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COMMUNICATION

Transition Metal-Free Functionalized Hydration of Alkynes: One-Pot Synthesis of fluorinated β-keto-imidates using Selectfluor

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ABSTRACT: The transition metal-free, four-component one-pot synthesis of polyfunctionalized fluorinated β-keto-imidates *via* functionalized hydration of alkynes has been described. The intermediate 1, 3-ketoamino moiety was obtained from easily accessible arylpropioladehyde and arlyhydroxylamine which was treated with selectfluor delivering fluorinated β-keto-imidates. The wide functional groups are tolerated under mild reaction condition and product applicability is highlighted.

Introduction

The introduction of fluorine element in the organic molecule has always been an important endeavor for drug designing purposes. Nevertheless, organic compounds containing fluorine next to the amino, imino and ketone functionalities have been found in anticancer, anticholinergic, anti-inflammatory drugs, and therapeutic β -peptides[1-3] (fig 1). Accordingly, their synthesis has captivated much attention resulting in numerous strategies for its construction.[4,5]

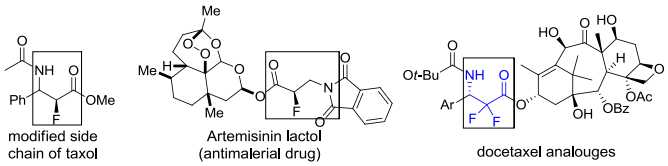
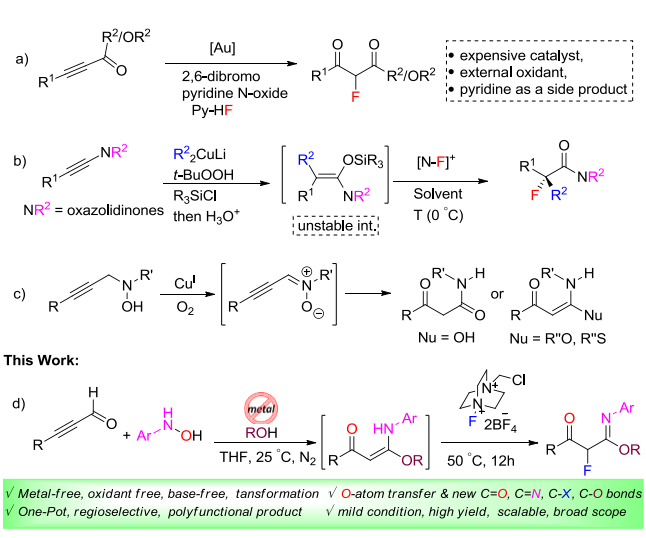


Figure 1. Biologically active fluorinated drug molecules.In this line, despite of various approaches for fluorinated compound synthesis, transition metal-catalyzed transformations using internal alkynes are exclusively studied in recent years.[6] In particular, Hammond *et al.*[7] reported gold-catalyzed regioselective synthesis of fluorinated 1,3-dicarbonyl compounds using alkynyl ketones or esters. The insertion of hydrogen fluoride take place across gold carbene generated from cationic gold-catalyzed addition of *N*-oxides to alkynyl ketones/esters. (Scheme 1a). While, Marek *et al.*[8] reported the diastereoselective synthesis of tertiary α-fluorinated carbonyl compounds from ynamide precursors *via* stereodefined fully substituted silyl-ketene hemiaminals intermediate (Scheme 1b). In addition, Liu *et al.*[9] reports, copper-catalyzed oxidations of 3-*N*-hydroxyaminopro-1-ynes with water, alcohols, or thiols to form 3-substituted 3-amino-2-en-1-ones *via* a formation of nitrone intermediate (Scheme 1c). It is found that, these types of transformations have several drawbacks. Therefore, it will be highly challenging if one can seek to achieve these transformations under the economical and metal-free conditions.[10,11] Moreover, preparation of synthetically important and biologically active compounds under transition metal-free condition have gained high importance in recent years.[12] In this context, herein, we report the transition metal-free one-pot synthesis of 3-substituted 3-imino-2-fluoro 1-ones from easily accessible 3-phenylpropiolaldehyde and *N*-phenylhydroxylamine. In this functionalized hydration of alkynes, commercially available alcohols acts as a nucleophile while



Scheme 1. Synthesis of functionalized fluorinated compounds

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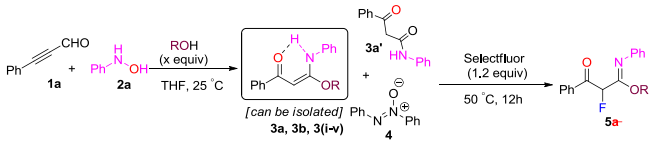
Selectfluor serves as electrophilic fluorine source. It is confirmed that, the present alkyne hydration proceeds *via in-situ* generated 3-substituted 3-amino-2- en 1-ones intermediate which is formed by Mannich reaction[13] between 3-phenylpropiolaldehyde, *N*-arylhydroxyimine and alcohol. The subsequent addition of Selectfluor to tetrahydrofuran solution furnished the desired 3-substituted 3-imino-2-fluoro 1-ones.

We commenced our studies by examining the reaction parameters in a reaction of 3-phenylpropiolaldehyde **1a** (0.5 mmol) and *N*- phenylhydroxylamine **2a** (0.55 mmol) in THF (3.0 mL) solvent at 25 °C. It is observed that, in absence of nucleophile, the formation of undesired *β*-oxoamide **3a'** takes place up to 67% in 24 h likely due to trace amount of water present in solvent, while azoxybenzenes (**4**) was obtained as a side product due to the

Table 1. Optimization of reaction condition arylaldehyde[a]



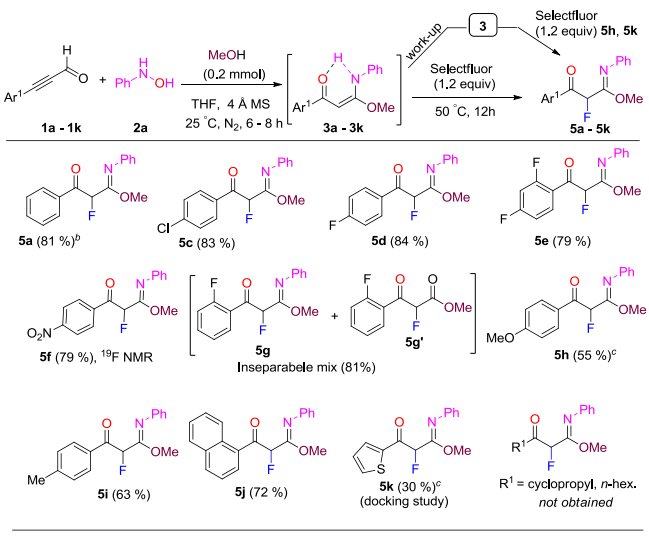
S.N	ROH (equiv-)	Solvent	*t* (*h*)	Compounds 3(%)/**3a'**(%)	5 (%)[b]
1	ROH = none	Wet toluene	24	**3a**(0)/**3a'**(67)	—
2	MeOH (4)	Wet toluene	15	**3a**(41)/**3a'**(26)	—
3	MeOH (4)	Toluene	15	**3a**(56)/**3a'**(trace)	—
4	MeOH (4)	THF	6	**3a** (91)/ **3a'**(trace)	—
5	MeOH (3)	THF	10	**3a** (76)/**3a'**(10)	—
6	MeOH (2)	THF	18	**3a** (58)/**3a'**(31)	—
7[c]	MeOH (4)	THF	6	**3a**(~95)/**3a'**(trace)	**5a**(81)
8[c]	MeOH (3)	THF	8	**3a**(~81)/**3a'**(14)	**5a**(72)
9[d]	ROH = EtOH	THF	10	**3b**(58)/**3a'**(21)	**5b**(44)
10	*t*BuOH(4)	THF	15	**3i**(trace)/**3a'**(38)	—
11	*n*-BuOH (4)	THF	18	**3ii**(trace)/**3a'**(41)	—
12	*i*-PrOH (4)	THF	18	**3iii**(10)/**3a'**(21)	—
13	PhOH (4)	THF	18	**3iv**(trace)/**3a'**(30)	—
14	BnOH(4)	THF	12	**3v**(10)/**3a'**(18)	—

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), ROH (0 - 4 equiv), molecular sieves (4 Å) in THF (3.0 mL) at 25 °C then (in case of entries 7 and 8) Selectfluor (1.2 equiv) at 50 °C. [b]yields are reported after purification form silica column (average of two run). [c]In these cases, **3a**/**3a'** are not isolated and their approx. TLC conversion is shown. [d]yields corresponds to Selectfluor addition to the purified **3b**.

decomposition of *N*-hydroxylamine[14] (Table 1, entry 1). To our delight, the alkyne hydration efficiency was significantly improved, when MeOH (4 equiv) was employed as a nucleophile and desired 3-substituted 3-amino-2-en 1-ones **3a** obtained up to 41% yield along with **3a'** (26%, entry 2). The compound **3a**, **3a**' and **4** are isolated by column chromatography and confirmed by NMR spectroscopy. The N-H proton of compound **3a** appears at 13.08 ppm in ^{1}H NMR presumably due to the intermolecular H-boding with carbonyl group. Next, when dry toluene is employed as a solvent in presence of 4Å MS under nitrogen atmosphere, the yield of **3a** is further increased to 56% with trace of **3a'** (entry 3). Surprisingly, change of solvent to dry THF exclusively furnishes **3a** in 91% yield (entry 4), while other solvents such as 1,4-dioxane, dichloromethane, acetonitrile are ineffective (See the supporting information for details). Furthermore, reaction with reduced amount of MeOH furnishes less yield presumably due to sluggish reaction process (entries 5 and 6). Notably, in the cases of entries 7 and 8, once the intermediate **3a** is formed (indicated by TLC), Selectfluor (1.2 equiv) was added to the THF solution under nitrogen atmosphere and the newly formed 3-substituted 3-imino-2-fluoro 1-ones compound **5a** was obtained (50 °C, 12 h) 81% and 72% yield respectively. The NOE study of **5a** indicates that, the geometry (*E* or *Z*) of *N*-penyl ring of **5a** is unspecified and therefore it is shown by wavy bond.[15a] It is observed that, the newly formed *β*-keto-imidates are stable in air while prolonged storage cause slow imine hydrolysis due to atmosperic moisture. In the later stage, the reactions with change in nucleophile to ethanol furnishes desired product **5b** in 44% yileld (entry 9), while other nucleophile such as *t*-BuOH, *n*-BuOH, *i*-PrOH, PhOH, and BnOH found to be inefficient presumably due to steric and electronic properties (entries 10–14) of these alcohols.[15b]

With the optimal conditions in hand (Table 1 entry 7), we first scrutinized the scope of 3-phenylpropiolaldehyde bearing various substituents in reactions with **2a** using MeOH as a nucleophile. Phenylpropiolaldehyde with an electron withdrawing group such as 4-chloro, 4-fluoro, 2,6-difluoro, 4-nitro works efficiently providing fluorinated compounds (**5c**–**5f**) in 79–84% yields; while, 2-fluoro phenylpropiolaldehyde furnishes the inseparable mixture of desired product **5g** along with its ester analogue **5g'** mainly due to expeditious imine hydrolysis.[16] On the other hand, electron donating substituents such as 4-methoxy, 4-methyl, furnishes desired product (**5h** and **5i**) albeit in moderate yield. However, replacing the phenyl

Table 2. Substrate Scope of arylaldehyde[a]



[a]Reaction condition: **1a–1k** (0.5 mmol), **2a** (0.55 mmol), MeOH (4 equiv), molecular sieves (4 Å) in THF (3.0 mL) at 25 °C then Slectfluor (1.2 equiv) at 50 °C. [b]yields are reported after purification form silica column (average of two run). [c]yields corresponds to Selectfluor addition to the purified **3h** , **3k**

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moiety of **1** by 1-napthyl group furnishes desired product **5j** in 72% yield. Further, the scope to heterocyclic propioladehyde was extended wherein **5k** was obtained in 30% yield from 3-(thiophen-2-yl) propiolaldehyde. While the 3-cyclopropylpropiolaldehyde and hex-2-ynal furnishes the complicated mixture of products. The fluoro-containing heterocyclic compounds are highly sought in medicinal chemistry as they contribute in the physicochemical properties and interactions with the target protein.[17] We studied the interaction of **5k** with Epidermal Growth Factor Receptor (EGFR) kinase, an important target in cancer (Figure 2). **5k** occupies the ATP binding site of kinase and shows H-bond interaction between compound's carbonyl and methionine 769 of kinase.

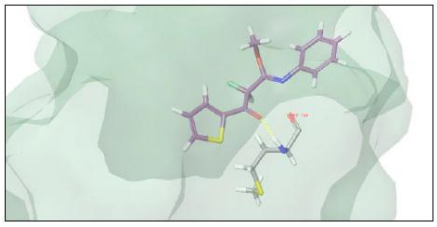
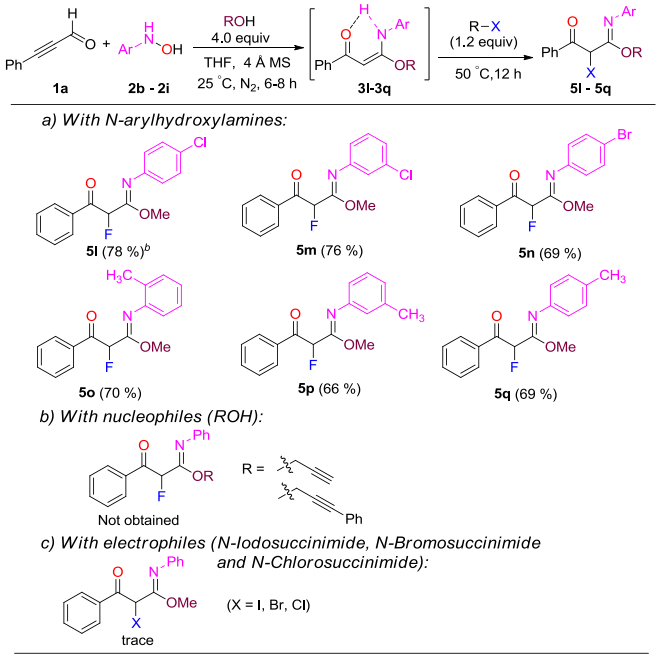


Figure 2: interaction of **5k** with EGFR kinase. Compound **5k** was docked in EGFR kinase (PDB ID: 1M17)

The scope with other reactants such as *N*-arylhydroxylamine (ArNHOH), nucleophiles (ROH), electrophiles (RX) are subsequently examined (Table 3). Initially, we tested *N*-phenylhydroxylamine bearing electron withdrawing substituent such as 4-chloro, 3-chloro, 4-bromo which reacted smoothly leading to the formation

Table 3. Scope with *N*-arylhydroxylamine, nucleophiles and electrophiles[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2b–2i** (0.55 mmol), ROH (4 equiv), Selectfluor (1.2 equiv), molecular sieves (4 Å) in THF (3.0 mL) at 25 °C then Selectflour (1.2 equiv) at 50 °C. [b]yields are reported after purification form silica column (average of two run).

of desired compounds (**5l–5n**) in 69–78% yields. Interestingly, when *N*-(*o*-tolyl)hydroxylamine is subjected for the reaction under the standard condition we have observed shiny crystals of corresponding intermediate (**3o**) which is unambiguously confirmed by X-ray crystallographic analysis indicating that 3-amino and 2-keto functionalities are *cis* to each other[18] (Fig 3, in dimeric form). Next, under one-pot condition, compound **5o** is obtained 70% yield showing –CH-F peaks at -189.3 ppm (J = 52 Hz) in ^{19}F- spectroscopy.

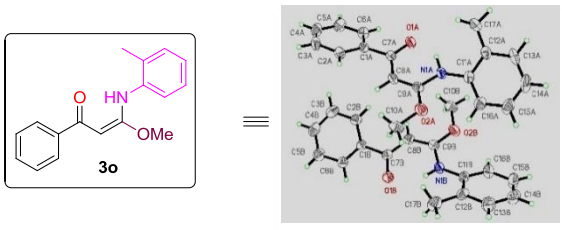
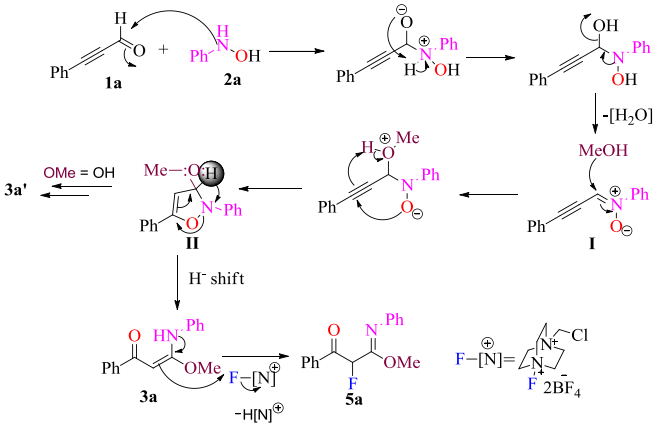


Figure-3: Crystal XRD image of **3o**(dimer: CCDC1865939)

In continuation, the analogous *N*-(*m*-tolyl)hydroxylamine and *N*-(*p*-tolyl)hydroxylamine also furnishes the desired **5p** and **5q** in 66% and 69% yield respectively. The reaction with *N*-alkylhydroxylamine such as *N*-(*tert*-butyl)hydroxylamine and *N*-isopropylhydroxylamine furnishes only trace amount of keto-amino products presumably due to the poor nucleophilicity induced by electron donating inductive effect of alkyl substituent and therefore analogous fluorination products are not obtained. Further, we have also tested the scope of reaction with the nucleophiles tethered with alkyne functionality such as propargyl alcohol, 3-phenylprop-2-yn-1-ol and they are found to be ineffective under the standard condition presumably due to steric and electronic properties. On the other hand, the electrophile other than selectfluor such as, *N*-iodosuccinimide, *N*- bromosuccinimide, and *N*-chlorosuccinimide are ineffective.

The plausible mechanism of alkyne hydration for the synthesis of 3-substituted 3-imino-2-fluoro 1-ones is depicted in Scheme 3 The proposed skeletal rearrangement mechanism supported by literature precedents.[9,14]

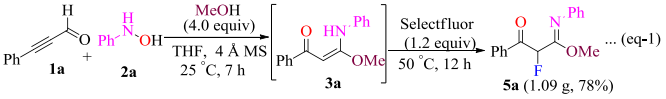


Scheme 3. Plausible mechanism for formation of **3a** and **5a**

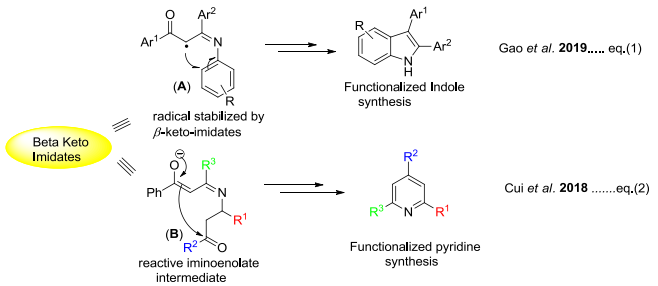
The condensation of aldehyde **1a** and *N*-phenylhydroxylamine **2a** leads to the formation of *N*-phenylhydroxylammonium intermediate **I**. The subsequent nucleophilic attack of alcohol on the electron

deficient imine carbon leads to the formation of cyclized intermediate **II**. As reported by Liu *et al*,[9] hydride shift followed by N-O bond cleavage[19] leads to the formation of 3-substituted 3-amino-2- en 1-ones **3a** through intramolecular oxygen atom transfer to alkynes.[20] while **3a'** is obtained as a side product. We believe that, the amide oxygen atom in **3a'** is from trace of water present in reaction medium but not from atmospheric O_2. This is strongly evidenced by the H_2O^{18} Vs $^{18}O_2$ labeling study shown by Liu *et. al*[9]. The subsequent treatment of **3a** with Selectfluor leads to the formation of final compound **5a**

Our protocol can be scaled up in gram scale without affecting the chemical yield (eq. 1). In addition, we performed tha acidic imine hydrolysis of **5a** to get synthetically importaint 1,3-β-keto methyl ester **6.**[21-22] (see the supporting information for more details).



Nevertheless, β-keto imidates are prone to form a stable and reactive free-radical and anions on the carbon atom which is between keto and imine group and therefore, they are widely involved in organic synthesis (Scheme 4). For instance, Gao *et al*.[22c] reported the synthesis of functionalized indole *via* intramolecular addition of free radical **A** to the aryl ring, followed by radical coupling, deprotonation (Scheme 4 , eq. 1). While, Cui *et al.*[22d] reported the synthesis of functionalized pyridine *via* stepwise intramolecular nucleophilic addition on iminoenolate intermediate **B** (Scheme 4, eq. 2).



Scheme 4: Stability and reactivity β-keto imidates

Conclusion

In conclusion, we have developed a transition metal-free functionalized hydration of alkynes for the synthesis of fluorinated β-keto-imidates under one-pot reaction condition. The wide range of substrates is compatible under the reaction condition and products are obtained in moderate to good yields. The formation of intermediate, its geometry is confirmed by X-ray crystallography. The reaction mechanism is well supported by literature evidences and the products suitability is featured. We are also intending to utilize fluorinated β-keto-imidates for the synthesis of bioactive drug like molecules and related investigations are ongoing in our laboratory.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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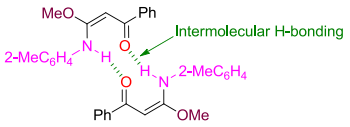

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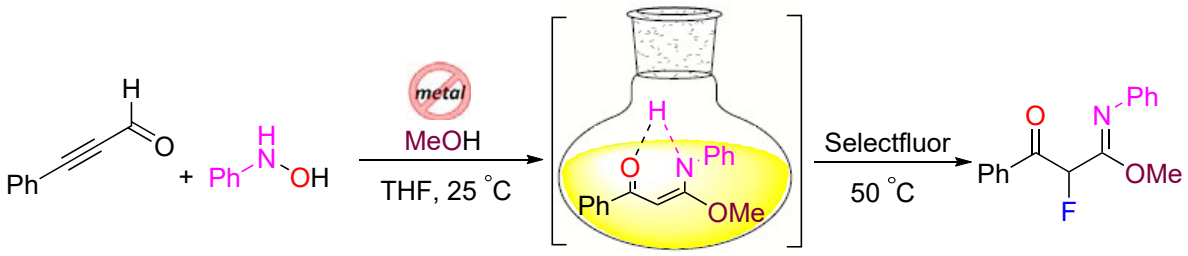

√Metal-free, oxidant free, base-free, tansformation √O-atom transfer & new C=O, C=N, C-X, C-O bonds
√One-Pot, regioselective, polyfunctional product √mild condition, high yield, scalable, broad scope