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Four component domino reaction for the synthesis of highly functionalized dimeric tetracyclic dilactam fluorophores: H-bond Aided Self-Assembly

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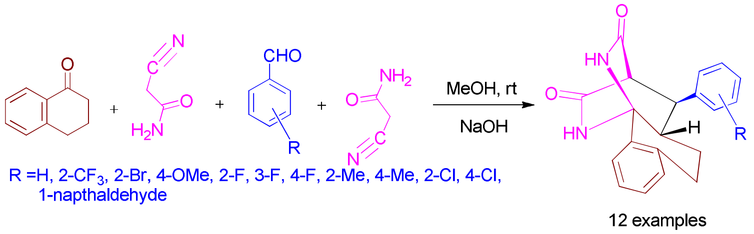
A series of new dimeric tetracyclic dilactam fluorophores (DTDF) consist of diazabicyclo-octane-dione (DBOD) fused to tetrahydronaphthalene (THP) was designed and synthesized from a simple precursor. The monomer showed enhanced emission in THF/water solvent and also benzene-dimer like absorption and fluorescence, originated from hydrogen-bonding aided self-assembly of dilactams. The crystal structure revealed water-mediated molecular aggregates with several hydrogen-bond bridges formed by water.

In chemistry and biology, the hydrogen bond plays an essential role characterized by a relatively weak interaction involving electronegative proton acceptor, a hydrogen, and an electronegative proton donor.[1-5] Several theoretical studies have been established at diverse levels of calculation to study the blue-emitting fluorophore possessing hydrogen bonds in OLEDs.[6-10] Dykstra and his co-workers[11-13] have built a hypothesis of shifts in vibrational frequency for hydrogen bonding based on monomer properties such as polarizabilities and electrical moments. For the past few decades of research in organic materials, significant importance have been devoted to design and synthesis of molecules possessing hydrogen bonded as well as π-conjugated molecules with specific properties[14-16]. Thus, highly emissive organic fluorescent materials are of vast interest to realize and investigate a new class of AIE chromophores. Benzene dimer association with π-π interaction between the aromatic rings has been a widely explored area of AIE chromophores[17-21]. Bridged lactams of self-assembly possessing intermolecular hydrogen bonding along with the water interaction between the molecules have not been reported so far. The accessible choices to mount both in one reaction are extremely limited; this interaction was introduced successfully into organic molecules by employing an efficient method to synthesize dimeric tetracyclic dilactams. Numerous methods have been developed to study AIE effect in organic materials, but still it remains challenging. The aggregated species showed π-π stacking between the benzene rings to form benzene dimer, intermolecular interaction between the lactam amides and also between water molecules with lactam amides. Indeed, such interactions between the lactam amides and water molecules exhibiting AIE effect have not been reported so far, to the best of our knowledge. For the first time, we designed and synthesized highly functionalized DTDF possessing four stereogenic centers from simple starting materials α-tetralone, aryl aldehyde, and cyanoacetamide.[21, 22] Molecular aggregates are characterized by quinoline dimers linked through dimeric N–H•••O hydrogen bonds. Examination of crystal structure clearly showed that these molecules consist of fused bridged dilactam showeing fluorescence behaviour due to the formation of aggregation in the crystal packing[23]. Another interesting phenomenon for the formation of aggregation in these systems was water hydrogen bonding between the molecules.

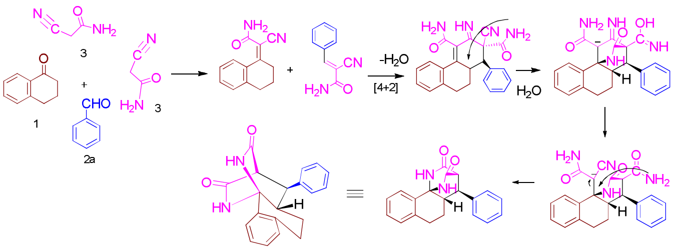
As an initial probe to study the reaction condition, we investigated the optimal condition to evaluate the efficiency of catalyst for this reaction under various conditions. In this model reaction, several metal hydroxides were screened to optimize the reaction conditions. From Table S1 (entry 1-9), it can be understood that the reaction proceeded only in presence of metal hydroxides, to form highly functionalized benzo[h]quinoline. The solvent effect was the next factor considered for better yield. Thus, experiments were carried out in various solvents such as polar protic, aprotic and nonpolar solvents using 0.5 mol% of NaOH as the catalyst for all the reactions. From table S1 it shows that the optimal condition for these reaction transformations was 0.5 mol% of NaOH in methanol. We then applied these conditions to synthesize a series of substituted DTDF. The synthesized DTDF possessed four stereogenic centers in which two quaternary amine functionalities were obtained. Such observation is certainly rare, fascinating and quite interesting in organic chemistry[21].

Table 1. Domino reaction for the synthesis of multifunctionalized tetracyclic dilactams



Entry	ArCHO	Product	Yield (%)[b]	Entry	ArCHO	Product	Yield (%)[b]
1	H	4a	58	7	4-F	4g	80
2	2-CF_3	4b	62	8	2-Me	4h	83
3	2-Br	4c	69	9	4-Me	4i	80
4	4-OMe	4d	45	10	2-Cl	4j	75
5	2-F	4e	89	11	4-Cl	4k	89
6	3-F	4f	65	12	1-napthaldehyde	4l	95

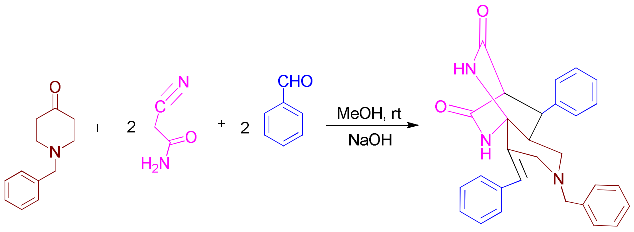
[a]Reaction conditions: α-tetralone (10 mmol); Benzaldehyde (10 mmol) and cyanoacetamide (20 mmol) at room temperature (30°C). [b]Isolated yield



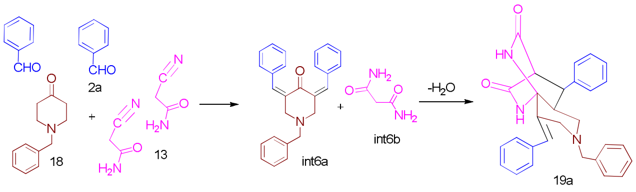
Scheme 1. A proposed mechanism for the formation of tetracyclic dilactams.

The proposed mechanism for the formation of this domino reaction is shown in Scheme1. The two different Knoevenagel condensations with cyanoacetamide using α-tetralone and benzaldehyde give two intermediates, which in turn rearrange to form C-C bond followed by [4+2] cycloaddition and intramolecular Michael-type addition. We also examined the scope and the limitation of these four component domino reactions (Table 1). When the reaction was carried out with other cyclic ketone as substrate instead of α-tetralone, the reaction proceeded in a different path. The behaviour of phenylacrylamide fluorophore and the reaction with other cyclic ketone is being studied in our laboratories. When the equivalence of cyanoacetamide used in the reaction was reduced to 1 eq. from 2 eq., the reaction proceeded in a different manner. Similarly we also tried these reactions with aliphatic aldehydes instead of aryl aldehydes under the same condition but failed to get the desired product.

Initially, we carried out this reaction using similar condition by using other cyclic ketone to obtain tricyclo dilactam fluorophore, but unexpectedly we got non-fluorescence compound of highly functionalized triazatricyclo $[6.2.2.0^{1,6}]$ dodecane-9,12–dione. In order to investigate further we focused on the mechanism to study the path in which the reaction proceeded and suggested that the mechanism followed aldol reaction / condensation / cyclisation followed by dehydration to give the desired product.



Scheme 2 Synthesis of highly functionalized triazatricyclo $[6.2.2.0^{1,6}]$ dodecane-9, 12 –dione



Scheme 3 Several reactions for the formation of 19a via int6a and int6b.

UV-visible absorption and fluorescence spectral (Fig 1) studies for these compounds were carried out to understand the electronic properties, and also to explore the influence of electron donating or electron withdrawing nature of the substituent on the electronic properties. The representative absorption spectra of **4h** measured in tetrahydrofuran (THF) solvent showed peaks at 255, 336, 348, 396, and 412 nm, which was found to exhibit concentration dependent behaviour. The lowest energy absorptions disappeared when the concentration of the sample was maintained in micromolar range.

The observed concentration-dependent behaviour could have originated from the dimer or aggregates of **4h**. Indeed, the electron withdrawing or donating nature of the substituent had only a subtle effect on the absorption spectrum. Notably, the chromophoric unit of these molecules was restricted to the benzene moiety alone, and the remaining non-conjugated skeleton did not influence the electronic properties to a significant extent (Table S2). Further, the electronic absorption spectrum of benzene was generally observed in the range of 300 nm. The significantly red-shifted absorption spectrum of tetracyclic dilactams is quite intriguing.

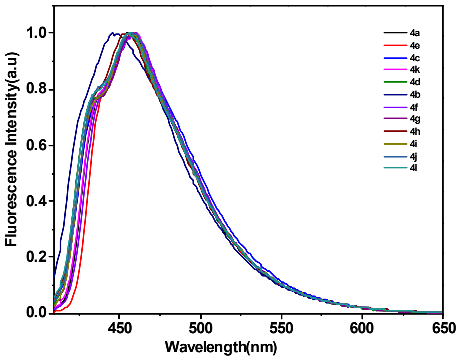


Figure 1: Emission spectra for the synthesized compound 4a-4l

To understand the electronic properties further, we calculated molecular orbital at B3LYP/6-31G level using Gaussian 03 programme.[24] Initially the geometry of tetracyclic dilactams was optimized at B3LYP/6-31G level using the single crystal X-ray structure as the input file. It was observed that the band gap between the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) corresponded to 5.72 eV in gas phase, a value corresponding to the transition from ground to excited state of monomeric benzene.[18] Hence, the transitions in the lower energy region might have been due to the dimeric or aggregated tetracyclic dilactams aided by the intermolecular hydrogen bonding interactions.

It has been known, particularly, for benzene based systems, that the dimer or higher aggregates absorbed at longer wavelengths than that of monomers. Nevertheless, trans-annular interactions between the benzene ring in cyclophane analogous systems led to longer wavelength absorption peak, which was observed below 300 nm (*19*). However, **4a** showed the longest absorption spectrum close to 400 nm. To the best of our knowledge, this is the first observation with benzene aggregates showing least energy absorption in the visible region. The fluorescence spectra of **4a** in THF solvent showed maximum emission wavelength at 426 and 448 nm, with mirror image relationship with the lowest energy absorption spectrum. The compound **4l**, naphtho[h]quinoline-2, 12(3H)-dione also showed concentration dependent absorption.

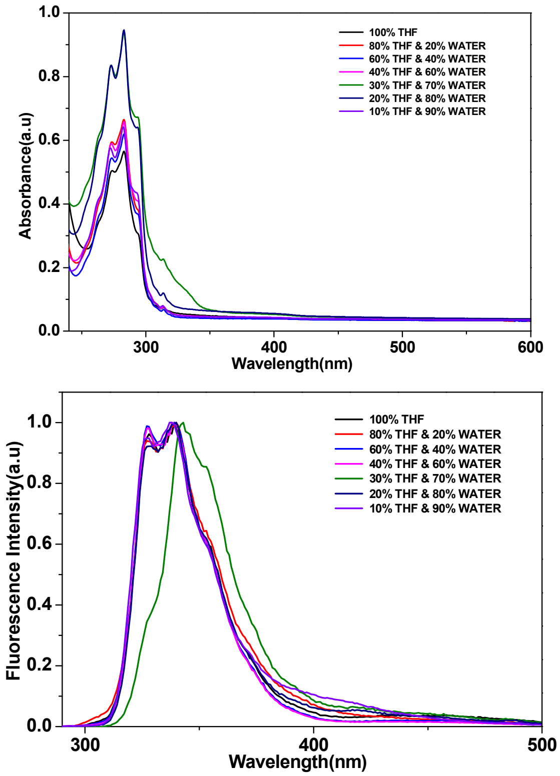


Figure 2. Absorbance and fluorescence (exi-270nm) spectrum of compound 4l in various percentage of water and THF

At higher concentration the ground state dimer absorption was predominant at 265, 336, 346, 378, 394 and 414 nm, while monomer spectra were noticed at lower concentrations. The observed spectra matched with the reported value for the dimer absorption where naphthalene moieties were tethered covalently to the dendrimer moiety[20]. Indeed, intense fluorescence at 438 and 459 nm, was observed for naphthalene dimers in THF solutions and that of monomer was observed at 328, 340 nm along with the shoulder at 354 nm (Fig 2). The red-shifted absorption and emission spectra at higher conc. occurred solely due to the self-assembly formation which was aided by the hydrogen bonding interaction.

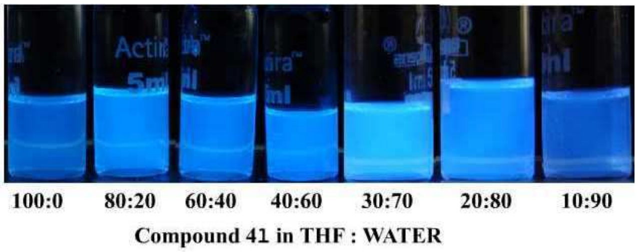


Figure 3. Fluorescent photographs of compound 4l in THF/water mixtures with different water fractions taken under UV illumination

To enable the self-assembly even at lower concentrations, we used the reprecipitation method where the concentrated **4l** was injected rapidly into the water and water-THF solvent mixtures in different ratios (V/V). The concentration of **4l** was maintained at 5.42 × 10^{-6} M, where only the monomer absorption was observed. Addition of **4l** to the water-THF mixture caused slight changes in the spectral maxima; however, a significant reduction in absorbance characteristic to the solvent ratio was noticed. Thus, we inferred that the formed self-assembly was quite stable as was evident from the lack of time-dependent absorption spectral changes and also due to the absence of precipitation. It should be noted that the solvent aided self-assembled structure formed in water-THF solvent mixture, at lower concentrations, did not form the naphthalene dimers at higher concentrations (Fig 3). Nonetheless, the fluorescence from the monomeric units became intense when the water-THF ratio was 20-80, 40-60, 60-40%. The dimer also existed in the solid state as can be understood from the UV-visible diffuse reflectance spectra of the solid samples.

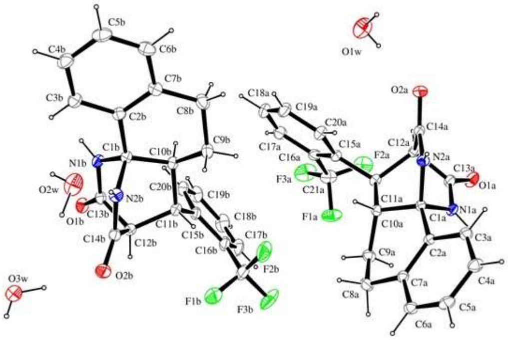


Figure 4. Molecular structures of 4b, together with the atomic-labeling scheme. Displacement ellipsoids are drawn at 30% probability levels and hydrogen's are shown as small spheres of arbitrary radii.

The diffraction quality crystals for **4b** were grown and examined using X-ray diffraction method. The molecular structure is illustrated in **Fig. 4**. The asymmetric unit comprised of 2 conformers (A and B) of **4b** hydrated with three water molecules. In the tetracyclic ring, the DBOD and THP were fused together. In the reported centrosymmetric structure, the stereogenic centers of DBOD rings (C10 & C11) in **4b** (A) and **4b** (B) assumed R, R configurations. The cyclohexene ring of THP adopted a twisted-chair configuration while the trifluoromethylbenzene substituent of DBOD ring was in equatorial position. Crystal packing of **4b** was characterized by N-H…O bonded molecular dimers and water-mediated molecular aggregation. Molecules associated along a-axis to form a channel occupied by water that formed multiple bridge interactions with one of the amide groups in DBOD bicyclic ring system. These channels at the unit cell corners (see Fig S3 in projected unit cell along a-axis) interacted via closed dimeric N1A-H1A…O1A interactions between amide groups of DBOD ring and got augmented by intermolecular C-H…F interactions (**Table S4**).

In summary, we report a novel four-component domino reaction for the synthesis of highly functionalized benzo[h]quinoline-2,12(3H)-dione which gave access to tetracyclic dilactam. The obtained molecules possessed four stereogenic centers with two quaternary carbon-amino functionalities. All the compounds existed as dimers at higher concentrations which were aided by the hydrogen bonding interactions between the amide groups. The dimers showed a higher red-shifted absorption spectrum than the monomer. To the best of our knowledge, this report is the first to specify an interesting finding of tetracyclic dilactam fluorophore which had an inherently strong effect on the generation of aggregation-induced red-shifted florescence properties. In fact, all the compounds showed intense blue fluorescence with a maximum at 460 nm. These molecules can be used as blue emitters. Also, the presence of amide group might help to use these molecules as fluorescent markers for probing biological functions.

Notes and references

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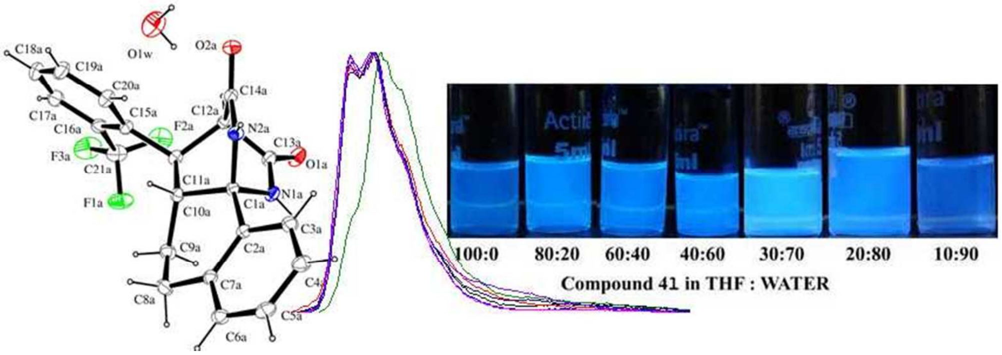

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