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Insights

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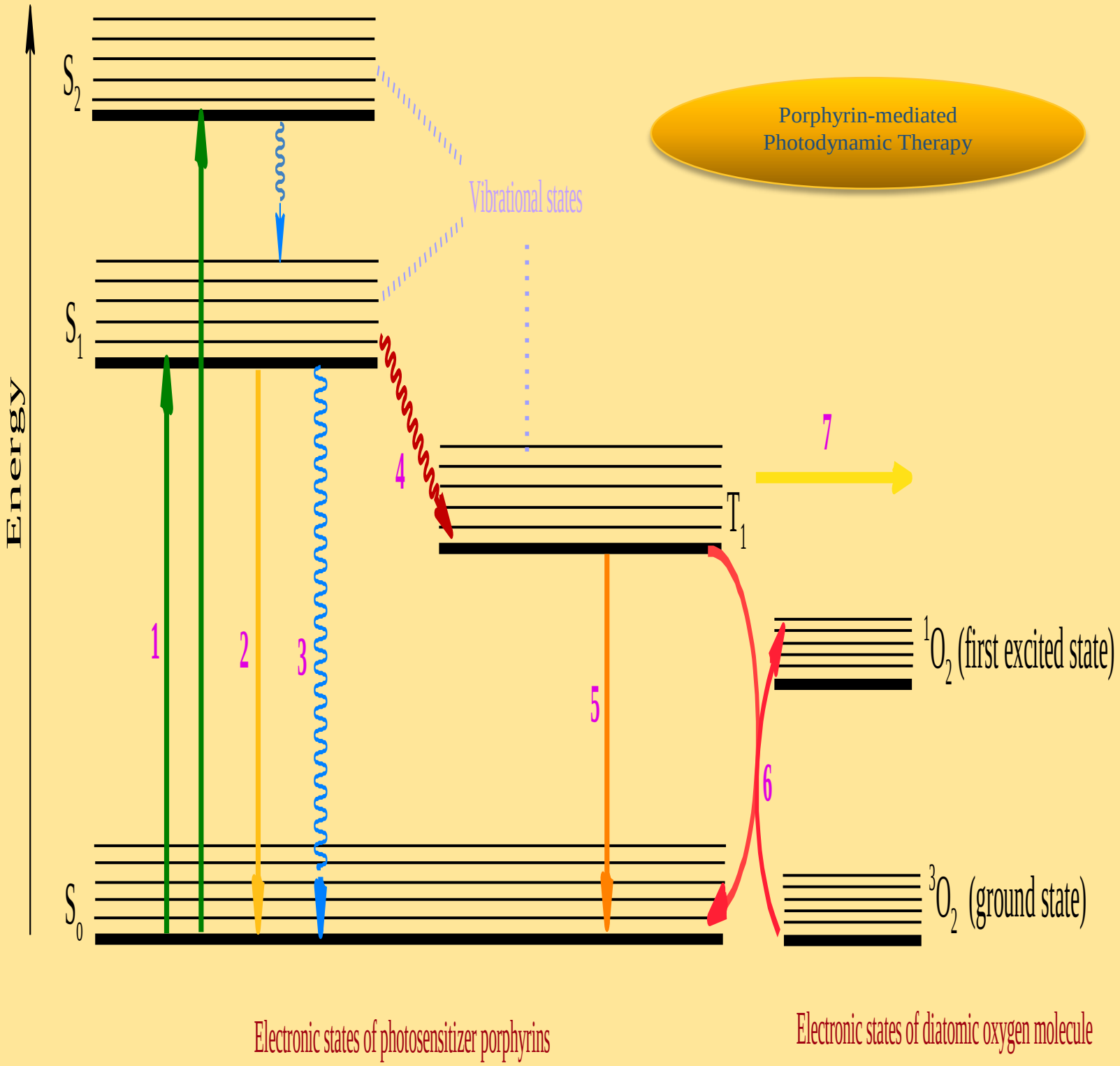

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Insights

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ISSN : 2590-0811

August 2018 | volume 1 | number 2

Table of contents

BTL NEDERLAND

Insights

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ISSN : 2590-0811

August 2018 | volume 1 | number 2

Porphyrin-mediated Photodynamic Therapy

Atef S. Iskander

Photodynamic therapy (PDT) is a promise approach which can pave the way for selectively tumor eradication. This medical treatment employs the combination of light and drug (photosensitizer) to bring about a cytotoxic or modifying effect to neoplastic tissues and their vasculature. Of great importance for the therapeutic efficacy of PDT is the quality of photosensitizer that can act as a good site-specific delivery for cancer cells and have remarkable optical properties. A class of compounds which have such qualities are porphyrins. They exhibit extraordinary characteristics. Herein, a short review is presented to shed light on porphyrin-based photosensitizers and the recent advances in the photophysical and chemical basis of PDT.

Introduction

Photodynamic therapy (PDT) is an emerging technique in the last decades which has opened new avenues in the treatment of cancer. This promising technique is based on the sensitization of molecular oxygen to its singlet exited state by using a molecule that can act as a photosensitizer (PS) and light of appropriate wavelength. When the photosensitizer molecule reaches the neoplastic tissues and their vasculature, an appropriate light dose is shone onto the diseased tissues[1-3]. Irradiation at visible

ISSN : 2590-0811
August 2018 | volume 1 | number 2

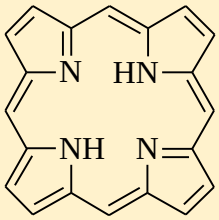
wavelengths of light can lead to a severe damage of tumor. Recent studies have shown that killing of tumor cells by PDT can lead to the creation of cancer vaccines[4].

Among the most photoactive based drug (photosensitizers) therapies utilize porphyrin-based chromophores. These molecules have the ability to absorb light at long wavelength, due to their large delocalized π-system, which upon their interaction with every present diatomic oxygen and in combination with light of appropriate wavelength lead to efficient singlet oxygen ($^1O_2$) generation. Singlet oxygen is the lowest excited electronic state of molecular oxygen. PDT is dependent on the presence of molecular oxygen. This short review is focused on the general aspects of these fascinating molecules, porphyrins, to understand their roles in the biological systems as well as recent advances in the photophysical and chemical basis of PDT.

Porphyrins

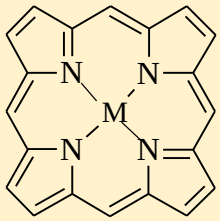
Porphyrins are essential to the reactivity of biological systems. They are involved in many electron transport systems a function that is vital to the life of all vertebrates. Their electronic structures are rich and diverse. Such diversity is also mirrored their applications in the field of advanced organic materials science. Porphyrins constitute important functional molecules in numerous fields including near-infrared dyes, photovoltaics and optoelectronic devices. These important functions rely on their highly conjugated, 18 π-electrons, aromatic core. The structure of porphyrin incorporates four pyrrole rings linked with four methine (=CH-) bridges to form a larger macrocycle ring (Figure 1). It refers to as free-base porphyrin because it is not complexed to a metal. This tetrapyrrole structure **1**, or porphin, can be substituted at the peripheral positions by various side chains forming a wide variety of porphyrins.

ISSN : 2590-0811
August 2018 | volume 1 | number 2



1

free-base porphyrin



2

metallated porphyrin

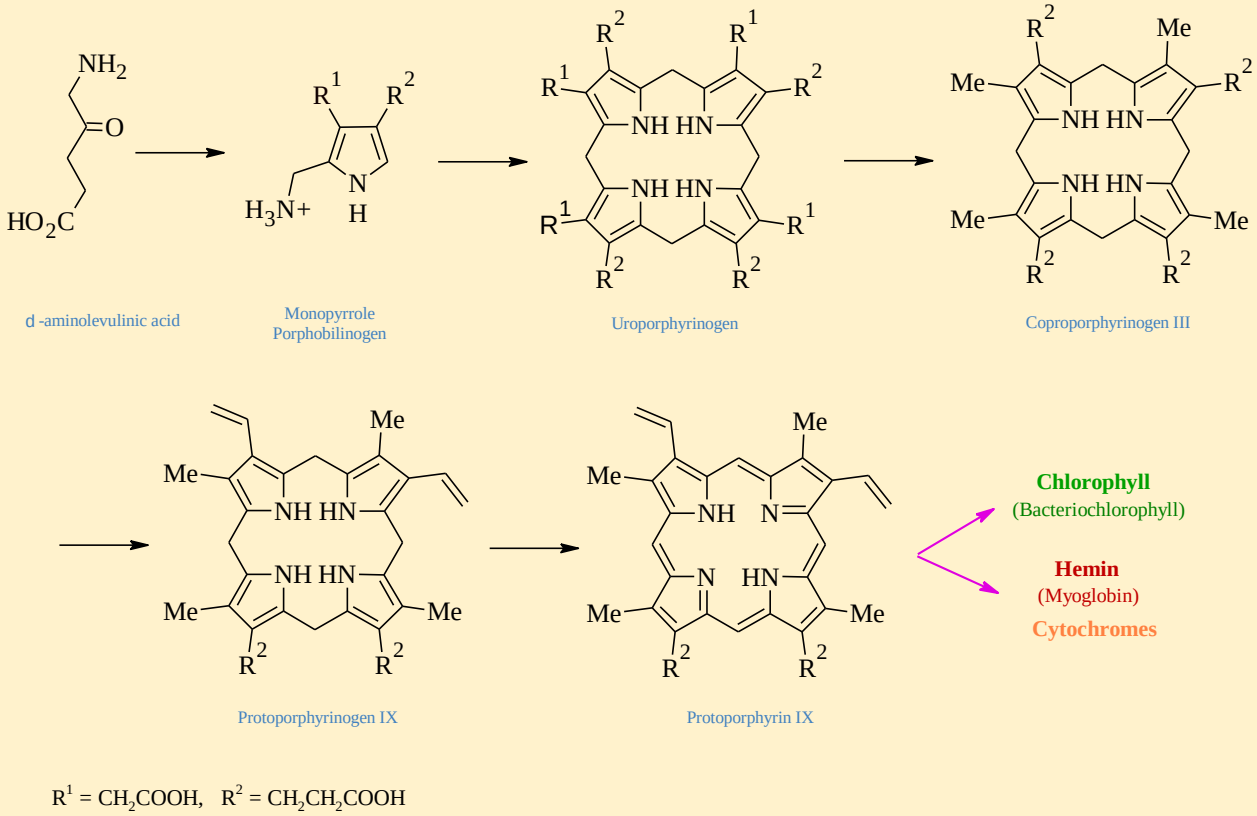
Figure 1: The structures of porphyrin macrocycle ring.

Metallated porphyrins **2** are present in hemoglobin and chlorophyll as well as a part of cytochrome P-450 enzyme systems. The starting material for all porphyrin biosynthesis is δ-aminolevulinic acid (Scheme 1)[5]. This compound is cyclized to form mono-pyrrole porphobilinogen. Through a process of enzymatic reactions this pyrrole is first cyclized to uroporphyrinogen. The uroporphyrinogen is then subjected to decarboxylation to give the reduced form of coproporphyrinogen III followed by protoporphyrinogen IX. Oxidation at this point, followed by metallation of protoporphyrin IX gives hemin which can be found as the co-factor in, for instance, hemoglobin and the cytochromes. In plants, protoporphyrin IX is taken onto chlorins such as chlorophyll while bacteria convert it into bacteriochlorins.

Porphyrins are also found in petroleum which are derived from the metabolism of chlorophyll by micro-organisms. Interestingly, these class of organometallic compounds are strikingly colored. Thus, the word porphyrin is derived from the Greek “porphura” meaning purple. Indeed, chlorophyll contains magnesium (green) whereas crude oils contains mostly vanadium (red) and nickel (orange) porphyrins. Hemoglobin contains iron by virtue of heme group, porphyrin-iron complex, and is the red protein of red blood cells.

All the molecular architecture of oxygen-carrying proteins are metalloproteins. The hemoglobin molecule is a tetramer composed of two globins (polypeptide chain) of unequal lengths. In the center of the protein lies a prosthetic group made of a porphyrin nucleus which acts as a ligand for the iron, Fe(II), ion and refers to as a hemoprotein. The role of hemoprotein is very important for both plants and mammalian and acts as oxygen transport to tissue; catalytic oxidation of organic compounds; decomposition of hydrogen peroxide and electron transfer.

BTL NEDERLAND
Insights
SCIENTIFIC LITERATURE REVIEW
ISSN : 2590-0811
August 2018 | volume 1 | number 2



Scheme 1: Biosynthetic pathway of hemin and chlorophyll.

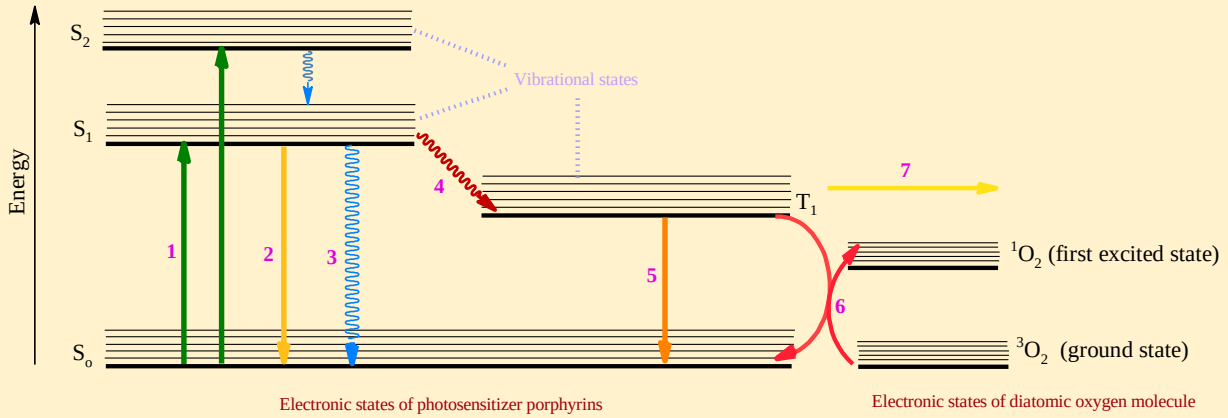
Singlet Oxygen Production

The generation of singlet oxygen is extremely crucial to the success of PDT. This can be achieved in the presence of molecular oxygen; light and photosensitizers. Photosensitizers are compounds which are capable of generation of singlet oxygen upon their interaction with every-present diatomic oxygen and light of appropriate wavelength.

Porphyrins belong to the group of photosensitizers. They are characterized by large excited state absorption, two-photon absorption, fast intersystem crossing (ISC), excellent stability and biocompatibility[6]. As a result of these features, porphyrins have attracted considerable attention in PDT.

BTL NEDERLAND
Insights
SCIENTIFIC LITERATURE REVIEW
ISSN : 2590-0811
August 2018 | volume 1 | number 2

The photophysical characteristics of porphyrin can be explained in the light of excited state dynamics which can be illustrated by a modified Jablonski energy diagram[7] (scheme 2). In these processes, a porphyrin is excited by light from the state S_o (ground state) to the state S_1 (singlet excited state) (process 1)**.** Then, there are several possible reaction pathways. The most important pathway is an intersystem crossing (ISC) (process **4**) leading to the triplet state T_1. Other two processes are either irradiative quenching (IC) (process **2**) or radiation in the form of fluorescence ($h\nu_f$) (process **3)**. The triplet state T_1 which involves a spin-inversion, then reacts with diatomic oxygen ($^3O_2$) in the vicinity of the sensitizer to produce singlet oxygen ($^1O_2$) (process **6)**. On such interaction is spin exchange (also corresponding to energy transfer) with the triplet oxygen, which generates the highly reactive singlet oxygen species. The other possibilities for quenching of the T_1 are irradiative processes (among them process **7**) or radiative as phosphorescence ($h\nu_F$) (process **5)**.



Scheme 2: Modified Jablonski diagram for a typical photosensitizer as porphyrin, 1: Absorption of light ($h\nu$), 2: Fluorescence ($h\nu_f$), 3: Internal conversion (IC), 4: Intersystem crossing (ISC), 5: Phosphorescence ($h\nu_F$), 6: Singlet oxygen production, 7: Hydrogen or electron transfer.

Singlet oxygen is a very reactive species with lifetime in water of about few microseconds[8]. It undergoes several reactions with biological substrates such as oxidation and cycloaddition leading to quite disruptive to biological processes. To define the efficiency of transferring the energy of absorbed light from the photosensitizer to triplet oxygen, there is an important photophysical property, specifically, the quantum yield of singlet oxygen (ϕ).

ISSN : 2590-0811
August 2018 | volume 1 | number 2

The profile of a suitable PDF drug

An optimal photosensitizer for use in PDF[9] would be (i) low dark toxicity (ii) strong absorption in the red part of the visible spectrum (> 650 nm); (iii) high quantum yield of triplet formation; (iv) high singlet oxygen quantum yield; (v) high extinction coefficient - the greater is the extinction coefficient, the smaller drug dosage is required to induce a cytotoxic response which may, in turn, decrease the cost of PDT[10] and greatly reduce the risk of provoking systemic toxic reaction; (vi) selectively for the enrichment in tumorous tissue *vs* healthy tissue; (vii) rapidly washed out from the body; and (viii) easy for derivatization for further enhancement.

Recent advances in the photophysical and chemical basis of PDF

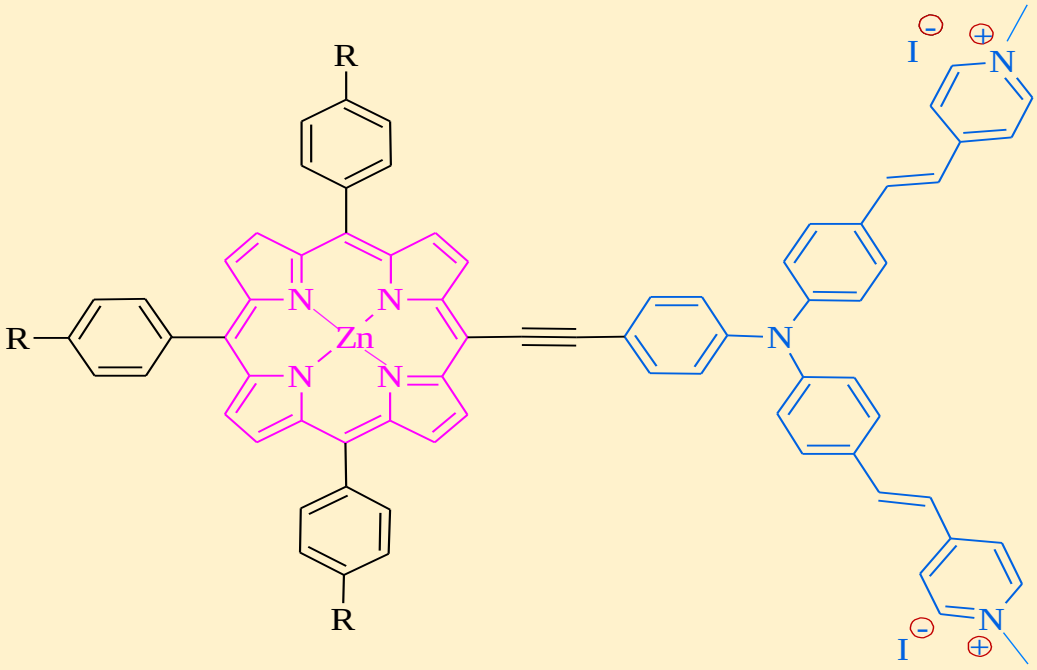
Ongoing research in both the application of light, light sources and applied techniques, and modifications of photosensitizers is trying to increase and optimize efficacy of PDT. D. Kessel[4] has demonstrated the ability of a sequential (two-sensitizer) PDT to enhance the efficacy of tumor eradication through sequentially evokes lysosomal, followed by mitochondrial photodamage where single agents are less effective. The team of Wilson and Anderson[11] have demonstrated an efficient two-photon activated PDT (2PA-PDT) which could allow precise three-dimensional manipulation of treatment volumes.

Two-photon activated drug

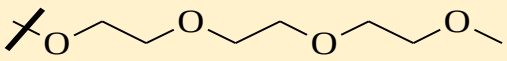
The strategy of two-photon absorption (2PA) technique is based on the simultaneous absorption of two photons to impose a high photonic density. It depends on the square of the light intensity and differs from linear absorption. It could be applied at the focal point of femtosecond pulsed lasers allowing a high spatial resolution. Furthermore, the applied wavelengths could be situated in the near infrared which effective light penetration through tissue could reach the centimeter scale. On the other hand, the π-conjugated photosensitizers that used in 2PA are highly hydrophobic and incompatible with biological media. Also, porphyrins are notoriously insoluble. To overcome this problem, the team of Hammerer and Mahuteau-Betzer[12] succeeded recently in preparation of novel π-conjugated porphyrin-triphenylamine hybrids photosensitizers bearing cationic charges which led to strongly increased water solubility and cellular penetration for use in two-photon activated PDT (2PA-PDT).

ISSN : 2590-0811
August 2018 | volume 1 | number 2

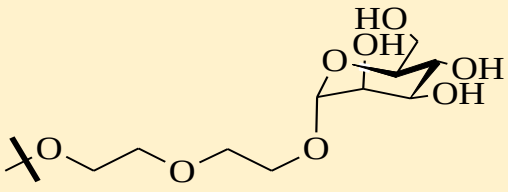
The biscationic compounds are functionalized by triethylene glycol (**P_{TEG}TP)** (Figure 2) or diethylene glycol-α-mannosyl groups (**P_{Man}TP)** in *para*-position of *meso*-phenyl moieties. The more conjugated tetracationic (**$P_{TEG}(TP)_2$**) contains two triphenylamine moieties. The synthetic strategy is based on systematically methylation on the pyridine rings to increase aqueous solubility that produced cationic hybrids bearing two or four charges. Moreover, the vinyl pyridinium triphenylamine (TP) motif was identified as a strong DNA minor groove binder. That is to say, this group is poorly emissive in aqueous solution as a result of fast non-radiative de-excitation, but upon DNA binding fluorescence emission increases dramatically. Also, they demonstrated earlier that these compounds were localized in mitochondria in live cells which represents a preferential target organelle for PTD.



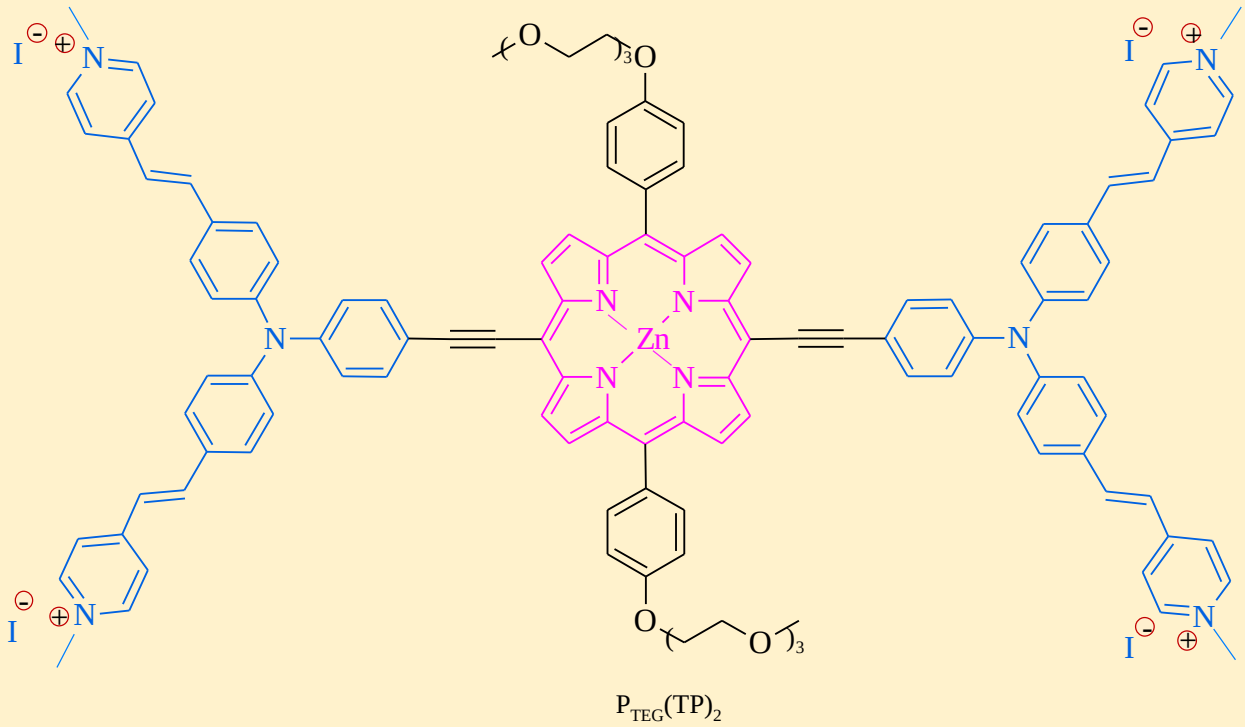
$P_{TEG}TP$: R = R^1 =



$P_{Man}TP$: R = R^2 =



BTL NEDERLAND
Insights
SCIENTIFIC LITERATURE REVIEW
ISSN : 2590-0811
August 2018 | volume 1 | number 2

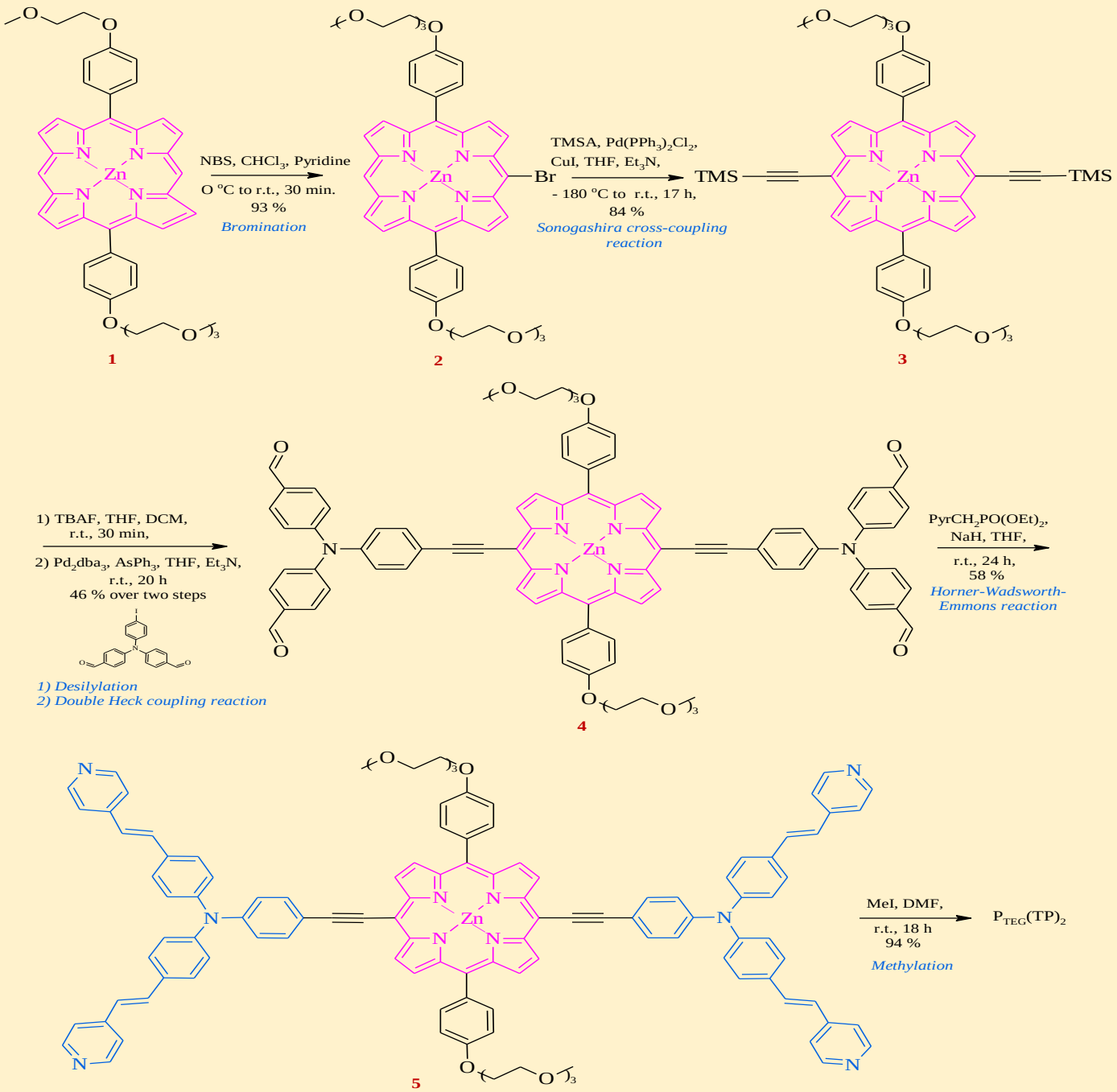


$P_{TEG}(TP)_2$

Figure 2: Structures of the cationic hybrids **P_{TEG}TP, P_{Man}TP** and **$P_{TEG}(TP)_2$.**

Synthesis of $P_{TEG}(TP)_2$

The synthetic pathway of **$P_{TEG}(TP)_2$** was achieved by bromination of **1** (scheme 3) to afford the dibromo zinc complex **2.** Then, Sonogashira cross-coupling reaction yielded **3** which further desilylated followed by a double Heck coupling reaction to give **4**. Whereas compound **5** was optained by a Horner-Wadsworth-Emmons reaction with diethyl[(pyridine-4-yl)methyl]- phosphate. Methylation of compound **5** produced the desired compound.



Scheme 3: Synthesis of compound PTEG(TP)2.

ISSN : 2590-0811
August 2018 | volume 1 | number 2

Photophysical properties

The absorption profiles for these compounds are typical of conjugated porphyrins with bathochromic shift of Soret band at 450 nm for **P_{TEG}TP** and **P_{Man}TP,** at 470 nm for **$P_{TEG}(TP)_2$** as well as intense and shifted Q bands between 570 and 720 nm. The fluorescence emission spectra of the methylated hybrids display typical red-shifted porphyrinic profiles with maxima around 650 nm for **P_{TEG}TP** and **P_{Man}TP** and 715 nm for **$P_{TEG}(TP)_2$**. These cationic hybrids show remarkable physicochemical properties for cellular application and cellular internalization.

Cellular imaging revealed the localization of hybrids partly in DNA-containing organelles, more precisely in the nucleus in fixed cells and in the mitochondria in live cells. Despite the low singlet oxygen production yields of the hybrids, the results revealed the generation of reactive oxygen species (ROS) due to oxidative stress such as hydroxyl radical or superoxide anion.

The cationic hybrids show improved one and two-photon photosensitizing properties against two different cancer cell lines. When two-photon imaging was performed on live cells using a 850 nm excitation wavelength and the recorded emission was in the rang of 521-705 nm, the results revealed a cytoplasmic localization of these compounds without nuclear staining. The two-photon cytotoxicity of the compounds showed cellular damages after 1 min. irradiation while non-treated cells submitted to the same light dose showed no cell death. The greater photocytotoxicity was achieved for **$P_{TEG}(TP)_2$** which possesses two cationic TP moieties. These results demonstrate the potential of these compounds as 2PA-PS for PDT applications.

Conclusion

PDT can be a useful approach to selective tumor eradication. The development of photosensitizers with high efficacy against cancer has significant impact on improved PDT effectiveness. In view of the remarkable optical properties of porphyrins, they continue to attract considerable attention for future research in this field.

ISSN : 2590-0811
August 2018 | volume 1 | number 2

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BTL NEDERLAND

Insights

SCIENTIFIC LITERATURE REVIEW

ISSN : 2590-0811

August 2018 | volume 1 | number 2

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

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Managing Director / Founder

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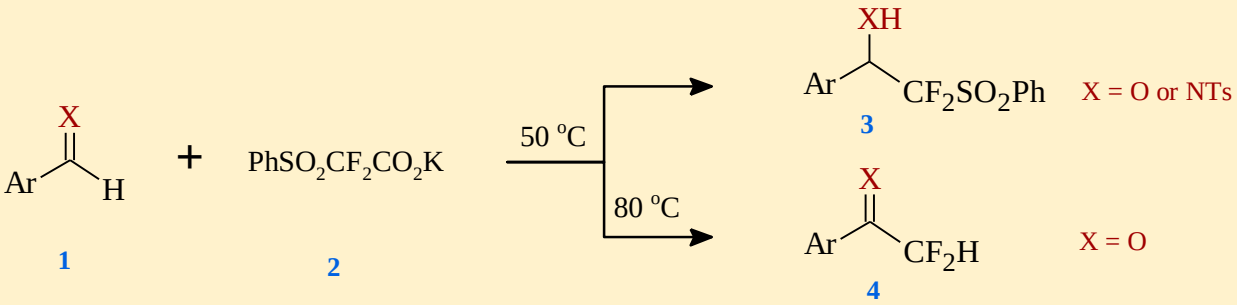
Insights
SCIENTIFIC LITERATURE REVIEW
ISSN : 2590-0811
August 2018 | volume 1 | number 2

Difluoromethylation of Organic Compounds

Free base and additive procedure for the formation of difluoromethyl ketones under mild thermal conditions is described.

Difluoromethylation groups (-CF_2H) are key functional features common to numerous fields, including drug discovery and agrochemicals. They serve as an effective lipophilic isostere of the carbinol, amide or thiol groups. Moreover, the presence of CF_2H moiety can enhance the binding selectivity of biologically active compounds via hydrogen bonding. Thus, development of new synthetic pathways that can efficiently introduce a CF_2H moiety into organic substrates is an important goal in contemporary organic chemistry.

In this context, Xiao *et al*. reported a simple free base and additive method for the introduction of nucleophilic (phenylsulfonyl)difluoromethyl moiety into aldehydes or imines **1** under mild thermal conditions (50 ^oC) using phenyl-sulfonyl difluoroacetate salt ($PhSO_2CF_2CO_2^-K^+$) **2** to generate $PhSO_2CF_2$-alcohols or –amines **3**, respectively (Scheme). The remarkable salt performance was attributed to the easily liberation of the carboxylic group under thermal reaction conditions to give an active anion $PhSO_2CF_2^-$. Subsequent thermal treatments at elevated temperatures (80 ^oC) led to the decomposition of $PhSO_2$ group and the formation of CF_2H-ketones **4**.



Scheme: synthesis of phenylsulfonyl difluoromethyl alcohols and – amines and difluoromethyl ketones.

Review:

J. Chen, J. H. Lin, J. C. Xiao, *Tetrahedron*, **2018**, *74*, 4295-4297.

BTL NEDERLAND

Insights

SCIENTIFIC LITERATURE REVIEW

ISSN : 2590-0811

August 2018 | volume 1 | number 2

New Designed Ligands for Ullmann-type C-N Coupling Reaction

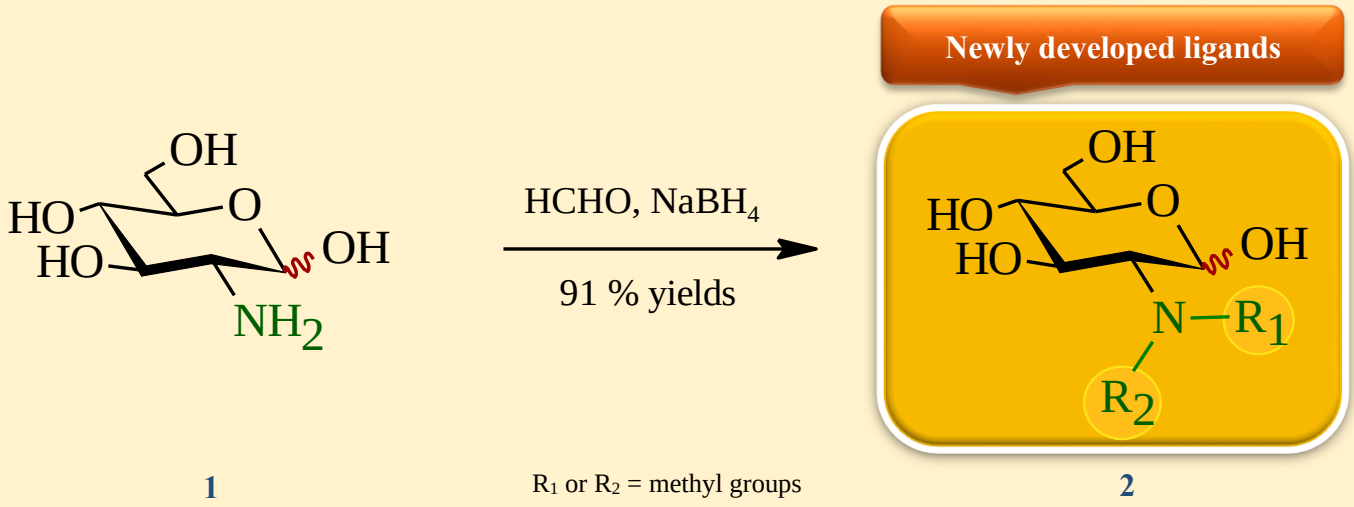
A new designed ligand is developed for the synthesis of *N*-aryl heterocycles by Ullmann-type C-N coupling reaction in the presence of Cu_2O.

Compounds that contain *N*-heterocycles have attracted intense interest in the chemical and biological communities. Key to the allure of these compounds are their extremely rich biological activities.

As a convenient synthetic strategy for constructing these classes of compounds is the copper-mediated Ullmann reaction which is proceeded in the presence of ligands as Cu-ligand composite catalysts. Despite the synthetic advantages of these ligands, significant challenges remain in their designs, such as economic viability, eco-friendly and limited substrates. To overcome these limitations, Xuan *et al.* reported new ligands derived from D-glucosamine to participate in Ullmann coupling reaction which were able to be compatible with a wide range of substrates.

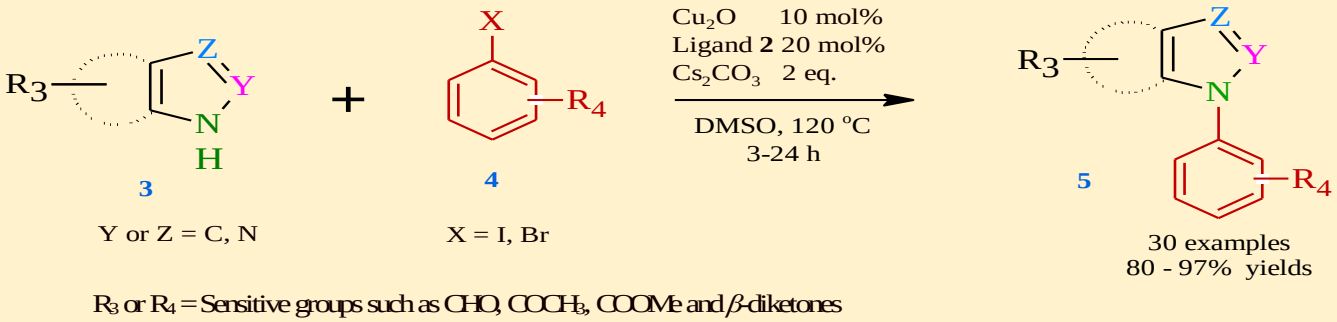
Among the best designed ligand they have achieved, was *N*,*N*-disubstituted D-glucosamine **2** which was obtained from the reduction amination of D-glucosamine **1** with formaldehyde (Scheme 1).

ISSN : 2590-0811
August 2018 | volume 1 | number 2



Scheme 1: The preparation of *N,N*-disubstituted D-glucosamine via the reduction amination of D-glucosamine with formaldehyde.

In view of the reaction conditions as well as the scope of the coupling, it was found that the coupling between N-H heterocycles **3** with sensitive substituents of aromatic halides **4** under the optimal reaction conditions as shown in (Scheme 2) afforded the corresponding products **5** in excellent yields.



R3 or R4 = Sensitive groups such as CHO, COCH3, COOMe and β-diketones

Scheme 2: C-N coupling of selected N-H heterocycles with aryl iodides.

ISSN : 2590-0811
August 2018 | volume 1 | number 2

Review:

J. J. Wei, W.B. Song,Y. F. Zhu, B. L. Wei, L. J. Xuan, *Tetrahedron*, **2018**, *74*, 19-27.

BTL NEDERLAND
Insights
SCIENTIFIC LITERATURE REVIEW
ISSN : 2590-0811
August 2018 | volume 1 | number 2

Carbon Dioxide Fixation

Native transition metals promote carbon dioxide hydrogenation to acetate and pyruvate under mild hydrothermal conditions.

The conversion of Carbon dioxide (CO_2) into fuels and chemicals is becoming an alternative option to fossil fuels and a way to mitigate global warming and diversity energy sources. Research in this area has adapted various strategies for turning waste gas into economic profit. In this context, we highlight the findings of the promotion of C-C bond formation from CO_2 in water under exceptionally mild hydrothermal conditions.

Moran and his colleagues investigate how could the native metals used by cofactors and metalloenzymes of acetyl-CoA (AcCoA) pathway, as one of the six known pathways of CO_2 fixation in nature, reduce CO_2 to furnish the same products of AcCoA pathway in the absence of enzymes? Herein, we focus on the applied reaction conditions as a model for CO_2 fixation.

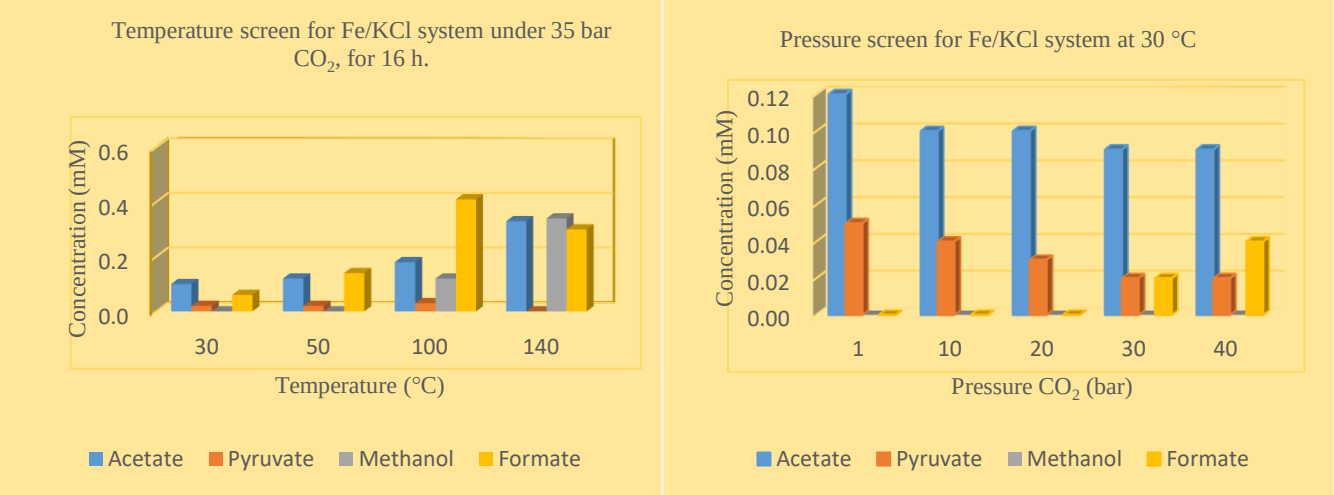
Reaction screening of Fe, Ni, Co, Mo, Mn and W powders (1mmol) in KCl solution (1 mmol) in deionized H_2O (1 ml) under the reaction conditions (100 °C, 35 bar CO_2 ,16 h., pH = 7) showed to produce acetate as a major product for all cases, whereas Fe, Ni, and Co produced exceptionally considerable amounts of pyruvate. Also, amounts of formate and methanol were observed in almost all cases (eq. 1).

$$\underset{\text{1 mmol}}{\text{M (powders)}} + \underset{\text{1 mmol}}{\text{KCl}} \xrightarrow[\text{2) KOH}]{\text{1) } H_2O \text{ (1 ml), 100 °C, 35 bar } CO_2\text{, 16 h.}} \underset{\text{Acetate}}{CH_3COO^-} + \underset{\text{Pyruvate}}{CH_3COCOO^-} + \underset{\text{Methanol}}{CH_3OH} + \underset{\text{Formate}}{HCOO^-} \quad (1)$$

(M = Fe, Ni, Co, Mo, Mn, W)

The influence of temperature, pressure and reaction time on the yield of Fe-mediated C-C bond formation were also studied and the results were shown in the Figure.

BTL NEDERLAND Insights
SCIENTIFIC LITERATURE REVIEW
ISSN : 2590-0811
August 2018 | volume 1 | number 2



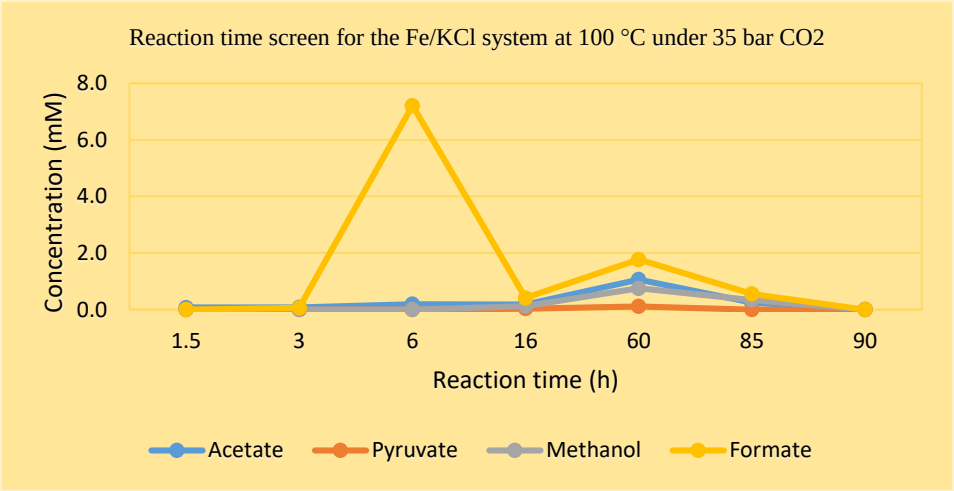


Figure : Effect of temperature, pressure and reaction time on the yield of iron-promoted C-C bond formation in aqueous solution.

These findings reveal that the exceptionally mild conditions of the proposed synthetic pathways could lead to exciting avenues of exploration in enhancing renewable fuel production.

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1. Sreejith J. Varma, Kamila B. Muchowska, Paul Chatelain and Joseph Moran. *Nat. Ecol. Evol.* **2018**, *2*, 810.

BTL NEDERLAND

Insights

SCIENTIFIC LITERATURE REVIEW

ISSN : 2590-0811

August 2018 | volume 1 | number 2

Simple and Efficient Route for C-Si Bond Formation

Green method for the preparation of β-silylcarbonyl compounds and carbonyl containing allylsilanes in high yields is described.

The team of Zhu and Wang have extended the work of Kobayashi *et al.*[1] and reported a green method for the silylation of α,β-unsaturated acceptors. Various substituted α,β-unsaturated substrates **2** reacted with the silylboron reagent [Me2PhSi-B(pin)] **1** in the presence of basic copper carbonate as catalyst; 2,2-bipyridine as ligand and Triton X-100 as additives in water at room temperature to afford the corresponding β-silylcarbonyl products **3** in excellent yields (Scheme 1). Moreover, α,β,γ,δ-unsaturated acyclic (**4a** & **4b)** as well as cyclic dienones (**4c & 4d)** could undergo silylation to produce the corresponding 1,4- (**5a & 5b**) and 1,6-addition products **(5c & 5d**), respectively (Scheme 2).

Notably, the ligand plays a dual role in this reaction. It may function as the coordination part with copper and as the Bronsted base for activation of water molecules. On the other hand, addition of limited amount of surfactant, Triton X114 or X-100, would enhance the productivity of the reaction as a result of increasing the reactivity of a solid substrate by offering external flexibility.

The method is characterized by a broad substrate scope including chalcone derivatives, esters, nitrile as well as α,β,γ,δ-unsaturated acyclic and cyclic dienones.

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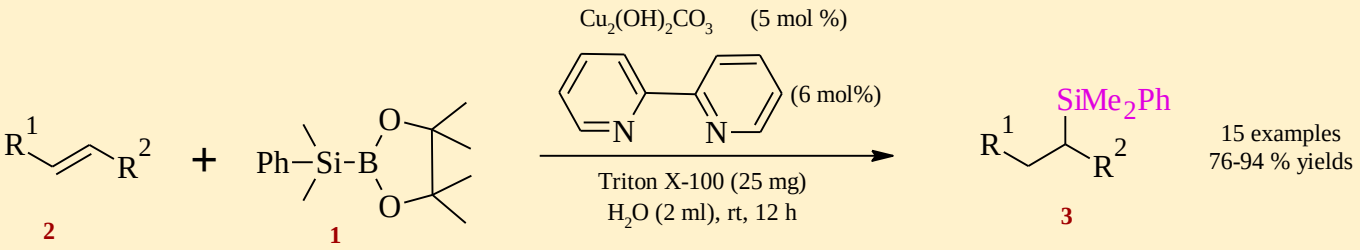
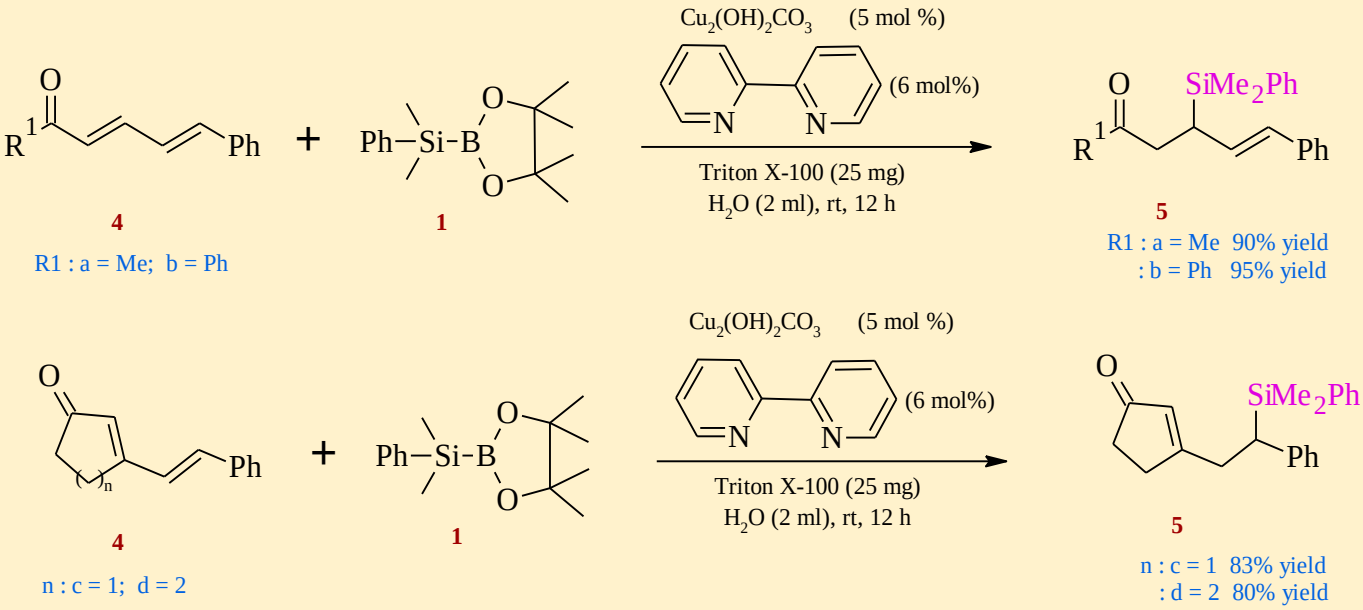


Scheme 1: The preparation of β-silylcarbonyl compounds.



Scheme 2: The preparation of carbonyl containing allylsilanes.

Review:

1) T. Kitanosono, L. Zhu, C. Liu, P. Xu, S. Kobayashi, *J. Am. Chem. Soc*. **2015**, *137*, 15422.
2) W. Wang, B.J. Li, Z.F. Xiao, F. Yan, P.R. Wei, L.S. Wang, L. Zhu, *J. Chin. Chem. Soc.* **2018**, *65*, 81-83.

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The Influence of Solvent on the Molecular Structure of Organotin Carboxylates

The effective role of solvent in the coordination of tin atoms in organotin carboxylates is highlighted.

The organotin carboxylates are well-known for their versatile and significant important therapeutic activities and wood preservatives. They have outstanding properties and structures. It was demonstrated that their structures depend on the ligand, Sn-R group, and the metal-to-ligand molar ratio. Xiao and his coworkers demonstrated here that the type of reactive solvent can influence the coordination of tin atoms in organotin carboxylates and also the internal mechanism of the reaction.

Organotin carboxylate complex **2** can be obtained by reaction of 3-(1,3-dioxo-2,3-dihydro-1*H*-phenalen-2-yl)benzoic acid (**HL**) with dibutyltin oxide as mentioned in the literature. The reaction has been applied with the same raw materials using benzene as a solvent instead of toluene. The outcome was a new complex **1** which shows antitumor activity.

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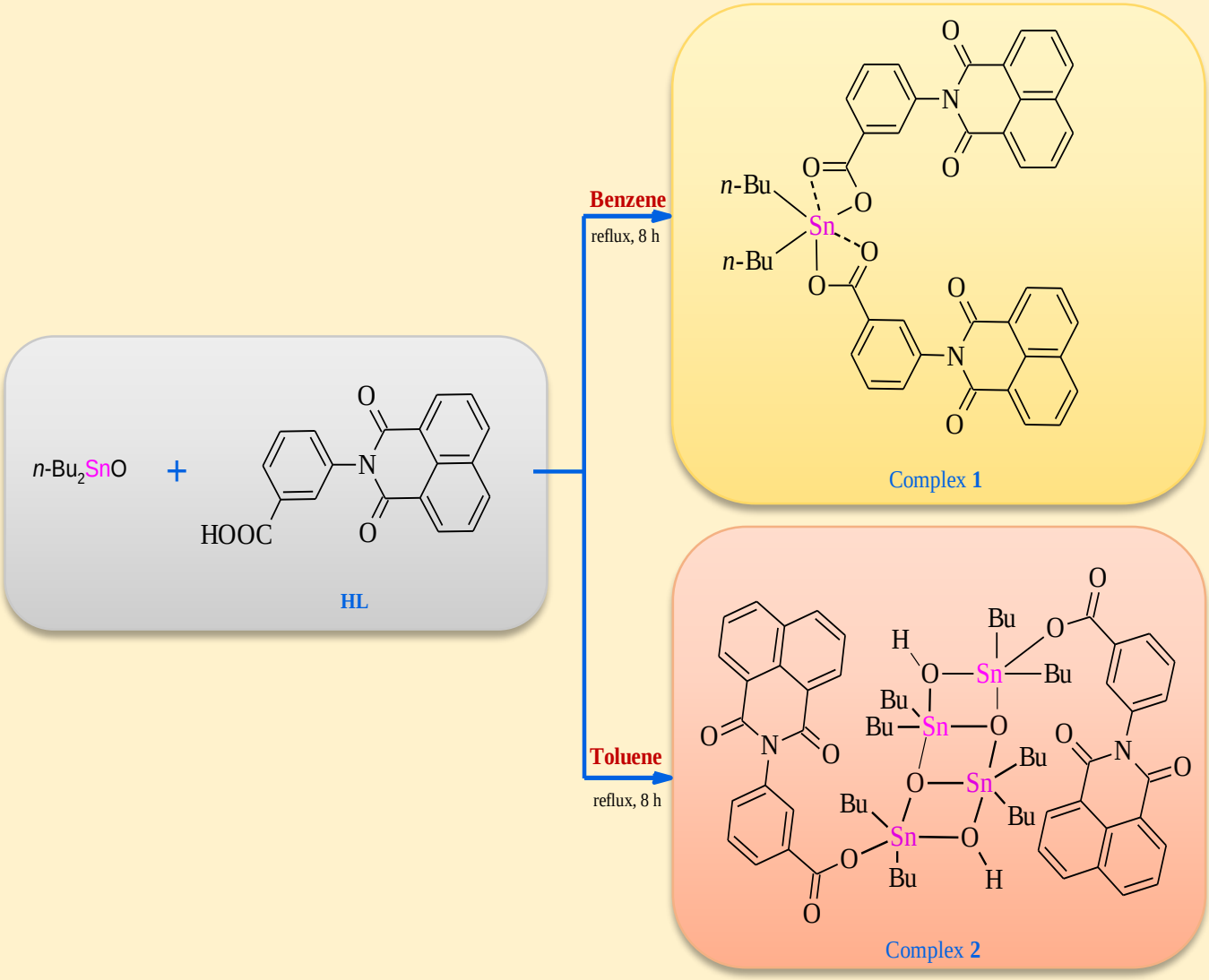

Scheme: Syntheses of complexes **1** and **2**.

Review:

X. Xiao, W. Li, N. Shi, H. Zhu, B. Feng, *Z. Anorg. Allg. Chem.*, **2018**, *644*, 23–28.