



# Advances in Organic Synthesis

Editor:  
**Atta-ur-Rahman, *FRS***

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# Advances in Organic Synthesis

*(Volume 15)*

Edited by

**Atta-ur-Rahman, *FRS***

*Kings College,  
University of Cambridge,  
Cambridge,  
UK*

## **Advances in Organic Synthesis**

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## PREFACE

The 15th volume of *Advances in Organic Synthesis* presents recent exciting developments in synthetic organic chemistry. The chapters are written by authorities in the field. The topics include a review of molecular halogens and N-halamines in the context of their applications as acid- and metal-free catalysts, recent fluorination methods involving phase transfer catalysts, synthesis and applications of small fluorescent molecules, achievements in the synthesis of aromatic five-membered heterocycles containing one heteroatom, and lastly, a discussion about triazole synthesis under green conditions in basic ionic liquids.

This volume should prove to be a valuable resource for organic chemists, pharmaceutical scientists and postgraduate students seeking updated and critically important information on recent important developments in synthetic organic chemistry. I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new developments in the field.

I am thankful to the efficient team of Bentham Science Publishers for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Editorial Director), Mr. Obaid Sadiq (in-charge Books Department) and Ms. Asma Ahmed (Manager Publications).

**Prof. Atta-ur-Rahman, *FRS***  
Kings College  
University of Cambridge  
Cambridge  
UK

## List of Contributors

- A. Bhattacharya** Amity Institute of Nanotechnology, Amity University, Noida, Uttar Pradesh-201303, India
- A. S. Khanna** Surface Engineering & Coating Consultant, Mumbai-400078, India
- Ajay Sharma** Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India
- Atul P. Singh** Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India
- Avni Sharma** Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India
- Bala Dhiman** Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India
- Bidyutjyoti Dutta** Department of Chemistry, Dibrugarh University, Dibrugarh-786004, Assam, India
- Bojan Božić** Institute of Physiology and Biochemistry “Ivan Djaja”, Faculty of Biology, University of Belgrade, Belgrade, Serbia
- Dau X. Duc** Department of Chemistry, Institute of Natural Sciences Education, Vinh University, Vietnam
- Diganta Sarma** Department of Chemistry, Dibrugarh University, Dibrugarh-786004, Assam, India
- Jasmin Sultana** Department of Chemistry, Dibrugarh University, Dibrugarh-786004, Assam, India
- Jaya Verma** CART, Indian Institute of Technology Delhi, New Delhi-110016, India  
Amity Institute of Nanotechnology, Amity University, Noida, Uttar Pradesh-201303, India
- Klara Čebular** Department of Physical and Organic Chemistry, Jožef Stefan Institute, Jamova 39, 1000 Ljubljana, Slovenia  
Jožef Stefan International Postgraduate School, Jamova 39, 1000 Ljubljana, Slovenia  
Lek Pharmaceuticals d.d, Verovškova 57, SI - 1526 Ljubljana, Slovenia
- Monika Mangla** Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India
- Rajesh K. Yadav** Department of Chemistry and Environmental Science, Madan Mohan Malaviya University of Technology, Gorakhpur, U.P., India
- Roktopol Hazarika** Department of Chemistry, Dibrugarh University, Dibrugarh-786004, Assam, India
- Sakshi Rana** Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India
- Sandip S. Shinde** Department of Chemical and Industrial Engineering, Institute of Chemical Technology Mumbai, Marathwada Campus, Jalna 431203, Maharashtra, India
- Stojan Stavber** Department of Physical and Organic Chemistry, Jožef Stefan Institute, Jamova 39, 1000 Ljubljana, Slovenia  
Jožef Stefan International Postgraduate School, Jamova 39, 1000 Ljubljana, Slovenia



# Metal-Free and Acid-Free Activation of Carbonyl Moiety Using Molecular Halogens or *N*-Halamines

Bojan Božić<sup>1\*</sup>, Klara Čebular<sup>2,3,4</sup>, Stojan Stavber<sup>2,3</sup>

<sup>1</sup> Institute of Physiology and Biochemistry “Ivan Djaja”, Faculty of Biology, University of Belgrade, Belgrade, Serbia

<sup>2</sup> Department of Physical and Organic Chemistry, Jožef Stefan Institute, Jamova 39, 1000 Ljubljana, Slovenia

<sup>3</sup> Jožef Stefan International Postgraduate School, Jamova 39, 1000 Ljubljana, Slovenia

<sup>4</sup> Lek Pharmaceuticals d.d, Verovškova 57, SI - 1526 Ljubljana, Slovenia

**Abstract:** In recent years, the growing environmental awareness has prompted an increasing demand for eco-friendlier technologies, acting consequently as a main driving force for exploring greener methodologies. One of the most fundamental approaches in organic synthesis is the activation of the carbonyl group. This step is essential for the performance of a plethora of organic reactions. Herein, we provide a brief overview of molecular halogens and *N*-halamines in the context of their application as acid- and metal-free catalysts. Susceptibility of the carbonyl group to the nucleophilic attack allows the construction of numerous organic compounds. The existence of oxygen lone pairs puts the carbonyl moiety into the context of a Lewis base, prone to activation in the presence of a Lewis acid, which has been observed and extensively investigated over the last decade. The noncovalent interactions – halogen bonds – provided by halogen atoms in haloorganic compounds may be assumed responsible for their catalytic activity. Molecular halogens and *N*-halamines act as convenient, easily-handled, low-priced catalysts/mediators and, more importantly, the ones that can presumably act as Lewis acids. These characteristics prompted this class of compounds in the research focus aiming at substantial advances in organic synthesis. Finally, an optimal reaction method (where the carbonyl moiety activation represents an essential step) should meet the following criteria: *i*) an easily-manipulable, low-cost, non-metal, water- and air-tolerant catalyst, *ii*) mild and solvent-free reaction conditions, *iii*) no need for simultaneous water removal, and, *iv*) stoichiometric amounts of activators or large excesses of reagents.

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\*Corresponding author Bojan Božić: Institute of Physiology and Biochemistry “Ivan Djaja”, Faculty of Biology, University of Belgrade, Belgrade, Serbia; E-mail: bbozic@bio.bg.ac.rs

**Keywords:** Carbonyl group, Catalysis, Green chemistry, Halogen bond, Molecular halogens, *N*-halamines.

## INTRODUCTION

From the early beginnings, civilizations use technology to improve the quality of life by extracting different metals from ores, producing ceramics, transforming fats into soap, fermenting beer and wine, extracting natural compounds from herbs for fragrance and therapeutics, creating glass, and making alloys. Nowadays, with the world's population outreaching 8 billion, a request for higher quality food, agrochemicals, and products, larger quantities of medicines and fuel, more manufactured goods, such as garments and machines, and most importantly, enhanced access to drinking water and clean air, dramatically escalates. Such needs have driven the advancement and growth of research in different scientific disciplines, including chemistry, for the last two centuries launching the road of invention, development, and discovery. However, scientists have undertaken this course without thoroughly understanding the effects of chemicals and different technologies on human health and the environment, in general, *i.e.*, the consequences of the galloping pace in breakthroughs related to both novel insight and accompanying methodologies had been only partially foreseen. In recent decades, with the tremendous accumulation of new information/data, the awareness about arising environmental issues has led chemists to challenge their work and actively mitigate the implications by adopting the principles of green chemistry [1]. The 12 principles were established by Paul T. Anastas in 1998 [2], standing as the essence of the green chemistry *modus operandi* [3]:

1. Analytical methodologies for pollution prevention;
2. Atom efficiency;
3. Catalytic rather than stoichiometric reagents;
4. Designing products for degradation;
5. Energy efficiency by design;
6. Inherently safer processes.
7. Innocuous solvents and auxiliaries;
8. Less hazardous/toxic chemicals;
9. Preferably renewable materials;
10. Safer products by design;
11. Shorter synthesis – avoiding derivatization;
12. Waste prevention instead of remediation;

Over the last decades, the growing acceptance of green chemistry in academic and industrial settings has resulted in a movement to develop a better, healthier, and more sustainable environment [4]. On 25 September 2015, the UN introduced a set of goals to reduce poverty, protect the earth and ensure sustainability for all, as a part of a new environmental sustainability strategy. The aims and targets should promote progress in areas of vital importance to humanity and the environment over the next 15 years [5]. In this context, the research and development of environmentally harmless chemical transformations and catalysis will play an increasingly important role in sustainable development and, generally, in the progress of organic chemistry.

### Catalysis

Green chemistry assumes the reduction or, ideally, elimination of waste products in the chemical industry, with the slogan: “*Prevention is better than cure.*” This objective calls for a paradigm shift in the organic synthesis performance from the higher-yield-based to waste minimization [3]. Over the last two decades, advances in green chemistry prompted catalysis protocols extensively applied in the pharmaceutical and fine chemical industries to minimize the enormous quantities of waste produced due to the inorganic stoichiometric reagents usage. Catalysts are used in 80 percent of all chemical manufacturing processes, producing global annual sales of about \$1500 billion, contributing directly or indirectly to about 35 percent of the world's GDP [6]. The term *catalyst* refers to the substance increasing the velocity of a reaction, *i.e.*, decreasing the reaction's activation energy without undergoing alteration during the process. At least, in theory, the catalyst can be used in small amounts and recycled continuously so that no waste material is produced in net effect.

Catalysis increases reaction kinetics. Although thermodynamics serves as a guide to the most stable products, kinetics evaluates the relative levels of many competitive pathways available for reactants. By reducing the activation energy, catalysts enable additional mechanistic routes with lower energy activation barriers, compared to those of non-catalyzed reactions, rendering quickly and selectively metastable products during catalytic processes. With new pathways available, catalyzed reactions follow at much faster rates and lower temperatures. A catalyst, however, can only shorten the period of reaching thermodynamic equilibrium, but cannot alter the position of the balance, *i.e.*, catalyze a thermodynamically unfavourable reaction [7].

## Anti-algal Study on Polymeric Coating Containing Metal@Metal Oxide Core-shell Nanoparticles Developed through Organic Synthesis for Marine Paint Applications

Jaya Verma<sup>1,2,\*</sup>, A. S. Khanna<sup>3</sup>, A. Bhattacharya<sup>2</sup>

<sup>1</sup>CART, Indian Institute of Technology Delhi, New Delhi-110016, India

<sup>2</sup>Amity Institute of Nanotechnology, Amity University, Noida, Uttar Pradesh-201303, India

<sup>3</sup>Surface Engineering & Coating Consultant, Mumbai-400078, India

**Abstract:** In this chapter, we studied anti-algal coating development with silica-titania core-shell nanoparticles using a novel organic synthesis approach; peptization. Development of nano core-shell through this peptization methodology improved the two different material properties in a single nanoparticle excellently *i.e.* core silica improved the mechanical strength, and shell titania enhanced the anti-algal property of the coating. These coatings were formulated in two model binders: solvent-based binder polyurethane and water-based emulsion poly-acrylic at various concentrations of nanoparticles against hazardous algae present in seawater. Obtained results confirmed these developed coatings are super protective coatings using silica-titania core-shell nanoparticles, which are highly anti-algal as well as mechanically-strengthened that can be useful as marine antifouling coatings for water boats or ships and when it would be applied to the underwater hull of ships, discourages or prevents the growth of organisms that attach to the hull. It would also improve the flow of water passing the hull of a fishing vessel or high-performance racing yacht because of the smoothness of the coatings. Additionally, the irradiation effect of low energy ions was also investigated on these coating surfaces and found excellent results towards application in marine paint.

**Keywords:** Algae, Anti-algal activity, Irradiation effects, Low energy ions, Mechanical strength, Nano-coating, Peptization process, Poly-acrylic, Polyurethane, Silica-titania core-shell nanoparticle.

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\*Corresponding author Jaya Verma: CART, Indian Institute of Technology Delhi, New Delhi-110016, India; Tel: +91-8744985777; Email: jayaverma@iitd.ac.in

## INTRODUCTION

At present, Marine biofouling', the undesired growth of marine organisms, such as microorganisms, barnacles, and seaweeds on submerged surfaces, is a global problem for maritime industries, with both economic and environmental penalties [1-3] The primary strategy for combating marine fouling is to use biocide-containing paints, but environmental concerns and legislation are driving science and technology towards non-biocidal solutions based solely on physicochemical and materials properties of coatings [4-7]. Advances in nanotechnology and polymer science, and the development of novel surface designs 'bio-inspired' by nature [8-10], are expected to have a significant impact on the development of a new generation of environmentally friendly marine coatings [11,12].

Recent approaches are based on the development of polymeric anti-algal surface by silica-titania core-shell nanoparticles through organic synthesis. Previously, various researchers worked on the anti-microbial effect of nanoparticles using  $\text{TiO}_2$ ,  $\text{ZnO}$  etc. nanoparticles, but no one worked with silica-titania core-shell nanoparticles in anti-algal study for marine anti-fouling paint application. In this core-shell structure, two different material properties improved in a single composite. Core silica improved the anti-scratch property of coating, which is already reported in our previously published research article [13] and the presence of titania as shell material improved the anti-algal properties of the coating. As we already know, titania-polymer nano-composites are intrinsically environmentally friendly and exert a non-contact biocidal action. Therefore, no release of potentially toxic nanoparticles (with unpredictable effects on human health) to the media is required to achieve disinfection capabilities [14, 15]. So, this type of coating can be useful as *anti-fouling coating* for the marine industry. When this nanocomposite based coating would be applied to the underwater hull of ships, it would improve the smoothness of the coating and the flow of water passing the hull of a fishing vessel that supports a high-performance racing yacht by prohibiting the growth of organisms attach to the hull. So in this anti-algal study, testing was performed against green and mixed algae because these types of harmful algae are mostly found in seawater.

## Synthesis and Characterization Approach for SiO<sub>2</sub>@TiO<sub>2</sub> Core-shell Nanoparticles

Peptization is the organic synthesis approach used for converting a fresh precipitate into a colloidal particle by shaking it in the dispersion medium in the presence of a small amount of electrolyte. Generally, an electrolyte is added whose one ion is common with one ion of the precipitate. The particles of precipitate absorb common ion of electrolyte. Then, they get dispersed due to electrostatic repulsion. This method not only avoids complicated processes such as the layer-by-layer technique and polymer/surfactant grafting methods. It also reduces costs due to its short reaction time and the use of inexpensive reactants. In this research work, we followed the peptization process for metal oxide core-shell nanoparticle synthesis. In the organic synthesis (Peptization process) of core-shell nanoparticle, core silica was prepared using tetraethyl orthosilicate (TEOS) in the presence of H<sub>2</sub>O, C<sub>2</sub>H<sub>5</sub>OH and NH<sub>4</sub>OH. Shell structure was developed on core silica using titanium tetra-isopropoxide with 1 ml of 70% nitric acid and stirred for 4 h at 70<sup>0</sup> C. After this, the whole material was centrifuged at 8000 rpm for 10-15 min and dried at 70<sup>0</sup> C for overnight. Core-shell nanoparticles were synthesized through the sol-gel process for comparative study on the anti-algal property as well as individual silica and titania nanoparticles also. Detailed synthesis methodology is already reported in our previously published research articles for the same nanoparticles [13].

Surface modification of synthesized nanoparticles was carried out using methyl trimethoxy-silane in the presence of ammonium hydroxide for better dispersion in the coating formulations. Further water-based binder poly-acrylic (PA) and solvent-based polyurethane (PU) coatings were developed on mild steel and bricks containing silica, titania, and silica-titania core-shell nanoparticles (from 1wt % to 6wt % in total coating formulations) individually prepared *via* both the processes, *i.e.*, sol-gel and peptization, for anti-algal testing as well as mechanical property testing.

The characterization of all the nanoparticles, such as dynamic light scattering (DLS), UV-Vis spectroscopy, XRD analysis, TEM, XPS, and Fourier transform infrared spectroscopy was successfully performed. In this study, DLS was used to measure the particle size of the as-prepared nanomaterials. The particle size of nano-silica was measured as 85 nm. Nano-TiO<sub>2</sub> was measured as 107 nm, and the size of the silica-titania core-shell nanoparticles was 240 nm, prepared *via* a sol-gel process. TiO<sub>2</sub> nanoparticles and SiO<sub>2</sub>-TiO<sub>2</sub> nano core-shell particles were also prepared by the peptization process with a particle size of 75 nm and 144 nm separately. All these characterizations of the same nanoparticles are briefly

# Functionalized Catalyst for Efficient Nucleophilic and Electrophilic Fluorination

Sandip S. Shinde<sup>1\*</sup>

<sup>1</sup> Department of Chemical and Industrial Engineering, Institute of Chemical Technology Mumbai, Marathwada Campus, Jalna 431203, Maharashtra, India

**Abstract:** Fluorination reactions are an important class of organic synthesis. Fluorine is a highly electronegative atom; thus, it has dual characteristics, such as being basic and nucleophilic in nature which produces various products. In this chapter, we have discussed the recent development of fluorination methods by using various phase transfer catalysts. The catalyst plays a significant role in aliphatic nucleophilic fluorination. The various tasks of specific tailor-made ionic liquids are developed and used for fluorination reactions. Ionic liquid catalyst is immobilized, covalently bonded on solid or liquid support to improve the catalytic efficiency in the reactions.

**Keywords:** Aliphatic nucleophilic substitution, Catalyst, Electrophilic, Fluorination, Halogenations, Ionic Liquids, Methodologies, Organic reactions.

## 1. INTRODUCTION

Ionic liquid (ILs) is the term that generally refers to salts of the organic or inorganic molecule, which exists in the liquid state at room temperature [1]. The ionic liquids are one of the environmental benign "green solvents" due to their series of characteristic features that include easy preparation, good thermal conductivity, chemical stability, recoverability, non-toxicity, *etc.* Most of the organic solvents are insoluble in ILs, thus they can be recoverable and recycled after the reaction process. ILs usually have a high boiling point, non-volatile, insoluble, and high-density features which have made them a favourable reaction media and catalyst in various organic transformations [2]. They can be used as a heterogeneous or homogenous catalyst as per the requirement of reaction conditions [3]. The applications of ILs are not limited to the chemistry field but also used in biomedical

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\*Corresponding author Sandip S. Shinde: Department of Chemical and Industrial Engineering, Institute of Chemical Technology Mumbai, Marathwada Campus, Jalna 431203, Maharashtra, India; E-mail: shinde88@gmail.com

applications [4]. Currently, numerous ILs are developed based on the heterocyclic organic skeleton to form cation and anion salts. However, the imidazole and pyridine-based modified ILs are widely being studied for various applications, including surfactants, polymer, therapeutics, insecticides, and lubricants [5].

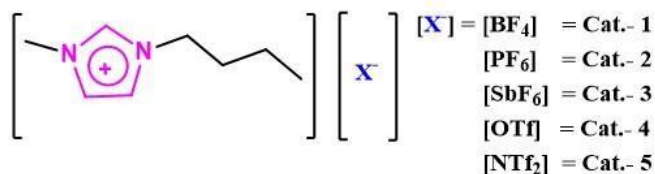
Substitution reactions are important class of organic reactions, in which a functional group is replaced by a new nucleophile or electrophile. In bioactive molecules, the polymer is synthesized by following substitution reactions. The halogenation compounds are usually achieved by applying the substitution reaction to the aliphatic or aromatic system. Among the various halogens such as F, Cl, Br, I, *etc.*, the fluorine has attracted attention due to significant physico-chemical properties, like increased receptor-binding, metabolic stability, and lipophilicity properties that are found in bioactive compounds [6]. Fluorine is one of the important elements in our daily life, which is widely present in toothpaste, mineral water, eatable salts, and kitchen utensils. The fluorination reaction is an attractive research area for organic synthesis researchers. The fluorine is not only limited to use in chemical biology or food chemistry research but also applied in clinical science research to detect the progress of cancer diseases. In the radiopharmaceutical field, fluorine with radiolabelling is high in demand due to its longer half-life (110 min). In recent years, fluorinated organic molecules have reached a commercial status in crop protection and pharmaceutical drug industries [7]. More than 600 agrochemicals have been developed and marketed; among them, low fluorinated compounds account for most of the commercially available crop protection agents [8], which include important insecticides, fungicides, herbicides, and the agrochemical blockbusters [9]. In the pharmaceutical field, many fluorinated compounds with the greatest activity and properties have been very successfully introduced to the market, as anti-depressants, anti-inflammatory, anti-malarial, anti-psychotic, antiviral agents, steroids and anaesthetics, *etc.* [10]. Considering this above-mentioned importance of fluorine, research has developed several reactions for the synthesis of fluorine-containing molecules [11]. Introducing fluorine to the organic molecule is a tedious task due to low availability of fluorine source, which is mostly available in salt, making it difficult for it to react with organic substrates. Fluorination is performed by substitution reactions using phase transfer catalyst due to the insolubility of fluoride metal salts in an organic solvent. Great progress is made in fluorine diazotization reaction, nucleophilic fluorination, electrophilic fluorination, and electrochemical fluorination [12]. ILs are used as solvent and phase transfer catalysts in various reactions, even though in transition metal catalyst reactions. This not only enhances the reaction rate of metal salts but also facilitates product separation after completion of the reaction process [13]. However, the applications of ionic liquid as a catalyst in fluorination reactions are an emerging



and interesting topic for organic chemists. In this book chapter, we have covered the two decades of research developments involving fluorination reactions in the presence of various catalysts; also, the role of reaction media or catalyst in various substitution reactions has been reviewed [14].

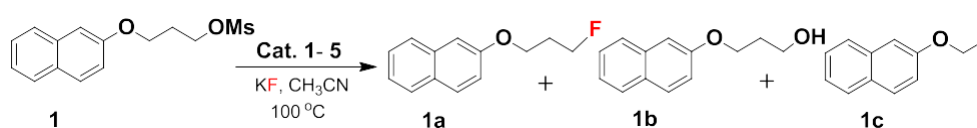
### 1.1. Imidazolium Ionic Liquid Catalyst

Ionic liquids are uncommon to use in halogenation reactions. Kim *et al.* found that nucleophilic fluorination reaction with some haloalkanes and mesylalkanes gave corresponding desired fluorinated products by using KF in the presence of IL catalysts [15]. The imidazolium-based ILs with various counter anions, as shown in Fig. (1), have been studied as a catalyst for nucleophilic substitution. The fluorination in ILs provides much better yield than classic organic solvent-mediated reactions.



**Fig. (1).** Imidazolium ILs studied in nucleophilic substitution reactions.

Kim and his group developed some new ionic liquids for nucleophilic substitution reactions, exhibiting good yield, as shown in Scheme 1. Fluorination of substrate **1** containing mesylate (leaving group) with the help of KF as a fluorinating agent in CH<sub>3</sub>CN at 100 °C took more reaction time, but the same reaction in the presence of [bmim] [BF<sub>4</sub>] **Cat.-1** involving BF<sub>4</sub> counter anion was completed in 2h, and the product 2-(3-fluoropropoxynaphthalene) formed with less amount of by-products such as alcohol **1b**; the by-product can be eliminated if the reaction is performed using a low amount of water.



**Scheme 1.** Classic ILs as a catalyst in fluorination reaction.

## Synthesis and Applications of Small Fluorescent Molecules

Avni Sharma<sup>1</sup>, Sakshi Rana<sup>1</sup>, Monika Mangla<sup>1</sup>, Bala Dhiman<sup>1</sup>, Ajay Sharma<sup>1</sup>, Atul P. Singh<sup>1\*</sup> and Rajesh K. Yadav<sup>2</sup>

<sup>1</sup> Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India

<sup>2</sup> Department of Chemistry and Environmental Science, Madan Mohan Malaviya University of Technology, Gorakhpur, U.P., India

**Abstract:** Fluorescent molecules play an important role in synthetic chemistry due to their vast applications from their applicability in sensors in the medicinal field. These molecules cover a range of systems from monomeric to polymeric but more attention has been given to the development of small molecules that are of high relevance. One can ask about the factors which direct small molecules as a core centre of research in sensor chemistry. Strong emission, better molar absorptivity, molar extinction coefficient and small molecular weight are some of the important points that govern the high applicability of fluorescent molecules in sensor chemistry. But first, it is important to know what these properties are, and how these properties play a crucial role to govern fluorescent molecules as a tool to utilize in various fields of sensor chemistry. Fluorescent molecules have been extensively used in the field of physiology of receptors, as sensors for metal ions (generally transition metals) and ROS (reactive oxygen species), bio-imaging and pharmacology, etc.

**Keywords:** Auxochrome, BODIPY, Biological Importance/Function, Chromophore, Energy Transfer Mechanism, Fluorescein, Fluorescent Probe, Fluorescence, Quantum Yield, Reactive Oxygen species (ROS), Sensors.

### INTRODUCTION

Fluorescent molecules are very important in synthetic chemistry due to their vast applications as a sensor in *in-situ* as well as *in-vitro*. These molecules range from monomeric to polymeric in nature, and are well-known, but researchers are working to discover small molecules that are of higher relevance. One can ask about the factors which cover or direct small molecules as a core centre of research in sensor chemistry. Strong emission, better molar absorptivity, molar

\* Corresponding author Atul P. Singh: Department of Chemistry, UIS, Chandigarh University, Mohali, Punjab, India; E-mail: atulpiitd@gmail.com

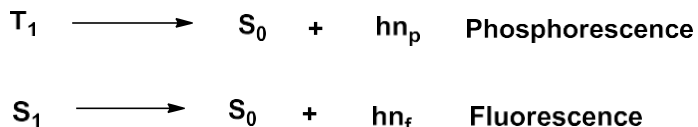
Extinction coefficient, and small molecular weight are some points that govern the high utility of fluorescent molecules in sensor chemistry [1, 2]. But first, it is important to know what these properties are, and how these properties play a crucial role to govern fluorescent molecules as a tool to utilize in various fields of sensor devices. Fluorescent molecules [3 - 5] have been extensively used in the field of physiology of receptors, as sensors for metal ions (generally transition metals) and ROS (reactive oxygen species), bio-imaging and pharmacology, etc.

It has been reported in South America that a terrestrial animal named polka-dot tree frog (*Hypsiboas punctatus*) [6] shows fluorescent properties on illumination with UV-Vis light and radiate bright green light. This bright green color emission was due to the molecule which absorbs red color light at a longer wavelength and emits its complementary color. This process is called fluorescence. There are basically two phenomena that work in the field of photochemistry (1) Fluorescence (2) Phosphorescence, but fluorescent molecules are based on the phenomenon of fluorescence. Various fluorescent molecules have been reported so far, which show this phenomenon and have many biological applications as reported with Fluorescein, Rhodamine, BODIPY, Pyrene-type molecules, and their derivatives. The question is why these molecules are fluorescent in nature and what properties they exhibit.

### Definition

Firstly, we need to know the above two phenomena which are well described and schematically illustrated in the Jablonski diagram (Fig. 1) given by Professor Alexander Jablonski in the year 1985 [7]. It is based on the emission of light which is termed Luminescence. When the light of a certain wavelength irradiates on a molecule, the electron in the molecule gets excited and move from singlet ground state to excited state and comes back from the singlet excited state ( $S_1$ ) to ground state, emission of light and energy takes place; this whole phenomenon is called fluorescence. In this diagram, the excited states are drawn vertically with increasing energy named singlet excited states, and triplet excited state which is lower in energy than their corresponding singlets. When two electrons with the spin, align in the opposite direction to each other, so the electrons have spin multiplicity equal to 1 hence called singlet state and denoted as S with the ground state ( $S_0$ ), first excited state ( $S_1$ ), and so on. Triplet state, on the other hand, when electrons which are unpaired and have parallel spin formulating the spin multiplicity equal to 3, hence called triplet state and denoted as T. As triplet ground state does not exist, so the triplet state starts with first triplet excited state ( $T_1$ ) which is lower in energy as compared to first singlet excited state. The diagram shows two types of processes 1.) Radiative process and, 2.) Non-radiative process [8].

Radiative processes are those in which the release of energy takes place in the form of light during the time of emission, while non-radiative processes are those in which there is no emission of energy or light takes place. Non-radiative processes are classified as internal conversion (IC), intersystem crossing (ISC), and vibrational relaxation. Similarly, radiative processes are classified in two ways as Phosphorescence and Fluorescence [9]. Phosphorescence basically a phenomenon in which the emission of a photon of light ( $h\nu_p$ ) takes place during the electron drops from triplet excited state ( $T_1$ ) to ground state ( $S_0$ ) after some time. Materials that show this phenomenon are kid's toys that glow-in-the-dark, clock dial, paints, and stickers. Even if we remove the source of radiation, phosphorescence will still occur because this triplet state is longer-lived than the singlet state. In the process of fluorescence, there is an emission of energy in the form of a photon ( $h\nu_f$ ) when an electron drops from the  $S_1$  state to  $S_0$ . It generally occurs within  $10^{-9}$  seconds. Generally, the organic compounds which are aromatic in nature show fluorescence (Table 1).



Generally, the compounds which show fluorescence are eosin, fluorescein, chlorophyll, and anthracene. The electron releasing group generally increases fluorescence, whereas the electron-withdrawing group reduces fluorescence. The fluorescein emission spectra of compounds are usually the mirror image of its absorption spectra.

**Table 1. Differences in fluorescence, phosphorescence, internal conversion, and intersystem crossing.**

-	Fluorescence	Phosphorescence	Internal Conversion	Intersystem Crossing
<b>Type of Radiation</b>	Radiative	Radiative	Non-Radiative	Non-Radiative
<b>Emission</b>	From $S_1$ to $S_0$	From $T_1$ to $S_0$	From $S_n$ to $S_{n-1}$ where n is any electronic state	From $S_n$ to $T_n$ where n is any electronic state
<b>Time Scale</b>	$10^{-9} - 10^{-7}$ sec	$10^{-1} - 10^2$ sec	$10^{-4} - 10^{-11}$ sec	$10^{-8} - 10^{-3}$ sec

## Recent Achievement in the Synthesis of Aromatic Five-Membered Heterocycles Containing One Heteroatom

Dau X. Duc<sup>1\*</sup>

<sup>1</sup>Department of Chemistry, Institute of Natural Sciences Education, Vinh University, Vietnam

**Abstract:** Furan, pyrrole and thiophene derivatives are aromatic five-membered heterocyclic compounds with one heteroatom. These compounds are widely distributed in a wide range of natural and non-natural compounds. Many of these derivatives have a diverse range of bioactivities such as antimicrobial, anticancer, antiparasitic, anti-inflammatory, antihypertensive antiviral, antitumor, activities, and several derivatives have been marketed as drugs for treatment of various diseases. Besides, the use of furan, pyrrole and thiophene derivatives also has been found in other fields such as organic materials, agrochemicals, flavors, dyes. They can serve as intermediate or building blocks for the preparation of natural product compounds or drugs.

With such a diverse range of applications, the preparation of furan, pyrrole and thiophene derivatives has drawn intensive attention of chemists. Several established synthetic approaches for example the Paal-Knorr, Feist-Benary, Gewalt, Knorr and Fiesselmann, Huisgen, and Hantzsch syntheses have been modified and improved. Moreover, an enormous number of new methods for the preparation of these heterocycles have been developed. This chapter will give an overview of published studies on the construction of pyrrole, furan, and thiophene skeletons which date back to 2012.

**Keywords:** 1,4-diketones, 2-aminothiophenes, 2,5-dimethoxytetrahydrofuran, 3-yne-1, 2-diols, Anticancer, Antihypertensive, Antiinflammatory, Antimicrobial, Antiparasitic, Antitumor, Antiviral, Clauson-Kaas synthesis, Cyclization, Feist-Benary Synthesis, Fiesselmann synthesis, Gewalt reaction, Hantzsch synthesis, Paal-Knorr synthesis, Primary amines, Tosylmethyl isocyanide, Van Leusen synthesis.

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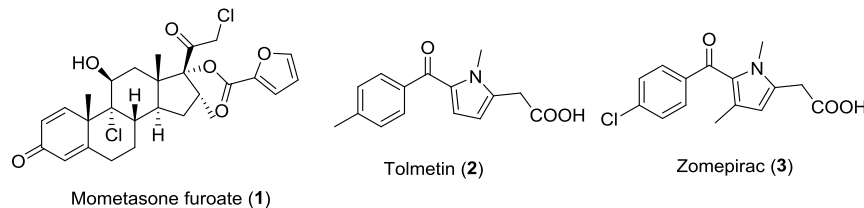
\* Corresponding author **Dau X. Duc:** Department of Chemistry, Institute of Natural Sciences Education, Vinh University, Vietnam; Tel: +84947588283; E-mail: xuanduc80@gmail.com

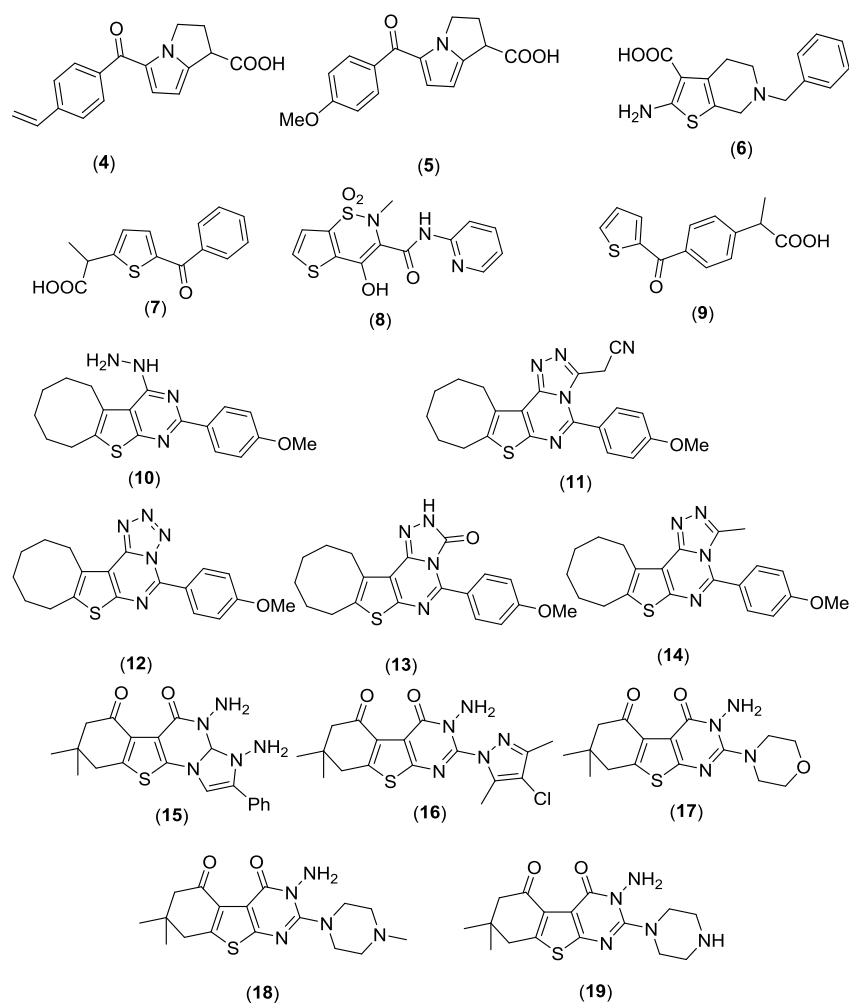
## 1. INTRODUCTION

Furan, pyrrole and thiophene derivatives are aromatic five-membered ring heterocycles with one heteroatom. These compounds are widely distributed in a wide range of natural and non-natural compounds. Many of these heterocycles have a broad range of bioactivities such as antimicrobial, anticancer, antiparasitic, anti-inflammatory, antihypertensive, antiviral, antitumor, activities, and some compounds have been marketed as drugs for treatment of various diseases. Besides, the use of furan, pyrrole and thiophene derivatives also has been found in other fields such as organic materials, agrochemicals, flavors, dyes. They can serve as intermediate or building blocks for the preparation of natural product substances or drugs.

### 1.1. Anti-inflammatory Activity

Mometasone furoate **1** has been used in the treatment of inflammatory skin disorders (Fig. 1) [1]. Tolmetin (**2**) and Zomepirac (**3**), are pyrrole-containing drugs used in the treatment of rheumatoid arthritis and pain in the market. Various 5-aryl-1,2-dihydro-3*H*-pyrrol [1,2-*a*] pyrrole-1-carboxylic acid derivatives were prepared by Muchowski *et al.* and evaluated for anti-inflammatory activity. The derivatives containing 4-vinylbenzoyl (**4**) and 4-methoxybenzoyl (**5**) moieties were the most active components (Fig. 1) [2]. Various thiophene compounds including Tinoridine **6**, Tiaprofenic acid **7**, Tenoxicam **8** and Suprofen **9** have been marketed as anti-inflammatory agents. Fayed *et al.* synthesized a new class of fused thiophene compounds and examined their anti-inflammatory activity using Indomethacin as the reference. Five of them, compounds **10**, **11**, **12**, **13** and **14** exhibited significant anti-inflammatory activity (Fig. 1) [3]. Five novel benzothino-pyrimidine compounds **15-19** prepared by Duaij *et al.* displayed stronger anti-inflammatory activity than Indomethacin over bioassay testing method in rats (Fig. 1) [4].





**Fig. (1).** Antiinflammatory activity of furan, pyrrole and thiophene derivatives.

## 1.2. Antimicrobial Activity

Ceftiofur **20**, Fumoxicillin **21**, Nitrofurantoin **22**, Nifuroxazide **23**, Nifurtinol **24**, Roseophilin **25**, and Cefuroxime **26** are furan-containing antibiotic drugs and widely used in medical practice (Fig. 2A) [5-10]. Furazolidone **27** has been used as an antibacterial agent in the treatment of diarrhea and enteritis caused by bacteria or protozoan infections (Fig. 2A) [11]. Nifurquinazol **28** (NF-1088) has been used as a nitrofuran antibacterial agent (Fig. 2A) [12]. A series of symmetric 2,5-diaryl-*NH*-pyrroles (**31**) constructed by Jana *et al.* showed strong

## CHAPTER 6

## Basic Ionic Liquid Catalyzed Cycloaddition Reactions for the Synthesis of 1, 2, 3-Triazoles

Diganta Sarma<sup>1,\*</sup>, Jasmin Sultana<sup>1</sup>, Roktopol Hazarika<sup>1</sup> and Bidyutjyoti Dutta<sup>1</sup>

<sup>1</sup> Department of Chemistry, Dibrugarh University, Dibrugarh-786004, Assam, India

**Abstract:** Ascribing to the superiority of possessing noteworthy physicochemical properties, ionic liquids engirdle a scientific interest in research area of chemistry as green solvent over past few decades. Being constituted entirely of ionic species, these solvents remain often as fluid at room temperature. The strength of the cation, anion or the combination of both governs the acidity or basicity of reactive ionic liquids. Due to some special properties like flexibility, non-volatility, non-corrosive, tunable property, high thermal stability and recyclability; ionic liquids offer a great potential to replace conventional solvents in chemical synthesis. Further, the use of acidic or basic ionic liquids reduces the necessity of using external acid or base along with the solvents. Therefore, implementation of these ionic liquids in chemical laboratory is widely accepted as one of the green techniques as it lessens the adverse environmental impacts.

1,2,3-triazoles are highly desired synthetic molecules in the field of chemical and pharmaceutical industries as triazole containing moieties possess potent biological activities such as anti-viral, anti-epileptic, anti-allergic, anti-microbial, anti-cancer, antituberculosis and anti-HIV properties. Its application is also extended to other areas such as organic synthesis, polymer science, material science and chemical biology. As the incorporation of basic condition favors the synthesis of these privileged classes of compounds from their starting reagents, use of basic ionic liquids as reaction media provides an alternative and greener approach for their facile construction. This chapter will discuss triazole synthesis under green conditions by following three different routes in basic ionic liquid:

- Direct azide-alkyne cycloaddition reactions affording 1,2,3-triazoles.
- Cascade synthesis of triazoles from azides and carbonyl compounds.
- One pot three component reactions leading to 1,2,3-triazoles.

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\* Corresponding author Diganta Sarma: Department of Chemistry, Dibrugarh University, Dibrugarh-786004, Assam, India; E-mail: dsarma22@dibru.ac.in

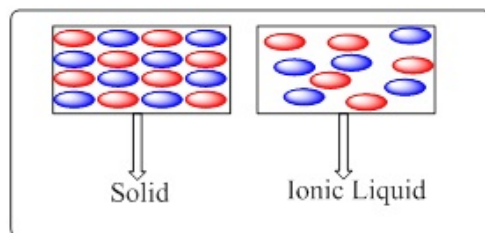


**Keywords:** 1, 2, 3-triazoles, Anti-microbial, Atom economy, Basic ionic liquid, Click-chemistry, CuAAC, Cascade synthesis, Green Chemistry, One pot reaction, Sustainable Solvents.

## INTRODUCTION

### Ionic Liquids: Combination of Molten State of Ions

Molecular solvents turned out to be the medium to accomplish most of the chemical reactions. Most of our efforts in dealing with chemistry have been drawn upon the reactions of molecules in solution phase in molecular solvents for decades. Of late, due to the aspiration for “green” solvents for reducing environmental hazards; “ionic liquid” has turned up as a new sort of sustainable solvent providing a few unique properties like high chemical and thermal stability, non-flammability, tremendous solvating power [1, 2] *etc.* Being composed wholly of ionic species, these solvents have many captivating assets such as they can be designed as per as to meet the specific necessity for a particular kind of reaction as they are composed of at least two fragments *i.e.*; organic cation part and organic/inorganic anion part, which can be varied. Using a distinct end from the two (cation and anion) in notice, these solvents can be designed to hold a set of specific properties *i.e.*; they are task specific [3]. Due to the huge deviation in size of cation and anion, they are not capable of forming lattice (Fig. 1); rather they are dispersed resulting them to usually be fluid at room temperature.



**Fig. (1).** Representation of the difference between a lattice and an ionic Liquid.

Ionic Liquids (ILs) can be synthesized by metathesis, direct-combination or acid-base neutralization reactions [4]. The thermodynamic and kinetics of reactions carried out in these designer solvents are poles apart compared to those traditional molecular solvents which make them of vital interest to all researchers as they have the prospective of functioning as catalyst too [5]. Moreover, ionic liquids do not emit any volatile organic compounds (VOCs) as these solvents have no quantifiable vapor pressure due to which they are a matter of interest for diverse synthesis that can be termed as “green”.

## History of Ionic Liquid

In 1888, ethanolanmonium nitrate emerged out to be the first ever ionic liquid reported by Gabriel and Weiner [6]. With the discovery of first room-temperature ionic liquid ethylammonium nitrate [7] by Paul Walden in 1914, the era of ionic liquid started its mark (Fig. 2).

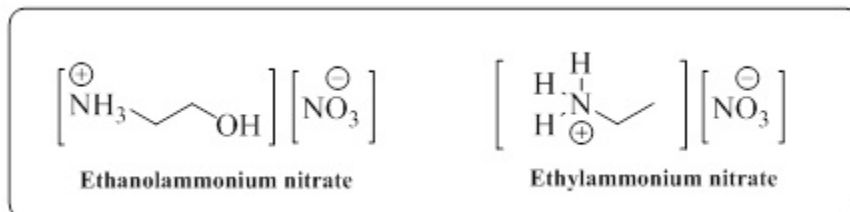


Fig. (2). Ionic liquids prepared by Gabriel & Warner and Paul Walden respectively.

This ionic liquid was the first to meet all the specifications to satisfy the present definition of ionic liquid bearing a melting point of 12 °C. It was obtained by treating  $\text{C}_2\text{H}_5\text{NH}_2$  with concentrated  $\text{HNO}_3$ . Though Walden discovered the first room temperature ionic liquid (RTIL) giving an account of the physical properties of it, owing to its explosive nature, literally the interest about ionic liquid had set about from the synthesis of binary ionic liquid dialkylimidazolium chloroaluminate by Hussey *et al.* in 1982 [8]. Osteryoung *et al.* in 1970 studied about  $\text{AlCl}_3$  and alkyl pyridinium halide system *i.e.* the first generation of ionic liquids [9] and Hussey published the debut prime review about ionic liquid [10]. Ever since late 1990s the study of ionic liquid and its uses have been grown astonishingly in various research fields covering organic synthesis [11], analytics [12], electrochemistry [13] and material science [14] as a medium for novel synthesis (Fig. 3).

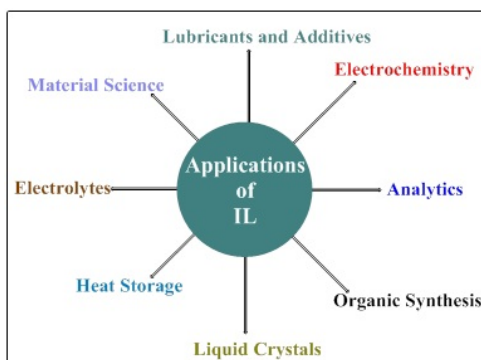


Fig. (3). Applications of ionic liquids in different fields.

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## **PROF. DR. ATTA-UR-RAHMAN, FRS**

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.