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Metadata Record: https://dspace.lboro.ac.uk/2134/13947

Version: Accepted for publication

Publisher: © American Chemical Society

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An Intermolecular Hydroamination of Allenamides Catalysed by Cationic Au(I) Salts

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RECEIVED DATE (will be automatically inserted after manuscript is accepted).

An intermolecular hydroamination of allenes has been achieved under mild Au(I) catalysis conditions delivering allylamine E-enamides stereoselectively and in high yield. The reaction is made possible via a convenient method for conjugated N-acyliminium formation.

The addition of the N-H bond over alkene and alkyne π-systems, the hydroamination transformation, represents a powerful method for the introduction of the amine functionality. Such transformations give access to a range of valuable nitrogen containing building blocks such as amines, imines and enamines. Within this group of reactions the intermolecular hydroamination of allenes has become increasingly important due to the regiochemical factors in such transformations. Allenes (1) can undergo either Markovnikov or anti-Markovnikov addition, giving rise to allylamines (2a) or imines (2b) (Scheme 1). This first group of substrates, allylamines, are vital synthetic building blocks since they are contained within a number of important biological systems and are key intermediates in organic synthesis.

A number of transition metal approaches towards the hydroamination of allenes have been reported, including the use of Zr (anti-Markovikov), Hg (Markovnikov), Pt (Markovnikov) and Pd (Markovnikov) salts. Additional to these transition metals, Au salts have proved to particularly attractive in hydroamination reactions due to their low toxicity and increased stability to moisture and air. Consequently, a number of groups have utilised Au salts in these transformation to great effect. 

SCHEME 1. The hydroamination of allenes.

Recently, we reported the first intermolecular hydroarylation of allenamides with electron rich aromatics using an Au(I) catalyst to give the corresponding enamides. Enamides are a class substrates that have become particularly topical due to their use in the construction of heterocycles, chiral amines and their presence in a number of natural product frameworks. This transformation was high yielding. 


for most substrates and gave exclusively the E-enamide. Importantly, unlike many of the methods\textsuperscript{10} for enamide preparation, the reaction required no exclusion of air and moisture and the reaction was extremely facile.

While there are reported methods for the Au catalysed intermolecular hydroamination of allenes to give allyl amines within the literature,\textsuperscript{3} methods for the intermolecular hydroamination of enamides remains untouched to our knowledge. Whereas the hydroamination of allenes delivers synthetically useful allamylanes, the intermolecular Markovnikov addition of an N-H bond over an enamide \textsuperscript{3} would deliver an allylamino enamide \textsuperscript{4}, a substrate that would contain both an allyl amine and an enamide within the one synthetic framework (Scheme 2). Therefore, in this communication we would like to share our results of the first intermolecular hydroamination of enamides using aniline derivatives under our Au(I) catalytic conditions.

**Scheme 2.** The proposed hydroamination of enamides.

The enamides used for this study are shown below in Scheme 3. Cyclic enamides \textsuperscript{5a} and \textsuperscript{5b} were synthesised using an adapted method of Heaney,\textsuperscript{11} and the acyclic enamide \textsuperscript{7} was synthesised via initial amide formation followed by base catalysed rearrangement.\textsuperscript{12}

Our starting point would be the conditions used for our hydroarylation protocol.\textsuperscript{6} Therefore a solution of enamide \textsuperscript{5a} (1.00 equiv.) and aniline \textsuperscript{8a} (1.05 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} was treated with a catalytic amount (5 mol\%) of cationic Au(I)PPh\textsubscript{3}OTf generated from AuPPh\textsubscript{3} and AgOTf at room temperature (Scheme 4). To our delight the hydroaminated product \textsuperscript{9a} was isolated in 86\% yield after chromatography. The enamide was obtained exclusively as the E-isomer, and the addition of the N-H bond to the activated enamide gave the Markovnikov product.

**Scheme 3.** Preparation of enamides \textsuperscript{5a,b} and \textsuperscript{7}.

A comparable yield of 84\% was also obtained using 5 mol\% of the Au(I) complex, AuPPh\textsubscript{3}(NTf\textsubscript{2}). The stereochemistry of the E-enamide double bond was supported by a combination of \textsuperscript{1}H and \textsuperscript{13}C NMR, IR spectroscopy (coupling constant 14.0 Hz and 1673 cm\textsuperscript{-1}) and single crystal X-ray analysis.\textsuperscript{13}

**Scheme 4.** Hydroamination of enamide \textsuperscript{5a}.

The applicability of this protocol was then further explored, the results of which are summarised in Table 1. Haloamelines \textsuperscript{8b} and \textsuperscript{8f} successfully added to the enamide giving the enamides \textsuperscript{9b} and \textsuperscript{9f} in good yield (entries 1 and 5). Introduction of an electron withdrawing ethyl ester para to the NH\textsubscript{2} gave the enamide \textsuperscript{9e} in a moderate 61\% yield (entry 2), while a nitro group at the ortho position was tolerated and gave the enamide \textsuperscript{9d} quantitatively (entry 3). 2,5-Dimethyl aniline \textsuperscript{8e} and 3-methoxyaniline \textsuperscript{8g} both successfully added to the activated enamide to give the hydroaminated products \textsuperscript{9e} and \textsuperscript{9g}, respectively (entries 4 and 6). Unfortunately, pentafluoroaniline \textsuperscript{8h} failed to add to the activated enamides, presumably due to its low nucleophilicity (entry 7). Finally, N-methyl aniline \textsuperscript{8i} readily participated in the hydroamination reaction giving the N-methyl enamine \textsuperscript{9i} in near quantitative yield (entry 8).

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\textsuperscript{13}(13) Crystal data for \textsuperscript{9a}: C\textsubscript{2}H\textsubscript{4}N\textsubscript{2}O\textsubscript{2}. M = 218.25, monoclinic, \textit{P2}1; \alpha = 16.015(3) Å, b = 5.4583(9), c = 25.143(5) Å, \beta = 99.848(2)°, \gamma = 2165.5(7) Å\textsuperscript{2}; D\textsubscript{calc} = 1.339 g/cm\textsuperscript{3}; \mu (Mo-K\alpha) = 0.093 mm\textsuperscript{-1}; \lambda = 0.71073 Å, T = 150(2) K; 12077 total reflections, 3283 unique data (R\textsubscript{int} = 0.0277); Solved by direct methods and refined on F\textsuperscript{2} values to give R1= 0.0428. See supporting information for further details.
TABLE 1. Substrate scope for the Au(I) catalysed hydroamination of allenamide 5a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H2N→Br</td>
<td>9b</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>H2N→CO2Et</td>
<td>9c</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>O2N→Me</td>
<td>9d</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>H2N→Me</td>
<td>8e</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>H2N→Me</td>
<td>8f</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>H2N→OMe</td>
<td>8g</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>H2N→F</td>
<td>No reaction</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>MeH→NO2</td>
<td>9i</td>
<td>98</td>
</tr>
</tbody>
</table>

“See experimental section for procedure; *data for all new compounds is contained within the supplementary information; †Isolated yields”

The hydroamination reaction was also performed with chiral and acyclic allenamides and the results are shown below in Table 2.

TABLE 2. Variation of the allenamide in the Au(I) catalysed hydroamination reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Aniline</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H2N→Bn</td>
<td>8a</td>
<td>10a</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>H2N→Bn</td>
<td>8f</td>
<td>10b</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>O2N→Me</td>
<td>8f</td>
<td>11a</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>O2N→Me</td>
<td>8g</td>
<td>11b</td>
<td>47</td>
</tr>
</tbody>
</table>

“See experimental section for procedure; *data for all new compounds is contained within the supplementary information; †Isolated yields”

Chiral allenamide 5b successfully underwent hydroamination with both aniline 8a and 2-iodoaniline 8f giving the chiral enamides 10a and 10b, respectively. No epimerization was observed, but slightly reduced yields as compared to the achiral allenamide 5a was seen (entries 1 and 2). The acyclic allenamide also underwent hydroamination with anilines 8f and 8g. A crude 1H NMR of enamides 11a and 11b indicated full conversion to the desired products, however the isolated yields were modest at best and we have attributed this to product degradation during purification.

A mechanistic rationale for this transformation is outlined in Scheme 5.

![Scheme 5](image)

SCHEME 5. Mechanistic rationale for the hydroamination reaction.

We believe that the cationic Au(I) salt activates the allenamide 12 to give an conjugated N-acyl iminium intermediate species 14. This can undergo either 1,2- or 2,3-addition by a suitable nucleophile. In the case at hand the anilines undergo 1,2-addition giving 15 which can then undergo protodemetalation to yield the observed E-enamide 16.

In summary, we have disclosed an Au(I) catalysed protocol for the intermolecular hydroamination of allenamides. The reaction is facile, high yielding and stereoselectively gives the E-enamide products. The products of this reaction, allenamino enamides, have the potential to be valuable building blocks in organic synthesis since they contain two vital functionalities, allyl amines and enamides, within one framework. The chemistry of this building block, the mechanistic insights and the addition of other nucleophilic species to the Au activated conjugated N-acyl iminium species are currently being studied in our group and will be reported on in due course.

Experimental section

Representative hydroamination method with allenamide 5a. To a solution of the allenamide 5a (63 mg, 1.05 equiv., 0.50 mmol) in dichloromethane (3.00 mL) at room temperature was added the aniline derivative (1.05 equiv.) followed by AuPPh₃OTf (from AuCIPPh₃ [12.40 mg, 5.00 mol%, 0.025 mmol] and AgOTf [6.60 mg, 5 mol%, 0.025 mmol]) and the resultant solution stirred for up to 1h at room temperature (monitored by tlc). The resultant reaction mixture was then filtered through a plug of Celite® and the crude mixture purified by column chromatography (ethyl acetate/petroleum ether mixture as indicated). 9a was obtained
as a pale yellow solid (Rf = 0.42) (93 mg, 86 %, MP 89 – 91 °C); [Found (ES): MNa\(^+\), C\(_3\)H\(_6\)N\(_2\)O\(_2\), 241.0944, requires MNa\(^+\) 241.0953]; IR (solution, CHCl\(_3\)) 3441, 3014, 2926, 1755, 1670, 1503, 1413, 1310, 1238, 1206 cm\(^{-1}\); \(^1\)H NMR (400 MHz; CDCl\(_3\)) δ 7.18 (t, J = 8.4 Hz, 2H), 6.91 (d, J = 14.0 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 6.62 (dd, J = 7.6 Hz, 2H), 4.96 (dt, J = 6.4, 14.0 Hz, 1H), 4.42 (dd, J = 8.0, 9.2 Hz, 2H), 3.80 (d, J = 6.4 Hz, 2H), 3.73 (bs, 1H), 3.69 (t, J = 8.0 Hz, 2H); \(^1\)C NMR (100 MHz; CDCl\(_3\)) δ 155.3(C), 147.8(C), 129.3(CH), 126.4(CH), 117.8(CH), 113.1(CH), 107.7(CH), 62.2(CH\(_2\)), 43.8(CH\(_3\)), 42.5(CH).

**Representative hydroamination method with allenamide 5b.** To a solution of the allenamide 5b (50 mg, 1.00 equiv., 0.232 mmol) in dichloromethane (2.00 mL) at room temperature was added the aniline derivative (1.05 equiv.) followed by AuClPPh\(_3\)OTf (from AuClPPh\(_3\) [5.80 mg, 5.00 mol%, 0.012 mmol] and AgOTf [3.00 mg, 5 mol%, 0.012 mmol]) and the resultant solution stirred for up to 1h at room temperature (monitored by tlc). The resultant reaction mixture was then filtered through a plug of Celite\(^6\) and the crude mixture purified by column chromatography (ethyl acetate/petroleum ether mixture as indicated). 10a was obtained as a colourless oil (Rf = 0.5) (48 mg, 68%); [\(\alpha\)]\(_D\)\(^{20}\) = 26.0 (c 1.00, CHCl\(_3\)) [Found (ES): MNa\(^+\), C\(_3\)H\(_6\)N\(_2\)O\(_2\), found 331.1413, requires MNa\(^+\) 331.1422]; IR (solution, CHCl\(_3\)) 3014, 2926, 1755, 1670, 1503, 1413, 1310, 1238, 1206 cm\(^{-1}\); \(^1\)H NMR (400 MHz; CDCl\(_3\)) δ 7.35 – 7.26 (m, 3H), 7.20 (t, J = 8.0 Hz, 2H), 7.15 – 7.13 (m, 2H), 6.84 (d, J = 14.4 Hz, 1H), 6.74 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 5.22 (dt, J = 6.4, 14.4 Hz, 1H), 4.27 – 4.17 (m, 3H), 3.87 – 3.83 (m, 2H), 3.21 – 3.18 (m, 1H), 2.81 – 2.76 (m, 1H); \(^1\)C NMR (100 MHz;CDCl\(_3\)) δ 155.8(C), 147.8(C), 135.2(C), 129.3(CH), 129.0(CH), 127.4(CH), 125.3(CH), 117.9(CH), 113.2(CH), 108.3(CH), 66.7(CH\(_2\)), 55.0(CH), 44.2(CH\(_2\)), 36.3(CH\(_3\)).

**Representative hydroamination method with allenamide 7.** To a solution of the allenamide 7 (50 mg, 1.00 equiv., 0.289 mmol) in dichloromethane (3.00 mL) at room temperature was added the aniline derivative (1.05 equiv.) followed by AuClPPh\(_3\)OTf (from AuClPPh\(_3\) [7.20 mg, 5.00 mol%, 0.014 mmol] and AgOTf [3.70 mg, 5 mol%, 0.014 mmol]) and the resultant solution stirred for up to 1h at room temperature (monitored by tlc). The resultant reaction mixture was then filtered through a plug of Celite\(^6\) and the crude mixture purified by column chromatography (ethyl acetate/petroleum ether mixture as indicated). 11a was obtained as a yellow oil (Rf = 0.35) (52 mg, 46%); [Found (ES): MNa\(^+\), C\(_7\)H\(_7\)N\(_2\)O, found 331.415271, requires MNa\(^+\) 331.415283]; IR (solution, CHCl\(_3\)) 3441, 3011, 1638, 1590, 1506, 1389, 1069 cm\(^{-1}\); \(^1\)H NMR (400 MHz; CDCl\(_3\)) (mixture of rotamers) δ 7.64 (d, J = 7.6 Hz, 1H), 7.49 – 7.40 (m, 5H), 7.20 (t, J = 7.2 Hz, 1H), 6.78 (bs, 1H), 6.50 (bs, 1H), 6.48 – 6.44 (m, 1H), 5.16 (bs, 1H), 4.17 (bs, 1H), 3.77 – 3.75 (m, 2H), 3.27 (bs, 3H); \(^1\)C NMR (100 MHz;CDCl\(_3\)) (mixture of rotamers) δ 170.9(C), 146.4(C), 139.1(CH), 135.7(C), 133.0(CH), 129.4(CH), 128.7(CH), 128.0(CH), 119.0(CH), 110.8(CH), 105.7(CH), 85.7(C), 44.1(CH\(_2\)), 30.4(CH\(_3\)).

**Acknowledgments.** The author thanks Loughborough University for financial support.

**Supporting Information Available.** Experimental procedures, \(^1\)H and \(^13\)C NMR spectra, characterization for 9a-9l, 10a, b, 11a,b and the crystallographic data for 9a. This material is available free of charge via the Internet at http://pubs.acs.org.