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Hydrogen Bond-Promoted Metal-Free Hydroamination of Alkynes

Janet Bahri, Thierry Ollevier, Marc Taillefer, Florian Monnier

1Ecole Nationale Supérieure de Chimie de Montpellier, Institut Charles Gerhardt, CNRS UMR 5253, AM2N, 8 rue de l'école normale, 34296 Montpellier Cedex 05 (France)
2Département de Chimie, 1045 avenue de la Médecine, Université Laval, Québec (Qc), G1V oA6 (Canada)
3IUF Institut Universitaire de France, 1 rue Descartes, 75231 Paris (France)

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 and are present in a plethora of natural substances. Among them, enamines are interesting building blocks because of their versatile reactivity toward alkylation, cycloaddition and some related bond-forming reactions for heterocycle synthesis. 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. This transformation is often catalyzed by systems involving lanthanides, alkaline earth metals, acids, bases, and transition metals. Catalytic systems based on Pd, Rh, and Au 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. While for decades, the ability of copper systems to catalyze intramolecular hydroamination of alkynes has been known, there are few intermolecular examples of this reaction. Recently, our group showed that this transformation can be catalyzed by CuCl to afford regioselectively (E,2E)-1,4-disubstituted-1,4-dienes, and by CuCN to produce anti-Markovnikov (E)-enamines. The use of hydroxylamines and hydrazines to perform metal-free hydroamination of alkynes has been disclosed. 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 CH3CN, 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 disymmetrical 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**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>2a (equiv)</th>
<th>T (°C)</th>
<th>3a (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>3</td>
<td>135</td>
<td>NR</td>
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<tr>
<td>2</td>
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<td>NR</td>
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<td>3</td>
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<td>NR</td>
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<td>DMSO</td>
<td>3</td>
<td>135</td>
<td>3</td>
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<tr>
<td>5</td>
<td>DMF</td>
<td>3</td>
<td>135</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>NMP</td>
<td>3</td>
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<td>12</td>
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<td>Catechol</td>
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</tr>
<tr>
<td>18</td>
<td>Ethylene glycol</td>
<td>3</td>
<td>MW[c]</td>
<td>15</td>
</tr>
</tbody>
</table>

[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-methylpyrrolidine 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 arylo- 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 enamine 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. The disubstituted substrates 1-ethyl-4-nitrobenzene and 1-ethyl-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**

**Table 3. Hydroamination Reaction of Various Substituted Heteroarylacetylenes 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 Hydroxy 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 D₂-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 57:4:15:14 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 D₂-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 D₂-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 1H NMR and 13C NMR spectra for all new compounds are provided. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION
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REFERENCES

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