JOC*Note*

PhIO as a Powerful Cyclizing Reagent: Regiospecific [3+2]-Tandem Oxidative Cyclization of Imine toward Cofacially Self-Aggregated Low Molecular Mass Organic Materials

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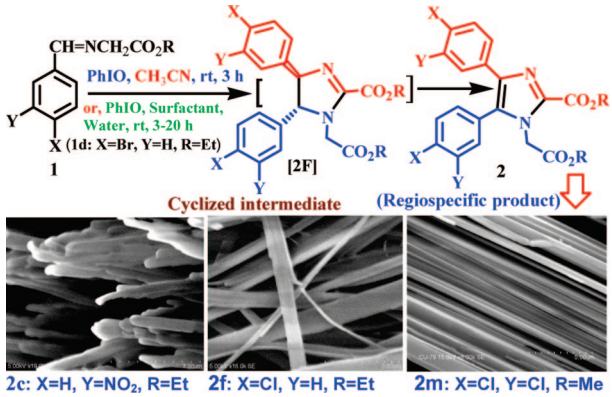
Received December 26, 2008



The powerful cyclization and tandem oxidation property of environmentally benign PhIO is developed for the first time, which leads to regiospecific [3+2]-tandem oxidative cyclization of imine at room temperature in rapid access to a new class of compounds, 1,2-functionalized 4,5-diarylimidazoles, in excellent yield with synthetic efficiency. Size, shape, and activity of the involved nanoreactors for the green approach built up from various surfactants are investigated. Spontaneous generation of low molecular mass self-aggregated organic materials, their cofacial one-dimensional packing, and interesting photophysical properties are reported.

Tandem oxidative cyclization (TOC) reaction is one of the fundamental organic transformations, and this versatile and powerful synthetic tool is capable of synthesizing complex biomolecules and natural products in one step.[1] However, most of the TOC reactions are investigated by using metal catalysts to maximize the regioselection. Development of the TOC property of an environmentally benign reagent for easy and rapid access to a new class of desired compounds using simple starting material under metal-free conditions is one of the paramount challenges in modern organic synthesis. Application of the TOC reaction in the synthesis of low molecular mass self-aggregated organic materials (LMSOM) is interesting in the context of achieving the target as they have attracted growing attention in the emerging fields of nanoscience and nanotechnology, mainly due to their promising applications in optical and optoelectronic nanodevices including semiconductors, fluorescence sensing abilities, and light emitting diodes.[2,3] Another important goal of achieving the target molecule by the TOC reaction is to address some aspects of modern criteria of synthetic efficiency[4] like regioselectivity, energy, time and atom economy, and use of nonconventional reaction media and environmentally benign reagent to reduce impact on the environment and hazards.

Polyvalent organo iodine compounds have found immense applications as environmentally benign, chemoselective, and smart oxidizing agents in synthetic chemistry.[5−10] Iodosobenzene (PhIO) has emerged as the most important family member because of its wide synthetic application as a starting material in the preparation of numerous iodine(III) compounds[5] and also as an oxygen donor in metal-catalyzed asymmetric epoxidation and other oxidation reactions.[6] Evolution of its oxidizing property is not that much investigated compared to the other hypervalent organoiodanes.[5] It is believed that due to poor solubility of polymerized iodosobenzene [$(PhIO)_n$] in organic

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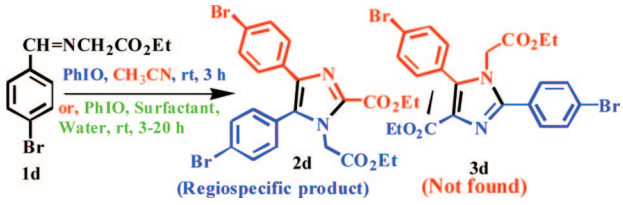
10.1021/jo8028136 CCC: $40.75 © 2009 American Chemical Society
Published on Web 02/27/2009

TABLE 1. Studies of TOC Reaction in Aqueous and Organic Media

entry	reaction media	surfactant	dimension of the nanoreactor (nm)	reaction time (h)	conversion (%)
1	CH_2Cl_2	no surfactant	N/A	4	100
2	CH_3CN	no surfactant	N/A	3	100
3	water	CTAB	290 (250−320)	3	100
4	water	SDS	380 (200−600)	5	100
5	water	tween 20	580 (490−700)	20	80
6	water	tween 80	460 (400−600)	20	100
7	water	triton CF-10	510 and 1110	48	20

SCHEME 1. Regiospecific [3+2]-Tandem Oxidative Cyclization of Imine by PhIO



solvent it is less reactive and thus activation is required to generate the actual oxidizing monomeric species in solution.[5b] Oxidation reactions of iodosobenzene have been carried out in the presence of Lewis acids,[7] catalysts,[8] and transition metal complexes[5] and also with its ortho carboxylic acid derivatives.[9] Only a few reactions like epoxidation of ketene,[10a] oxidative decarboxylation,[10b] and oxidation of amine[10c] and alkene[10d] are reported with PhIO alone as an oxidant. Recently, we have reported the chemoselective oxidizing property of PhIO to generate nitrile oxides from aldoximes.[10e] In this Note, we report for the first time excellent [3+2]-cyclization and tandem oxidation property of PhIO. It has transformed imines (**1**) in common organic solvent and in neutral aqueous media (Table 1) at room temperature in rapid access to designed compounds, 1,2-functionalized-4,5-diaryl-imidazoles (**2**, Scheme 1), with complete regiospecificity which have expectantly shown interesting self-assemble and photophysical properties suitable for designing fluorescent biosensor and optoelectronic nanodevices.[2]

The concept of green chemistry and its application in organic synthesis has emerged as a major solution for the development of cleaner and more benign chemical processes.[11] Initially, we have studied the TOC in common organic solvents (entries 1 and 2, Table 1) and the progress of the reaction is very fast (3−4 h) with complete dissolution of PhIO. We are very keen to develop a complete green [3+2]-TOC reaction using the environmentally benign reagent PhIO and water as reaction medium. After extensive studies this reaction is developed in aqueous media by making a confined reactor[12] built up from molecular assemblies of cationic (CTAB), anionic (SDS), and neutral amphiphilic surfactants (Table 1). The shape of the nanoreactors is nearly spherical as is observed with an optical microscope (Figure 1) with use of its thin film. We have

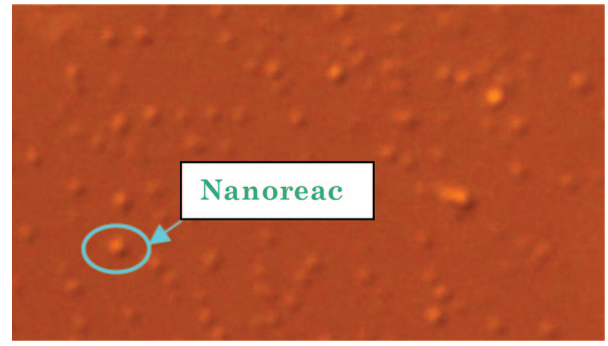


FIGURE 1. Optical microscope image of the nanoreactor formed by aqueous surfactant.

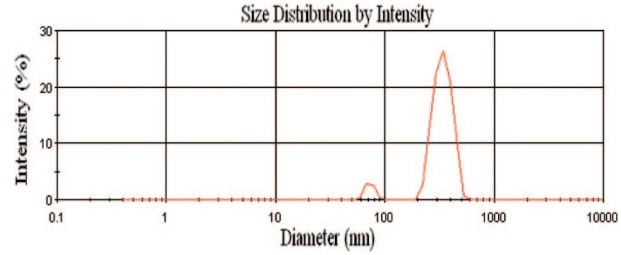


FIGURE 2. DLS size distribution data of the spherical nanoreactors formed by aqueous SDS.

measured their dimension (290−1110 nm) by dynamic light scattering (Figure 2 and Supporting Information). They are sufficiently hydrophobic in nature to solubilize the organic compounds like imine (**1**) and PhIO into their hydrophobic cores and protect water labile substances from decomposition. Our studies reveal that the reaction rate depends on the size and population of the nanoreactors. The dimensions of the nanoreactors formed by CTAB and SDS are optimum (300−400 nm) for their efficiency (entries 3 and 4). However, they are very large (350−1240 nm) and too small (ca. 10 nm) made by neutral surfactants (entries 5−7) and thus are not effective. Kita and co-workers have studied sulfide oxidation by PhIO[8a] and $PhIO_2$[8b] under miceller and reverse miceller environment and found quaternary ammonium salts as indispensable in solubilization and activation of the hyperiodanes. They have considered surfactants as catalysts enhancing the chemical and optical yield of the reactions. However, our investigation with DLS and an optical microscope has confirmed that the role of the surfactant is not as catalyst but forming nanometer micelles (nanoreactor) to perform the organic transformation with comparable reaction rate studied in organic media (Table 1).

Imidazoles are ubiquitous motifs in pharmaceuticals as well as in important natural products.[13] New and straightforward methods to access these substrates are thus highly desirable. There are numerous accounts in the literature on the synthesis of imidazoles mainly by using acid- and metal-catalyzed reactions.[13a] Synthesis of 4,5-diarylimidazoles is not much investigated[13b] although their analogues have been identified as potential candidates for antibacterial, antirheumatoid arthritis, anti-inflammatory, and other bioactivities.[13b,c] This green approach is highly efficient in synthesizing a variety of imidazoles (Table 2) containing functional groups and a heteroatomic and

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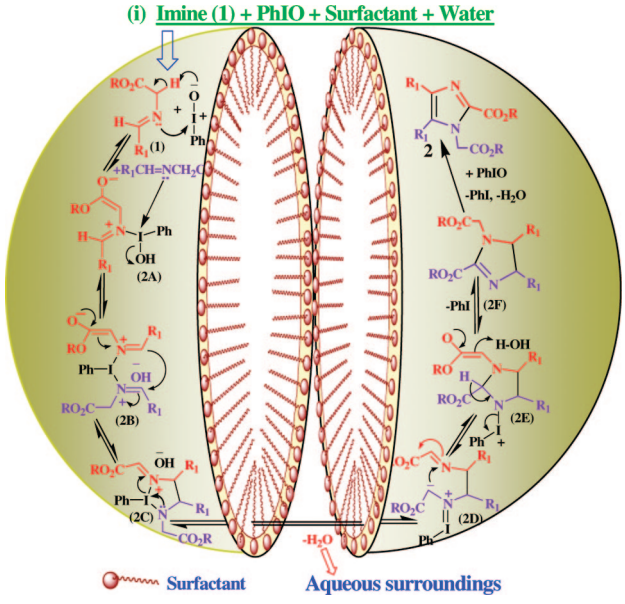
TABLE 2. Regiospecific [3+2]-TOC Reaction of Imine by PhIO

entry	imine	R_1	R	time (h)	product	yield (%)
1	**1a**	4-methoxyphenyl	Et	3.0	**2a**	72
2	**1b**	4-nitrophenyl	Et	4.0	**2b**	80
3	**1c**	3-nitrophenyl	Et	4.0	**2c**	82
4	**1d**	4-bromophenyl	Et	5.0	**2d**	75
5	**1e**	4-methoxyphenyl	^{n}Bu	5.0	**2e**	80
6	**1f**	4-chlorophenyl	Et	4.0	**2f**	70
7	**1g**	2-allyloxyphenyl	Et	3.5	**2g**	81
8	**1h**	4-cyanophenyl	^{t}Bu	6.0	**2h**	77
9	**1i**	2-furyl	Et	5.0	**2i**	68
10	**1j**	3-pyridyl	Et	6.0	**2j**	67
11	**1k**	2-quinyl	Et	7.0	**2k**	80
12	***1l***	2-methoxyphenyl	^{t}Bu	5.0	***2l***	82
13	**1m**	3,4-dichlorophenyl	Me	5.0	**2m**	79

SCHEME 2. Proposed Path for the TOC Reaction That Occurred Inside the Surfactant Assembled Nanoreactor

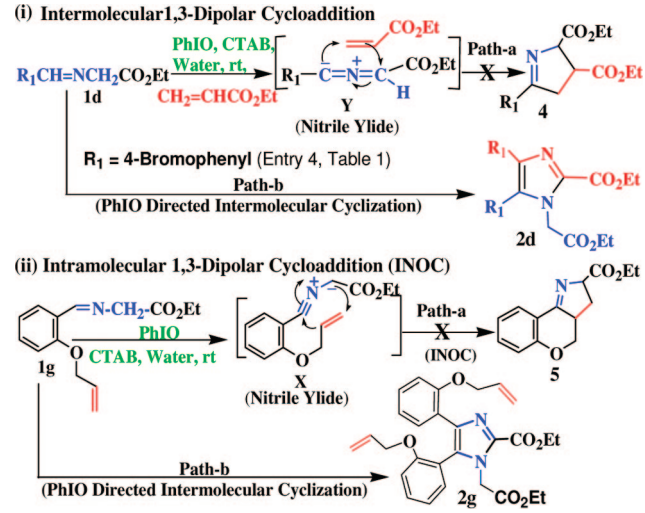


substituted aromatic nucleus essential for favorable binding interactions with the receptors to achieve the desired biological activities.[13c]

The proposed path of the TOC of imines to the corresponding imidazoles by PhIO is shown inside the nanoreactor (Scheme 2). The nitrogen atoms of two imines are captured by PhIO to form cyclized intermediate **2C** and followed by loss of PhI generating the oxidative cyclized intermediate **2F**. Oxidative dehydrogenation by PhIO in the final step leads to generation of **2**. We have successfully trapped the intermediate **2F** supporting the proposed path. We have investigated whether the regiospecific formation of imidazoles (**2**) has progressed through dimerization of possible nitrile ylides which may be generated by the oxidant PhIO.[10e] Failure in both the attempts for intermolecular (**4**, **i**) and intramolecular (**5**, **ii**) 1,3-DC reactions with olefins proves that the reactions follow solely path b toward **2** due to the strong cyclization property of the oxidant PhIO (Scheme 3). The [3+2]-tandem oxidative cyclization ability of PhIO is so powerful that the two sterically hindered aromatic groups have been placed side-by-side (**2**) without generation of the other regioisomer (**3**, Scheme 1).

Design and easy access to LMSOM is now a new challenge in organic synthesis wherein macrocyclic compounds or optically insensitive alkyl chains/steroidal groups substituted compounds have usually been utilized for the fabrication of 1D

SCHEME 3. Studies of the Reaction Path for the TOC Reaction



organic nanomaterials.[2,3] In this regard, the generation of the submicrotube from 2,4,5-triphenylimidazole by the reprecepitation method under heating and sonication is important.[3a] In a bid to our continuous effort to design and synthesize new heterocycles and to study their self-assembly properties,[2a] we report herein a new class of LMSOM from **2c**, **2f**, and **2m** (Table 2) which are easily accessible by the one-step green synthesis protocol. Elegant approaches have been devised to achieve the self-assembled nanostructured materials.[3] However, these small organic molecules spontaneously form tunable nanomaterials in common organic solvents (Supporting Information). To gain insight into the aggregation morphology of the nanomaterials formed by compound **2c**, two different solvents have been subjected to SEM. In ether medium it forms organic material of spherical dimension with a coral-like well-defined shape constructed by highly self-aggregated linear nanofibers about 200 nm in width (panel a, Figure 3) whereas a flat sheet-like nanomaterial is obtained in ethyl acetate at about 250 nm in width (Supporting Information). Spontaneous self-aggregated nanobelts (panel b, Figure 3), nanorods, and spiral fibrils (Supporting Information) are generated by compound **2f**, and also stack nicely (panel c, Figure 3) by compound **2m** in different solvents. The large red shift in UV measured in the self-aggregated solid state compared to their dilute solutions (panel d, Figure 3) is probably due to their unidirectional $\pi-\pi$ stacking. Unusual fluorescent amplification is also observed from dilute solution to its higher concentration (Supporting Information) and it becomes extremely large in the solid state (panel e, Figure 3). These 1D LMSOM (panel f, Figure 3) with strong photophysical properties are important in the generation of biosensor[14] and optoelectronic nanodevices of higher sensitivity.[2,3]

In conclusion, we have for the first time demonstrated the powerful [3+2]-cyclization and tandem oxidation property of the environmentally benign reagent PhIO leading to regiospecific TOC of imines with synthetic efficiency. The nanoreactors formed by various surfactants in aqueous media were studied by DLS and optical micrography. CTAB and SDS are found to be efficient for the TOC reaction. Using this robust green

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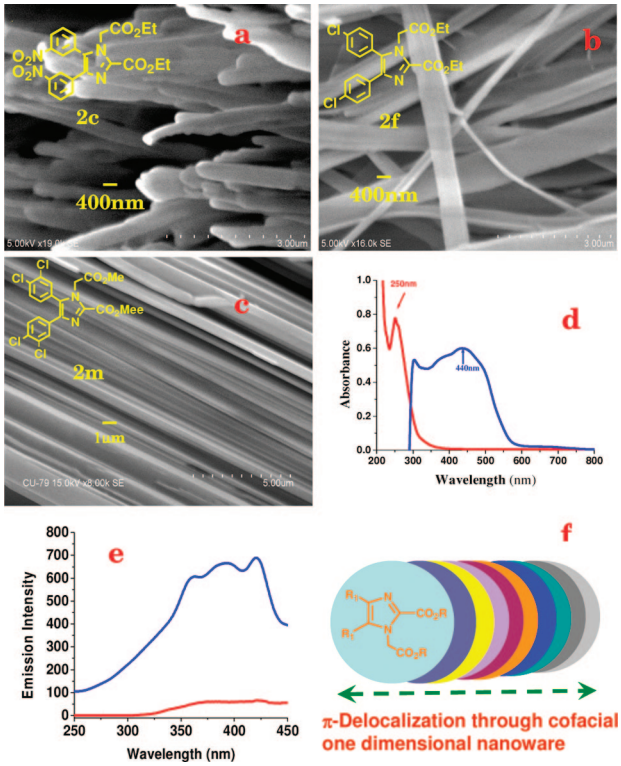

FIGURE 3. Cofacially self-aggregated one dimensional organic nanomaterials and their photophysical properties.

protocol we have synthesized three UV and fluorescence active LMSOM forming tunable cofacial 1D stacking suitable for designing biosensor and optoelectronic nanodevices. Extension of this strategy toward new heterocycles, novel LMSOM and their application as biosensor and nanodevices, and DFT calculations for geometry optimization and self-assembly is in progress.

Experimental Section

General Procedure for the TOC Reaction. A mixture of imine **1** (1.0 mmol), surfactant (0.33 mmol), and water (15 mL) in a round-bottomed flask (25 mL) was stirred at 10−15 °C for 15 min to build up the nanoreactor in aqueous media. PhIO (500 mg, 2.25 mmol) was added, and the content was allowed to attain room temperature. The reaction was complete after 3−7 h. The postreaction mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic portion was washed with a brine solution (2 × 10 mL), dried on activated sodium sulfate, and concentrated in a rotary evaporator under reduced pressure at room temperature. The crude product was chromatographed on silica gel (60−120 mesh) and eluted with ethyl acetate−petroleum ether. Thus, the reaction with [(4-bromobenzylidene)amino]acetic acid ethyl ester (**1d**, 270 mg, 1.0 mmol) using CTAB (120 mg, 0.33 mmol) afforded 1-ethoxycarbonylmethyl-4,5-bis(4-bromophenyl)-1*H*-imidazole-2-carboxylic acid ethyl ester (**2d**) after processing in an isolated yield of 75% (400 mg, 0.75 mmol). Compound **2d** and others (**2a**−**m**) were characterized by ^{1}H and ^{13}C NMR (NDC and DEPT), FT-IR, and mass (EI-MS and HR-MS) spectral analysis. The structure is established by 2D NMR spectra.

Compound 2d: yellow semisolid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.2 Hz), 1.18 (3H, t, J = 7.2 Hz), 4.07 (2H, q, J = 6.9 Hz), 4.20 (2H, q, J = 7.2 Hz), 4.37 (2H, s), 7.22 (2H, s), 7.43 (2H, d, J = 7.5 Hz), 7.55 (4H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.1, 46.8, 60.6, 62.3, 124.2, 124.5, 126.9, 127.6, 128.1, 128.5, 130.1, 130.8, 131.7, 132.0, 138.6, 147.8, 162.5, 167.4; EI-MS (*m*/*z*) 534 (M^+), 504, 440, 404, 365; IR (neat, cm^{-1}) 1199, 1378, 1474, 1723, 2377, 2926; HR-MS (*m*/*z*) for $C_{22}H_{21}Br_2N_2O_4$ (M + H) calcd 536.9848, found 536.9895 (highest ion peak).

Acknowledgement. We acknowledge the financial support of this work by the DST (SR/S1/OC-22/2006), India and Center for Research in Nanoscience and Nanotechnology, C.U. We thank Prof. Anjan Dasgupta, Prof. Arup Mukherjee, and Dr. Prabir K. Maiti of C.U. for providing optical microscope, mass spectrometry, and SEM (TEQIP) instrumental facilities. N.C. and S.H. thank CSIR, and P.P. thanks UGC, India for research fellowships. We also thank P. Ghosh, S. Chatterjee, and S. Bhowmik for running spectra of our samples.

Supporting Information Available: General methods, experimental procedures, imaging pictures, elucidation of structure by 2D NMR, spectroscopic data, and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8028136