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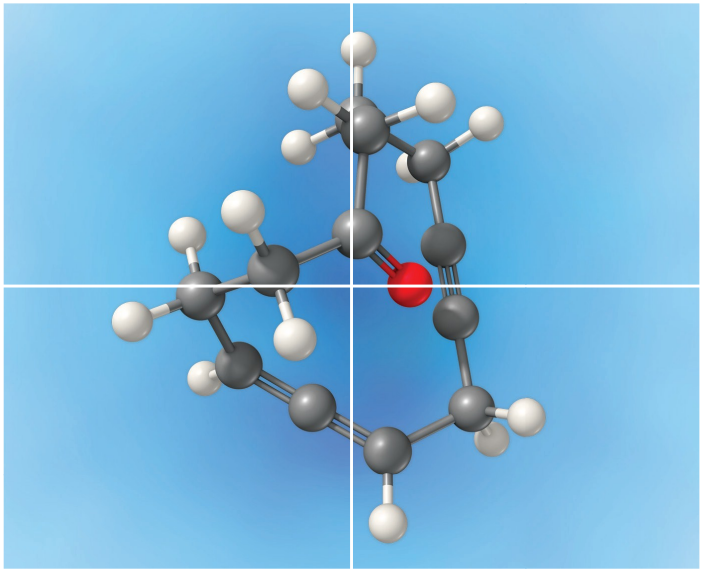

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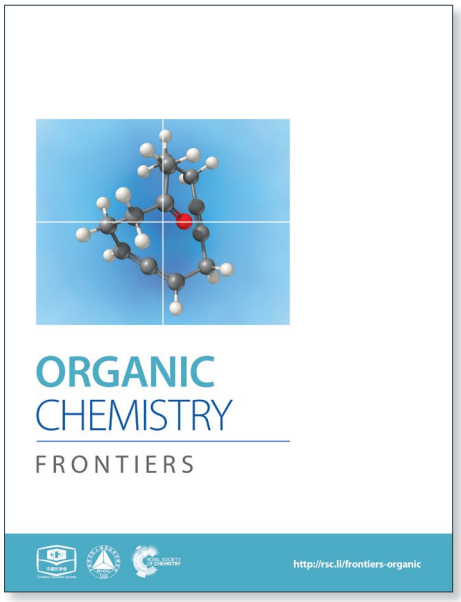

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Journal Name

ARTICLE

Triphenylphosphine Promoted Regio and Stereoselective α-Halogenation of Ynamides

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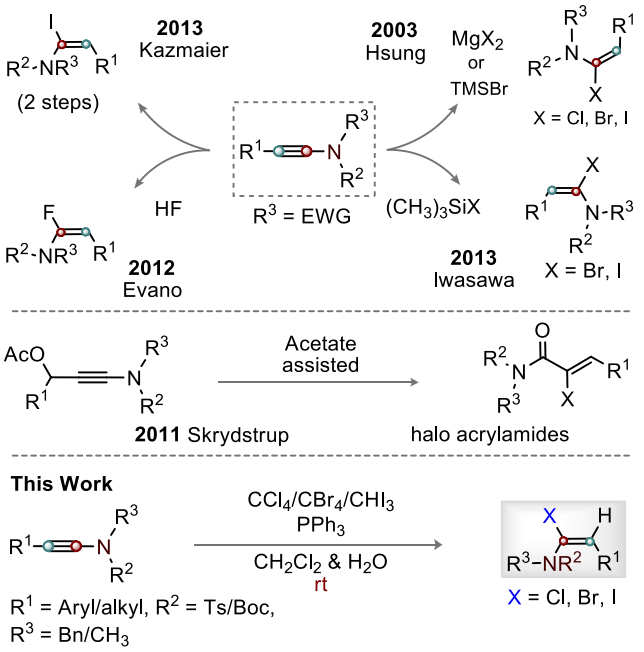
In this study, we demonstrate metal free regio- and stereoselective α-halogenation (Cl, Br and I) of ynamides. Halogenation of ynamides in the presence of PPh_3 and CCl_4, CBr_4 or CHI_3 in moist CH_2Cl_2 at room temperature provides good-to-excellent yields of a wide varieties of stable (*E*)-α-haloenamides; thus, the reaction has a broad scope. Chlorination of ynamide at room temperature is particularly notable. The sequential one pot α–iodination and alkynylation of ynamides provides synthetically useful amidoenynes. The chlorination of 3-acetoxy ynamide delivers 3-acetoxy-α-chloro enamide without the migratory-assistance of acetoxy moiety.

Introduction

Enamides are versatile motifs, and are widely present in various natural products and complex molecular entities.[1] In general, enamides are more stable than enamines; thus, enamide scaffolds are synthetically viable and broadly useful.[2] Notably, delocalization of the nitrogen lone-pair readily assist the functionalization of the β-position of enamides.[3] By contrast, modification of the α-position of enamides is challenging. α-Haloenamides are particularly notable in this context because functionalization of their α- and β-carbons is easy.[4] The β-carbon of α-haloenamides is nucleophilic and is therefore useful for stereoselective C–C/X bond formation; while their α–halo group can effectively be replaced by organometallic reagents through transition-metal-catalyzed cross-coupling reactions.[5]

Hsung et al. first reported the stereoselective synthesis of α-haloenamides through the hydrohalogenation of ynamides with MgX_2 and TMSBr in moist CH_2Cl_2; ynamide chlorination was possible at an elevated temperature (Scheme 1).[6] The Kazmaier group showed Mo-catalyzed hydrostannylation of ynamide followed by Sn-iodine exchange to afford α-iodoenamide (Scheme 1).[7] The Skrydstrup group exhibited a novel method for the synthesis of α-iodo/bromo acrylamides/acrylimides through NIS/NBS promoted reaction on 3-acetoxy ynamide; while the identical reaction with NCS displayed poor conversion (Scheme 1).[8] Stereoselective hydroflourination of ynamides was described by Evano and co-workers (Scheme 1).[9] Iwasawa et al. demonstrated the regio- and stereospecific synthesis of (*E*)–α–haloenamide from ynamides in the presence of halotrimethylsilane and H_2O (Scheme 1).[10] Thus, the synthesis of α–haloenamides from ynamides involves step-wise conversion from Sn-species to iodo, regioselective addition of HX to ynamide, control of the double-bond geometry, or harsh conditions. Thus, the efficient introduction of common halo groups (Cl, Br or I) at the α-position of ynamides are considerably challenging. Therefore, an operationally simple and competent protocol for the regio- and stereoselective α–halogenation of ynamides is required. With our ongoing research on ynamides,[11] we expect to trap halophosphonium salts generated from Ph_3P and CCl_4, CBr_4 or CHI_3 with the keteniminium ion species,



Scheme 1 Synthetic Strategies for α-Haloenamide.

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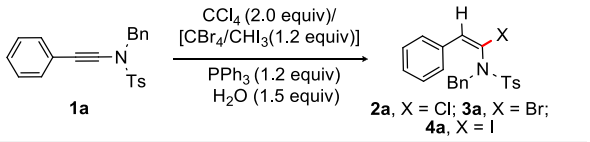
[c] This manuscript is dedicated to Dr. J. S. Yadav, IICT-Hyderabad, INDIA for his out-standing contribution to Organic Chemistry and his 65th Birthday.
[d] †Electronic supplementary information (ESI) available: Copies of the ^1H NMR, ^{13}C NMR and HRMS data for all products. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of the Reaction Conditions[a,b]



entry	reagent	solvent	temp (°C)	time (h)	yield (%)[b] 2a/3a/4a
1	PPh_3	CCl_4	60	16	50
2	PPh_3	CCl_4	24	24	NR
3	PPh_3	CCl_4	80	12	68
4	PPh_3	CCl_4	80	24	98
5	–	CCl_4	80	24	NR
6	$P(Et)_3$	CCl_4	80	24	50
7	$P(Me)_3$	CCl_4	80	24	25
8	$P(^iPrO)_3$	CCl_4	80	24	10
9	$P(EtO)_3$	CCl_4	80	24	45
10	**PPh_3/CCl_4**	**CH_2Cl_2**	**24**	**02**	**98**
11	PPh_3/$SOCl_2$	CH_2Cl_2	**24**	02	86
12[c]	PPh_3/CCl_4	CH_2Cl_2	**24**	02	84
13[d]	PPh_3/CCl_4	CH_2Cl_2	**24**	02	26
14[e]	PPh_3/CCl_4	CH_2Cl_2	**24**	02	48
15[f]	PPh_3/CCl_4	CH_2Cl_2	**24**	02	59
16[g]	PPh_3/CCl_4	CH_2Cl_2	**24**	02	68
17	PPh_3/$CHCl_3$	CH_2Cl_2	**24**	04	NR
18[h]	**PPh_3/CBr_4**	**CH_2Cl_2**	**24**	**05**	**94**
19[i]	**PPh_3/CHI_3**	**CH_2Cl_2**	**24**	**05**	**96**
20[k]	**PPh_3/ICl**	**CH_2Cl_2**	**24**	**02**	**60**
21[l]	**PPh_3/I_2**	**CH_2Cl_2**	**24**	**02**	**83**

[a]Reactions were carried out using **1** (0.5 mmol), CCl_4 (2.0 equiv), PPh_3 (1.2 equiv) in solvent (2.0 mL) at rt. [b]Isolated yield. [c]CCl_4 (1.2 equiv) was used. [d]absence of water, [e]0.5 equiv of H_2O, [f]1.0 equiv of H_2O, [g]1.5 equiv of H_2O, [h]bromination of **1a,** [i]iodination of **1a**, [k]formation of **2a** (60%) along with 40% mono hydration, [l]formation of **4a** [E/Z(1:1)]. NR = no reaction.

the reactive resonance hybrid unit of ynamides,[12] and finally produce stereoselctive (*E*)–α–haloenamides (Scheme 1).

We herein report a general, reliable, efficient, and gram-scale synthetic approach for the convergent and stereoselective synthesis of geometrically defined α–halo (Cl,/Br/I)-enamides from ynamides in the presence of the metal-free reagents [Ph_3P and CCl_4/CBr_4/CHI_3] in CH_2Cl_2 and H_2O at rt; the halo moiety is successfully used for the synthesis of diverse molecular entities.

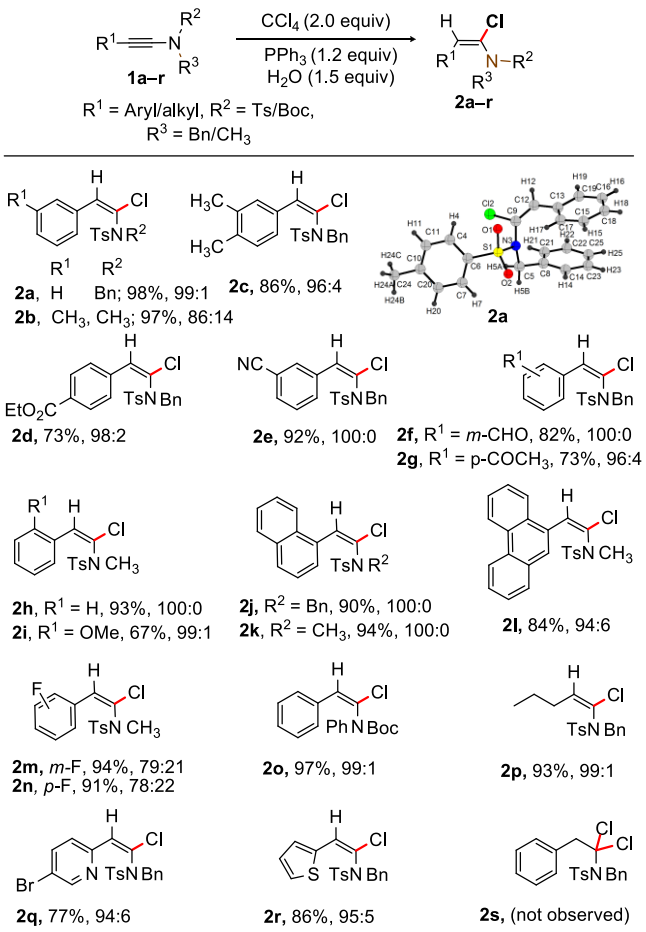
Results and discussion

Investigation was initiated examining α–chlorination of **1a** (Table 1). Thus, mixture of **1a** (0.5 mmol), PPh_3 (1.2 equiv), CCl_4 (2.0 equiv) and H_2O (1.5 equiv) was heated at 60 °C for 16 h; gratifyingly the desired (*E*)-α-chloroenamide **2a** was isolated in 50% yield with the incomplete consumption of **1a** (entry 1). Disappointingly, the reaction did not proceed at rt; the inadequate solubility of PPh_3 in CCl_4 at rt is presumably responsible for the poor outcome, an established fact reported by R. Apple (entry 2).[13] Good to excellent yield of **2a** was obtained, when the reaction conducted at 80 °C (entries 3 and 4). The structure of **2a** was confirmed by X-ray crystallographic analysis (Scheme 2).[22] In the absence of PPh_3, there was no consumption of starting material (entry 5). Other phosphine reagents such as trialkylphosphine and trialkylphosphite provided moderate yield of **2a** (entries 6–9). Apparently the more nucleophilic trialkylphosphines should work better than triarylphosphines; however, the requirement of H_2O in this transformation makes the pyrophoric trialkylphosphines ineffective, resulting poor reaction outcome (entries 6 and 7). Whereas the corresponding phosphonium salts of the phosphite esters are unstable and are readily transformed to dialkyl phosphonate esters, hampering the reaction productivity (entries 8 and 9).[14] To our surprise, reaction of **1a** with PPh_3 and CCl_4 in CH_2Cl_2 (2.0 mL) was found efficient at rt, producing **2a** in 98% yield in 2 h with excellent stereo-control (entry 10). Presumably, solubility of PPh_3 in CH_2Cl_2 enables faster interaction with CCl_4 at rt to offer better results.[15] *Thus, stereoselective α-chlorination of ynamide at rt is truly notable*. Despite the toxicity of CCl_4, the current method requires only 2.0 equiv of CCl_4 rather than solvent. The formation of $[Ph_3PCl]^+$ species from PPh_3 and $SOCl_2$ is known.[16] Accordingly, reaction of **1a** with [PPh_3 and $SOCl_2$] was conducted at rt; pleasingly, the desired α–chloroenamide **2a** was obtained in 86% yield (entry 11). The use of CCl_4 (1.2 equiv) led to the decrease of product yield (entry 12). Furthermore, the reaction in the absence of water produced **2a** in 26% yield (entry 13). Use of different amount of H_2O in the reaction provided 48–68 % of **2a** in 2 h (entries 14–16). The results from entries 12–16 suggest that H_2O plays critical role in this transformation. We believe that the attack of H_2O to the phosphonium species terminates the reaction and liberates $PPh_3(O)$ by-product, which eventually controls the efficiency of the reaction. The isolation of $PPh_3(O)$ further supports the need of H_2O in this study. The reaction of **1a** with PPh_3 and $CHCl_3$ in CH_2Cl_2 did not proceed (entry 17, Table 1). The use of other solvents such as chloroform, dioxane and acetone instead of CH_2Cl_2 provided inferior yields of **2a**.

Next, α–bromination and iodination of ynamides were investigated (Table 1). As expected, reaction of **1a** with a mixture of PPh_3, CBr_4 and H_2O (1.5 equiv) in CH_2Cl_2 at rt led to α-bromoenamide **3a** in 94% yield (entry 18). To accomplish iodination of ynamides, **1a** was exposed to PPh_3, iodoform (CHI_3) and H_2O (1.5 equiv) in CH_2Cl_2; gratifyingly, 96% of the desired α-iodoenamide **4a** was obtained at rt (entry 19). The reaction of **1a** with PPh_3, ICl, and H_2O (1.5 equiv) in CH_2Cl_2 provided a mixture of chlorination product **2a** along with the monohydration compound (60:40) (entry 20). In contrast, 83% of iodination product **4a** (*E/Z* = 1:1) was obtained, when the reaction was performed with PPh_3 and I_2 (entry 21).

With the optimized conditions shown in entry 10, Table 1 in hand, the scope of α-chlorination of various ynamides was explored; the results are summarized in Scheme 2. Wide ranges of N-(Ts/Boc)-benzyl/methyl-ynamides having aryl, heteroaryl and alkyl substitution at the alkyne terminus were subjected to the optimized conditions (entry 10, Table 1); the corresponding (*E*)-α-chloroenamides **2a–r** were obtained in good yields. The electro-neutral/-rich aryl-moiety bearing ynamides provided *E*-α-chloroenamides **2a**–**c** in excellent yields. Easily modifiable ester, –CN, formyl, and –COMe functional groups did not show adverse effect, affording **2d**–**g** (73–92%) yield. The N-methyl protected ynamides were no

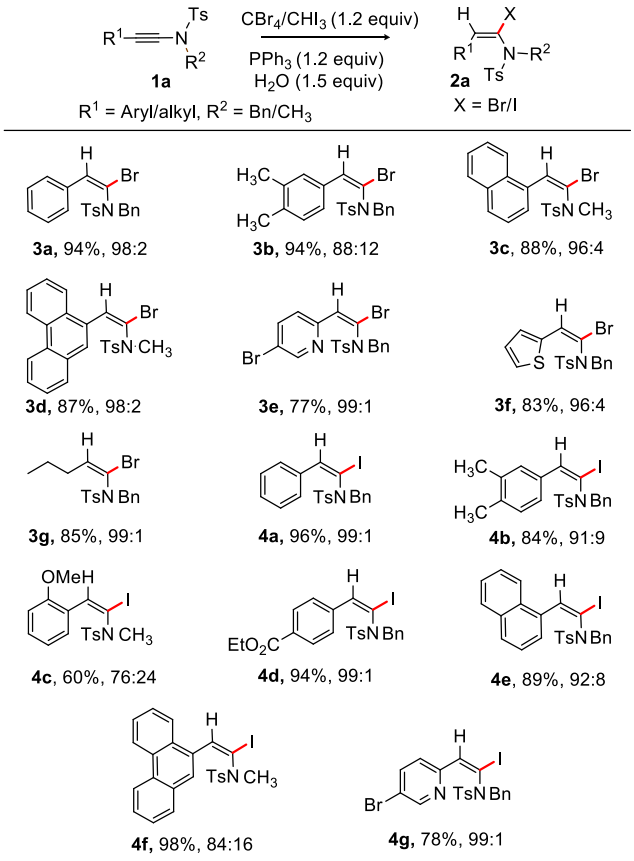
exception [**2h** (93%) and **2i** (67%)]. The naphthalene and phenanthrene bearing α-chloroenamides **2j**–**l** were readily synthesized. The fluoro group in ynamide did not affect the reaction outcome, providing **2m** [*E*/*Z* = 79:21] and **2n** [*E*/*Z* = 78:22] in 94% and 91% yield, respectively. The labile and easily removable N-Boc group was survived, affording 97% of **2o**. The alkyl-bearing (*E*)-α-chloroenamide **2p** (93%) was smoothly accessed. The pyridyl, and thiophenyl bearing ynamides were effectively reacted to provide **2q** and **2r** in good yields.



Scheme 2 α–Chlorination of Ynamides[a,b]: [a]Reactions were carried out using **1** (0.5 mmol), CCl_4 (1.0 mmol), PPh_3 (0.6 mmol) in CH_2Cl_2 (2.0 mL) and H_2O (0.75 mmol) at rt for 2 h; stereoisomers are mentioned in *E*/*Z* ratio (determined by 1H NMR). [b]Isolated yield.

The β-position of α-chloroenamide is generally nucleophilic; the formation of α,α'-gem-dichloroamide product is therefore anticipated from α-chloroenamide under the optimized conditions. To further assess the reaction feasibility of α-chloroenamide, compound **2a** was subjected to excess amount of Ph_3P (2.5 equiv) and CCl_4 (4.0 equiv) in CH_2Cl_2 at rt. Disappointingly, we did not observe the expected gem-dichloroamide product **2s** (Scheme 2). We therefore believe that the α-position of ynamide **1a** is more susceptible to chlorination with $[Ph_3PCl]^+$ than the enamide moiety in **2a**.

Next, α-bromination of ynamide **1** under the optimized conditions (entry 18, Table 1) was examined at rt. The reaction proved to be general and broad; the results are depicted in Scheme 3. The phenyl substituted α-bromoenamide **3a** (94%) was obtained with high selectivity; while **3b** (*E*/*Z* = 88:12) was isolated in 94% yield. The 1-naphthyl bearing N-methyl protected bromoenamide **3c** was produced in good yield. Phenanthrene substituted **3d** (*E*/*Z* = 98:2) was formed in 87% yield. The heteroaryls such as 5-bromopyridinyl and thiophenyl bearing ynamides were compatible [**3e** (77%) and **3f** (83%)]. The alkyl group bearing ynamide was not exception, providing 85% of **3g**.



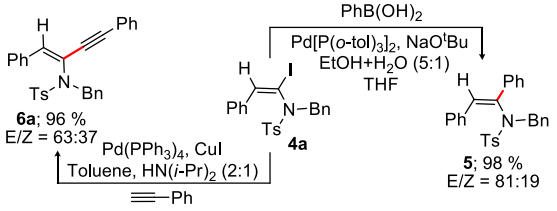
Scheme 3 α–Bromo and α–Iodination of Ynamides[a,b]: [a]Reactions were carried out using 1 (0.5 mmol), CBr_4/CHI_3 (0.6 mmol), PPh_3 (0.6 mmol) in CH_2Cl_2 (2.0 mL) and H_2O (0.75 mmol) at rt, 5 h; stereoisomers are mentioned in *E*/*Z* ratio (determine by 1H NMR). [b]Isolated yield.

We next tested the α-iodination of ynamide under the conditions shown in entry 19, Table 1. The ynamide having electron-neutral and electron-rich aryl moieties on alkyne terminus was reacted efficiently to deliver **4a** and **4b** with high selectivity; whereas the *o*-substituted aryl ynamide yielded **4c** [*E*/*Z* = 76:24] with moderate selectivity. The exact reason for the moderate selectivity is unknown; however, we believe the participation of *o*-OMe group in the reaction intermediate and the size of iodine plays crucial in determining the observed selectivity. Iodination of ynamide having the easily modifiable electron withdrawing ester group on aryl ring provided **4d** (94%). The naphthalene and phenanthrene bearing substrate did not affect reaction efficiency affording **4e** and **4f** in fruitful yields. Pleasingly, pyridyl bearing ynamide effectively

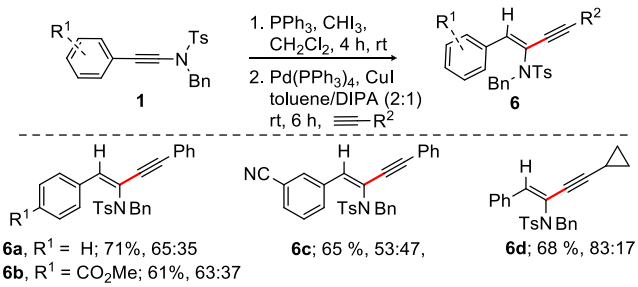
participated in the iodination process, constructing **4g** (78%) in excellent selectivity (Scheme 3). The current method provided moderate to excellent E/Z selectivity of α-iodo/bromo-enamides, while the Iwasawa protocol exclusively delivered the corresponding E-α-Br/I-enamides.

We next investigated to explore the synthetic potential of α-haloenamides. The iodo group of α-iodoenamide **4a** was successfully utilized for the Suzuki and Sonogashira reactions to provide non-separable mixture of tri-substituted enamides **5** (98%, *E/Z* = 81:19) and **6a** (96%, *E/Z* = 63:37), respectively (Scheme 4).[17, 18]

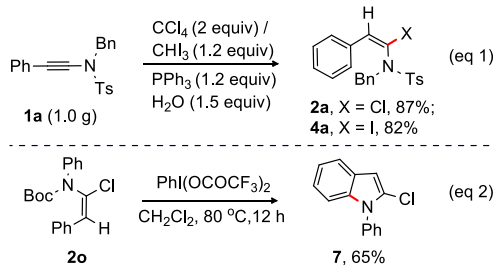
Regioselective alkynylation of ynamide (alkyne–ynamide cross coupling) readily constructs amidoenynes, the intermediates



Scheme 4 Synthetic Manipulation



Scheme 5 One Pot Sequential Iodination and Alkynylation of Ynamides



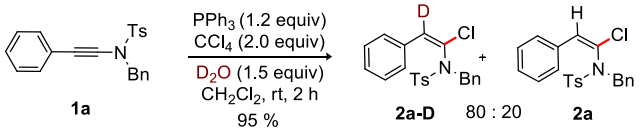
Scheme 6 Gram Scale Preparation & Synthesis of Indole

widely used for the fabrication of complex molecular entities. The facile reactivity of α-iodoenamide to Sonogashira reactions shown in Scheme 4 inspired us to survey one pot α-iodination and alkynylation on ynamide **1**. Gratifyingly, α-iodination of **1** under the optimized conditions followed by Sonogashira reaction with a range of alkynes readily produced synthetically valuable non-separable *E/Z* stereoisomers of amidoenynes **6a–d** in overall good yields in a single-pot (Scheme 5).[19]

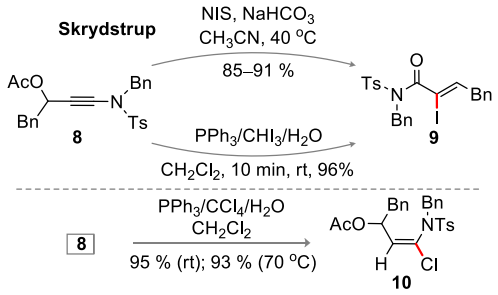
Finally, chlorination and iodination of ynamide **1a** in gram scale were successfully tested under the optimized conditions at rt. Pleasingly, the desired products **2a** (959 mg) and **4a** (1.1 g) were isolated in 87% and 82% yield, respectively from 1.0 g of ynamide **1a** (eq 1, Scheme 6). Interestingly, 2-chloro-N-phenyl indole **7** was readily accessed from **2o** under the oxidative conditions [$PhI(OCOCF_3)_2$ at 80 °C] (eq 2, Scheme 6).[20] Deprotection of N-Boc followed by intramolecular oxidative coupling between NH and o–C–H of alkenyl-phenyl moiety allowed the formation of **7** from **2o**.[20]

To examine the role of H_2O in the halogenation of ynamide, a control experiment reacting **1a** with PPh_3, CCl_4 and D_2O in CH_2Cl_2 was conducted at rt. Pleasingly, product **2a-D** (80%) with a D-incorporation at the β-carbon of **1a** was isolated; this suggests the occurrence of protonation in the final step of the reaction (Scheme 7).

The base mediated iodination of 3-acetoxy ynamide **8** produced *Z*-α-iodoacrylamides **9** at 40 °C, an elegant



Scheme 7 Reaction in Deuterium Oxide



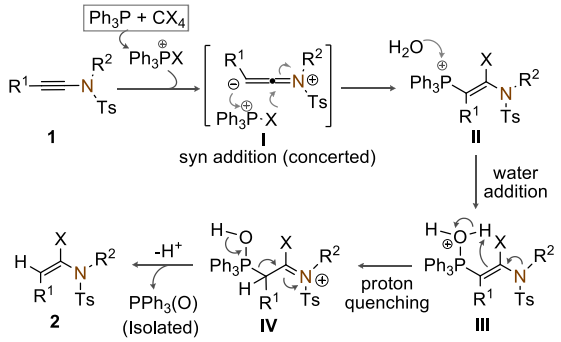
Scheme 8 Halogenation of 3-Acetoxy Ynamide

observation disclosed from Skrydstrup group; this reaction proceeds through 1,3-acetate shift (Scheme 8).[8] Not surprisingly, compound **8** was efficiently converted to **9** under the optimized iodination conditions (entry 19, Table 1) at rt within 10 min (Scheme 8). Unexpectedly, chlorination of **8** under the optimized conditions (entry 10, Table 1) exclusively delivered 3-acetoxy-α-chloro enamide **10** in excellent yield, when the reaction independently conducted at rt or 70 °C; the formation of corresponding α–chloroacrylamide was not detected (Scheme 8).[8] Thus, two distinct products **9** and **10** can independently be accessed from **8** under different conditions.

To validate the probable path and the role of PPh_3 in the reaction, we have performed a series of ^{31}P NMR measurements. To begin with, ^{31}P NMR spectrum of a crude mixture containing $PPh_3/CHI_3/CH_2Cl_2$ and H_2O in the absence of ynamide was recorded in a regular interval. An instant shift of PPh_3 in the ^{31}P NMR from –6.30 ppm to –8.41 ppm was observed; the respective peak at [28.1 ppm] for triphenylphosphine oxide [$Ph_3P(O)$] was not detected. We believe that the peak at –8.41 ppm corresponds to the reactive species derived from PPh_3 and CHI_3, which is responsible initiating the reaction with ynamide. In other experiment, ^{31}P NMR of the reaction mixture containing $PPh_3/CHI_3/CH_2Cl_2$ and H_2O in the presence of ynamide was examined in regular interval. Interestingly, the peak at 28.1 ppm corresponds to [$Ph_3P(O)$] was started appearing after 10

mins. From this observation, we anticipate that the reaction is terminated with the liberation of $Ph_3P(O)$, which was isolated and characterized.

On the basis of the results from entry 11, Table 1 and the ^{31}P NMR experiments, we believe the reaction initiates with the syn-addition of phosphonium salt, generated in situ from PPh_3 and $CCl_4/CBr_4/CHI_3$, to the reactive ambivalent ynamide (**1**) in a concerted manner (**I**) to yield the regio- and stereoselective cationic β–phosphonium-α–haloenamide (**II**).[21] Next, the addition of water to the cationic β–phosphonium–α–haloenamide (**II**) generates intermediate (**III**); subsequently proton quenching of (**III**) gives (**IV**). Finally, extrusion of [$PPh_3(O)$] from **IV** leads to the desired (*E*)–α–haloenamide (Scheme 10).[22] The formation minor *Z*-isomer is possible from the intermediate **IV**.



Scheme 9 Plausible Mechanistic Path

Conclusions

In conclusion, we showcase a general, efficient, gram-scale synthetic method for the construction of stereodefined α–halo(Cl/Br/I)-enamides from ynamides under the metal-free reagents [Ph_3P and $CCl_4/CBr_4/CHI_3$ in CH_2Cl_2 and H_2O] at rt. The chlorination of ynamide at room temperature under metal-free condition is notable. The role of H_2O in the halogenation of ynamide is also elucidated through deuterium labelling experiment. The reaction displays broad scope with the synthesis of wide array of *E*-α-halo(Cl/Br/I)-enamides. Novel molecular scaffolds, such as tri-substituted enamides, amidoenynes, and 2-chloroindole are readily accessible. 3-Acetoxy ynamides distinctly delivers diverse compounds under different conditions. Investigations to unravel synthetic applications of the current method are underway.

Acknowledgements

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