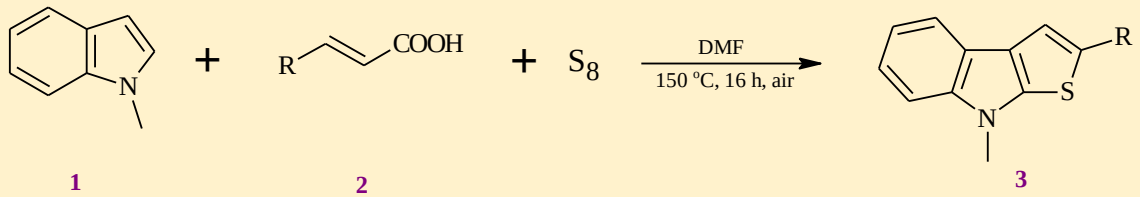
An Efficient Route for thieno[2,3-*b*]indoles

A simple route for the synthesis of thieno[2,3-*b*]indoles by a one-pot, three-component reaction of indoles and *α,β*-unsaturated carboxylic acids in the presence of sulfur is described.

The development of a selective method for the construction of thieno[2,3-*b*]indole skeletons is important for organic synthesis and has proved to be particularly useful for the reactions that involve fused heterocyclic moiety. In this context, Zhang *et al.* reported a facile method for the synthesis of 2-substituted thieno[2,3-*b*]indole derivatives **3** through an one-pot, three component reaction of indoles **1** and *α,β*- unsaturated carboxylic acid **2** in the presence of elemental sulfur (Scheme 1).



Scheme 1. Preparation of thieno[2,3-*b*]indole derivatives.

The role of DMF is crucial to convert the starting materials into the cyclization products. A proposed mechanism is described as follow: i) reaction of **2** with sulfur and DMF to afford ***A*** through decarboxylation (Willgerodt Kindler reaction), or via resonated route of ***B***; ii) reaction of 1-methyl-indoles **1** with ***A*** to give ***C***; iii) subsequent cyclization of ***C*** to afford ***D***; and iv) aromatization of ***D*** to furnish the desired product and dimethylamine (Scheme 2).

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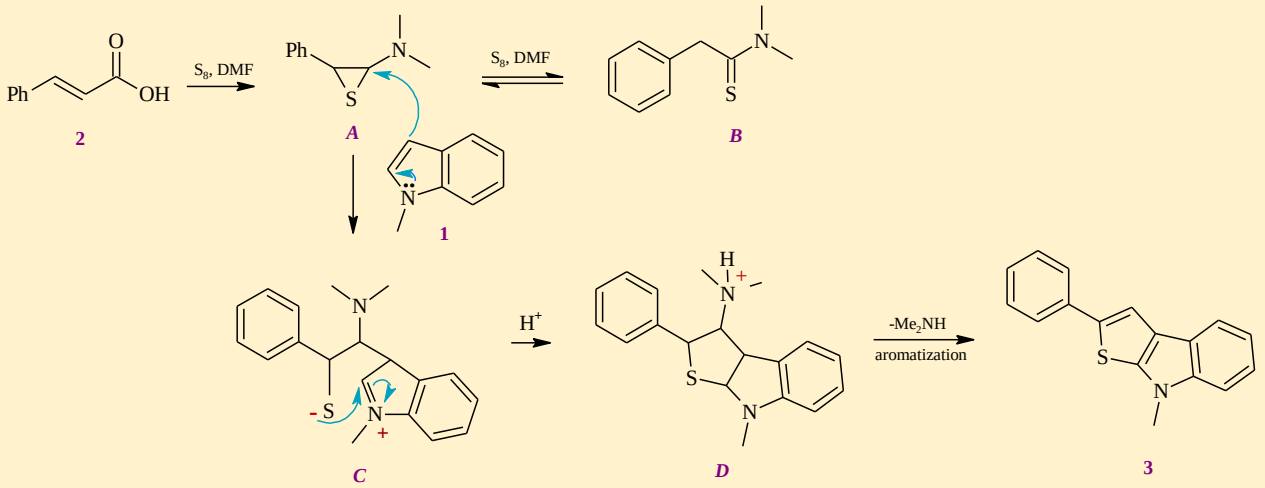

Scheme 2. Proposed reaction mechanism.

The procedure is characterized by catalyst-free, simplicity, and a broad scope of substrates.

Review

H. L. Zhang, F. Wen, W. B. Sheng, P. Yin, Ch. T. Zhang, C. Y. Peng, D. M. Peng, D. F. Liao, R. G. Fu, *Tetrahedron Lett.*, **2019**, *60*,80-83.

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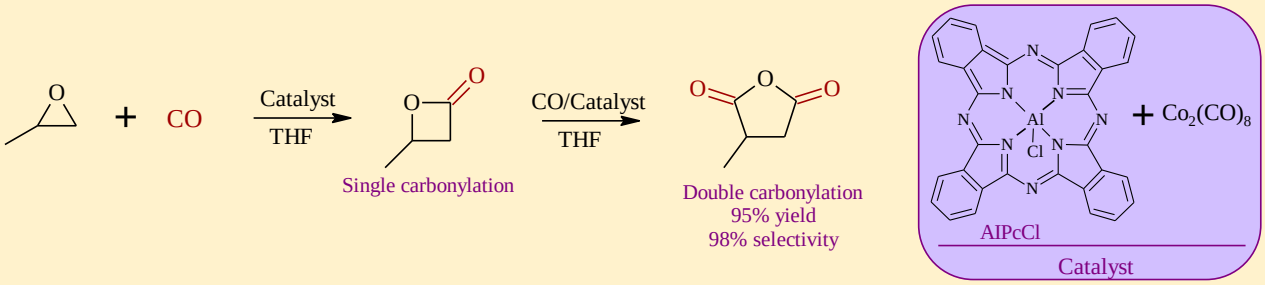
An *in-situ* Catalyst for Double Ring-Expanding Carbonylation of Epoxide to Anhydride

A one-pot double carbonylation of epoxide to anhydride is described. The reaction is achieved using an *in situ* generated catalyst from aluminum phthalocyanine chloride and dicobalt octacarbonyl.

Synthesis of *β*-lactones and succinic anhydride derivatives through ring-expanding carbonylation of epoxides is an efficient one-step procedure. However, the employed catalysts in these reactions suffer from many drawbacks such as difficult synthetic procedures, purification process, low yield, and high cost. In this regard, Jiang and co-workers proposed a highly efficient catalytic system for epoxide carbonylation based on an *in situ* generated catalyst from cost-effective aluminum phthalocyanine chloride (AlPcCl) and dicobalt octacarbonyl ($Co_2(CO)_8$) (Scheme).



Scheme Propylene oxide carbonylation catalyzed by an *in situ* generated catalyst from AlPcCl and $Co_2(CO)_8$.

The AlPcCl disproportionates $Co_2(CO)_8$ into $[AlPc]^+ [Co(CO)_4]^-$. The generated Lewis acid $[AlPc]^+$ binds and activates the propylene oxide (PO) for nucleophilic $[Co(CO)_4]^-$ attack on the less hindered carbon to form the ring-opened intermediate. At high pressure, rapid CO insertion into Co-alkyl bonds, followed by ring-closure affords *β*-lactone.

It is anticipated that the *in situ* generated catalyst from $Co_2(CO)_8$ and co-catalyst will have promising applications for other catalytic transformation reactions.

Review

J. Jiang, S. Rajendiran, S. Yoon, *Asian J. Org. Chem.*, **2019**, *8*, 151-154.