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ARTICLE

Reactant cum solvent water: generation of transient λ^3 -hypervalent iodine, its reactivity, mechanism and broad application

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An outstanding amidation/imidation process is demonstrated under metal-free benign reaction conditions by grafting terminal alkynes with varied amines and reactant cum solvent water. We explored diverse substrate scope in the nonconventional approach for synthesis of several classes of valuable compounds bearing amide linkages such as *N*-tosyl, *N*-aminotosyl, *N*-oxobenzyl, *N*-alkylated sugar-based secondary and tertiary chiral amides and also exploiting it for synthesis of valuable cyclic imides through simultaneous activation of triple bond and sp^2 C-H of aldehyde. The insitu-generated powerful reagent $\text{PhI}(\text{OH})_2$ enables selective cleavage and functionalization of terminal C-C triple bonds through simultaneous construction of C-N and C=O bonds. A measurable breakthrough in time-resolved ATR-MIR spectroscopy of the ongoing λ^3 -hypervalent iodine controlled reaction revealed formation of the unknown intermediates. The ATR-MIR technology is used for identifying infrared (IR) spectra of the individual intermediate/component present in the reaction mixture, which contains several compounds. The structures of the intermediates and their IR spectra were determined by DFT study. This unprecedented combination of experimental results and theoretical prediction provided useful information regarding the reaction insights such as the cleavage of triple bond, amination and amidation in the complex reaction process involving λ^3 -hypervalent iodine-bearing labile intermediates to the desired amide. The NMR and labelling (^2H and ^{18}O) studies supported the DFT-IR predicted reaction pathway.

Introduction

Water is one of the important ingredients cum reaction media for essential biochemical processes. In contrast to the traditionally used toxic, expensive and volatile organic solvents, the unique physical and chemical properties of water, environmentally benign nature, large abundance, low cost and easy product isolation have grown interest for exploiting it as a universal solvent.¹ Water can also be used as a reactant cum solvent, which found scant application. Recently developed metal catalyzed splitting of water to hydrogen and oxygen is interesting.² It is especially challenging to switch a frequently used anhydrous reaction such as amidation and imidation into operationally simple aqueous process using oxygen from reactant water. The λ^3 -hypervalent iodines are attractive for their easy preparation and application,³ compatibility with water as a reaction medium,⁴ fast reaction rate,⁵ efficient Lewis acid-like oxidant,⁶ catalytic activity⁷ and metal mediated transformations⁸ towards easy access to diverse compounds especially under benign reaction conditions.³⁻¹⁰ $\text{PhI}(\text{OAc})_2$ ⁹ and PhIO ¹⁰ are commercially available inexpensive hypervalent iodines. $\text{PhI}(\text{OAc})_2$ is converted into polymeric PhIO under alkaline conditions using strong base such as aqueous NaOH or KOH .^{9a} However, $\text{PhI}(\text{OAc})_2$ may be

transformed into highly reactive $\text{PhI}(\text{OH})_2$ under the mild basic conditions, and its novel chemical properties will be exploited in organic synthesis. The understanding of reaction insights¹¹ is desirable to improving the knowledge of new hypervalent iodine chemistry, enhancing the reactivity, selectivity and yield of the desired products. The major obstacle for investigating the reaction process is the low volatile, thermally labile and transient nature of the hypervalent iodine and its intermediates. It is attempted to detect simple hypervalent iodine reagents such as 4-substituted iodosylbenzene and iodosobenzene by mass spectrometry.¹² Expectantly the labile hypervalent iodines provided several peaks for ions under the instrumental conditions. Thus, it is practically impossible to identify relatively large and complex hypervalent iodine intermediates-bearing organic precursor from the reaction mixture because of their low volatility, less stability, high reactivity and labile nature under the experimental conditions. It is desirable to exploit the insitu-generated new λ^3 -hypervalent iodine reagent under benign reaction conditions to improve the substrate scope towards diverse syntheses of amides and imides, and also to identify the involved λ^3 -hypervalent iodine - bearing intermediates in the novel unorthodox organic transformations. The modern Mid-IR^{13,14} experimental technique of the ongoing reaction and the theoretical Gaussian approach^{6,10,15-17} can be attempted together to overcome this difficulty.

The construction of amides is a fundamental reaction and often used in our body for keeping it functioning,^{18c} syntheses of invaluable natural products (antibacterial MSX 47401, I, Figure 1),^{18e} medicinal products,^{18a} agrochemicals,^{18d} catalysts^{18b} and

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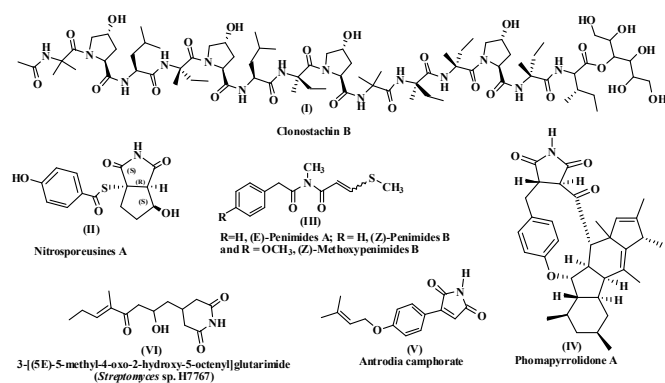
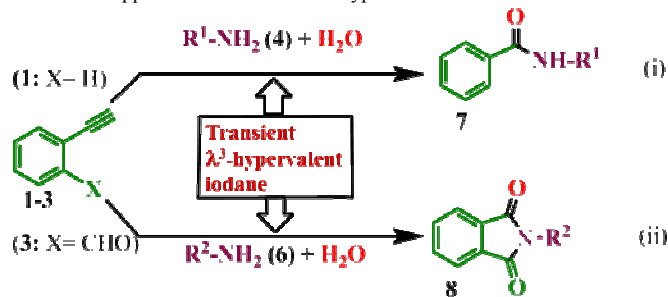


Figure 1. Amide and imide-bearing bioactive natural products

semiconducting materials for organic electronics.^{18f} The cyclic imides also revealed a wide range of medicinal properties (II-VI).¹⁹ There are increasing interest on direct synthesis of amides and imides especially due to their presence in most of the drugs of pharmaceuticals industry. The traditional syntheses of amides and imides through dehydrative coupling of carboxylic acids and amines under strongly heating conditions, microwave irradiation and metal-catalyzed stringent processes have a very limited substrate scope.²⁰ The usefulness of the compounds leads to development of several interesting strategies in recent time such as for amides metal catalyzed processes,^{21a-c} umpolung approach,^{21d} silatropic switch strategy^{21e} and decarboxylative method^{21f}, and imides by palladium catalyzed carbonylation with carbon monoxide, amines and haloarenes,^{22a-d} Rh-catalyzed C-H activated imidation of amide with CO,^{22e,f} and *trans*-imidation.^{22g-j} Recently we have communicated²³ a new λ^3 -hypervalent iodine chemistry under basic reaction conditions for synthesis of amides and ketoesters. In this article we have explored the wide-spread application, reactivity and mechanistic study of the transient λ^3 -hypervalent iodine for grafting functionalized-terminal alkynes with several types of amines and water towards synthesis of important classes of valuable compounds such as *N*-tosyl, *N*-aminotosyl, *N*-oxobenzyl, *N*-alkylated sugar-based secondary and tertiary chiral amides (**7**, eq. i, Scheme 1) under benign reaction conditions. The scope of the strategy is exploited for synthesis of valuable cyclic imides through simultaneous activation of triple bond and sp^2C-H of aldehyde (**8**, eq. ii). We have also executed the DFT-transition states, NMR, and labeling experiments of the new amidation strategy to achieve reaction insights of the unorthodox processes.

Scheme 1: Application of transient λ^3 -hypervalent iodine



Experimental

Materials and methods

All reagents were purchased from commercial suppliers and used without further purification, unless otherwise specified. Commercially supplied ethyl acetate and petroleum ether were distilled before use. Dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) were dried by distillation over P_2O_5 . Petroleum ether used in our experiments was in the boiling range of 60°-80 °C. Column chromatography was performed on silica gel (60-120 mesh, 0.120 mm-0.250 mm). Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Reported melting points are uncorrected. 1H NMR and ^{13}C NMR spectra were recorded using 300 MHz spectrometers (300 MHz for 1H and 75 MHz for ^{13}C). Chemical shift is reported in ppm from internal reference tetramethylsilane and coupling constant in Hz. Proton multiplicities are represented as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). Infrared spectra were recorded on FT-IR spectrometer in thin film. HR-MS data were acquired by electron spray ionization technique on a Q-tof-micro quadruple mass spectrophotometer. Optical rotation of the chiral compounds was measured in a polarimeter using standard 10 cm quartz cell in sodium-D lamp at ambient temperature. Optical purity of the chiral amides and imide were determined by chiral HPLC using normal phase semipreparative chiral column. MIR-ATR spectroscopy of the inline reaction was executed by React IR 15 instrument using iC IR 4.3 software.

General procedure for amidation

Terminal alkyne (**1**, 1.0 mmol, 102 mg) and iodobenzene diacetate (3.0 mmol, 966 mg) were stirred for 30 min. and allowed to react with aqueous sodium bicarbonate solution (2.1 mmol, 176 mg in 2.0 mL of water) under stirring conditions at ambient temperature. After one hour amine (**4**, 1.5 mmol) was added in a drop-wise manner. The reaction was monitored by thin layer chromatography (TLC). The post-reaction mixture was extracted with EtOAc (2x15 mL), and the combined organic layer was washed successively with saturated sodium bicarbonate solution (1x10 mL) and brine (1x10 mL). It was then dried over anhydrous Na_2SO_4 , filtered and evaporated in a rotary evaporator under reduced pressure at room temperature. Thus, the reaction with phenylacetylene (**1a**, 102 mg, 1.0 mmol) and *N*-tosylamine (1.5 mmol, 256 mg) afforded *N*-tosylbenzamide (**7a**) after purification by column chromatography on silica gel (60-120 mesh) with ethyl acetate-petroleum ether (1:24, v/v) as an eluent in a yield of 65% (179 mg, 0.65 mmol). The synthesized amide (**7a**)²⁴ and other compounds were characterized by means of NMR (1H and ^{13}C), FT-IR and mass (HR-MS) spectral analyses.

Labeling experiment with H_2O^{18}

On treatment of phenylacetylene (**1a**) with *n*-butylamine (**6a**) in presence of sodium bicarbonate and iodobenzene diacetate in H_2O^{18} (eq. iii, Scheme 2) for 4 h at room temperature the desired amide was formed with incorporated O^{18} -isotope (**9b**). It was confirmed by performing GC-MS analysis of the post reaction mixture which showed appearance of 179 (**9a**+2) for **9b** (ESI). The

peak at 177 indicates formation of **9a** by reaction with the insitu generated H_2O^{16} .

Labeling experiment with D_2O

A mixture of phenyl acetylene (**1a**, 1 mmol, 102 mg), *n*-butylamine (**6a**, 1 mmol, 73 mg) and iodobenzene diacetate (322 mg) were allowed to stir for 24 h in D_2O to obtain **9c**. The post-reaction mixture was extracted with EtOAc (2x15 mL), and the combined organic layer was washed successively with dilute HCl, saturated aqueous sodium bicarbonate solution (1x10 mL) and brine (2x10 mL). It was then dried over anhydrous Na_2SO_4 , filtered and evaporated in a rotary evaporator under reduced pressure at room temperature. The product ($\text{PhCOCD}_2\text{OAc}$) was isolated and characterized (ESI) by NMR, FT-IR and mass spectroscopy (m/z 180.0752).

Investigation reaction mechanism by NMR study

The particular amidation reaction with similar composition was performed in D_2O or water and ^1H -NMR of the reaction mixtures were recorded (ESI). The NMR experiments were performed using CD_3CN as a NMR solvent at different time intervals and the relevant spectra are uploaded in the ESI.

Trapping of intermediate VIII

To a suspension of 2-ethynylbenzaldehyde (**3**, 1.0 mmol, 130 mg) and iodobenzene diacetate (1.0 mmol, 322 mg) in water (2.0 mL) sodium bicarbonate (2.0 mmol, 168 mg) was added and allowed to stir for one hour. *n*-Benzylamine (**6c**, 1.5 mmol, 160 mg) was added drop-wise under stirring condition at room temperature. The reaction was monitored by the thin layer chromatography (TLC). After three hours the reaction mixture was quenched by addition of NH_4Cl and subsequently extracted with EtOAc (30 mL). The organic layer was washed successively with saturated sodium bicarbonate solution (1 x 10 mL) and brine (1 x 10 mL). It was dried over anhydrous Na_2SO_4 , filtered and evaporated in a rotary evaporator under reduced pressure at room temperature. The intermediate 2-benzyl-3-methylene-2,3-dihydro-isoindol-1-one (**VIII**) was isolated after purification by column chromatography on silica gel (60-120 mesh) using ethyl acetate-petroleum ether (1:24, v/v) as an eluent in a yield of 50% (120 mg, 0.50 mmol). The synthesized compound (**VIII**) was characterized by means of NMR (^1H and ^{13}C), FT-IR, Mass (HR-MS) spectral analysis and comparing with the literature spectroscopic data.²⁵

General procedure for synthesis of imides (**8**)

To a suspension of 2-ethynylbenzaldehyde (**3**, 1.0 mmol, 130 mg) and iodobenzene diacetate (4.0 mmol, 1.288 g) in water (2.0 mL) sodium bicarbonate (3.1 mmol, 260 mg) was added and allowed to stir for one hour. Primary aliphatic amine (1.5 mmol) was added drop-wise under stirring condition at room temperature. The reaction required nine to ten hours to complete, which was confirmed by TLC monitoring. The post reaction mixture was extracted with EtOAc (2x15 mL) and the combined organic layer was washed successively with saturated sodium bicarbonate solution (1x10 mL) and brine (1x10 mL). It was dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness in a rotary evaporator under reduced pressure at room temperature. Thus, the reaction

with 2-ethynyl benzaldehyde (1.0 mmol, 130 mg) and benzylamine (1.5 mmol, 160 mg) afforded 2-benzylisoindole-1,3-dione (**8a**) which was isolated after purification by column chromatography on silica gel (60-120 mesh) using ethyl acetate-petroleum ether (1:24, v/v) as an eluent in a yield of 65% (154 mg, 0.65 mmol). All synthesized compounds including **8a**²⁶ were characterized by means of NMR (^1H and ^{13}C), FT-IR, Mass (HR-MS) spectral analysis data (ESI).

Results and discussion

Development of alkyne-amine-water coupling reactions

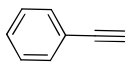
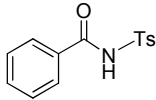
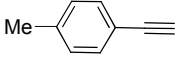
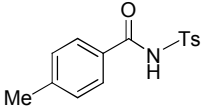
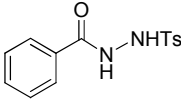
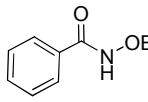
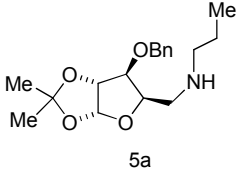
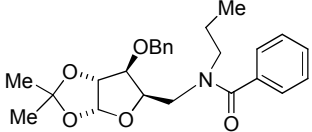
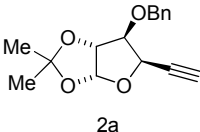
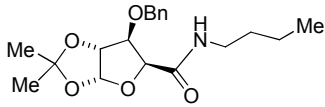
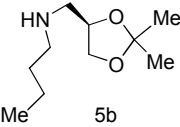
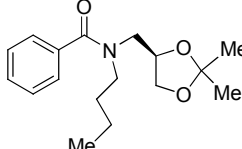
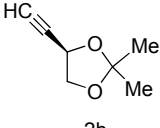
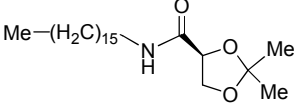
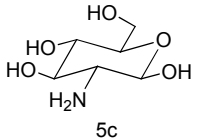
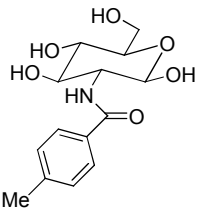
Simultaneous coupling of *N*-tosylamine (**4a**) for C-N and water for C=O bonds was achieved through grafting of phenyl acetylene (**1a**) using NaHCO_3 (2.1 mmol) and $\text{PhI}(\text{OAc})_2$ (3 mmol) to afford directly the primary amide (entry 1, Table 1) equivalent *N*-tosylbenzamide (**7a**, entry 1, Table 2). The amidation reaction was rapid (3 h) and subsequent SiO_2 -chromatographic separation of the post reaction mixture provided the desired product in 65% yield. To optimize the reaction we have employed stronger base NaOH , K_2CO_3 and KOH and a comparable yield was obtained in each experiments (entries 2-4, Table 1). The reaction was very slow (20 h) and low yielding (20%) on use of polymeric PhIO (entry 5). As expected the amidation reaction was completely arrested in absence of base and water (entries 6-9). To understand the amidation process by the insitu-generated hypervalent iodine we have installed one aldehyde group at *ortho*-position of the aromatic alkyne (**3**, eq. ii, Scheme 1). Interestingly the $\text{sp}^2\text{C-H}$ of aldehyde

Table 1. Optimization of the amidation and imidation reactions

Entry	Hypervalent iodine ^a	Solvent ^b	Base ^c	Time (h)	7a/8a , Yield (%) ^d
1	$\text{PhI}(\text{OAc})_2$	H_2O	NaHCO_3	3	7a , 65
2	$\text{PhI}(\text{OAc})_2$	H_2O	NaOH	4	7a , 62
3	$\text{PhI}(\text{OAc})_2$	H_2O	K_2CO_3	10	7a , 62
4	$\text{PhI}(\text{OAc})_2$	H_2O	KOH	4	7a , 63
5	PhIO	H_2O	NaHCO_3	24	7a , 20
6	$\text{PhI}(\text{OAc})_2$	H_2O	-	48	7a , nd ^e
7	$\text{PhI}(\text{OAc})_2$	CH_2Cl_2	NaHCO_3	48	7a , nd
8	$\text{PhI}(\text{OAc})_2$	MeCN	Na_2CO_3	48	7a , nd
9	$\text{PhI}(\text{OAc})_2$	MeOH	Na_2CO_3	48	7a , nd
10	$\text{PhI}(\text{OAc})_2$	H_2O	NaHCO_3	6	8a , 51
11	$\text{PhI}(\text{OAc})_2^f$	H_2O	NaHCO_3	4	8a , 65
12	$\text{PhI}(\text{OAc})_2^f$	H_2O	NaOH	5	8a , 62
13	$\text{PhI}(\text{OAc})_2^f$	H_2O	KOH	5	8a , 63
14	PhIO^f	H_2O	NaHCO_3	24	8a , 25

^a3 mmol. ^b2 mL. ^c2.1 mmol. ^dYield of the isolated product after column chromatography. ^eNot detected. ^f4 mmol.

Table 2. Synthesized amides utilizing alkynes, water and amine analogues

Entry	Alkyne (1-3)	Amine (4-6)	Product (7)	Time (h)	Yield (%)
1	 1a	TsNH ₂ 4a		3.0	7a, 65
2	 1b	4a		3.0	7b, 72
3	1a	TsNHNH ₂ 4b		3.0	7c, 60
4	1a	NH ₂ OBn 4c		3.5	7d, 60
5	1a	 5a		3.5	7e, 68
6	 2a	ⁿ BuNH ₂ 6a		3.0	7f, 75
7	1a	 5b		3.0	7g, 75
8	 2b	Me-(CH ₂) ₁₅ -NH ₂ 6b		4.5	7h, 68
9	1b	 5c		3.5	7i, 60

was also involved in the amidation process with phenylethylamine (**6a**), (entry 10, Table 1) to afford directly a valuable cyclic imide **8a** (entry 1, Table 3) through dual amidation. Initially we applied the similar reagents and reaction conditions (entry 10, Table 1) and the desired compound was obtained in a moderate yield (51%). The yield and reaction time were improved (entry 11) on use of little excess amount of $\text{PhI}(\text{OAc})_2$ (4 mmol). Herein also comparable yield was obtained on switching the reaction using strong bases (entries 12,13) and the yield was drastically reduced on employing neutral λ^3 -hypervalent iodine PhIO (entry 14) under the similar reaction conditions.

Substrate scope for amidation and imidation reaction

With the developed synthetic strategy in hand (entry 1, Table 1) we explored the scope of the metal-free unorthodox synthesis with substituted alkyne (**1b**, entry 2, Table 2), which smoothly produced the desired amide **7b** in 3 h. Surprisingly the benign strategy was also equally efficient for synthesis of valuable amides bearing *N*-tosyl amino (**7c**) and benzyloxy (**7d**) groups (entries 3,4) in 3.0-3.5 h. We successfully installed sugar-based 2° -amine towards synthesis chiral amide **7e** with interesting structural features (entry 5). We then turned our attention to prepare and use the sugar-based alkynes (**2a,b** entries 6-8) in the benign approach to afford successfully corresponding sugar-based chiral amides bearing lipophilic hydrocarbon chain (**7f-h**) with good yield (68-75%). The amidation reaction with water was also validated for amidation of highly polar free-amino sugar (**5c**, entry 9) with alkyne (**1d**) towards

chemoselective benzylation product **7i**. Thus this green strategy has tremendous importance in glycoscience as well as medicinal chemistry. Several types of cyclic imides (**8a-e**, entries 1-5, Table 3) and its chiral analogue (**8f**, entry 6) were synthesized under the reaction conditions.

Labelling experiment

To understand reaction insight of the new unorthodox process we first performed labelling experiments of a relatively simple amidation (eq. iii, Scheme 2) using phenyl acetylene (**1a**) and *n*-butylamine (**6a**) to afford *n*-butyl benzamide (**9a**, eq. iii, Scheme 2) in 4 h. On use of H_2^{18}O as a reaction medium under basic conditions a high level of incorporation of ^{18}O into the product **9a** was observed (**9b**, eq. iv), which was isolated, characterized and confirmed by mass spectrometry (ESI). In absence of NaHCO_3 complete cleavage of the C-C triple bond did not occur in D_2O and eventually produced deuterium incorporated end-product **9c** (eq. v) after a long period of time (~ 24 h).

Scheme 2. Labelling experiments

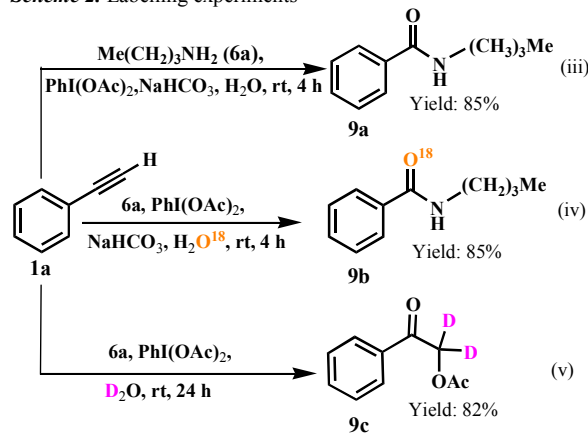


Table 3. Synthesized cyclic imides with 2-ethynylbenzaldehyde (**3**)

Entry	Amine	Product	Time(h)	Yield(%)
1			9.0	8a, 65
2			10.0	8b, 60
3			9.0	8c, 60
4			9.0	8d, 70
5			9.0	8e, 64
6			10.0	8f, 61

NMR study of the ongoing amidation reaction

On the other hand, the ^1H NMR studies of the reaction mixture in D_2O and the precipitated out solid material from water medium also supported the formation of a complex-adduct (ESI), with new broad peaks appearing in the aromatic region (7.39-8.69 ppm) and simultaneous disappearance of the *sp*-*C-H* ($\equiv\text{C-H}$; δ 3.47 ppm) with progress of time (~ 1 h). Subsequent addition of amine (**6a**) and breaking of the C-C bond is expected to have produced the desired amide **9a** after 1.5 h. We found a peak at 8.42 ppm in the ^1H NMR and 181.3 ppm in the ^{13}C NMR spectrum, which persisted in the ^{13}C -

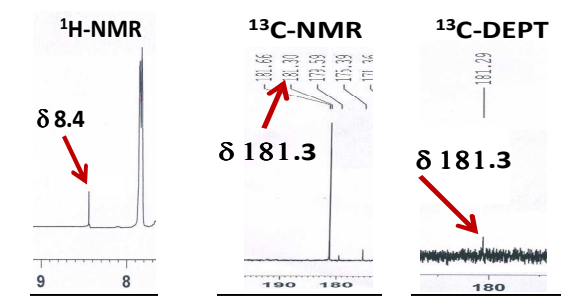


Figure 2: ^1H and ^{13}C -NMR spectra of the reaction mixture

DEPT NMR experiment (181.3 ppm, Figure 2) indicating the existence of a $-CHO$ bearing byproduct such as sodium formate and/or $PhI(OH)-CHO$. PhI was isolated from the post reaction mixture and characterized.

Inline ATR-MIR spectroscopy

With this preliminary observation in hand we have evaluated the reaction insights of the base-tuned new hypervalent chemistry by exploiting time-resolved Mid-IR spectroscopy (React-IR) combined with ATR (attenuated total reflectance) technology, which recently found tremendous application.^{13,14} To the best of our knowledge this is the first application of ATR-MIR spectroscopy for investigating insights of a λ^3 -hypervalent iodine reaction. The physical appearance of the reaction mixture over time (panels A-D, Figure 3), solvent-deducted 3D-reaction surface monitored by inline ATR-Mid-IR (Figure 4) and combined FT-IR spectra of the reaction mixture at selected point of time such as at 2 min. 27 sec./40 min. 27 sec. (Figure 5) and 1 h 31 min. 14 sec., 1 h 35 min. 14 sec. (Figure 6) were captured. The texture and colour of the reaction mixture

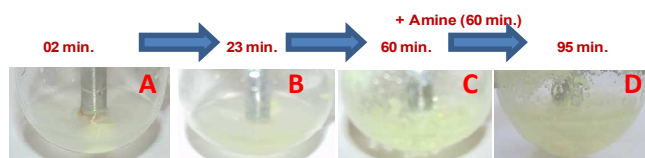


Figure 3. Outlook of the reaction mixture with progress of amidation

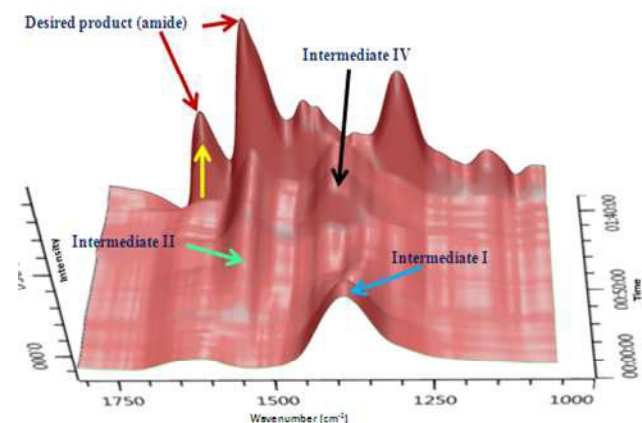


Figure 4. Mid-IR-ATR 3D-Surface of amidation reaction. $PhI(OAc)_2$, alkyne (**1a**) and water (5 mL) were mixed together and stirred for 30 min., added $NaHCO_3$, and progress of the reaction was monitored through continuously recording FTIR spectra (3D surface) at room temperature by insertion of an ATR-MIR probe. *n*-Butyl amine (**6a**) was added after 1 h for initiation of the amidation process towards generation of desired amide **9a**.

changed very quickly to form a fluorescent gel-like material (panels A to C, Figure 3), which (panel C) was ready for coupling with *n*-butyl amine (**6a**), in 1 h (Figure 3). Upon addition of **6a** the amidation reaction proceeded quickly. Transformation of the gel-like material to an oily product (**9a**, Scheme 2) was observed that was deposited in the reaction container as an oil (panel D).

The $PhI(OAc)_2$ -alkyne (**1a**) complex is expected to have formed within 2 min. in the water medium (panel A, Figure 3) through preactivation of the triple bond. FTIR-peaks of the probable intermediate I (Figure 4) were observed in the 3D reaction surface and captured FTIR spectrum showed intense characteristic peaks at

1384 cm^{-1} (2 min. 27 sec., red line, Figure 5). It might be due to generation of a charged-complex species. Characteristic peaks (2141 and 2051 cm^{-1} , blue line) for a C-C triple bond of phenyl acetylene disappeared in the red line (Figure 5), which confirmed cleavage of the triple bond. Surprisingly the 3D-reaction surface of ATR-Mid-IR was drastically changed on addition of $NaHCO_3$ into the reaction mixture. The captured FTIR spectrum at 40 min 27 sec revealed generation of three intense peaks 2010, 1563 and 1365 cm^{-1} (green line) with the disappearance of intense peak 1384 cm^{-1} (red line). It clearly indicates that $NaHCO_3$ played a crucial role in replacing the acetate groups from $PhI(OAc)_2$ with HO^- towards formation of a highly reactive new transient hypervalent iodine $PhI(OH)_2$ leading to immediate construction of another intermediate II (Figure 2).

On addition of *n*-butylamine (**6a**, pink dotted line) two intense peaks were observed at 1551 and 1421 cm^{-1} after 1 h 31 min. 14 sec. (green line, Figure 6) due to formation of a new intermediate (IV, Figure 4). Interestingly break down of the intermediate IV into the desired amide **9a** was very fast because we could not identify

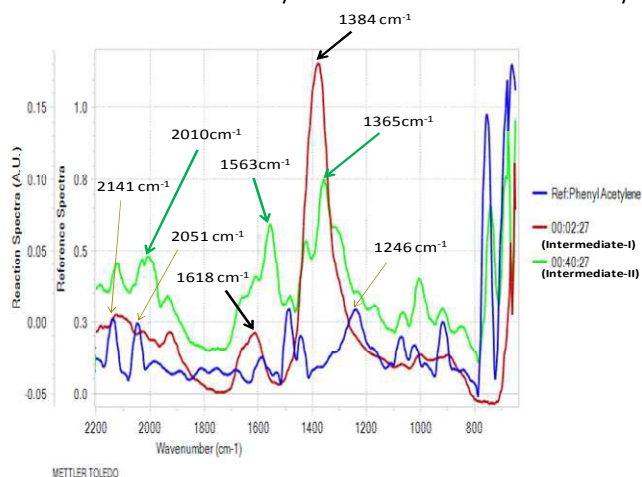


Figure 5. FTIR spectra of the intermediates before adding **6a**. (i) FTIR spectrum of precursor phenyl acetylene (**1a**) is displayed as blue line. (ii) FTIR spectrum (red line) of the mixture of alkyne (**1a**) and $PhI(OAc)_2$ in water was recorded at 2 min 27 sec. (for intermediate I) (iii) FTIR spectrum (green line) of reaction mixture with $NaHCO_3$ at 40 min 27 sec revealed formation of intermediate II.

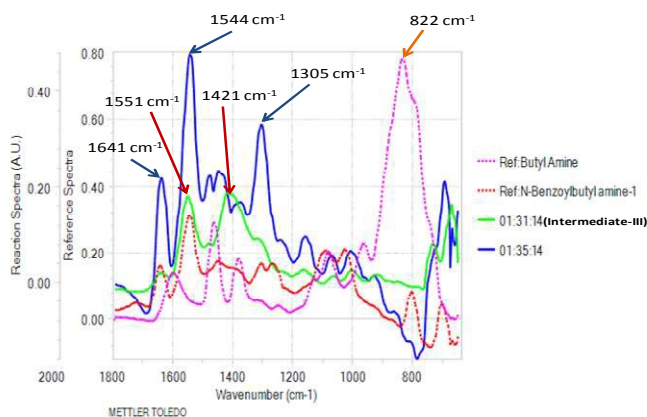


Figure 6. FTIR spectra of the intermediates towards amide **9a**. (i) The FTIR spectra of reactant *n*-butyl amine (**6a**) and product amide (**9a**) are presented in pink and red dotted line respectively. (ii) FTIR spectrum at 1 hr 31 min and 14 sec (green line) showed generation of intermediate III. (iii) The FTIR spectra at 1 hr 35 min 14 sec displayed appearance of the desired amide **9a**.

FTIR spectrum for any other intermediate(s). React-IR monitoring revealed sharp enhancement of the amide threshold only after 4 min. (blue line, at 1 h 35 min. 14 sec.) in the 3D energy surface with the characteristic FTIR peaks at 1641 and 1544 cm^{-1} , which were also comparable with the standard peaks of the authentic amide sample (red dotted line). The 3D energy surface of the MIR spectroscopy showed that consumption of precursor **6a** was very fast as its characteristic threshold at 822 cm^{-1} (pink dotted line) was sharply reduced due to formation of the desired product **9a** (eq. iii, Scheme 2).

DFT study for transition states and intermediates

In a continuous effort to study DFT calculation,^{6,10b,16} we attempted DFT investigation of the fast unorthodox amidation process to determine the probable transition state and intermediates involved in the reaction. To the best of our knowledge only a limited number of DFT studies were devoted on metal-free λ^3 -hypervalent iodine mediated organic transformations.^{6,16,17} Herein, all calculations were carried out with the Gaussian 09 package of programs. The stationary points of the structures were optimized in the gaseous phase using the LSDA method and LANL2DZ and/or 6-31G basis sets. Vibration analyses were performed to check stable geometries of both the structures at ground and transition states. All possible transition states were calculated using QST3 model. We executed IRC transition states calculation for every individual steps for better understanding of the correlation between the reactant(s), transition state and the product(s). The energy profile of the amidation reaction is displayed in panel Figure 7 and the DFT optimized structures of the intermediates (**Int-I** to **Int-IV**) and the corresponding transition

states (**TS-II**) in Figure 8. Results of DFT calculation reveals that transformation of intermediate **II** to **IV** is very fast, which was observed in the ATR-Mid-IR spectroscopy. It is expected that $\text{PhI}(\text{OAc})_2$ transformed to transient $\text{PhI}(\text{OH})_2$ rapidly under the mild basic conditions. The highly reactive $\text{PhI}(\text{OH})_2$ is susceptible for dehydration process to build polymeric PhIO compound.^{5,10} Herein, under the mild reaction conditions the insitu-generated $\text{PhI}(\text{OH})_2$ rapidly formed an adduct with the electron rich triple bond of phenylacetylene (**Int-I**) and was considered as the zero energy in the energy profile diagram in the Figure 7. The insitu-generated hypervalent iodine $\text{PhI}(\text{OH})_2$ was added to the terminal of C-C triple bond *via* **TS-1** with addition of another molecule of $\text{PhI}(\text{OH})_2$ and simultaneous transfer of hydroxyl group to generate a stable **Int-II** with the energy barriers +1.141 and +0.082 kcal/mol. **Int-II** rapidly transformed into intermediate **Int-IV** in presence of the *n*-butylamine (**6a**). The successive energy barriers for the two steps towards formation of the product **9a** were very low (+0.03 kcal/mol). Thus DFT studies strongly supported formation of the desired amide **9a** from the imine intermediate (**Int-IV**) in a fast process, which passes through six-member cyclic transition state **TS-5**.

DFT-MIR spectroscopy

Inline ATR-Mid-IR spectroscopy is the most emerging technology to probe reaction mechanism. However, mechanistic study of a reaction using this modern technology is applicable only if the structures and FTIR spectra of the intermediates of the ongoing reaction are known in the literature. Thus, the emerging technology is not so helpful for a reaction going through unknown intermediates or forming new types of bonds. Another problem is the assignment of the FTIR frequencies of the different bonds,

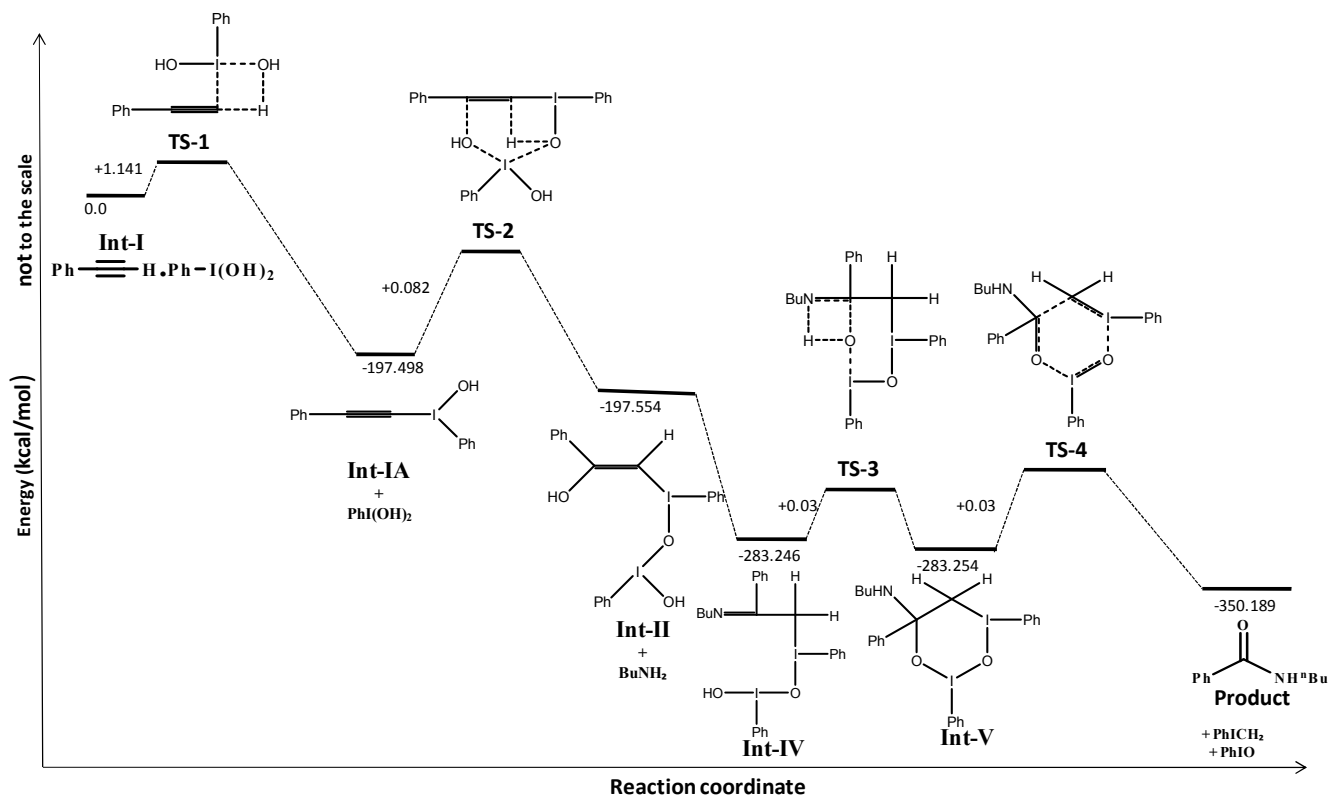


Figure 7. Important transition states and intermediates expected to be formed as predicted by DFT calculation (Gaussian 09)

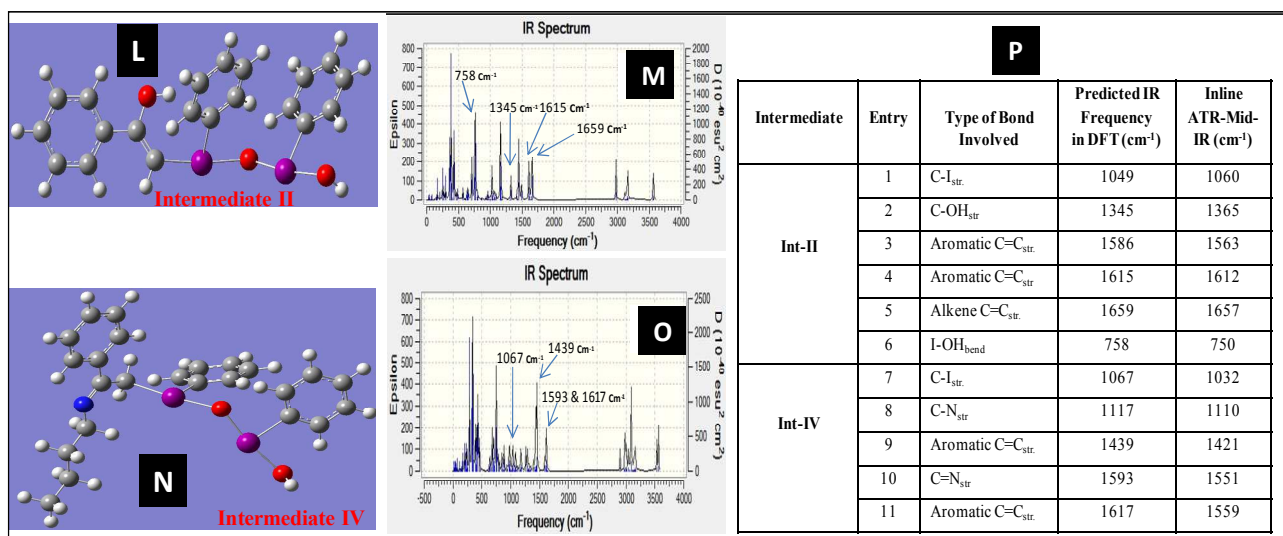


Figure 8. DFT optimized structures of intermediate **II** and **IV**, predicted and experimental IR peaks

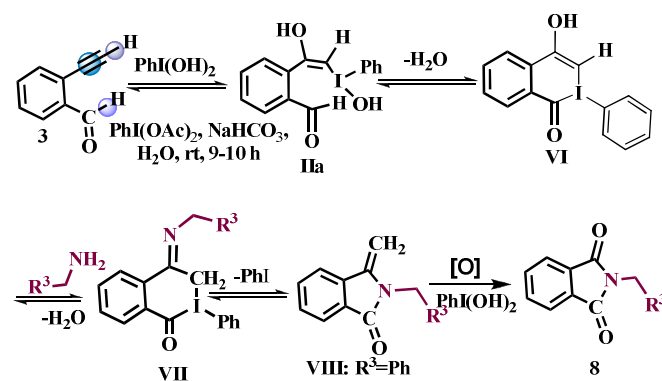
functionalities or groups of the unknown intermediates. For the first time we resolved it by watching their animation mode and correlating the corresponding DFT-IR peaks (panels G-K, Figure 5 and Figure 6). In our experiments the characteristic vibrational frequencies obtained from ATR-Mid-IR spectroscopy were comparable with the theoretical IR frequencies of the intermediates **Int-II** and **Int-IV** (panels L,N). The structure of the intermediate **Int-II** established convincingly through assignment of new bonds such as C-I (entry 1, panels P), two different hydroxyl groups (entries 2,6), aromatic and alkyne double bonds (entries 3-5). Similarly vibrational frequencies such as C-I, C-N, C=N and C=C (entries 7-11) from experimental and theoretical values suggested the structure of the intermediate **Int-IV** (panel N). Thus, we successfully determined the two important intermediates (**Int-II** and **Int-IV**, Figure 3) formed in the ongoing unorthodox amidation reaction and the possible reaction path by introducing a combination of theoretical DFT-IR and modern MIR-ATR technology. However, formation of the desired amide (**9a**, eq. iii, Scheme 2) is expected to have undergone through the cyclic transition state **TS-4** involving C-C cleavage of **Int-IV** (Figure 7). We could not find the corresponding DFT-IR peaks of the **Int-III** in the 3D-reaction surface (Figure 3) of the Mid-IR spectroscopy. It indicates that intermediate **Int-III** is a very unstable species, which immediately transformed into the relatively stable imine intermediate **Int-IV**, which subsequently transformed to the desired product **9a**. The low energy barriers (~ 1 kcal/mol) found for corresponding transition states (Figure 7) in DFT studies also strongly support this mechanistic path.

Validation through substrate-guided imidation

Formation of the important intermediate **II** (Figure 3 and Figure 7) bearing the insitu-generated active hypervalent iodine $\text{PhI}(\text{OH})_2$ was also verified by installation of an aldehyde group at the *ortho* position of phenylacetylene (**3**, eq. ii, Scheme 1), which produced imides (**9**). Herein, the possible enol intermediate **IIa** was generated through cleavage of C-C triple bond and subsequently nonmetallic intramolecular activation of the $\text{sp}^2\text{C-H}$ bond of aldehyde²⁷ was performed involving $\text{I}^{\text{III}}\text{-OH}$ at the close vicinity to generate cyclic intermediate **VI** (Scheme 3). It was smoothly transformed into corresponding cyclic imine **VII**, which on reductive expulsion of PhI

led construction of vinyl cyclic amide **VIII**. This intermediate was trapped ($\text{R}^3=\text{Ph}$) and fully characterized (ESI). Oxidative cleavage of olefins to ketone and/or aldehyde is a useful method in organic synthesis and performed *via* formation of diols or ozonides. Nicolaou and colleagues established the OsO_4 -mediated direct cleavage of alkene to ketone.²⁸ Herein, oxidative cleavage of C=C bond of **8** occurred smoothly under the metal-free benign reaction conditions using insitu-generated reactive $\text{PhI}(\text{OH})_2$ to afford cyclic imide **8**.

Scheme 3. Possible mechanistic path for imidation process



Conclusion

In contrast to the conventional metal catalyzed and/ thermal dehydrative amidation and imidation, we have demonstrated a general, simple and metal-free green strategy for synthesis of a wide range of amides, imides and their chiral analogues using water as a source of carbonyl oxygen and nontoxic reaction medium at ambient temperature. A new λ^3 -hypervalent iodine reagent $\text{PhI}(\text{OH})_2$ was generated insitu from inexpensive $\text{PhI}(\text{OAc})_2$ and aqueous NaHCO_3 for selective scissoring of a terminal triple bond and subsequent joining with water, amine and aldehyde to construct amides and imides through C=O and C-N coupling. Amidation occurred through coupling of amines to imines, which was confirmed using inline ATR-MIR and introducing theoretical DFT-IR spectroscopy. The DFT-MIR approach enabled to identify an

alkene-hypervalent iodine complex-adduct in the neutral water medium and generation of two successive intermediates of unknown structure under the basic conditions, and rapid reduction of the amine threshold with the enhancement of desired amide. We have found useful information regarding reaction-insight by NMR and labeling (^2H and ^{18}O) experiments. These synthetic and introduced mechanistic studies open up new prospects for establishing reaction pathway, hypervalent iodine chemistry for the nonmetallic activation of various bonds, developing innovative chemistry and robust synthetic strategies for valuable functionalized molecules, which are significantly important for chemical science and green industrial processes.

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Reactant cum solvent water: generation of transient λ^3 -hypervalent iodane, its reactivity, mechanism and broad application

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Abstract:

We have demonstrated a general, simple, benign and metal-free green strategy for synthesis of a wide range of amides, imides and their chiral analogues using water as a source of carbonyl oxygen and nontoxic reaction medium at ambient temperature. A combination of theoretical DFT and MIR technology and other controlled experiments were employed for understanding mechanism of an unorthodox amidation and imidation reactions with in situ generated labile $\text{PhI}(\text{OH})_2$ -bearing intermediates. It opens up a new avenue for studying hypervalent iodane mediated synthesis with water and understanding the reaction mechanism.

