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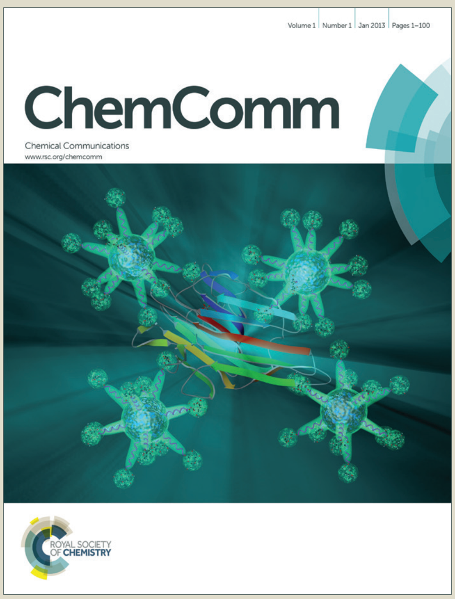

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ARTICLE TYPE

General base-tuned unorthodox synthesis of amides and ketoesters with water

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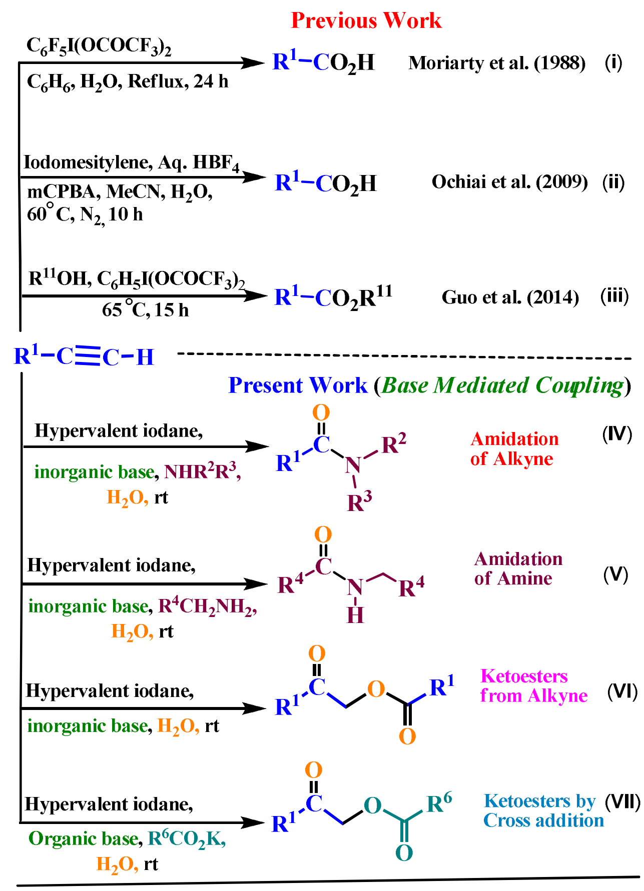
We discovered a highly reactive λ^3-hypervalent iodane species using inorganic/organic base for unorthodox synthesis of amides and ketoesters through grafting terminal alkynes. In contrast to the metal-catalyzed dehydrative approaches the insitu generated nonmetallic reagent efficiently created C-N/C-O and C=O bonds with amine/alkyne and water at rt.

Synthesis of amides and esters occurs naturally in plants and animals, and these compounds are essential for cellular function, construction of lipids for the cell membrane, many biological operations and directing groups in various metal-catalyzed reactions.[1] These fundamental processes are widely utilized in academia and industry to access valuable pharmaceuticals, agrochemicals, materials, natural products and synthetic compounds.[1-4] Development of a general synthetic strategy for R-CO-Nu compounds such as amides and esters remains a long standing challenge in chemical science, particularly if it is capable of addressing crucial issues such as operational simplicity, robustness, speed, high yield, metal-free benign conditions for broader substrate scope, diverse syntheses of valuable compounds, low cost and environmental safety. Conventional synthesis of amide and ester relies on dehydrative C-N/C-O coupling between activated carboxylic acid analogues and amine or alcohol under anhydrous, solid phase, metal-catalyzed and/or heating reaction conditions.[2a,b] In the last two decades, a few pioneering amidation reactions were developed using new precursors, such as the umpolung approach of 1,1-bromonitroalkanes,[3d] [Mn(2,6-Cl_2TPP)Cl]-mediated oxidative addition of amines to terminal carbon of alkynes,[3a] the nucleophilic carbene method of 2-haloaldehydes,[3b] Ru-complex mediated oxidative addition of alcohols and amines,[3c] decarboxylative amidation[3f] and the acid-activated silatropic switch strategy.[3e]

Complete cleavage of C-C terminal triple bond into functional group(s) is challenging and a limited number of approaches have been described in the literature.[5,6] In a continuous effort to develop new properties of λ^3-hypervalent iodanes[7,8] we wanted to screen inexpensive $PhI(OAc)_2$[8,9] for the nonmetallic cleavage of alkynes towards synthesis of amides and esters through coupling with amine/alkyne and water. However, only three nonmetallic approaches have been developed so far for cleavage cum functionalization of terminal alkynes: Moriarty and colleagues reported fluorine-protected hypervalent iodane $C_6F_5I(OCOCF_3)_2$ in benzene (six examples),[6a] Ochiai *et al*. reported the process of heating iodomesitylene (10 mol %), m-CPBA, HBF_4 (2.2 equiv,



Scheme 1. Cleavage of terminal alkynes with λ^3-hypervalent iodane

48% aq) in acetonitrile-H_2O (9:1) (five examples)[6b] to afford the corresponding carboxylic acids (eq. i, ii, Scheme 1); and recently Guo and co-workers reported an interesting approach (eq. iii) to synthesize ester using fluorine-protected λ^3-hypervalent iodane and alcohol under the heating conditions.[6c]

We envisioned the manipulation of the two loosely bound acetoxy groups of $PhI(OAc)_2$ leading to an enhancement of its reactivity towards organic precursors. This manipulation also enables organic transformation in water as the environmentally benign reaction medium as well as the reactant. $PhI(OAc)_2$ was used as a Lewis acid-like oxidant for the activation of the terminal alkyne phenyl acetylene (R^1=Ph, eq. IV, Scheme 1) for the amidation reaction with n-butylamine (R^2=^{n}Bu, R^3=H,) and water. Gratifyingly, simultaneous coupling of C-N and C=O bonds to construct secondary amide functionality at the nonterminal carbon of the alkyne was achieved on addition of a mild base, $NaHCO_3$ (2.1 mol) into the aqueous suspension of

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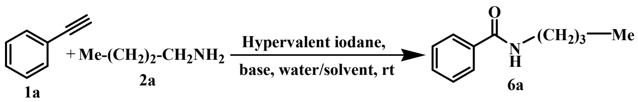
†Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, NMR spectra and CIF file. See DOI: 10.1039/c0xx00000x

Table 1. Development and optimization of the amidation reaction

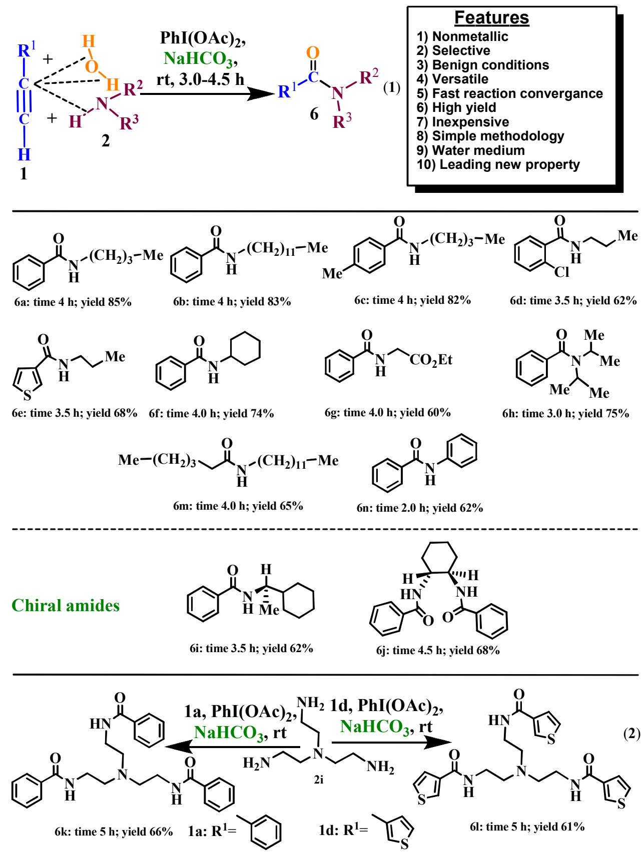


Entry	Hypervalet iodane[a]	Solvent[b]	Base[c]	Time (h)	6a,Yield (%)[d]
1	**$PhI(OAc)_2$**	**H_2O**	**$NaHCO_3$**	**4**	**85**
2	$PhI(OAc)_2$	H_2O	Na_2CO_3	12	80
3	$PhI(OAc)_2$	H_2O	NaOH	4	83
4	$PhI(OAc)_2$	H_2O	K_2CO_3	12	82
5	$PhI(OAc)_2$	H_2O	KOH	4	85
6	PhIO	H_2O	$NaHCO_3$	24	25
7	$PhI(OAc)_2$	H_2O	-	48	nd[e]
8	PhIO	H_2O	-	48	nd
9	$PhI(OAc)_2$	CH_2Cl_2	$NaHCO_3$	48	nd
10	$PhI(OAc)_2$	MeCN	Na_2CO_3	48	nd
11	$PhI(OAc)_2$	THF	$NaHCO_3$	48	nd
12	$PhI(OAc)_2$	$PhCH_3$	Na_2CO_3	48	nd
13	$PhI(OAc)_2$	MeOH	Na_2CO_3	48	nd

[a]2 mmol. [b]5 mL. [c]2.1 mmol. [d]Yield of the isolated product after column chromatography. [e]Not detected

phenyl acetylene and $PhI(OAc)_2$ at ambient temperature, and the reaction was complete within 4 h (entry 1, Table 1) affording the n-butyl benzamide (**6a**, Scheme 2) in 85% yield. For optimization of the reaction other inorganic bases such as Na_2CO_3, NaOH, K_2CO_3 and KOH were employed (entries 2-5, Table 1), and comparable yields (80, 83, 82 and 85% respectively) were obtained. During reaction optimization, we also observed that the reaction time was reduced to just 1 h if $PhI(OAc)_2$ and alkyne (**1a**) were stirred together for a few minutes and treated with aqueous $NaHCO_3$ before the addition of n-butyl amine (**2a**) instead of adding all reactants simultaneously. The physical appearance, texture and colour of the reaction mixture changed over time. It transformed into a fluorescent gel-like material, which was ready for coupling with amine (**2**) in 1 h. Upon addition of precursor n-butyl amine (**2a**), the amidation reaction proceeded quickly as we observed transformation of the gel-like material to an oily product that was deposited in the reaction container. The catalytic amount of $NaHCO_3$ was instrumental for this nonmetallic benign process. Two equivalents of $NaHCO_3$ were spared to neutralize the insitu-generated acetic acid from $PhI(OAc)_2$. To overcome the problem of using excess amounts of $NaHCO_3$, another λ^3-hypervalent iodane PhIO[13] was employed (entry 6, Table 1); however, the yield was drastically reduced (25%). Herein, the base played the pivotal role because the reaction was completely blocked in absence of $NaHCO_3$ (entries, 7,8). As expected, the reaction was unsuccessful on replacing the water medium with commonly-used volatile toxic organic solvents such as CH_2Cl_2, MeCN, THF, toluene and MeOH (entries 9-13).

The tolerance of various functionalities were successfully examined for this new methodology (eq. 1, Scheme 2) through synthesis of a wide range of compounds bearing both unsubstituted (**6a**,**b**) and substituted (**6c**,**d**) aromatic rings, heterocycles (**6e**,**l**), secondary (**6a-f**), activated secondary (**6g**) and tertiary amides (**6h**). The benign strategy was successfully used to transform cyclic amine (**6f**), substituted aromatic rings (**6c**,**d**), heterocycles (**6e**,**l**), secondary (**6a-f**), activated secondary (**6g**) and tertiary amides (**6h**). The benign strategy was successfully used to transform chiral monoamine (**2g**) and diamine (**2h**) into the corresponding optically pure amides (**6i**,**j**) without formation of racemization

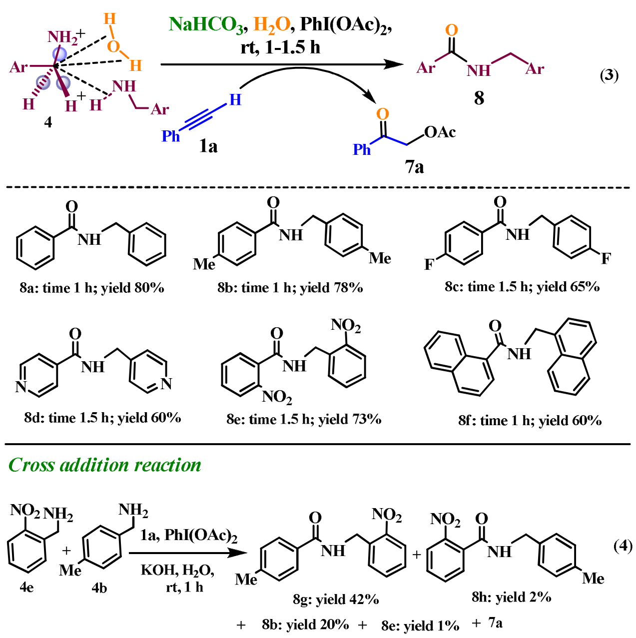


Scheme 2. Synthesis of amides with $NaHCO_3$-tuned-hypervalent iodane

products, which was confirmed by the chiral HPLC technique (SI). The unorthodox benign amidation strategy for functionalized amides (**6a-l**) was rapid (2.0-5.0 h) and high yielding (60-85%). However moderate yields (60-65%) were obtained for the amides **6g**, **6m** and **6n** on use of activated aliphatic amine, aromatic amine and aliphatic alkyne respectively.

To explore the scope of the operationally simple strategy, we attempted the direct synthesis of tripodal ligands which were recently found to have tremendous application as chemosensors for the detection and estimation of unsafe metal and nonmetallic ions.[10] Interesting results were obtained using the tripodal ligand tris(aminoethyl)amine (**2i**, eq. 2, Scheme 2), in which all three amine groups were simultaneously converted into their respective benzamide and thiophene amide analogues (**6k**,**l**) within 5 h. Herein we have introduced creative hypervalent iodane involving an unorthodox synthetic approach using water as a source of carbonyl oxygen, an amine for C-N bond formation and a carboxylate moiety for direct O-C couplings with the precursor alkyne in nontoxic ('green')[11] aqueous media at ambient temperature as the C-C triple bond can now be selectively grafted to various molecules. Terminal alkynes are inexpensive precursors that can be synthesized using calcium carbide and alkyl halide (R-X) or aldehyde using a simple green approach.[12] The mechanistic inside of the amidation process involving the active λ^3-hypervalent iodane reagent $PhI(OH)_2$ is under progress with an innovative DFT and Mid-IR techniques, which will be reported in due courses.

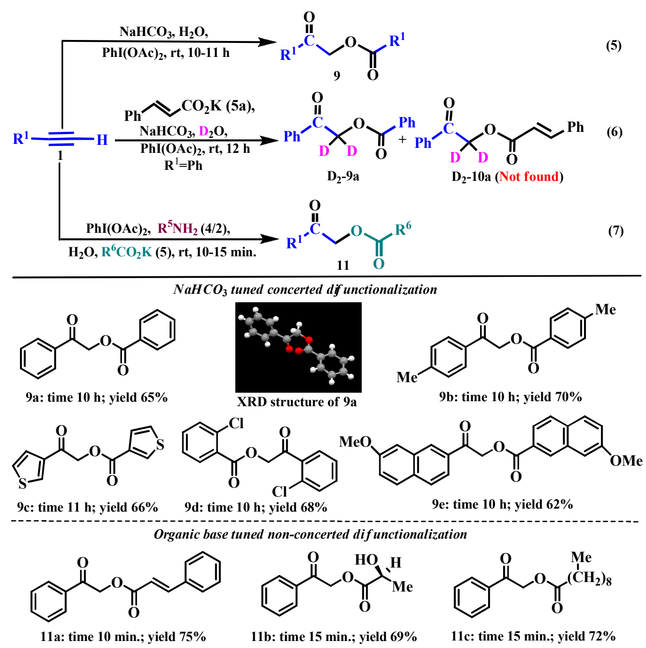
The activation of C-H and C-C triple bonds, and their transformation into carbon-heteroatom bonds was a revolutionary achievement in modern chemical science.[13,14] In comparison to the great success using metal-activated transformations,[13] only a few nonmetallic bond-activated functionalization processes have been achieved.[14] Activation of sp^{3}C-H and sp^{3}C-N bonds of a primary amine and its selective transformation have tremendous potential in organic synthesis. However, the high reactivity of primary amine functionality towards most reagents is the main obstacle to execute the reaction.[13e] To explore the reactivity of the $NaHCO_3$-activated-λ^3-hypervalent iodane species toward both the benzylic sp^{3}C-H and amine sp^{3}C-N bonds of a primary amine, a mixture of phenylacetylene (**1a**) and benzyl amine (**4a**) was treated with $PhI(OAc)_2$ in aqueous sodium bicarbonate solution at ambient temperature to obtain **8a** (eq. 3, Scheme 3). The benzylic sp^{3}C-H and sp^{3}C-N bonds were activated, and amidation took place by coupling between two molecules of **4a**. It is expected that the insitu-generated λ^3-hypervalent iodane reagent selectively activate both the benzylic sp^{3}C-H bonds and the sp^{3}C-N bond of amines (**4**) and simultaneously allowed the creation of C-N and C=O bonds by reacting with amine and water, respectively, leading to the construction of amides (**8**).



Scheme 3. Amidation through C-N and C-H cleavage

Direct involvement of the terminal triple bond was verified by performing a reaction without phenylacetylene, in which case the amide formation reaction became slow (24 h) and low yielding (30%). Herein, the exact role of phenylacetylene (**1a**) is unknown to us, which eventually transformed to α-acetoxyacetophenone (**7a**). The reaction is rapid enough (1.0-1.5 h) for methyl-, nitro-, fluoro-substituted benzylamines to afford the secondary amide **8a-f** with good yield (60-80%). During cross over experiment (eq. 4, Scheme 3) with activated 4-methylbenzylamine and deactivated 2-nitrobenzylamine, all four possible amides [**8g** (42%), **8b** (20%), **8h** (2%) and **8e** (1%)] were isolated after purification by column chromatography. The result revealed that a benzylamine derivative bearing activated aromatic ring is more favourable for benzylic sp^{3}C-H activation and that an amine bearing an electron-deficient group is preferred for C-N coupling.

α-Oxycarbonyl-β-ketone is an important class of compounds that recently exhibited excellent bioactivity against prostate cancer.[4a] Surprisingly only two approaches were found in the literature for synthesis of complex α-oxycarbonyl-β-ketones which were based on lactonization of keto acids[2d] and gold-catalyzed coupling of carboxylic acid.[4b] However, transfer of the acetate group from $PhI(OAc)_2$ was investigated to afford simple α-ketoacetates.[15] The limited number of reported methodology for complex α-oxycarbonyl-β-ketones led us to develop a new efficient approach for their synthesis utilizing the insitu-generated transient λ^3-hypervalent iodane. To our delight, it was found to be a powerful reagent under the alkaline condition undergoing cleavage of the terminal C≡C bond. On treatment with alkynes (**1**) with the insitu-generated λ^3-hypervalent iodane reagent in aqueous $NaHCO_3$, α-oxycarbonyl-β-ketones (**9a-e**, eq. 5, Scheme 4) were obtained in 10-11 h with good yield (62-70%). The reaction is expected to pass through a concerted pathway because in the presence of potassium cinnamate (excess) in D_2O the corresponding cross over ester (**D$_2$-10a**, eq. 6) was not found. The deuterium incorporated **D$_2$-9a** was furnished as the sole product. Structure of **9a** was confirmed through XRD analyses.[16]



Scheme 4. Inorganic and organic base-tuned synthesis of ketoesters

To investigate the reaction course with organic base, we added excess (4 mmol) potassium *trans*-cinnamate (**5a**), optically pure lactate (**5b**) and decanoate (**5c**) in the reaction mixture containing phenylacetylene (**1a**) and benzylamine (**4a**, eq. 7). Surprisingly the organic base played an important role, allowing the formation of the corresponding α-oxycarbonyl-β-ketones (**11a-c**). Significantly, a non-concerted reaction path with an excellent reaction rate (10-15 min.) was observed by exchanging the inorganic base with an organic base (eq. 7).

In conclusion, we have demonstrated base-tuned preparation of a new λ^3-hypervalent iodane species from inexpensive $PhI(OAc)_2$ and used for selective cleavage of spC-H, sp^{2}C-H, sp^{3}C-H, sp^{3}C-N and triple bonds under metal-free benign reaction conditions. The valuable amides and ketoesters were directly synthesized in the unprecedented general unorthodox approach through construction of C=O and C-N/C-O bonds with amines/alkynes and water.

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