J. Chem. Sci. (2021)133:6
https://doi.org/10.1007/s12039-020-01880-4

REGULAR ARTICLE

Reactivity of ynamides with $AlCl_3$ and ICl: Ready access to (*E*)-α-chloroenamides and (*E/Z*)-α-chloro-β-iodo-enamides

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MS received 10 November 2020; accepted 29 November 2020

Abstract. $AlCl_3$ acts as a chlorinating agent for ynamides in the presence of stoichiometric amount of water in the environmentally benign solvent dimethylcarbonate, affording efficient access to (*E*)-α-chloroenamides via hydrochlorination, with water as a protic source. The role of water in the reaction was proven by deuterium labelling experiment. Epoxy-ynamides undergo iodochlorination in addition to the cleavage of the epoxy ring to afford (*E/Z*)-α-chloro-β-iodo-enamides. Regio- and stereochemical assignments for the products are based on X-ray crystallographic studies.

Keywords. Ynamide; hydrochlorination; iodochlorination; enamide; epoxy-ynamide; stereoselective; X-ray structure.

1. Introduction

Ynamides are reactive alkynes and hence are useful precursors that can be utilized in different organic transformations due to the presence of the triple bond directly attached to the nitrogen atom.[1] The divergence in the reactivity or the regio- and stereo-selective transformations of these precursors when compared to simple alkynes, is presumably due to the formation of a reactive keteniminium ionic species (Scheme 1).[2]

Ynamides are well-explored in several organic transformations, including those involved in the formation of carbocycles, heterocycles and enamides.[3–5] Especially during the last decade, several protocols for the synthesis of enamides from ynamide substrates have been developed, illustrating the versatility of these precursors.[5–9] Significantly, the reports mainly included halogenation,[7] reaction with carbonyl compounds[8] and addition of phosphite/alkyne/hydrostannane.[9] However the α-halogenation of ynamides is a simple approach to prepare enamides; the products can be readily derivatized further.[7,10–13] Hsung and coworkers accomplished stereoselective access to enamides by the hydrohalogenation of ynamides using the magnesium halides in wet DCM (Scheme 2a).[10a] Another report from Matsuo *et al.,* involved the titanium tetrachloride mediated addition of carbonyl compounds to terminal ynamides (Scheme 2b).[10b] Sahoo and coworkers developed a triphenylphosphine promoted stereoselective hydrohalogenation of ynamides using carbon tetrahalides as a halogen source (Scheme 2c).[10c] The report from Zhu *et al*., involved the chloro-allylation of ynamides under palladium catalysis (Scheme 2d).[10d] The most recent paper by Tang *et al.,* utilized aq. hydrohalic acids in DCM (Scheme 2e).[10e] Thus there is a significant interest in these reactions- in particular with respect to regio- and stereoselectivity. Additionally, it should be noted that enamides themselves are versatile building blocks in organic synthesis.[11,12]

Initially, our idea was to use $AlCl_3$ which may readily activate the alkyne because of its strong Lewis acidic character.[13] It should be noted that even though $AlCl_3$ has been used in some transformations of ynamides either in catalytic or stoichiometric amounts, they did not include the involvement of chloride ion transfer from the $AlCl_3$.[14] To our knowledge, the use of $AlCl_3$ as a chlorinating agent, in particular for ynamides, has not been explored. Consequently, our interest to develop new synthetic strategies by using

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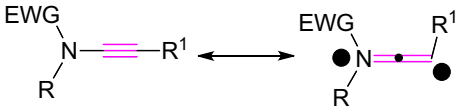
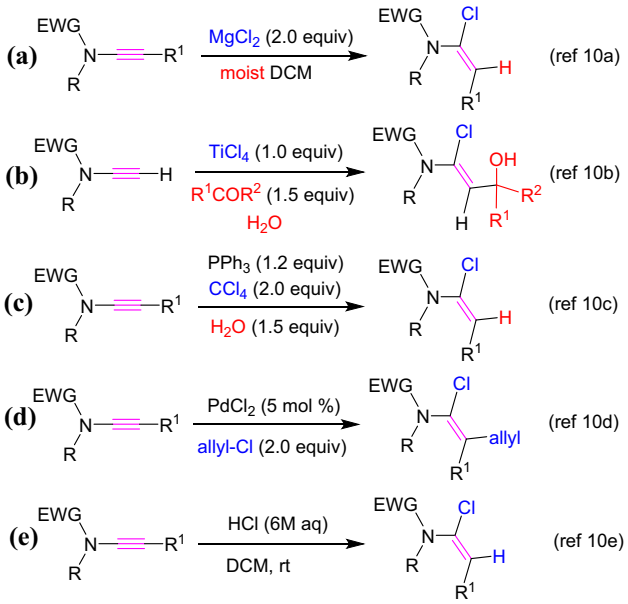
Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-020-01880-4) contains supplementary material, which is available to authorized users.

Published online: 04 February 2021



Scheme 1. Special Reactivity of Ynamide Precursors.



Scheme 2. Reports on α-chlorination of ynamides.

ynamides[15] prompted us to explore this aspect. Herein, we report an elegant approach to (*E*)-α-chloroenamides by the chlorination of ynamides using $AlCl_3$ as a chlorinating agent in a regio- and stereoselective manner; we have used dimethyl carbonate, a non-halogenated solvent in the present work.

In addition to the above, iodochlorination of ynamides using the inexpensive ICl could lead to functionalized enamides, with regiospecific iodination/chlorination. Iodochlorination of only alkynyl esters has been reported earlier by Ogilvie *et al.,* although iodobromination is known[16] This aspect has not been explored with ynamides so far (although the products could be useful synthons) and hence we briefly dwell upon this reaction also in this paper. Use of epoxy-ynamides led to epoxide ring-opening in addition to iodochlorination.

2. Experimental

General experimental set up with the details of equipment used, including X-ray structural analysis are given in the Supplementary Information. The known precursors used in the present study are prepared by methods reported in the literature.[15,17]

(i) Synthesis of enamide compounds **2a-2w**

Representative procedure for the synthesis of compound 2a. To an oven-dried Schlenk tube was added 4,*N*-dimethyl-*N*-phenylethynyl-benzenesulfonamide **1a** (0.20 mmol), $AlCl_3$ (0.22 mmol), dimethyl carbonate (1 mL) and H_2O (0.20 mmol). The tube was sealed under a nitrogen atmosphere and heated at 80 °C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude mixture was cooled to room temperature. The mixture was then passed through celite, washed with ethyl acetate (20 mL) and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford (*E*)-*N*,4-dimethyl-*N*-styrylbenzenesulfonamide **2a**. Compounds **2b-w** were prepared following the same procedure and the same molar quantities.

(*E*)-*N*-(1-chloro-2-phenylvinyl)-*N*,4-dimethylbenzenesulfonamide (2a): White solid. Yield 0.059 g (92%); M.p. 104-106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.5 Hz, 2H), 7.63-7.61 (m, 2H), 7.40-7.36 (m, 2H), 7.35-7.32 (m, 3H), 6.68 (s, 1H), 3.06 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 134.2, 133.1, 132.4, 129.8, 129.5, 128.9, 128.8_1, 128.7_8, 128.7, 35.7, 21.6; IR (KBr) 3060, 2926, 1634, 1593, 1443, 1361, 1164, 1092, 963, 808, 756, 689 cm^{-1}; HRMS (ESI): Calcd. for $C_{16}H_{16}ClNO_2SNH_4$ ($M^+ + NH_4$): *m/z* 339.0934. Found: 339.0935.

(ii) Synthesis of compounds **6a-c**

General procedure for 6a. To an oven dried 10 mL RBF, 4-methyl-*N*-(oxiran-2-ylmethyl)-*N*-(phenylethynyl)benzenesulfonamide (**5a**; 0.100 g, 0.3 mmol), 1M ICl in acetonitrile (1 mL) solution was added at 0 °C. The mixture was stirred at 0 °C to rt (25 °C) for 1 h. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure and purification by column chromatography (hexane/ethyl acetate 9:1) afforded compound **6a**. Compounds **6b–6c** were prepared following the same procedure and by using the same molar quantities.

(*E*)-*N*-(3-chloro-2-hydroxypropyl)-*N*-(1-chloro-2-iodo-2-phenylvinyl)-4-methylbenzene sulfonamide (6a): Yield 0.143 g (89% with *E:Z* in 53:47 (^{1}H NMR), M.p. 124-126 °C; IR (KBr): 3534, 2926, 1595, 1490, 1441, 1353, 1167, 1090, 1025, 816, 701, 658 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): Isomer 1: δ 7.89–7.86 (m, 4H), 7.41–7.40 (m, 5H), 4.22–4.18 (m, 1H), 3.76–3.73 (m, 1H), 3.69–3.66 (m, 1H), 3.59–3.54 (m, 1H), 3.44–3.40 (m, 1H), 2.47 (s, 3H). Isomer 2:

7.39–7.32 (m, 9H), 4.29–4.25 (m, 1H), 4.05–4.02 (m, 1H), 3.85–3.81 (m, 1H), 3.66–3.62 (m, 1H), 3.37–3.33 (m, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): Isomer 1: δ 145.3, 141.3, 134.3, 129.9, 129.2, 129.0, 128.5, 128.5, 128.4, 128.2, 103.6, 68.6, 52.2, 46.1, 21.7. *Isomer 2:* 145.2, 141.1, 134.3, 129.8, 129.1, 128.9, 128.5, 128.4, 127.7, 102.9, 69.3, 51.3, 47.9, 21.7. HRMS (ESI): Calcd. for $C_{18}H_{19}^{35,37}Cl_2INO_3S$ (M^++H): *m/z* 525.9507, 527.9477, 529.9447. Found: 525.9506, 527.9475, 529.9429. This compound was crystallized from DCM/ethyl acetate (2:1) mixture at 25 °C. X-ray structure was determined for *E*-isomer.

Full characterization data for the products **2a**–**2w** (compounds **2j**, **2k** and **2w** are known[7j, 10e]) and **6a**–**6c** are given in the Supplementary Information.

3. Results and Discussion

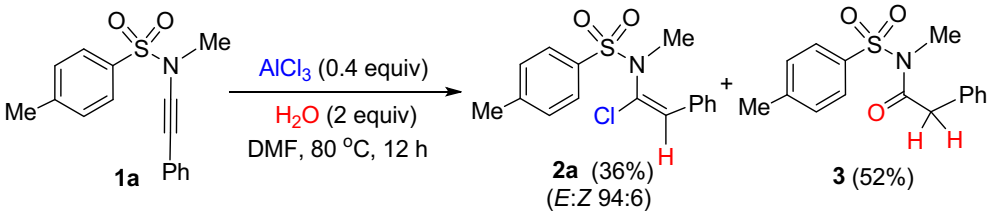
Initially, we performed the reaction of *N*-alkynyl benzenesulfonamide **1a** with $AlCl_3$ (0.4 equiv) using H_2O (2 equiv) as a proton source in DMF solvent at 80 °C for 12 h (Table 1, entry 1). Delightfully, the α-chloroenamide **2a** was isolated in 36% yield in addition to the water addition by-product **3** in 52% yield. To further improve the yield and stereoselectivity of the desired product **2a** (Scheme 3), we then moved to the optimization of the reaction conditions (Table 1).

The reaction using 1 equiv. of water also led to the formation of both the products **2a** and **3**. However, the use of stoichiometric amounts of $AlCl_3$ (1.1 equiv.) furnished the desired product **2a** in good yield. It is noteworthy that, no over-chlorination was observed even with an excess of $AlCl_3$ (3 equiv.). Variation of solvents from DMF to THF and PEG-400 improved the stereoselectivity. Unexpectedly, the reaction was not clean in the ethanol solvent. Both the yield and stereoselectivity decreased when we performed the reaction in toluene. Interestingly, the product was obtained in good yield and stereoselectivity by using acetonitrile as the solvent. Further, to our surprise, the reaction proceeded cleanly by the use of dimethyl carbonate as a solvent affording the product **2a** in 92% isolated yield in a regio- and stereo-selective manner. We noticed that the reaction also proceeded at the room temperature (25 °C) but with a slower reaction rate, reduction in the yield of the product with some unreacted starting material. More importantly, no product formation was observed in the absence of $AlCl_3$. We also checked other Lewis acids. While $TiCl_4$ gave a mixture of products, $SnCl_4$ led predominantly to the water addition product **3** with only traces of the desired product. In fact, $AlCl_3$ $6H_2O$ is also suitable as a chlorinating agent, though with decreased reaction rate. Hence the optimized condition for the regio- and stereo-specific hydro-chlorination of ynamides was **1a** (0.20 mmol), $AlCl_3$ (0.22 mmol) in

Table 1. Optimization study for the synthesis of (*E*)-*N*-(1-chloro-2-phenylvinyl)-*N*,4-dimethylbenzenesulfonamide **2a** from ynamide **1a**[a]

Entry	$AlCl_3$ (equiv.)	Solvent	Yield (%)[b] 2a (*E:Z*)
1[c,d]	$AlCl_3$ (0.4)	DMF	36 (94:6)
2[d]	$AlCl_3$ (0.4)	DMF	42
3	$AlCl_3$ (1.1)	DMF	85
4	$AlCl_3$ (3)	DMF	86
5	$AlCl_3$ (1.1)	THF	90 (96:4)
6[d]	$AlCl_3$ (1.1)	PEG-400	82 (99:1)
7	$AlCl_3$ (1.1)	EtOH	traces
8	$AlCl_3$ (1.1)	toluene	76 (92:8)
9	$AlCl_3$ (1.1)	CH_3CN	92 (96:4)
10	$AlCl_3$ (1.1)	$(MeO)_2CO$	92 ('99:traces)
11[e]	$AlCl_3$ (1.1)	$(MeO)_2CO$	46
12	–	$(MeO)_2CO$	No reaction
13	$TiCl_4$ (1.1)	$(MeO)_2CO$	traces
14[d]	$SnCl_4$ (1.1)	$(MeO)_2CO$	traces

[a]Ynamide (0.20 mmol), $AlCl_3$ (x equiv.), solvent (1 mL) and H_2O (1 equiv.) at 80 °C for 12 h. [b]Yield of the isolated product and stereoisomeric ratio in parenthesis was based on ^{1}H NMR.[c]H_2O (2 equiv.) used. [d]**3** was observed. [e]performed at rt (25 °C).



Scheme 3. Reaction of ynamide **1a** with $AlCl_3$ affording products **2a** and **3**.

dimethyl carbonate (1 mL) and H_2O (0.20 mmol) at 80 °C for 12 h [Table 1, entry 10].

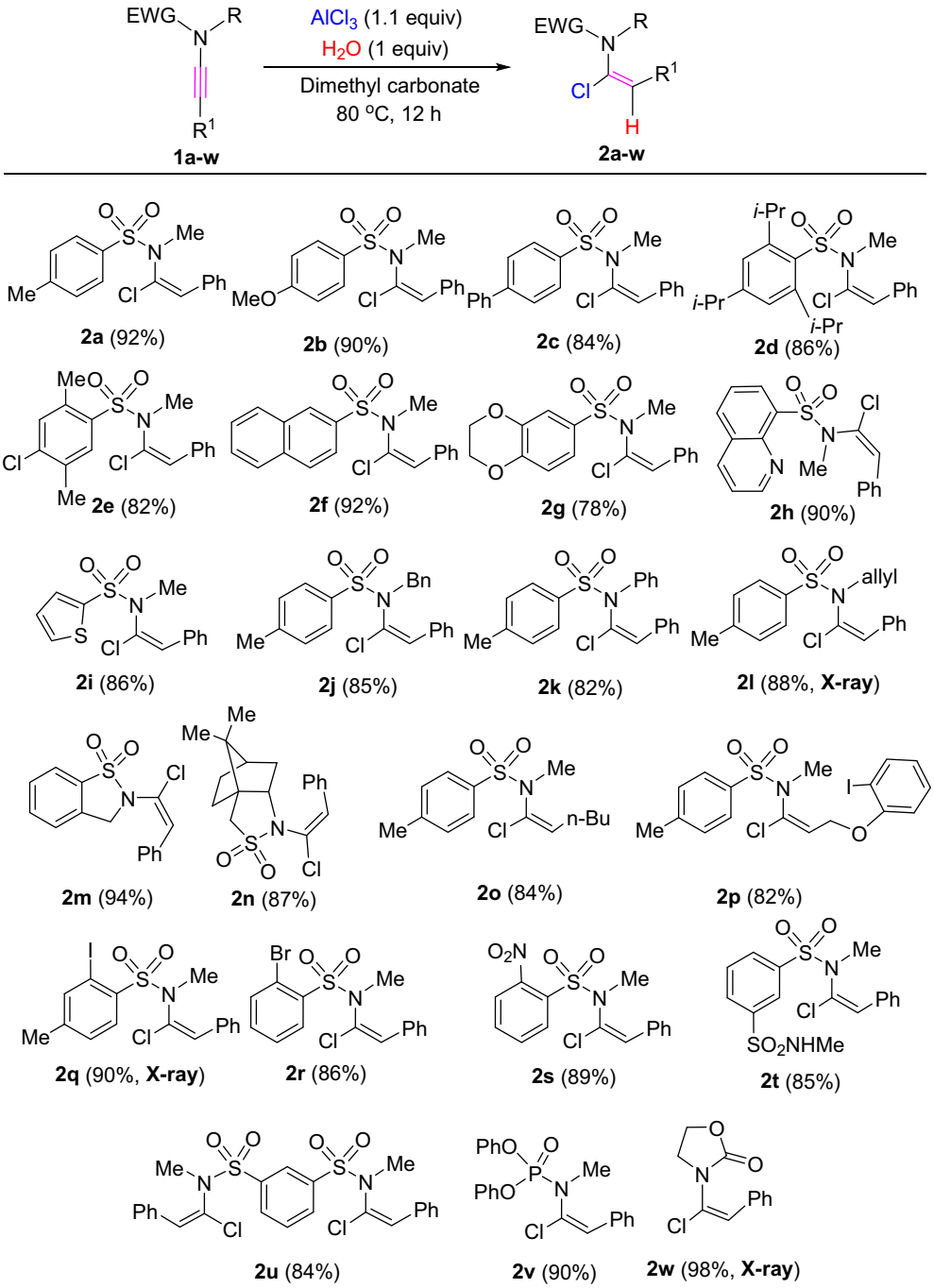
After having the above-optimized reaction conditions in hand, we then sought to explore the substrate scope for this chloride ion transfer from $AlCl_3$ to ynamides. As illustrated in Scheme 4, various types of ynamides are transformed into the corresponding (*E*)-enamides in good to excellent yields in a regio- and stereo-selective manner using $AlCl_3$ as the hydrochlorinating source. Precursors with substituents on the aryl moiety attached to sulfonyl group afforded products **2a–c** in excellent yields. Ynamides with bulky, bicyclic or heterocyclic moiety also offered the corresponding products **2d–i** in good yields. Ynamides with different substituents on the nitrogen atom of ynamides too produced the enamides **2j–l**. The reaction proceeded well with cyclic ynamides to provide the related products **2m–n**. In addition, this transformation worked well with precursor having an aliphatic substituent on the alkyne functionality, delivering the compound **2o** in good yield and selectivity. Functionalities such as halo, nitro and free sulfonamide functionalities on the ynamides were compatible with this reaction and produced the enamides **2p–t** in good yields. Interestingly, bis-hydrochlorination could be effected to yield the enamide **2u** in good yield by using 2.2 equiv of $AlCl_3$. Furthermore, the present method could be extended by varying the electron-withdrawing groups. Thus replacing the sulfonyl group with the phosphoryl group or carbonyl group did not affect the regio- and stereo-selectivity, and afforded the corresponding products **2v–w** in excellent yields. The structures of compounds **2l**, **2q** and **2w** were confirmed by X-ray crystallographic analysis (Figure 1 and Figure S3, Supplementary Information). X-ray structures of these compounds showed strong hydrogen bonding between the chlorine and the alkenyl hydrogen atom which may account for the observed stereo-specificity.

To elucidate the probable pathway for this chloride ion transfer from $AlCl_3$ to ynamides, we have done the following control experiments. Thus the reaction of ynamide **1a** with $AlCl_3$ (1.1 equiv) and D_2O (1 equiv) in dimethyl carbonate solvent delivers the compound **2a'** with about 76% deuteration at one of the olefinic positions (Scheme 5a). The fact that the isolation of monodeuterated α-chloroenamide **2a'** suggested the crucial role of water as a proton source in the reaction. No reaction occurred when we treated *N*-propargylated sulfonamide **4** under similar reaction conditions due to the nonexistence of reactive keteniminium ion (Scheme 5b).

It is known that $AlCl_3$ reacts vigorously with water (excess) to liberate HCl. Thus in the above reaction, it is possible that hydrolysis of $AlCl_3$ takes place leading to the liberation of HCl which then reacts with the ynamide. However, it can be noted that $AlCl_3.6H_2O$ is commercially available and hence it is difficult to say whether the reaction takes place with the liberated HCl or not. We have not done further experiments since the idea was to get the chloroenamides. Also, as pointed above, for reactions of ynamides in which $AlCl_3$ is used as a catalyst,[14a] traces of moisture could lead to hydrochlorination and one has to be careful.

3.1 *ICl addition reactions of epoxy ynamides*

In principle, the interhalogen compound $I^{\delta+}Cl^{\delta-}$ can also be used for iodochlorination of ynamides, but it is possible that it can act as an oxidizing agent. To test this, initially, we conducted the reaction with epoxy ynamides. We treated epoxy-ynamides **5a-c** with a 1M solution of ICl in CH_3CN (0.5 mL) at 0 °C for 10 min and obtained highly regioselective *E/Z*-isomeric mixture (1:1) of α-chloro-β-iodoenamide derivatives **6a–c** in good yields. In this transformation, along with addition reaction, intermolecular S_N2 nucleophilic ring-opening of epoxide part of the ynamide occurs simultaneously (Scheme 6). A band due to OH group is observed at ~ 3534 cm^{-1} in the IR spectra as expected. Here, electrophilic addition reactions are highly favored in contrast to the corresponding 5-*exo-dig* and/or 6-*endo-dig* cyclization reactions of epoxy-ynamides.[15d-e] Although *E/Z* isomeric mixture was obtained, the *E*-isomer preferentially crystallized. The structures of the addition products **6a** and **6c** (Figure 2) were confirmed by single-crystal X-ray



Scheme 4. $AlCl_3$ Mediated Synthesis of (*E*)-α-chloroenamides from the Ynamides[a]. [a] Conditions: **1** (0.20 mmol), $AlCl_3$ (0.22 mmol) in dimethyl carbonate (1 mL) and H_2O (0.20 mmol) at 80 °C for 12 h. Isolated yields after column chromatography are given in parenthesis. For the preparation of compound **2u** we used $AlCl_3$ (0.44 mmol), H_2O (0.40 mmol).

diffraction; although the data was not great for **6c** due to low quality of the crystals, the structure could be readily ascertained. In compound **6a**, the C8-C9 distance [1.340(10) Å] proved the presence of a double bond between these two atoms. Three single bonds Cl(1)-C(8), C(l2)-C(18) and I(1)-C(9) are newly formed. Similar structural features are observed in compound **6c** also. Crystal structures of the compounds **6a** and **6c** show I•••O halogen bonding interactions (Figure 2).[18] We did perform a similar reaction of **1a** with ICl but ended up in obtaining a mixture that contained the hydrolyzed product. We did not succeed in obtaining a product without opening of the epoxide ring. Hence we did not pursue this further.

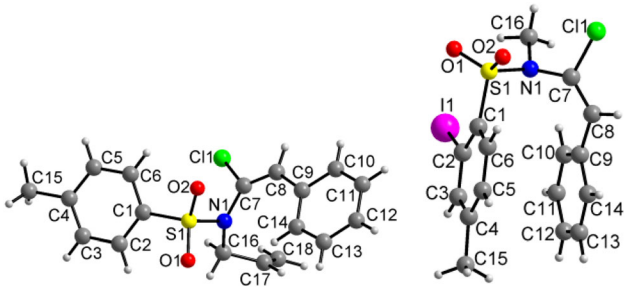
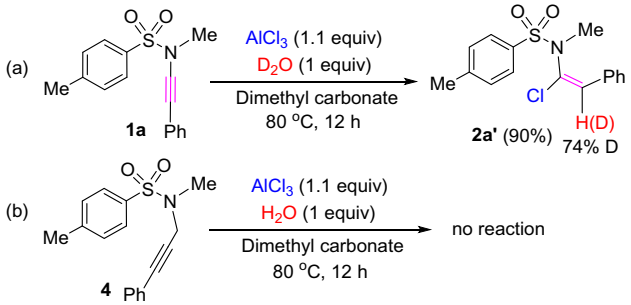
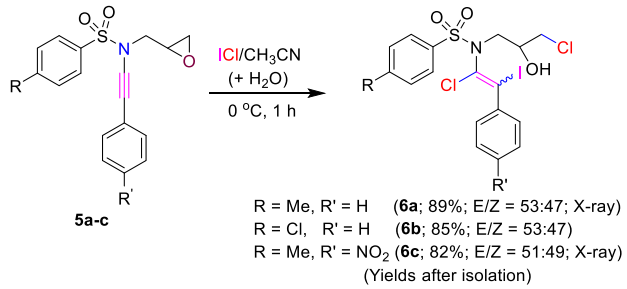


Figure 1. X-ray structures of compounds **2l** (left; CCDC 2033589) and **2q** (right; CCDC 2033590). Selected bond parameters: **2l** Cl1-C7 1.758(2), S1-N1 1.6520(15), N1-C7 1.404(2), C7-C8 1.326(3), C8-C9 1.468(3), C9-C10 1.396(3), C9-C14 1.390(3) (Å). **2q** Cl1-C7 1.770(3), S1-N1 1.662(2), N1-C7 1.414(3), C7-C8 1.316(4), C8-C9 1.484(4), C9-C10 1.385(4), C9-C14 1.388(4) (Å).



Scheme 5. Control Experiments.



Scheme 6. Reaction of epoxy ynamides with ICl.

4. Conclusions

An operationally simple approach for the regio- and stereo-selective synthesis of (*E*)-α-chloroenamides by the hydrochlorination of ynamides using $AlCl_3$ (as the source for hydrochlorination) is developed. This is complementary to other approaches reported in the literature, but emphasizes the point that $AlCl_3$ can also act as a hydrochlorinating agent (cf. ref. 14a) in the presence of even one equivalent of water; we also point out that a non-halogenated solvent, dimethyl carbonate, has been used in the present work. This

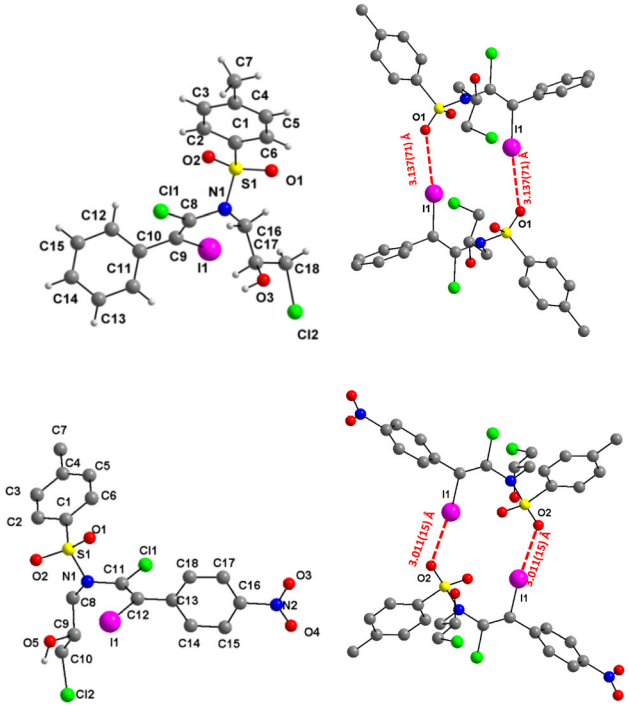


Figure 2. Molecular structures of compounds **6a** (Top; CCDC 2033592) and **6c**·CH_2Cl_2 (Bottom, solvent molecule is omitted; CCDC 2033593). Selected bond lengths [Å] with esds in parentheses: **6a** I1-C9 2.099(7), C9-C8 1.340(10), Cl1-C8 1.754(8), C16-C17 1.494(15), C18-C17 1.44(2), O3-C17 1.550(18), Cl2-C18 1.908(15), I•••O 3.137(71). **6c**·CH_2Cl_2 I1-C12 2.116(10), C11-C12 1.315(13), C12-C13 1.447(13), Cl1-C11 1.747(10), Cl2-C10 1.789(15), O5-C9 1.464(16), N1-C11 1.411(12), I•••O 3.011(15). Data quality for **6c** was only moderate but structure could be readily refined. The I•••O distances are considerably shorter than the sum of the corresponding van der Waals radii of O (1.52 Å) and I (1.98 Å) i.e. they are <3.50 Å [***Note***: Average I-O covalent bond distance: 2.14 Å].

methodology is also applicable to phosphoramidate and carbamate derived ynamide substrate illustrating its utility. Deuterium labelling experiment demonstrated the essential role of water as a proton source in the reaction.

Supplementary Information

Experimental details; X-ray crystallographic data (cif files; CCDC nos. 2033589-2033593); ORTEPS of **2l**, **2q**, **2w**, **6a** and **6c**; ^{1}H / ^{13}C/ ^{31}P NMR spectra. This material is available free of charge at www.ias.ac.in/chemsci.

Acknowledgements

We thank the Department of Science and Technology (DST, New Delhi) and University Grants Commission (UGC, New Delhi) for support. ASR, MA and Suraj thank UGC (New

Delhi) for fellowships. KCK thanks SERB for the J. C. Bose fellowship.

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