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Metal-free synthesis of alkynyl imines using an oxophosphonium-mediated approach at ambient temperatures

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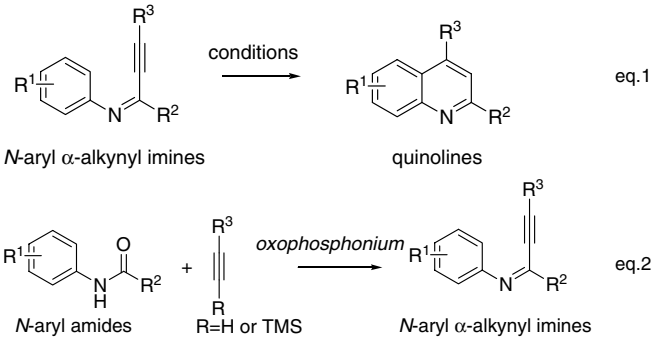
Abstract

A metal-free approach was developed for the mild synthesis of *N*-aryl α-alkynyl imines from corresponding amide precursors for the first time. The electronic effects of substrates and the reaction mechanisms were investigated and discussed. This newly developed oxophosphonium-triggered one-pot multiple-step method presents the advantages of mild conditions, ease of operation and satisfactory efficiency.

Quinolines have been found as substructures in many natural products, drugs and drug leads, as well as functional polymers.[1] Some recent syntheses of quinolines have been reported using the multiple-step protocols,[2,3] amongst which *N*-aryl α-alkynyl imines were frequently regarded as the suitable precursors (Scheme 1, Eq. 1).[4–7] Due to the weak acidity of α-proton of imines, most known methods for the preparation of *N*-aryl α-alkynyl imines require the use of reactive and sensitive organometallic reagents. Difficult operations and high costs make these methods less impractical in the laboratory, especially for those cases to raise materials in a larger scale. Therefore, development of milder, more efficient and easily operative procedures for *N*-aryl α-alkynyl imines is of great value.

Very recently, we developed a generally efficient strategy for the total syntheses of camptothecin-family alkaloids.[8] In this mild cascade reaction, an oxophosphonium salt (Hendrickson reagent)[9] was used to the convert the stable aniline amides to corresponding imidates (part of the active diene) at ambient temperatures and triggered the intramolecular Diels–Alder reaction and the following cascade sequence. The above mechanism suggests that an intermolecular version of this reaction might provide a new mild access to the quinolines via *N*-aryl α-alkynyl imines without using those sensitive organometallic reagents (Scheme 1, Eq. 2). The Use of a metal-free method in preparation of α-alkynyl imines and/or quinolines will broaden the applications of these compounds as intermediates in organic synthesis, especially in those sensitive to the



Scheme 1.

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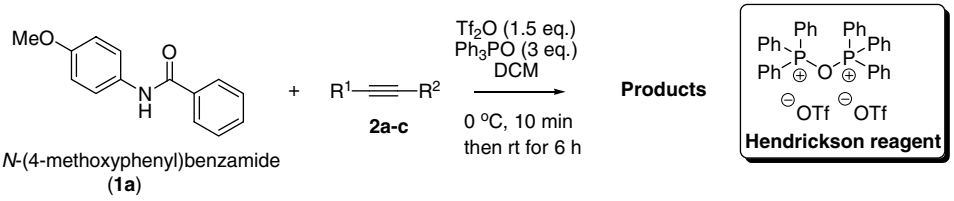
organometallic reagents. To best of our knowledge, no metal-free approach has been reported yet for the synthesis of *N*-aryl α-alkynyl imines.

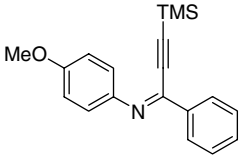
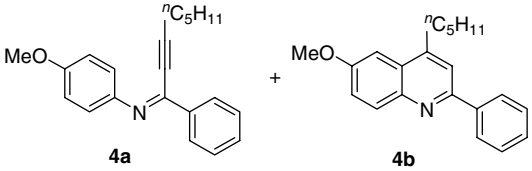
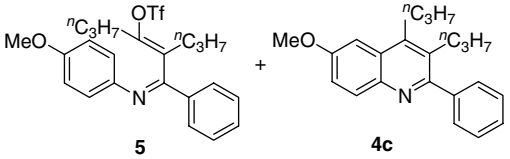
Hendrickson reagent can be conveniently prepared in situ by simply mixing Tf_2O and 2 equiv of Ph_3PO in dichloromethane as an oxophosphonium salt at room temperature. Due to the high affinity of phosphorous to oxygen atom, conversion of an amide to the corresponding imidate can be achieved in high efficiency by using Hendrickson reagent.[8,9] To screen the reaction with alkynes in the presence of Hendrickson reagent, *N*-(4-methoxyphenyl)benzamide (**1a**) was chosen as the amide substrate. Three mono- or di-substituted aliphatic alkynes **2a**–**c** were examined as the first batch of reactants. These reactions were performed and carried out in dichloromethane at 0 °C to room temperature (Table 1). The results showed two reactions (entries 2 and 3) worked, producing quinoline derivative and *N*-aryl α-alkynyl imine (entry 2) or its equivalence (entry 3) in similar yields. This mentions that at least two competitive pathways exist in this reaction (Fig. 1). Quinolines were generated by a pathway of intermolecular Diels–Alder reaction followed by eliminative aromatization, and the other cationic process provided *N*-aryl α-alkynyl imine or its equivalence (which is not able to cyclize under the same conditions). However, its reaction with trimethylsilyl acetylene afforded trace amount of *N*-aryl α-alkynyl imines **3a** only (entry 1). Electronic property of an alkyne is thus mentioned to be critical for this multiple-step reaction by stabilizing the active intermediates in the reaction process.

As mentioned above, choose of proper acetylenes is critical to improve the yields of *N*-aryl α-alkynyl imines. Theoretical inference suggests commercially available bis(trimethylsilyl)acetylene would be a better electron donor, in which the TMS group can play not only as a good electron-donating group, but also a 'super proton'[10] for the final elimination to generate acetylene **3a** (Fig. 2). Using similar conditions, the reaction of *N*-(4-methoxyphenyl)benzamide (**1a**) with bis(trimethylsilyl)acetylene gave *N*-aryl α-alkynyl imine **3a** in 70–72% yield. Attempts to use more equivalents of Hendrickson reagent could not improve the chemical yields.

To explore the generality of this reaction, a variety of aniline amides were then examined and the results are shown in Table 2. The substrates bearing electron-donating groups (entries 1, 2, 4 and 6) afforded the corresponding products in better yields, and those having electron-withdrawing groups (entries 3, 5, 10, 11 and 12) gave relatively lower yields. Due to the strong acidity of TfOH generated in this reaction, substrate **1m** (bearing an *N*,*N*-dimethyl

Table 1
Reactions of amide **1a** with aliphatic alkynes **2a**–**c**



Entry	2	Product(s)	Yields (%)
1	**2a**: $R^1 = H$; $R^2 = TMS$	 **3a**	Trace
2	**2b**: $R^1 = H$; $R^2 = n\text{-}C_5H_{11}$	 **4a** + **4b**	43 (**4a**) 32 (**4b**)
3[a]	**2c**: $R^1 = R^2 = n\text{-}C_3H_7$	 **5** + **4c**	42 (**5**) 37 (**4c**)

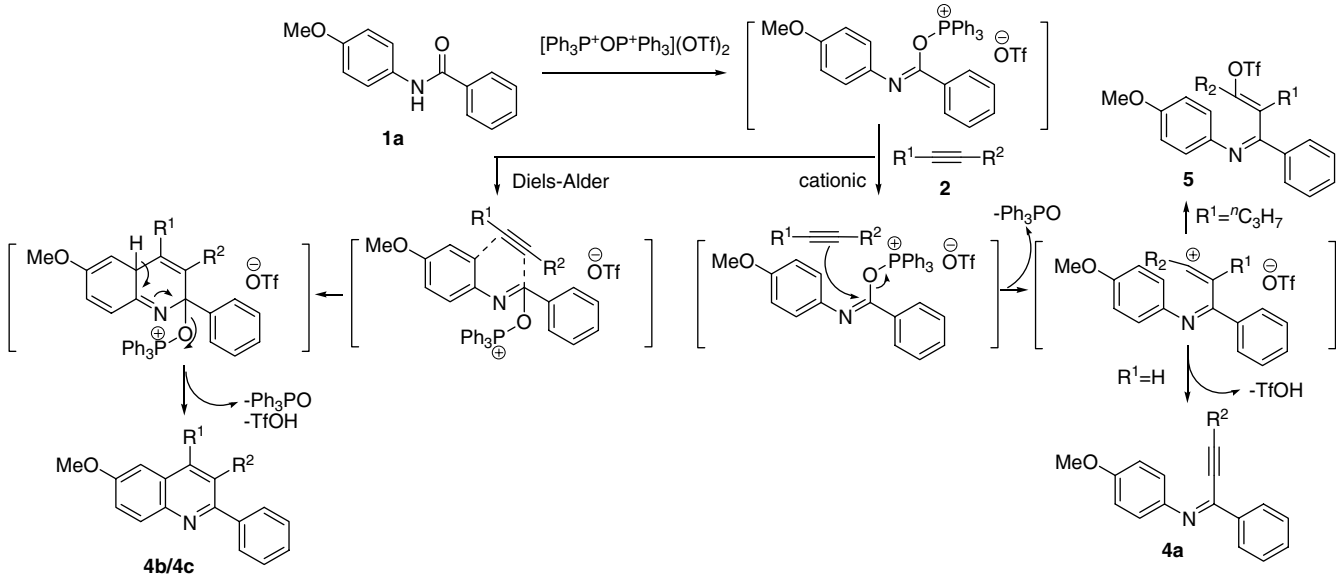


Fig. 1. Proposed mechanism for the competitive pathways.

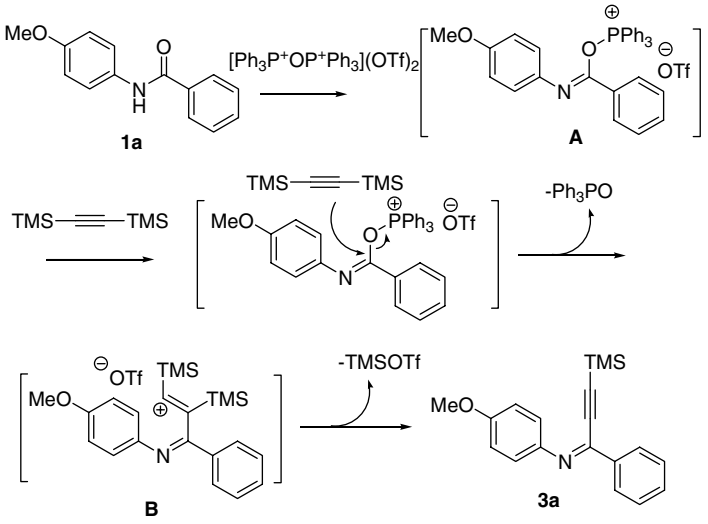


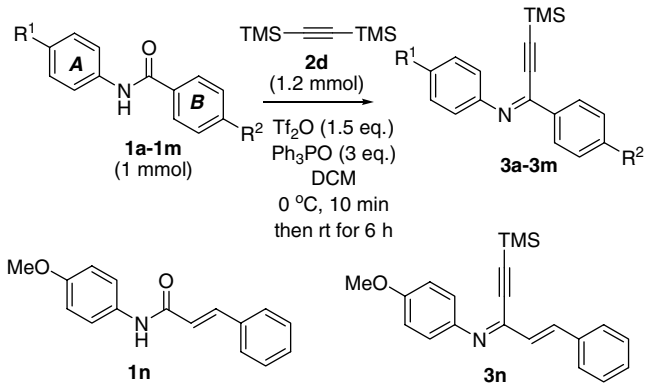
Fig. 2. Proposed mechanism for the reaction of *N*-(4-methoxyphenyl)benzamide (**1a**) with bis(trimethylsilyl)-acetylene.

group) was in situ converted to the ammonium salt, an electron-withdrawing group, and gave a lower yield (entry 13). In addition, the vinylogous amide (**1n**, entry 14) mentions that aryl ring B is not an essential for this reaction, though only a medium yield of product **3n** was achieved.

Improvement of competitive products distribution (favoured to *N*-aryl α-alkynyl imine) was verified by the reaction of **1b** with 1-trimethylsilyl-1-octyne (**2e**). In this reaction, the final cationic elimination of TMSOTf was devised in replace of HOTf (Scheme 2). Under similar conditions for the previous reaction with 1-heptyne (Table 1, entry 2), both *N*-aryl α-alkynyl imine (**3o**, 53%, cationic pathway) and quinoline derivative (**4o**, 24%, Diels–Alder pathway) were afforded. However, *N*-aryl α-alkynyl imine **3o** was improved to be a major product after such a treatment by enhancing the driving force of final cationic elimination of TMSOTf.

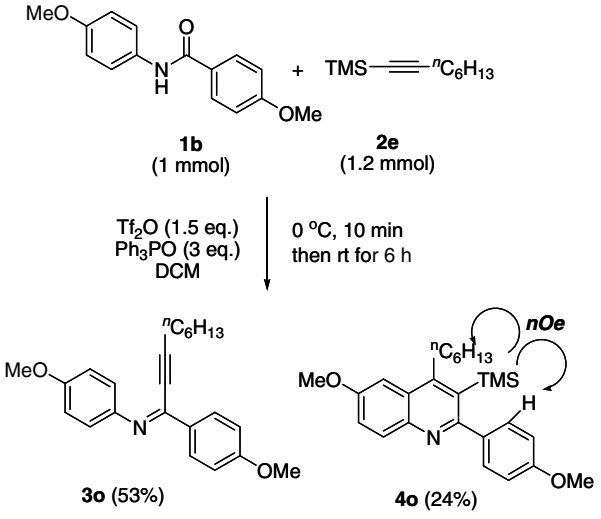
Reactions of amide **1a** with phenylacetylene (**2f**) and 1-phenyl-2-trimethylsilylacetylene (**2g**) were also examined under the above conditions (Scheme 3). Similar to the previous observations, both *N*-aryl α-alkynyl imine (**3p**, 35%) and quinoline derivative (**4p**, 28%) were produced in the reaction of amide **1a** and acetylene **2f**. When a TMS group-bearing acetylene **2g** was used, the reaction afforded a quinoline derivative (**4q**, 33%) and a lower yield of imine (**3p**, 13%), as well as other unidentified byproducts. The later results might be due to the spatial crowd in corresponding intermediate (**B**, Fig. 2). Such a situation dramatically decreased the rate to form a planar intermediate structure which was required for the next elimination of

Table 2
Generality examination of amide substrates



Entry	Reactants	Products	Yields (%)
1	**1a**: $R^1 = OMe$; $R^2 = H$	**3a**	71
2[a]	**1b**: $R^1 = OMe$; $R^2 = OMe$	**3b**	86
3	**1c**: $R^1 = OMe$; $R^2 = Cl$	**3c**	44
4	**1d**: $R^1 = OMe$; $R^2 = {}^tBu$	**3d**	81
5	**1e**: $R^1 = OMe$; $R^2 = NO_2$	**3e**	28
6	**1f**: $R^1 = Me$; $R^2 = OMe$	**3f**	80
7	**1g**: $R^1 = Cl$; $R^2 = OMe$	**3g**	69
8	**1h**: $R^1 = H$; $R^2 = OMe$	**3h**	65
9	**1i**: $R^1 = F$; $R^2 = OMe$	**3i**	59
10	**1j**: $R^1 = NO_2$; $R^2 = OMe$	**3j**	50
11	**1k**: $R^1 = CN$; $R^2 = OMe$	**3k**	57
12	**1l**: $R^1 = CO_2Me$; $R^2 = OMe$	**3l**	65
13	**1m**: $R^1 = NMe_2$; $R^2 = OMe$	**3m**	50
14	**1n**	**3n**	45

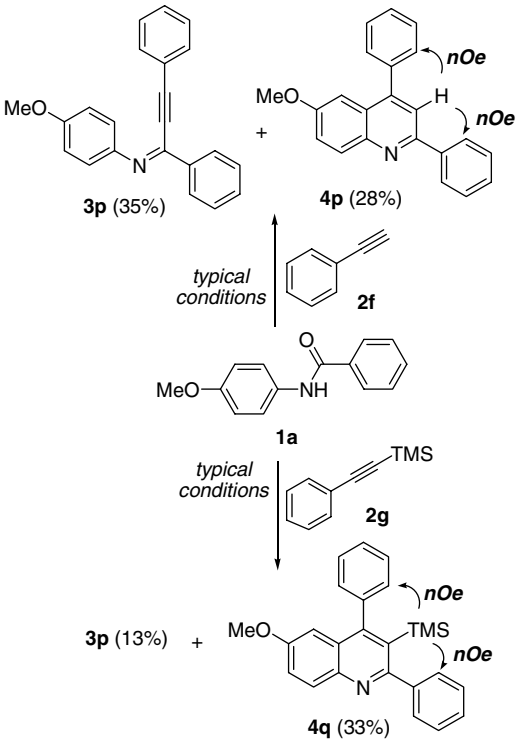
[a] Product **3b** was confirmed by the X-ray single crystal diffraction method.



Scheme 2.

TMSOTf, and finally gave the imine product **3p** in a lower yield.

In summary, a novel metal-free synthesis of *N*-aryl α-alkynyl imines[11] from stable amide precursors is developed. The electronic effects of substrates and the reaction mechanisms were investigated and discussed. This oxophosphonium-triggered one-pot multiple-step method presents advantages of mild conditions, ease of operation, satisfactory efficiency. Further, the improvement of this reaction and the transformation of *N*-aryl α-alkynyl imines to the functional quinolines are underway in our laboratory.



Scheme 3.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.024.

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11. *General procedure:* To a solution of triphenylphosphine oxide (0.83 g, 3 mmol) in dry CH_2Cl_2 (7 mL) was slowly added trifluoromethanesulfonic anhydride (0.25 mL, 1.5 mmol) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. The amide (solid, 1 mmol) and a solution of alkynes (1.2 mmol) in dry CH_2Cl_2 (2 mL) were successively added at this temperature. The reaction temperature was then allowed to warm to room temperature, and the reaction progress was monitored by TLC. The reaction was quenched with 10% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude products were purified by flash chromatography on silica gel.