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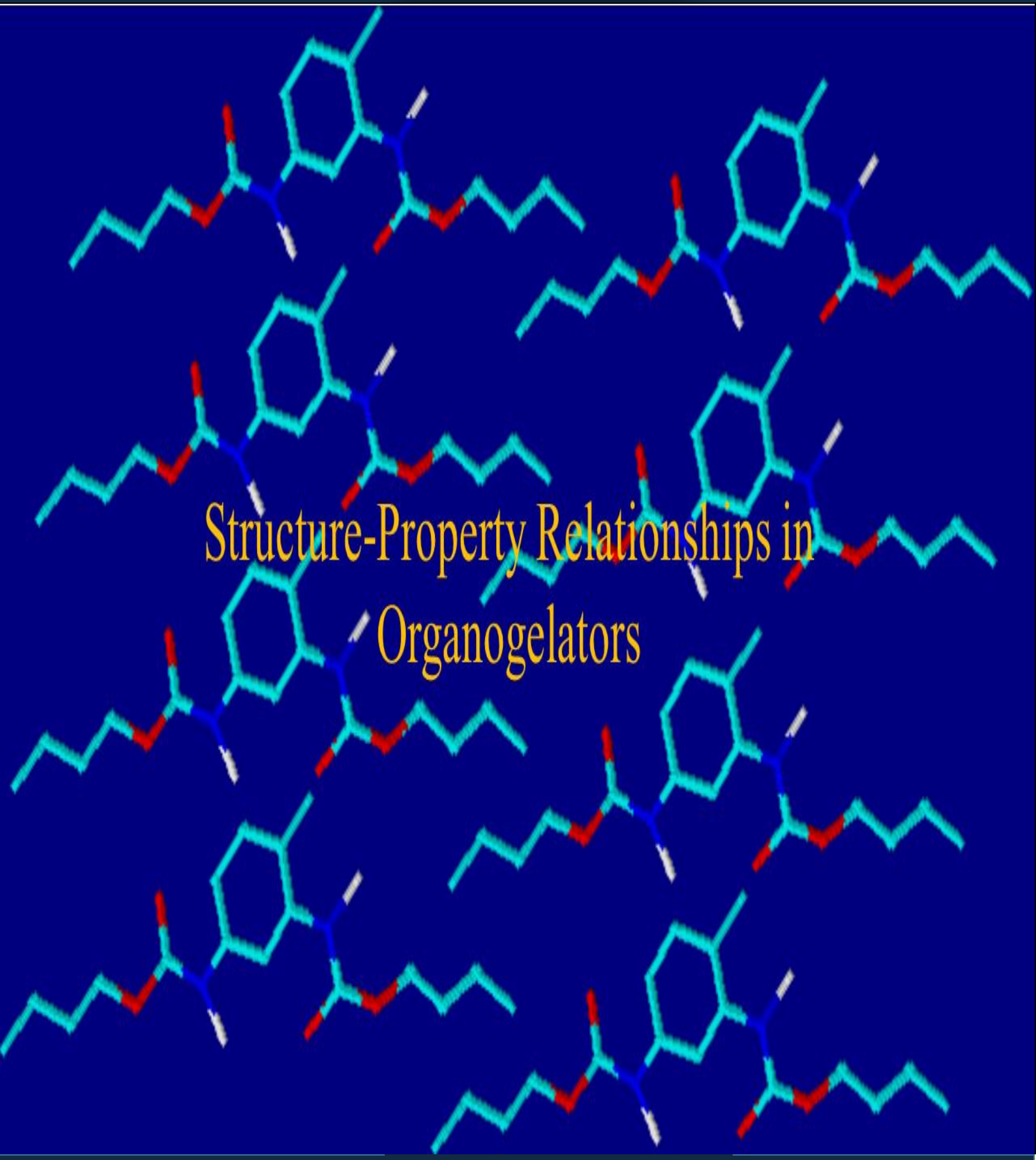

Structure-Property Relationships in Organogelators

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Structure-Property Relationships in Organogelators

Atef S. Iskander

Gelation processes are an increasingly important area of study due to their many applications throughout the fields of biomedicine, electronics, energy, and environment. Currently, the progress in organogelators relies on empirical approaches to construct smarter molecules with better gelation abilities. The gelling performances have, to a large degree, been dependent on the structures of these gelators, and their intermolecular interactions, which contribute to their self-assembly. This article aims at providing a brief view on the interplay between the gelator's structural characteristics and the driving forces for the self-assembly of small molecules.

1. Introduction

Organogelators have attracted widespread attention due to their outstanding properties for a wide range of applications including drug delivery[1], light harvesting[2], sensors[3], catalysis[4], and displays[5]. In fact, organogels are soft materials in which an organic liquid is immobilized by a three-dimensional network of self-assembled molecules leading to semi-solid supramolecular gel.[6] Basically, these materials are classified according to the type of organogelator used as well as the nature of organic liquid and its intermolecular interactions. Therefore, they can be divided into polymeric organic gelators (POGs) and low molecular-weight organic gelators (LMOGs). POGs are capable of jellifying organic liquids through intermolecular cross-linking, whereas LMOGs are gelled the organic liquids through the formation of weak interactions such as hydrogen bond, van der Waals, π-π stacking, and dipole-dipole forces.

LMOGs have several advantages over POGs regarding their preparation, stability, toxicity, gelling capacity, and biocompatibility. Moreover, LMOGs are characterized by their ability to tune their gelation properties and morphologies through rational design. Based on the molecular structure, LMOGs can be constructed taking different classes such as organogelators bearing one or more heteroatoms, e.g., *N*-octyl-D-gluconamide **1**, and 2-acryloylamide-dedecane-1-sulfonic acid **2**, or organometallic gelators, e.g., gold(I) *N*-heterocyclic carbene complexes **3** (Figure 1). Furthermore, based on the kinetic properties of

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aggregates, LMOGs can be classified into "strong" organogel (solid fiber network) and "weak" organogel (fluid fiber network).[7] Many natural or synthetic molecules can form clusters or thermo-reversible physical aggregates in solution, due to physical interactions between the molecular chains. If the supersaturation of the solution takes place, 3-dimentional fiber networks can be formed in certain solvents.

Several interesting strategies have been proposed to rationalize the gel formation by LMOGs which based on two main features: i) the conformation of molecules changes from random coil state to a partially helical state forming self-complementary and unidirectional intermolecular interactions that imposes one-dimensional self-assembly at high temperature; and ii) the helical parts aggregates to form network junctions on cooling. In the latter step, the control of fiber-solvent interfacial energy must be taken into account in order to prevent bulk crystallization.[8,9]

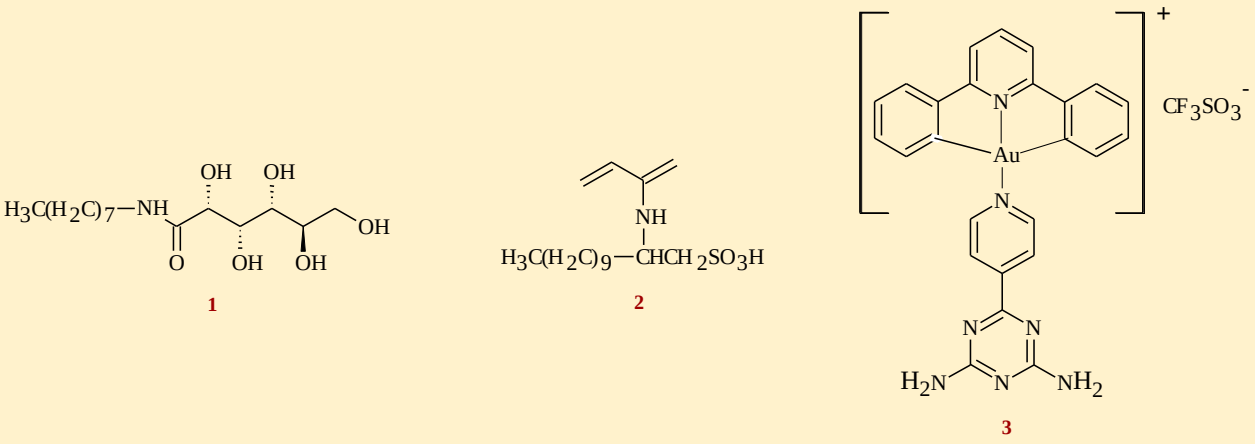

Figure 1. The chemical structures of LMOGs, **1**: *N*-octyl-D-gluconamide, **2**: 2-acryloylamide-dedecane-1-sulfonic acid, **3**: gold(I) *N*-heterocyclic carbene complexes.

Progress in gelators of organic liquids has, to a large degree, been dependent on the ability to construct gelator molecule based on the liquid that need to be jelled, and to tune its properties through rational design. As a most stringent test, the assembly and disassembly of the constituent molecules often serves as a measure of the power of the interconversion between gel and solution phases. Surveys of relevant applications of enabling processes are, therefore, of importance in that they not only help to underscore the scope and generality of such processes in organogelators design, but they also serve to place into perspective that particular design within the field, and to inspire future improvements and new applications. This article highlights briefly how the molecular structure of the gelator molecule impacts the gelling performances in the light of the driving forces for small molecular self-assembly, and I hope to underscore its power in gel design.

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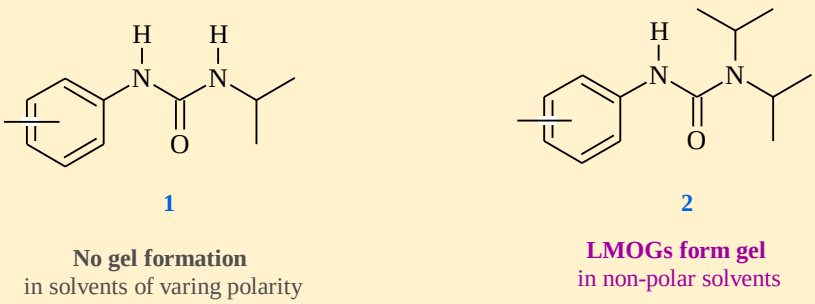
2. Influence of the molecular structure on gel formation

The design of a new LMOGs in a particular liquid is a challenging task, and most achieved attempts are based on rational design. Such design relies often on a known model compound of gelator, that can be functionalized for further versatility. Therefore, building an understanding of the interactions forces between the constituent molecules, which impact the gelling performances, is an essential prerequisite.

2.1 Influence of hydrogen bonding on gelation

It was demonstrated that LMOGs of urea derivatives formed a strong and elastic gel and considered as a motif for controlling self-assembly and gelation.[10] Remarkably, it was demonstrated that these urea molecules with a double H-bond potential **1** (Figure 2) did not form stable gels.[11] On the contrary, the restriction of available hydrogen bonding sites **2** (Figure 2) to a single bond by incorporation of the second diisopropyl group into urea moiety and an increase in steric bulk resulted in better gel formation through improved balance between energy of solvation and energy of crystallization. Moreover, a small modification in gelator structure has a large impact on the self-assembly properties of the materials. Due to the physical effect of the tolyl substituent position on self-assembly **2** (Figure 2), the gel showed very different properties depending on this moiety, in which the *para*-position exhibited the most stable gels with low critical gelation concentration (CGC). Notably, the diisopropylamine group prevents effective π-π interaction between the aromatic rings. Thus, adding more H bonding sites to a compound could not be a basic approach to improve the gelation performance, but rather through incorporating a small alkyl group as an auxiliary driving force for self-assembly could improve the properties.



1

No gel formation
in solvents of varing polarity

2

LMOGs form gel
in non-polar solvents

Solvents : DMSO, Chloroform, Petroleum ether, Cyclohexane, 1-Octadecene

Figure 2. Structure of urea gelators.

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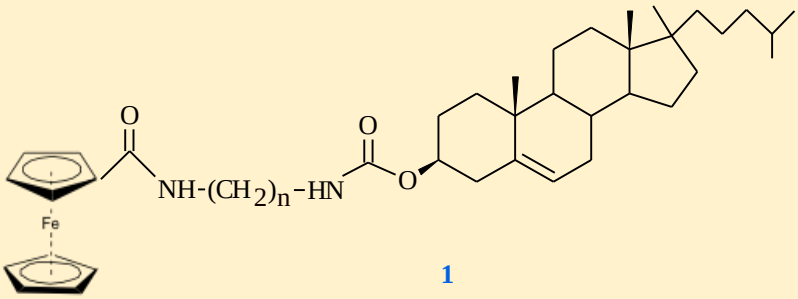
2.2 Influence of the length of linkers on gelation

The length and structures of the linker presents a key role in the gelation ability of organometallic compounds. In the design of an organometallic gelator with multiple-stimulus responsive properties, different units of carbonyl amide groups as linkers between one redox-active ferrocenyl moiety and one cholesteryl residue were incorporated, in order to give the compounds some H-bond formation sites and to enhance their aggregation ability, as well as to extend their structures (Figure 3).[12] It was shown that the supramolecular gels formed by LMOGs exhibit unique properties when they contain one methylene unit to gelatinize cyclohexane **1** (Figure 3). Such outstanding features include a supergelator (CGC = 0.09 wt%); formed at room temperature; molded into films of a certain flexibility; and responsive to various stimuli. Hence, LMOGs contain short linkers can jellify easier than those with long linkers leading to better gels properties.

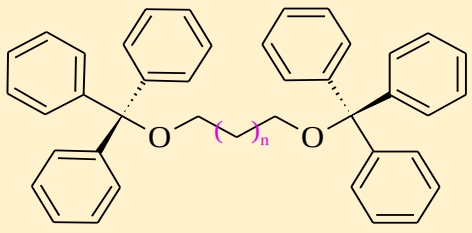


1

Figure 3. Cholesterol-appended ferrocene derivatives.

2.3 Influence of hydrophobic forces on gelation

Hydrophobic interactions have shown an important implication in the gelling process, which enhance the strength of the structure through π-π stacking between aromatic units. In triphenylmethyl-based organogelators, it was shown that the presence of hydrophobic interactions alone, i.e., in the absence of H-bond forming structural components, is sufficient for gel formation in some polar solvents due to the interaction between the alkyl chains and the triphenylmethyl moieties as the case in 1,8-Bis(trityloxy)octane, the ditrityl derivative of 1,8-octanediol (Figure 4).[13] Moreover, the optimal length of the alkyl chain for gel formation was found to be an octyl unit. An interesting feature of these gelators is that they are impervious to an acidic solution.



n = 6

Figure 4. Chemical structure of π-1,8-Bis(trityloxy)octane organogelator.

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2.4 Influence of hydrophilic-hydrophobic balance on gelation

LMOGs with both hydrophilic and lipophilic groups, which lend effective self-assembly to form 3D network structures, have a relationship with the length and structure of side alkyl chains. In fact, they are often amphipathic, and impacts the phase-selectivity of the gelling performances. Thus, the phase-selectivity is obtained by adjusting hydrophilic-hydrophobic balance. It was shown that gelators with intermediate alkyl side chain lengths have best gelling abilities.[14]

Generally, the formation of supramolecular gelation of some compounds arise from the combinations of H bonds, π-π stacking and van der Waals force, etc. Due to the strength and high directionality, H bonds interaction presents the main force for gel formation. It exhibits the polarity of the gelator that becomes more solvophobic, and capable of self-assemble. In addition, the van der Waals and π-π stacking have an important implication in the molecule's ability to self-assemble to form 3D network (Figure 5).

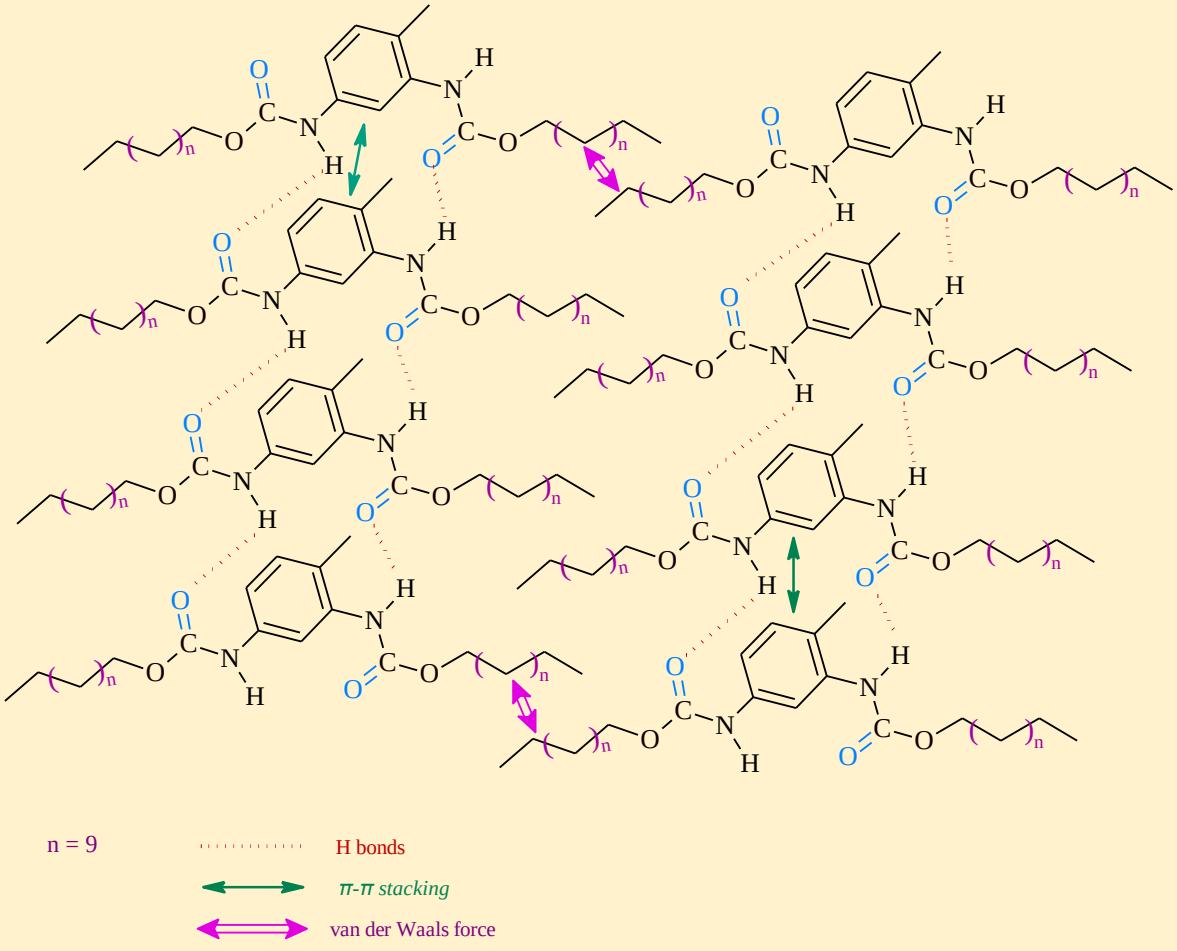

Figure 5. Schematic representation of the driving forces for the self-assembly of small molecules.

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The length or structure of side alkyl chains, with long methylene units, is the most extensively used strategy in the design of gelators, in order to extend van der Waals interactions. However, there are a number of surrogate groups with good lipophilicity features, that could be considered as potential gelling structural components in the design of molecular gelators, namely pentafluorosulfanyl **1**, bicyclo[1.1.1]pentanyl (BCP) **2**, cyclopropyl-trifluromethyl **3** substituents (Figure 6).

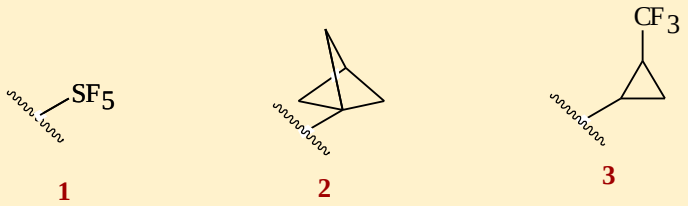

Figure 6. The structures of pentafluorosulfanyl **1**, bicyclo[1.1.1]pentanyl (BCP) **2**, cyclopropyl-trifluromethyl **3** substituents.

2.5 Influence of Chirality on gelation

The spatial conformation of the gelator is not crucial for gelling organic solvents. However, the majority of supramolecular gelators have one or more stereogenic center. Molecular chirality is transferred to individual fibers, that twist leading to maximize van der Waals interactions forming helical superstructures.[15]

3. Conclusion

Gelators with different designed molecular structures have been discussed. These molecular structures operate by self-assembly into fibrillar networks in organic solvents to form gel. The driving forces for self-assembly are realized through the formation of weak interactions including H bonding, van der Waals, π-π stacking, etc. These interaction forces impact the gelling performances. Although, H bonds interactions present the main driving forces for gelation, there are compounds that under the influence of their hydrophobic interactions alone can exhibit a better supramolecular gelation. The van der Waals and π-π stacking play an important role in the formation of 3D network structures and the balance between them and H bonding can lead to an efficient organogelation. In the light of these model compounds, the cooperative impact of the linkers, the side chain hydrophobicity, steric volume and conformational flexibility has been found to be important in the tuning of the gelation properties.

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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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Synthesis of Five-membered Heterocycles Bearing *exo*-difluoromethylene Units

Nucleophilic 5-*endo-trig* cyclization of 2-(trifluoromethyl)allylic ketones and imines *via* their metal enolates and enamides is highlighted. The formed carbon-heteroatom bonds during cyclization afforded five-membered heterocycles with two *exo*-alkylidene units including a *gem*-difluoromethylene group.

Fluoroalkenes play a key role as versatile building blocks in multidisciplinary fields. In this context, Ichikawa and co-workers took advantage of their reactivity and developed a method for nucleophilic 5-*endo-trig* cyclization of 2-(trifluoromethyl)allylic ketones and imines.

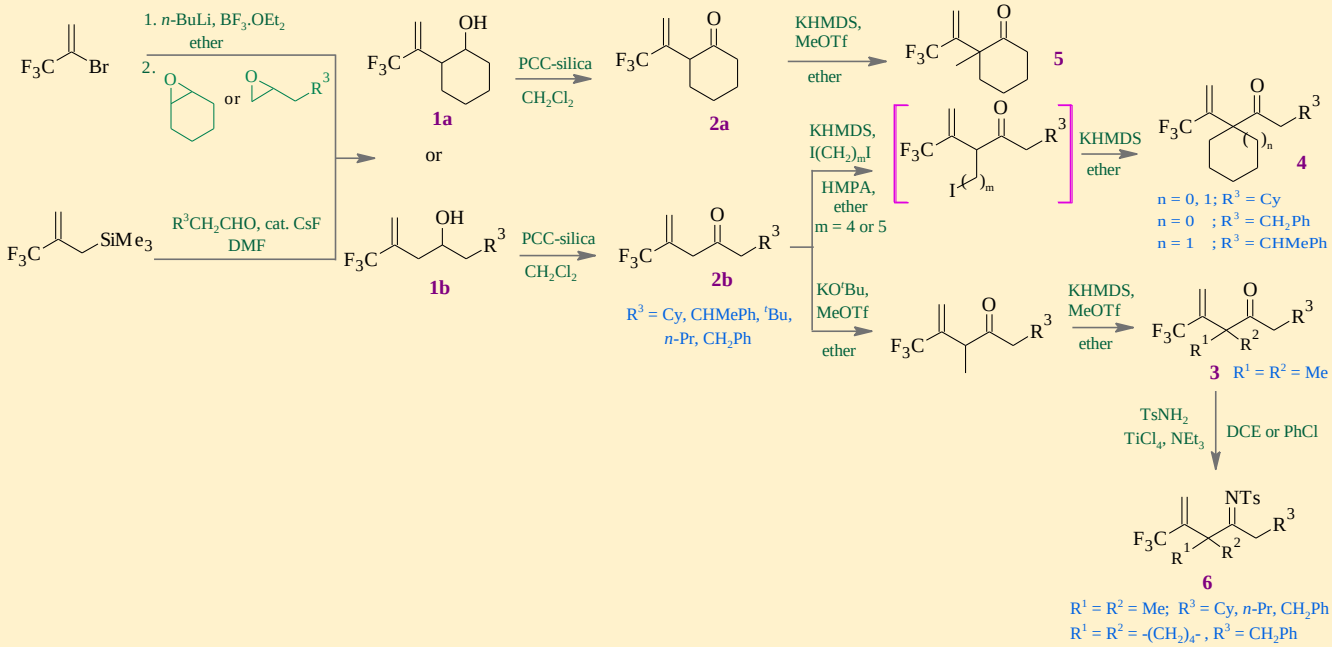
Preparation of 2-(trifluoromethyl)allylic ketones and imines

2-(trifluoromethyl)allylic ketones **3** were obtained through the preparation of (trifluoromethyl)homo-allylic alcohols **1b**, which were achieved either *via* ring-opening of epoxides with (trifluoromethyl)-vinyllithium or *via* allylation of aldehydes with trimethyl[(trifluoromethyl)allyl]silane (Scheme 1). Oxidation of alcohols **1a** & **1b** with pyridinium chlorochromate (PCC) on silica gel afforded the corresponding ketones **2a** & **2b**.

Next, synthesis of 2-(trifluoromethyl)allylic ketones bearing two methyl groups **3**; a cycloalkane moiety **4**; and cyclohexanone framework **5** were achieved in the presence of appropriate bases *via* stepwise dimethylation by trifluoromethanesulfonate; stepwise dialkylation using diiodoalkanes; and methylation of 2-(3,3,3-trifluoropro-1-en-2-yl)cyclohexane-1-one, respectively. Furthermore, 2-(trifluoromethyl)allylic imines **6** were obtained through the treatment of ketones **3** with *p*-toluenesulfon-amide in the presence of $TiCl_4$ and trimethylamine.

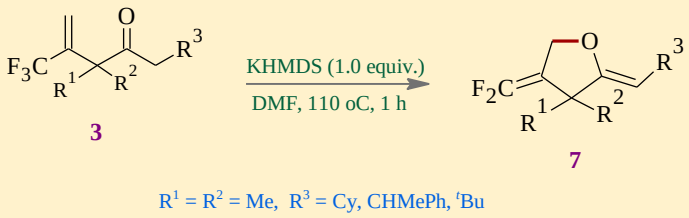
Cyclization of 2-(trifluromethyl)allylic ketones

5-*endo-trig* cyclization of 2-(trifluoromethyl)allylic ketones **3** were accomplished in the presence of potassium hexamethyldisilazide (KHMDS) as bases in *N*,*N*-dimethylformamide (DMF) at 110 °C for 1 h to afford tetrahydrofuranes bearing an *exo*-difluoromethylene unit **7** (Scheme 2). Nuclear Overhauser



Scheme 1. Preparation of 2-(trifluoromethyl)allylic ketones and 2-(trifluoromethyl)allylic imines.

effect (NOE) correlation of **7**, which was obtained as a single isomer, revealed that it exhibited correlation between the vinyl proton (H^a, Figure 1) and protons of the two methyl groups on the tetrahydrofuran ring. No NOE correlation was detected between the allylic proton (H^b, Figure 1) and methyl protons. Thus, the stereochemistry of **7** was *Z*-isomer.



Scheme 2. Preparation of tetrahydrofuranes bearing an *exo*-difluoromethylene unit.

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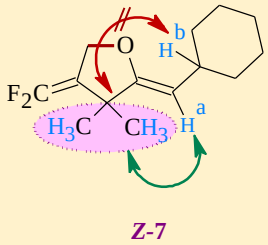
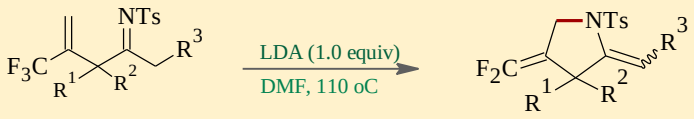


Z-7

Figure 1. NOE correlation of **7a.**

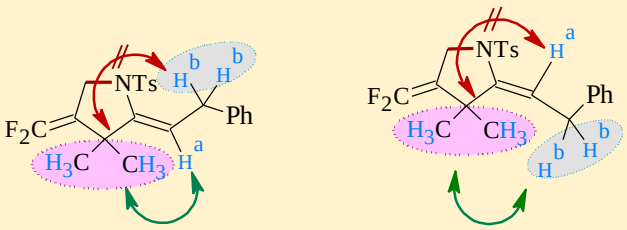
Cyclization of 2-(triflurormethyl)allylic imines

Cyclization of 2-(trifluoromethyl)allylic imines **6** was achieved in the presence of LDA as bases in DMF at 110 °C to afford the corresponding pyrrolidines **8** as *E*/*Z* mixture, which *Z*-isomer was the major product (Scheme 3). NOE revealed that the major *Z*-isomer exhibited correlation between the vinylic proton H^a and the protons of the two methyl groups on the pyrrolidine ring, whereas the minor *E*-isomer exhibited correlation between the allylic proton H^b and the methyl protons (Figure 2).



6 **8**

Scheme 3. Synthesi of pyrrolidines **8** bearing an *exo*-difluoromethylene unit.



***Z*- 8 (*Major*)** ***E*- 8 (*Minor*)**

Figure 2. NOE correlation of **8.**

The fluorine-containing tetrahydrofuranes and pyrrolidines can serve as constituents of bioactive pharmaceuticals and agrochemicals.

Review

T. Fujita, M. Hattori, M. Matsuda, R. Morioka, T. C. Jankins, M. Ikeda, J. Ichikawa, *Tetrahedron*, **2019**, *75*, 36-46.

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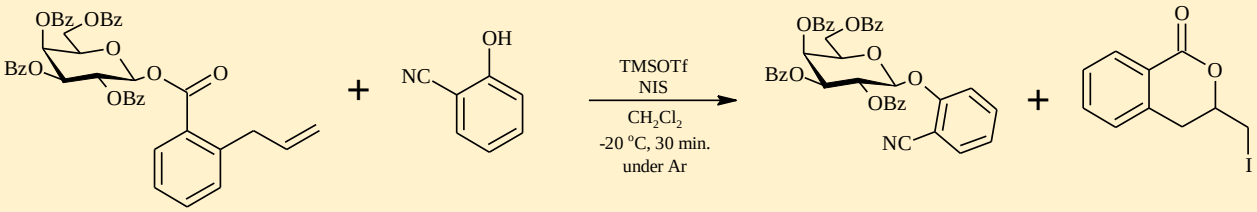
Iodonium-Promoted Glycosylation with Glycosyl *o*-allylbenzoates as Donors

A facile synthetic pathway for glycosylation is described. The approach is based on the construction of glycosides using glycosyl *o*-allylbenzoates as donors, and *N*-iodo-succinimide (NIS) as the electrophilic halogen source.

Study of glycosylation reactions helps to understand the biological functions of complex oligo-saccharides and glycolconjugates, and open a field of intensive research. Xue *et al.* reported an efficient glycosylation method which based on iodonium-induced cyclization of glycosyl *o*-allylbenzoates with a wide range of alcohols (Scheme).



Scheme Iodonium-promoted glycosylation reaction with donor.

Using *o*-allylbenzoic acid as a good anomeric ester precursor, they prepared a range of protected glycosyl *o*-allylbenzoates as donors. Then, glycosylation of a wide range of alcohols was promoted by trimethylsilyl triflate (TMSOTf) in combination with *N*-iodosuccinimide (NIS), as the electrophilic halogen source, under mild reaction condition (in CH_2Cl_2 at -20 °C) to afford the corresponding products in high yield (77-95%).

Among the synthesized glycoside, long-chain glycoside bearing cyano. halo, and azido groups are functional building blocks that are potentially applicable to bioconjugation chemistry.

Review

H. Liang, L. Ma, C. Li, Q. Peng, Z. Wang, Z. Zhang, L. Yu, H. Liu, F. An, W. Xue, *Tetrahedron Lett.*, **2019**, *60*, 84-87.

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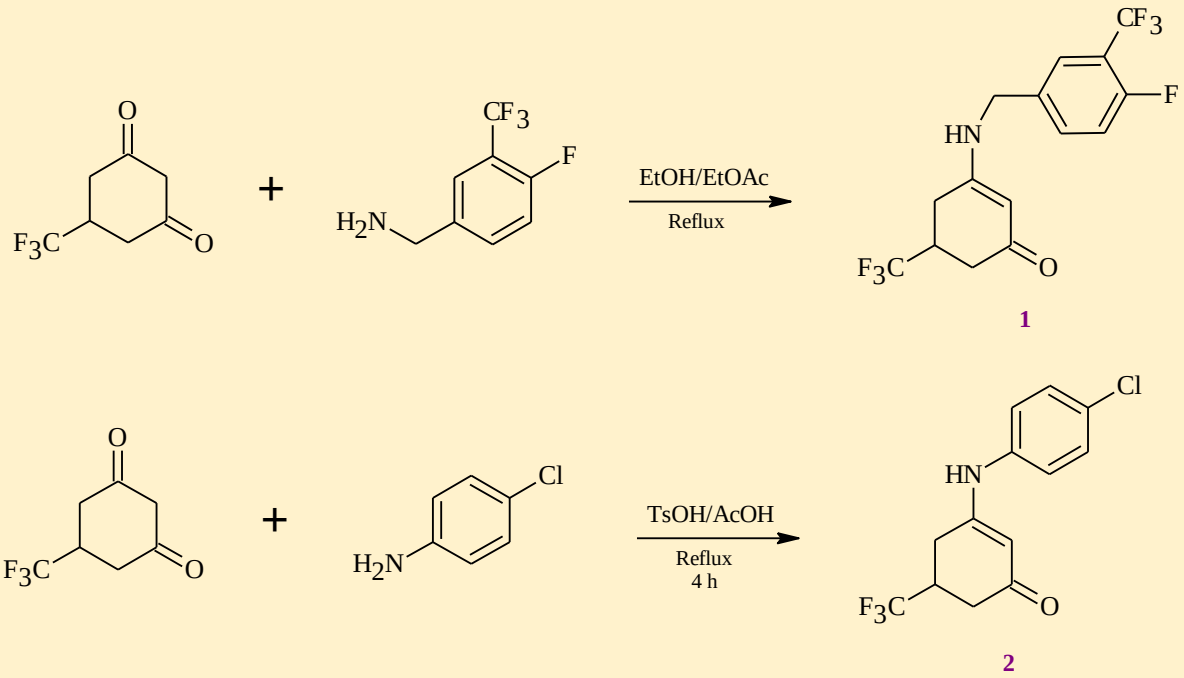
Potential Anticonvulsant Agent for The Treatment of Epilepsy

Fluorinated cyclic enaminones have been identified as potential anticonvulsant agent effective to suppress seizure.

The current antiepileptic drugs are associated with various side effects. In order to eliminate such side effects, Apraku and Okoro employed an enaminone derivatives bearing a highly lipophilic trifluoromethyl group taking advantage of these enaminones as potential anticonvulsant agent devoid of neurotoxicity. Among the synthesized compounds, compounds **1** and **2** (Scheme) showed significant anticonvulsant activity. Moreover, they have the potential to cross the Blood-brain barrier and act as the central nervous system (CNS) active agent. Notably, substitution of –F or $–CF_3$ at *meta*- or *para*-positions of benzyl amine ring favors the anticonvulsant activity.



Scheme Synthesis of enaminones analogs.

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J. Apraku, C. O. Okoro, *Bioorganic & Medicinal Chemistry*, **2019**, *27*, 161-166.

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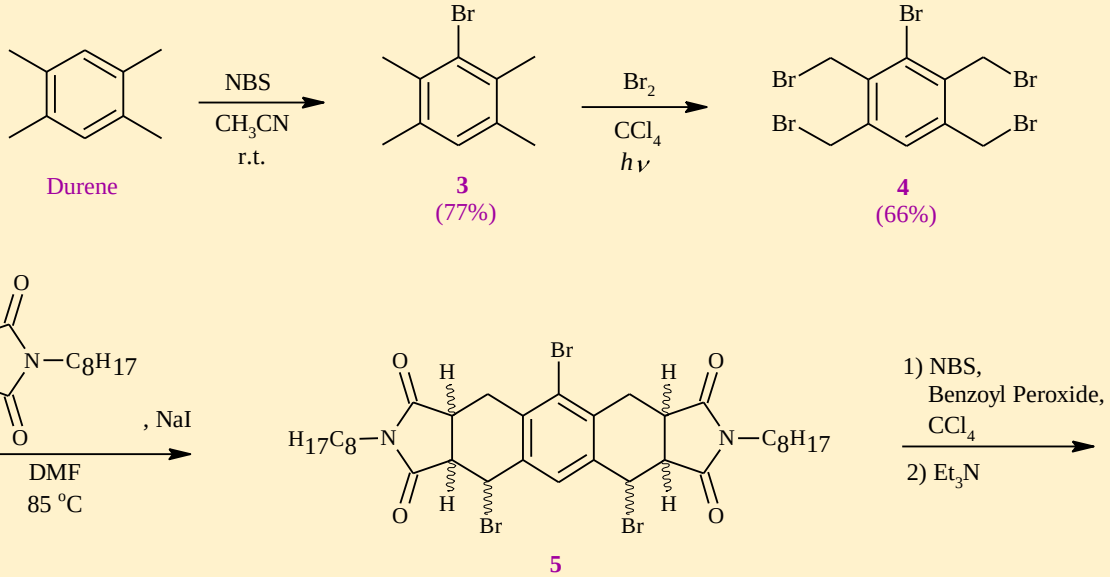
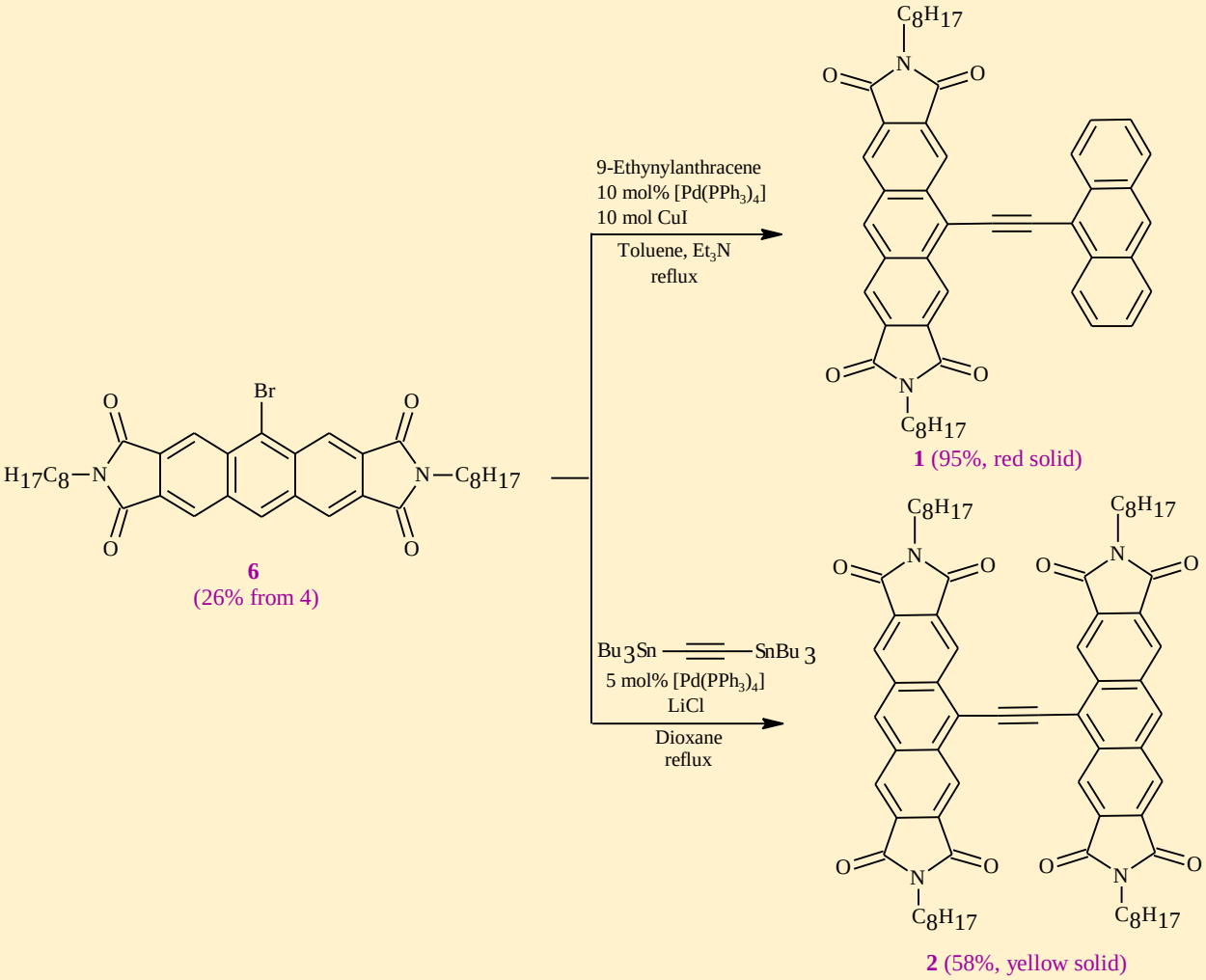
Synthesis of Ethynylated Anthracene Bisimide Derivatives

Incorporation of an arylethynyl group on an anthraces bisimide core is described. The synthesis was accomplished by Sonogashira and Stille couplings.

In the light of the progress in electronic devices, synthesis of extended π-conjugated molecules constitutes one of the top priority in this field. Among these compounds, antheracene-2,3:6,7-bisimides (ABIs) have the potential for the molecular design of new π-conjugated compounds. In this context, Iwanaga and co-workers designed a donor-acceptor type ABI derivatives **1** & **2** containing a 9-anthrylethynyl group at the 9 position in which the ABI unit serves as a terminal acceptor unit.

The synthesis of a key precursor for ethynylation, 9-Br-ABI **6**, was accomplished by the Diels-Alder approach of the product of the doubly bromination of durene, pentabromide **4** (Scheme). The Diels-Alder adduct **5** was obtained as a mixture of diastereomers from the reaction of **4** with *N*-octylmaleimide in the presence of NaI. Then aromatization by radical bromination followed by elimination afforded compound **6**. The Sonogashira coupling of bromide **6** with 9-ethynylanthracene gave compound **1**, while the Stille coupling of **6** with bis(tributylstannyl)ethyne in the presence of $[Pd(PPh_3)_4]$ and LiCl as additive in dioxane gave compound **2**.





6
(26% from 4)

1 (95%, red solid)

2 (58%, yellow solid)

Scheme Synthesis of ethynylated ABI derivatives **1** and **2**.

Compound **1** exhibited a significant bathochromic effect (λ_{max} = 570 nm), which is attributed to the intramolecular charge-transfer between the acceptor ABI unit and the donor anthracene unit across the acetylene linker. The absorption onset of **2** shifted bathochromically (λ_{max} = 486 nm). The fluorescence spectra showed emission peaks for compounds **1** and **2** at 575 and 507 nm respectively, while the absolute fluorescence quantum yields Φ_f of **1** and **2** were 0.51 and 0.65, respectively.

Review

T. Iwanaga, R. Tanaka, S. Toyota, *Chem. Lett.*, **2014**, *43*, 105-107.