A Study of [2+2] Cycloaddition–Retroelectrocyclization in Water: Observation of Substrate-driven Transient Nanoreactor Induced New Reactivity

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ABSTRACT: Organic solvents limit [2+2] cycloaddition-retroelectrocyclization (CA–RE) in biological fields. We examined the formation of 1,1,4,4-tetracyanobuta-1,3-dienes (TCBDs) through CA–RE reactions and their unusual reactivity to produce *N*-heterocyclic compounds when surfactant nature and concentrations were varied in the aqueous phase. An environment in which transient self-assembly (vesicles) was induced by substrate and surfactant molecules initiated new reactivity through H_2O addition on the TCBD generating enol form of the intermediate which results in the formation of the 6,6-dicyano-heteropentafulvene (amidofulvene) compound while lamellar sheets at higher concentrations favored TCBD generation. Interestingly, the amidofulvene underwent a clean transformation to 6-membered-heterocycles *via* keto-enol tautomerism mediated by a polar aprotic solvent which resembles cardiotonic drugs (milrinone, amrinone), opening up a new avenue for drug discovery. Unlike organic solvent-mediated CA–RE reactions, the present nanoreactor-mediated approach enabled the selective production of TCBDs as well as new heterocycles using H_2O as a green solvent. Besides the widely explored organic electronics/materials, we believe that this study would help overcome the long-standing limitation of CA–RE reaction applicability in biological fields.

INTRODUCTION: The organic non-planar strong push-pull chromophores are formed *via* a thermal [2+2] cycloaddition followed by retroelectrocyclization (CA–RE) between electron-rich alkynes (substituted with an electron-donating group (EDG)) and electron-deficient olefin (TCNE, TCNQ, *etc*) and can occur with/without organic solvents (Figure 1a).[1] In 1981, Bruce and coworkers invented this reaction using metal-ylides as EDG (Figure 1b).[2,3] Later, Michinobu and Diederich uplifted this field to significant heights using organic amines as EDG, thus expanding its application in organic materials including polymers.[4,5] So far, applications like optoelectronics (NLO, TFT, OLED, solar cell, hole transporting materials),[6,7] NIR,[8] and white-light[9] emission, sensing,[10] *etc* have been demonstrated. The [2+2] CA–RE reaction has received tremendous attention due to its promising features such as atom economic, one-pot synthesis, ambient conditions etc.[1,7] So far, the CA–RE reaction of TCNE with electron-rich alkynes generally provides TCBD except in a 2011 report by Bruce and coworkers wherein a ruthenium-substituted lithiated acetylide provided lithiated TCBD intermediate which during the column chromatography (CC) yielded not only TCBD but also 5 and 6-membered heterocycles with the isolated yields of 32, 20, and 16%, respectively without much selectivity (Figure 1b).[11] The formation of amidofulvene was postulated to proceed via water addition on Ru-delocalized nitrile (CN) group to provide amide intermediate which upon subsequent cyclization step furnished amidofulvene.

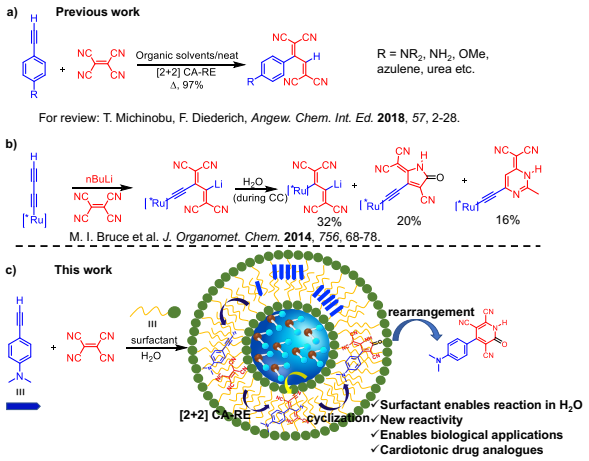


Figure 1. Organic solvents mediated a) formation of organic-TCBDs, (b) metal-substituted TCBDs and heterocycles, c) Surfactant mediated tunable selective synthesis of TCBDs and heterocycles

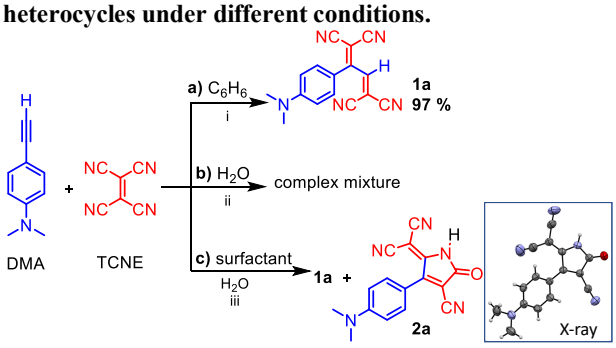
In the present work, we are trying to address the major limitations of [2+2] CA-RE reactions, i.e., (i) their poor or messy

reactivity in water arising as a result of precipitation/insolubility of reactive substrates; (ii) the CA-RE reaction has not been explored beyond the organic electronics device field primarily due to the use of biologically unfriendly solvents which also makes it not a perfect "click reaction"[12] though this reaction is regarded as click-type[1] as it majorly satisfies the criteria set for the click reaction except for the use of organic solvents. There is a need of urgent importance, in this context, for a greener synthetic protocol. So, we envisioned that the issues associated with the insolubility of substrates can be resolved by taking advantage of the well-known area of aqueous micellar chemistry (Figure 1c).[13] *i.e.,* replicating the CA-RE reaction in a green medium of water/surfactant replacing the organic solvents, which will pave a way for their scope and applicability in the living system and may bring about a new reactivity and leading to new a class of organic molecules of medicinal value.

RESULTS AND DISCUSSION:

Surfactant mediated reactions with *N,N'*-dimethylaniline (DMA)-substituted alkyne and TCNE: The [2+2] CA-RE reaction between *N,N'*-dimethylaniline (DMA)-substituted alkyne as electron-rich alkyne and TCNE as the acceptor to form the **DMA-TCBD 1a** was chosen as the reference reaction (Scheme 1). This reaction is known to occur very cleanly in organic solvent (C_6H_6) with a yield of 97% for **1a** as a purple solid (Scheme 1a).[4] Initially, we tested whether this reaction would occur in an aqueous condition (Scheme 1b). However, the TLC has indicated that although the starting material was consumed, no selective product formation observed in a complex mixture (see, Supporting Information (SI), Scheme S1).

Scheme 1. Synthetic scheme for the formation of TCBD and heterocycles under different conditions.



Reagents and conditions: i) C_6H_6, 20 °C, 2-3 h, **1a** (97 %),[4] ii) H_2O, 25 °C, 24 h, complex mixture, iii) surfactant, 25 °C, 24 h (see Table 1 for more details). Inset: ORTEP plot of **2a** with vibrational ellipsoids shown at the 50% probability level.

To overcome the challenge, we envisaged that the use of surfactants may stabilize the products in their hydrophobic environments created by hierarchical self-assembly depending on the concentration by facilitating any particular pathways and preventing other side reactions (Scheme 1c). It is well-known that different types of surfactants self-assemble differently with varied concentrations.[13] To understand which type of transient structures (produced by hierarchical molecular self-assembly) provide a better medium for CA-RE reactions, we have evaluated the role of surfactants in the aqueous phase. For this study, we chose non-ionic- (Tween 20 and Brij 30), anionic- (SDOSS and SDS), and cationic (CTAB) surfactants and varied the concentration at, above (up to 17-93 fold) and below (up to 1.8-6.0 fold) corresponding critical micellar concentration (CMC) values of each surfactant (Table 1, see Section A4, SI).

Table 1. Optimization of reaction conditions for surfactant-mediated CA-RE between DMA and TCNE.[a]

Entry	Surfactant Type	Concentration (mM)	Conversion (%)[b]	Selectivity[b] (%)	
				1a	**2a**
1	Tween 20	0.5	58	79	21
2	(Non-ionic)	0.9 (CMC)	70	83	17
3		5	76	92	8
4		20	64	53 (51)[c]	47 (5)[c] (30)[d]
5		41	84	97 (92)[c]	3 (0)
6	Brij 30	1.5 (CMC)	68	76	24
7	(Non-ionic)	10	76	60	40
8		50	52	54	46
9		75	58	59	41
10		125	52	88	12
11		140	43	98	2
12	SDOSS	0.5	52	77	23
13	(Anionic)	3 (CMC)	52	79	21
14		10	81	85	15
15		56	98	87	13
16		113	71	79	21
17	SDS	4	67	91	5
18	(Anionic)	9 (CMC)	75	68	32
19		30	60	95	5
20		150	82	92	8
21	CTAB	0.9 (CMC)	78	84	16
22	(Cationic)	5	64	65	35
23		20	97	75	25
24		41	81	85	18

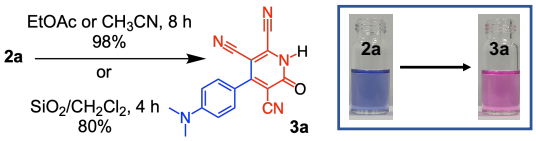
[a]DMA (1 equiv), TCNE (1 equiv), surfactant (in H_2O, 3 mL), 25 °C, 24 h. [b]Conversion and selectivity were determined by ^{1}H-NMR analysis. [c]Isolated yield by CC. [d]Isolated yield by separation of crystals.

After completion of the reaction for 8 h, the surfactant was separated by performing a workup with ethyl acetate (EtOAc), and the crude reaction mixture was quantified by ^{1}H-NMR using bromonitromethane ($BrCH_2NO_2$) as standard. The results indicated that all the surfactants at CMC concentration provided moderate conversion (52–78%) and selectivity (68–84%) for TCBD formation (entries 2,6,13,18,21). Whereas, at the highest concentration the TCBD was observed with remarkable selectivity in both non-ionic surfactants with a very good conversion yield of 84% in Tween 20 and 43% in Brij 30 (entries 5 and 11). Interestingly, in general, it was observed that at moderate concentrations, for e.g., Tween 20 at 20 mM and Brij 30 at 10–75 mM yielded ~1:1 ratio of unusual 6,6-dicyano-heteropentafulvene namely 3-*N,N'*-dimethylaminophenyl-substituted 4,6,6-tricyanoamidofulvene (hereafter named as amidofulvene) **2a** along with the conventional TCBD **1a**, with the good conversion of 52–76% yield (entries 4, 7, and 8). Unlike non-ionic surfactants, the ionic surfactants have facilitated the conversion yield significantly (82–98%) with excellent selectivity (75–92 for TCBD (entries 15, 20, and 23). However, the selectivity for compound **2a** was not obtained in good conversion in SDOSS,

SDS and CTAB with maximum selectivity of 23, 32 and 35%, respectively. To isolate and characterize compounds **1a** and **2a**, after the micellar reaction under the entry 4 condition, the surfactant residue was extracted in H_2O and the organic layer is recovered by EtOAc. Upon subjection to column chromatography (CC; CH_2Cl_2/hexane 1:1) in silica gel (SiO_2), the **1a** obtained 41% yield while only 5% for **2a**, along with a new compound **3a** with 38%, indicating the **2a** was not stable in SiO_2 and transforms into **3a**. Hence, compound **2a** was separated by performing flash chromatography for the crude reaction mixture separating **1a** and the mixture of **2a** and **3a**. The identity of compound **1a** was verified by comparing the TLC-R_f and physical nature with TCBD synthesized using C_6H_6 and also by NMR.[4] The mixture **2a** and **3a** were further subjected to crystallization, thus able to isolate **2a** in a moderate yield of 30% (entry 4).

Upon successful characterization of **2a** and **3a** by FT-IR, ^{1}H-, ^{13}C-, and 2D-NMR, and ESI-MS techniques, the unambiguous characterization for compound **2a** was successfully carried out because of X-ray suitable single crystals were obtained from the saturated solution of CH_2Cl_2/hexane 1:1 (Scheme 1c, for packing details see Section C, SI), however X-ray quality crystal of **3a** could not be obtained even after many attempts to grow under various conditions. It was observed in the X-ray structure that compound **2a** exists as a dimer with two complementary H-bondings between C=O and NH moiety (Figure S11).

Scheme 2. Synthetic scheme for the conversion of 2a to 3a under different conditions (inset: solution images)



Due to the fact that compound **2a** consists of a 5-membered fulvene ring, and despite its stability in solid-state with a high melting point (346 °C) and in solutions with aprotic nonpolar solvents (CH_2Cl_2, CH_2ClCH_2Cl, and $CHCl_3$), it readily undergoes keto→enol tautomerization with the subsequent formation of stable six-membered compound **3a** in polar aprotic solvents (EtOAc, acetone, CH_3CN and THF). The quantitative transformation from **2a** to **3a** was feasible in EtOAc and CH_3CN in 8 h even without stirring with an isolated yield of 98% (Scheme 2). Similarly, SiO_2 also catalyzed the transformation with an isolated yield of 80%. Further, we observed an interesting solvatochromism property of **2a** during the UV/Vis studies which also indicated the **2a** to **3a** transformation phenomenon (Figure S15d). These results are intriguing because the previous report by Bruce, with Ru-metal as EDG, did not facilitate such transformation.[11] Interestingly, compound **3a** resembles currently practiced cardiotonic drugs such as milrinone and amrinone.[14] Thus opening up a new window for discovering potential drug analogues of new derivatives of this class.

A plausible mechanism for the transformation of TCBD 1a to 2a and then 3a: The formation mechanism of TCBD **1a** from the reaction of TCNE with alkyne has been quite established by Diederich and co-workers, and also recently by Nielsen and co-workers with cyclobutene intermediate (Figure 2a).[15,16] Whereas, the H_2O addition to EDG-delocalized CN group on **1a** to generate 4-donor-substituted merocyanine dye/5-membered heterocycles **2a** was proposed by Bruce and co-workers.[11] It was proposed that amide forms an intermediate upon water addition to the TCBD which then further cyclizes to produce amidofulvene. However, we believe that the water addition on **1a** generates enol-intermediate-**I** instead of the keto form, which upon further cyclization provides amidofulvene **2a**. To validate this, we have performed a controlled study using compound **4**. In which the dicyanovinyl is absent to stop at the amide stage (see SI, Scheme S6). The study reveals that no reaction has taken place indicating the dicyanovinyl moiety is required to stabilize the enol form through the nucleophilic addition of enolic-*N*. Further to verify that the amide proton did come from water, we have performed the reaction in surfactant/D_2O and the ^{1}H-NMR of the **2a** in $CDCl_3$ did not exhibit a singlet peak at 7.93 ppm corresponding to the -NH proton (Figure S12). The disappearance of the peak at 7.93 ppm indicates that the amide proton comes from the water. Owing to the strong electron donating ability of the DMA group, unlike the Ru-metal atom, the lone pair on the *N*-atom of enol-form of intermediate **IV** undergoes nucleophilic attack at the C6-position creating fused 5 and 3-membered rings of intermediate **IV** (Figure 2b). Such systems are quite stable as exist in carzinophillin natural products.[17] The intermediate-**V** further undergoes Claisen-type rearrangement to afford 6-membered pyridinol-type heterocycle intermediate-**VI**. This subsequently rearranges to provide the stable cyclic-amide-based heterocycle **3a**.

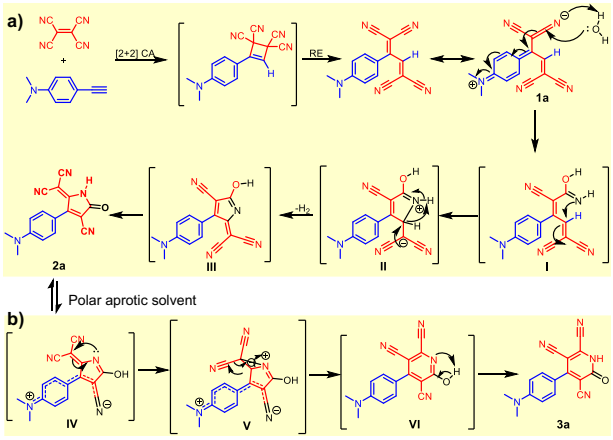


Figure 2. Proposed mechanisms a) for the formation of amidofulvene through substrate-assisted transient nanoreactor mediated water addition to TCBD **1a** and b) polar aprotic solvent-mediated keto-enol tautomerism initiated the transformation of **2a** to 6-membered heterocycles **3a**.

Water addition on TCBD to form 2a mediated by transient nanoreactor: A number of mechanistic approaches have been found to accelerate the organic transformations in H_2O viz., the hydrophobic effect, *H*-bonding, cohesive energy density, soft and dispersed interface-rich aqueous systems, and the nano-to-nano effect etc.[18]

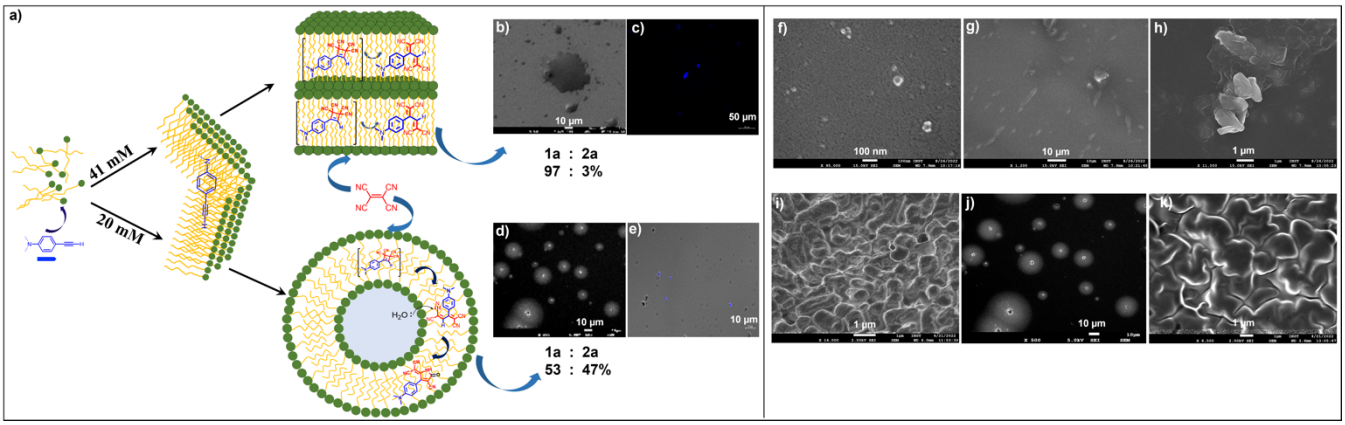


Figure 3. (a) Schematic representation of substrate-induced nanoreactors for the precise generation of polycyano-olefins. (b-c) FE-SEM and confocal images of Tween 20 at 41 mM with DMA. (d-e) FE-SEM and confocal images of Tween 20 at 20 mM with DMA. FE-SEM images of f) 10 mM of Brij 30 with DMA, g) 52 mM of SDOSS with DMA, h) 20 mM of CTAB with DMA, i) 20 mM of Tween 20, j) 20 mM of Tween 20 with DMA, k) 20 mM of Tween 20 after reaction with DMA and TCNE.

We have performed some control studies to shed insights on which type of mechanism occur on forming TCBD **1a** and its subsequent conversion in to amidofulvene **2a** mediated by surfactants. From the concentration study (Table 1), regardless of types of surfactants, all at very high concentration range (17–93 fold above CMC, highlighted in green in Table 1) provided TCBD **1a** as the major product (85–97%). As the concentration of surfactants was decreased to moderate or low, the effect of concentration was pronounced depending on the types of surfactants. For example, ionic and non-ionic surfactants provided <35% yield for **2a** at the 1.8–6.0 fold below CMC (highlighted in biege in Table 1), whereas, non-ionic surfactants Tween 20 and Brij 30 at 20mM and 50mM concentrations, respectively have showed an exceptional enhancement (41–47%) suggesting new type of hierarchical self-assembly (host system) formed in non-ionic surfactants. These results intrigued us for an extensive investigation on the surfactants and their self-assembling properties in the presence/absence of substrates. The studies related to morphology, shape transition, and size change detection were performed by FE-SEM & fluorescent confocal microscopy, fluorescence spectroscopy, and DLS experiments, respectively. Although Brij 30 and Tween 20 had similar selectivity profiles between **1a** and **2a** at low and high concentrations (entries 4 & 5; 8 & 11) due to Brij 30 being relatively more concentrated, this study focused on 20 and 41 mM concentrations of Tween 20, which produced **2a** (47%), and **1a** (97%), respectively. The FE-SEM imaging revealed that the 41 mM solution of Tween 20 forms sheet like morphology (Figure 3b) whereas, the 20 mM solution showed vesicles (Figure 3d) in presence of only DMA substrate. To support the FE-SEM observation, and to probe the hydrophilic compartment in the vesicle core, a hydrophilic dye (methylene blue) encapsulation study was performed for the same conditions by using confocal fluorescent microscopy (CFM). The CFM study revealed a clear image of a blue fluorescent core with shell indicating methylene blue a hydrophilic dye is present inside the core of the vesicle, whereas, the same experiment with 41 mM solution has showed sheet like structure as corroborated by the FE-SEM study (Figure 3e &c). Interestingly, in the absence of DMA showed completely different morphology with no vesicle signatures also after the reaction with TCNE, the reaction mixture did not exhibit vesicle suggesting DMA is assisting for the formation of vesicle similar to cholesterol mediated noisome formation (Figure 3i-k). Similar to Tween 20, the Brij 30 at lower concentration (10 mM) has showed vesicle formation (Figure 3f), whereas, the vesicles were not observed for ionic surfactants SDOSS and CTAB even with DMA even though they provided 23–25% yield for **2a** (Figure 3g & h) presumably due to micelle mediated reactivity. These observations substantiate the mechanism postulated in Figure 2, wherein, the transient nanoreactor *i.e.,* vesicle (20 mM Tween 20) having water core, yields **2a** exclusively by facilitating H_2O addition to EDG-delocalized CN group on **1a** which is formed by the conventional CA–RE reaction. Further, the concentration dependent shape transformation was investigated by fluorescence spectroscopy using methylene blue as a probe[19] and DLS technique. The fluorescence measurements were carried out for a series of concentrations of Tween 20 (0.5 – 44 mM) and the fluorescence intensity *vs* concentration plot (Figure S13a) shown a sudden fall at 20 mM concentration while below and above the 20 mM showed a normal trend indicating the transient self-assembled structure formation, which was also observed in the DLS experiments (Figure S13b). These results suggest co-assembling of non-ionic surfactants with substrate (DMA) to generate transient nanoreactor leading to the new reactivity of stable organic TCBD to transform into 5-membered heterocycle upon water addition.

Photophysical and substrate scope studies: The photophysical properties and dye characteristics of **2a** and **3a** have been investigated in comparison with already known TCBD **1a**[4] *via* optical, electrochemical and computational investigations and the results are discussed in detail in Section E, SI. Interestingly, the compound **2a** exhibited quite remarkable panchromatic absorption (250–800 nm) characteristics with a lower HOMO–

LUMO gap than TCBD **1a** (see Figure. S14). Lastly, to demonstrate the substrate scope of the present work, we have screened more mono-substituted alkynes (**1b-1e**) with varying the electron-donating ability of the donor group (entries 1–5, Table S5) and also di-substituted alkynes with varied donors (DMA, urea and NH_2) groups under similar conditions (see SI, Section E4). In brief, majorly, two observations have been made in this study, i) *N,N'*-dialkylated amines as EDG for mono-substituted alkynes generally undergoes similar reactivity profile yielding both TCBD and amidofulvene which can be tuned depending on the concentration, however, the less electron-donating alkynes such as –OMe, –urea (in water) did not undergo any transformations, ii) in the case of disubstituted alkynes only TCBD formation occurred irrespective of change in concentrations with *N,N'*-dialkylated amines as EDG and with or without urea EDG. This is understandable because of the leaving group for the cyclisation is H_2 in the mono-substituted alkynes (Figure 2), whereas the disubstituted alkynes will be alkanes which is energetically not favorable.

CONCLUSION: Herein, we report for the first time, the successful demonstration of the thermal [2+2] CA-RE reaction under greener condition replacing organic solvents by a surfactant/water medium. The conventional CA-RE product, i.e., TCBD which was formed with excellent yields (98%) in all types of surfactants (ionic and non-ionic) at higher concentration range mediated by lamellar bilayer sheet like structure. Interestingly, the TCBD formed in the reaction underwent distinct reactivity, at particular lower concentrations of non-ionic surfactants due to the formation of vesicles based transient nanoreactor facilitating H_2O addition in the hydrophilic core forming an 6,6-dicyanoamidopentafulvene. This transient nanoreactor was probed in detail through ^{1}H NMR, FE-SEM, CFM and DLS techniques revealing co-assembling of DMA-substrate generating a transient nanoreactor similar formation of niosomes by cholesterol. This unique mechanism of action is similar to the recently evolving field namely "substrate induced generation of transient self-assembled catalytic systems".[20] In addition, amidopentafulvene went through a clean transformation to a stable 6-membered cyclic amide in polar aprotic solvents *via* keto-enol tautomerism. In the substrate scope study, mono-substituted alkynes provide both TCBD and amidopentafulvene, which are tunable by surfactant concentrations, while di-substituted alkynes provide only TCBD. A further broadening of this system is currently being explored in our lab through the addition of other electron-donating groups to the monosubstituted alkynes. Overall, the present approach in water accounts for synthetic liability in biological systems and extends its application potential beyond TCBDs.

ASSOCIATED CONTENT

The Supporting Information (SI) is available:

- Experimental procedures, compound characterizations, NMR spectra, X-ray structural data for **2a**, spectroscopic, electrochemistry, and ab initio calculations data (PDF)

Accession Codes

CCDC 2216738 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Table of Contents (TOC)