Hydrogen-Bond-Promoted Metal-Free Hydroamination of Alkynes

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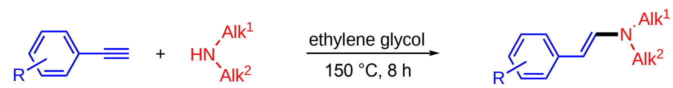
Supporting Information Placeholder



ABSTRACT: An original metal free regio- and stereoselective intermolecular hydroamination of alkynes is described. Various (*E*)-enamines have been obtained from arylacetylenes and aliphatic secondary amines in the presence of ethylene glycol as the solvent. The latter is assumed to play a major role in the mechanism *via* hydrogen bonding and proton exchange.

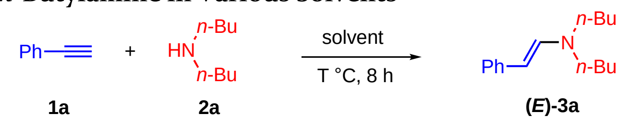
Developing and streamlining the construction of C–N bonds constitutes an important goal in organic synthesis. Indeed, nitrogen-containing molecules are often used as synthetic intermediates[1] and are present in a plethora of natural substances.[2] Among them, enamines are interesting building blocks because of their versatile reactivity toward alkylation, cycloaddition and some related bond-forming reactions for heterocycle synthesis.[3] Hydroamination of alkynes is an atom-efficient process that affords enamines *via* Markovnikov or anti-Markovnikov direct addition of an amine onto an unsaturated triple C–C bond.[4] This transformation is often catalyzed by systems involving lanthanides,[5] alkaline earth metals,[6] acids,[7] bases,[8] and transition metals.[9] Catalytic systems based on Pd,[10] Rh,[11] and Au[12] have been successfully used but they exhibit limitations such as their cost and toxicity, or their low reaction scope and functional group compatibility. Copper also showed interesting catalytic activity for this transformation.[13-14] While for decades, the ability of copper systems to catalyze intramolecular hydroamination of alkynes has been known,[13] there are few intermolecular examples of this reaction.[14] Recently, our group showed that this transformation can be catalyzed by CuCl to afford regioselectively (1*E*,3*E*)-1,4-disubstituted-1,4-dienes,[15] and by CuCN to produce anti-Markovnikov (*E*)-enamines.[16] The use of hydroxylamines and hydrazines to perform metal-free hydroamination of alkynes has been disclosed.[17-18] Inspired by these results, we investigated the possibility of conducting a catalyst-free hydroamination of alkynes, i.e. the formation of enamines starting from arylacetylenes and secondary aliphatic amines. We report herein the first example of metal-free/additive-free hydroamination of alkynes with secondary amines. This original method is stereoselective and effective for the synthesis of anti-Markovnikov enamines.

Our initial experiments were performed using phenylacetylene **1a** and di-*n*-butylamine **2a** (3 equiv) as model substrates in various solvents at 135 °C. No reactivity was detected in CH_3CN, THF and toluene, but traces of the anti-Markovnikov enamine **3a** were obtained in DMSO, DMF, and NMP (Table 1, entries 1–6). Slightly better yields were observed in alcoholic media, such as *n*-hexanol and *n*-butanol, and an encouraging yield of 50% of **3a** (exclusive formation of the *E* isomer) was obtained using ethylene glycol (EG) as solvent (Table 1, entries 7–9). In diethylene glycol (DEG), triethylene glycol (TEG), polyethylene glycol (PEG 400), pinacol, and catechol, a lower yield was observed (Table 1, entries 10–14). In ethylene glycol, raising the temperature from 135 °C to 150 °C afforded an excellent 98% yield of the anti-Markovnikov enamine (*E*)-**3a** (Table 1, entry 15). Decreasing the amount of the amine from 3 to 1 equivalent lowered the yield down to 40% (Table 1, entries 16–17). Microwave activation was also unsuitable for this transformation, as only

15% of expected product was observed after 0.25 h at 150 °C (Table 1, entry 18).

We then explored the scope and tolerance under the optimized conditions (Table 1, entry 15). Symmetrical and dissymmetrical aliphatic secondary amines, such as di-*n*-pentylamine **2b**, di-*n*-propylamine **2c** and *n*-butylethylamine **2d**, reacted smoothly with phenylacetylene and afforded anti-Markovnikov enamines **3b–d** in good to excellent isolated yields (60–96%, Table 1).

Table 1. Hydroamination of Phenylacetylene with di-*n*-Butylamine in Various Solvents [a],[b]



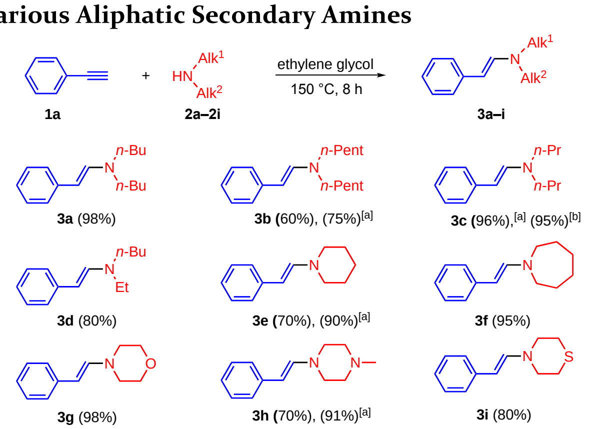
Entry	Solvent	2a (equiv)	T (°C)	3a (%)
1	CH_3CN	3	135	NR
2	THF	3	135	NR
3	Toluene	3	135	NR
4	DMSO	3	135	3
5	DMF	3	135	5
6	NMP	3	135	9
7	*n*-Hexanol	3	135	17
8	BuOH	3	135	19
9	Ethylene glycol	3	135	50
10	Diethylene glycol	3	135	34
11	Triethylene glycol	3	135	28
12	Pinacol	3	135	26
13	PEG (400)	3	135	20
14	Catechol	3	135	NR
15	**Ethylene glycol**	**3**	**150**	**98**
16	Ethylene glycol	2	150	70
17	Ethylene glycol	1	150	40
18	Ethylene glycol	3	MW[c]	15

[a] **1a** (0.5 mmol), **2a** (1.5 mmol) of di-*n*-butylamine, 250 µL of solvent at 135 °C for 8 h, sealed vessel. [b] NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [c] Reaction performed in microwave oven at 150 °C and 200 °C for 0.25 h.

Some examples of cyclic secondary amines bearing different heteroatoms, such as piperidine **e**, azepane **f**, morpholine **g**, *N*-methylpiperazine **h**, and thiomorpholine **i** afforded the desired anti-Markovnikov compounds **3e–i** with good to excellent isolated yields (70–98%, Table 2). Using a higher amount of amines slightly increased the yields of products **3b** and **3h**. This transformation was also efficient on gram-scale, as illustrated with the synthesis of **3c** (Table 2, see **3c**). It should be noted that no reactivity was observed with aliphatic and internal alkynes and/or aromatic amines.

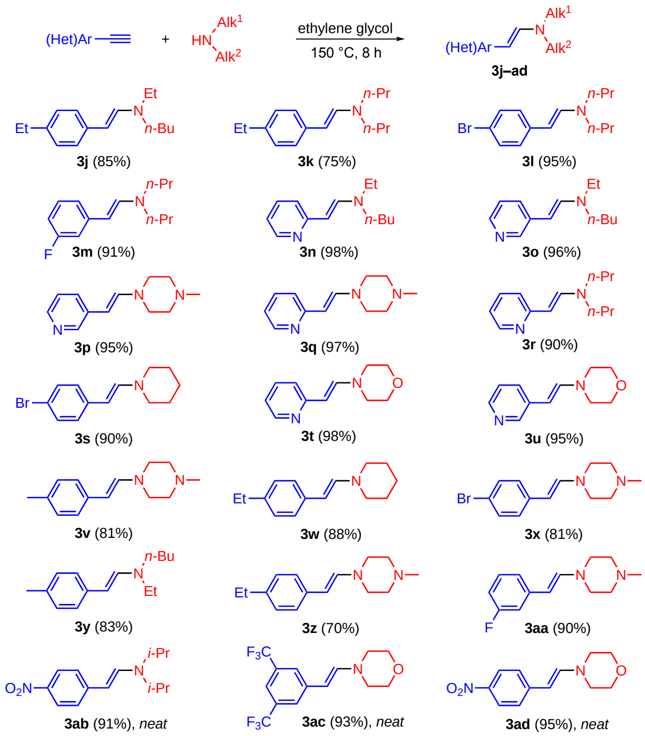
Next, we studied the influence of different substituents on aromatic terminal alkynes (Table 3). Derivatives of aryl- or heteroarylacetylenes bearing either electron-donating or withdrawing and halogen substituents in *meta* or *para* positions reacted well with various secondary cyclic or acyclic amines and afforded the anti-Markovnikov *E* enamines **3j–3ad** with good to excellent yields (70–98%). This synthetic method exhibits excellent regio- and stereoselectivity and is practically simple to carry out (no purification needed). At the end of the reaction, a simple extraction to remove ethylene glycol would suffice. The excess of amine was then evaporated under vacuum.[19] The disubstituted substrates 1-ethynyl-4-nitrobenzene and 1-ethynyl-3,5-bis(trifluoromethyl)-benzene were also converted into the corresponding enamines **3ab**, **3ac**, and **3ad** with excellent yields in neat conditions. Thus, the hydroamination of electronically-activated C–C triple bonds by electron-withdrawing groups apparently does not require the presence of any catalyst or additive.

Table 2. Hydroamination of Phenylacetylene with Various Aliphatic Secondary Amines



General conditions (isolated yields): **1a** (0.5 mmol) with various amines (1.5 mmol) at 150 °C for 8 h in ethylene glycol (250 µL). [a] General conditions with 2.5 mmol of amine. [b] Performed on gram-scale

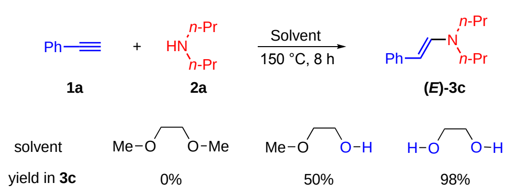
Table 3. Hydroamination Reaction of Various Substituted Hetero)arylacetylenes with Different Aliphatic Secondary Amines



General conditions (isolated yields): arylacetylene (0.5 mmol) with various amines (2.5 mmol) at 150 °C for 8 h in ethylene glycol (250 μL).

First, a radical mechanism was ruled out following the addition of trapping agents, such as Galvinoxyl, TEMPO, or 2,6-di-*tert*-butylphenol, which did not inhibit at all the hydroamination reaction of phenylacetylene with di-*n*-propylamine **2c** (no products derived from a radical species were detected in these conditions). Then, the possible involvement of hydrogen bonds between the amine and ethylene glycol as the driving force for this reaction to occur was examined by conducting the model reaction in methoxyethanol and 1,2-dimethoxyethane in standard conditions (150 °C, 8 h, Scheme 1). Providing one hydrogen bond with methoxyethanol cut the yield of enamine by half (50%). When eliminating both H-bonding sites, by using 1,2-dimethoxyethane, the reaction did not proceed at all. Thus, the presence of the two hydroxyl groups of ethylene glycol seems to be crucial to reach quantitative yields (98%, Scheme 1).

Scheme 1. Impact of the Number of Hydroxyl Groups of the Solvent on the Yield of Enamine 3c



The hydroamination of phenylacetylene **1a** with di-*n*-propylamine **2c** was then carried out in standard conditions (150 °C, 8 h) in D_2- ethylene glycol to test for scrambling (Figure 1). This experiment led to the formation of a mixture of four compounds **3c**/**3c'**/**3c''**/**3c'''** in a 57:14:15:14 ratio. The detection of **3c** as the major product could correspond to the addition of the nitrogen atom on the less-hindered carbon atom followed by the reduction of the triple bonds by abstracting the hydrogen from the amine (Figure 1, way **A**). The formation of **3c'**, albeit to a lesser extent, could result from the abstraction of the deuterium from D_2-ethylene glycol (Figure 1, way B).

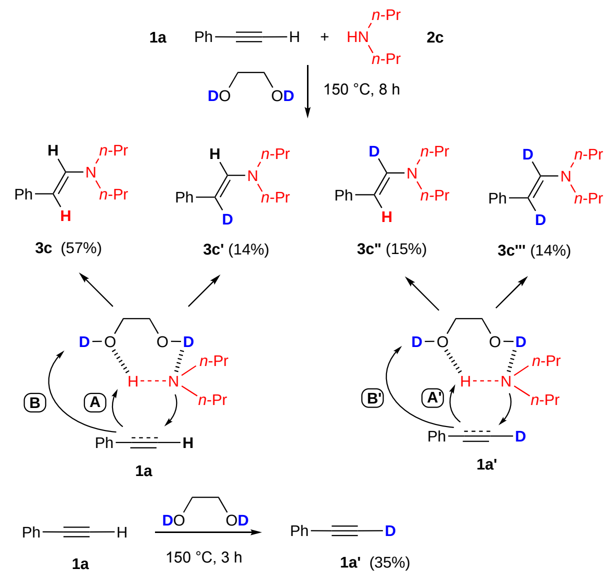


Figure 1. Control Experiments Involving Deuterated Species.

Products **3c''** and **3c'''** are a result of the same type of mechanism (route A' and B', respectively) performed from the *in-situ*-formed deuterated phenyl acetylene **1a'**. We indeed observed in blank experiments that, in standard conditions, a significant amount (35%) of **1a'** resulting from an exchange between the acetylenic proton of phenylacetylene and D_2-ethylene glycol, is formed (Figure 1). A preliminary exchange between the deuterated ethylene glycol and the N–H proton of the di-*n*-propylamine could also partly explain the formation of **3c'** and **3c'''**, respectively from **1a** and **1a'**. These results thus confirm that in our conditions ethylene glycol facilitates the proton transfer between the amine and alkyne reactants.

In summary, we have discovered an unprecedented methodology in metal-free conditions leading to the regio- and stereoselective hydroamination of various acetylenes with different aliphatic secondary amines. Ethylene glycol, used as a solvent, hypothetically promotes this reaction through a mechanism, which may involve hydrogen bonding and proton exchange. Work is now in progress to extend the application field and better understand the mechanism of this system.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds are provided. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

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(19) It is also possible to recover the unused amine in the cold trap and then totally recycle it.