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Citation: SINGH, S., ELSEGOOD, M.R.J. and KIMBER, M.C., 2012. An Au(I)-catalysed allenamide cyclisation giving access to an \( \alpha \)-vinyl-substituted tetrahydroisoquinoline building block. Synlett, 23 (4), pp. 565 - 568

Additional Information:

- This article was published in the journal, Synlett [© Georg Thieme Verlag]. The definitive version is available at: http://dx.doi.org/10.1055/s-0031-1290335

Metadata Record: https://dspace.lboro.ac.uk/2134/13935

Version: Accepted for publication

Publisher: © Georg Thieme Verlag

Please cite the published version.
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An Au(I) catalysed allenamide cyclisation giving access to a α-vinyl substituted tetrahydroisoquinoline building block

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Received: The date will be inserted once the manuscript is accepted.

Abstract: An Au(I) catalysed intramolecular hydroarylation of an enantiopure allenamide has been achieved and has given access to a key α-vinyl substituted tetrahydroisoquinoline. Additionally this has been accomplished in very high yield and high diastereoselectivity.

Key words: Alkaloids, allenamide, tetrahydroisoquinoline, Au(I)-catalysis, diastereoselective.

Tetrahydroisoquinolines are highly significant synthetic subunits contained within many biologically active alkaloids (Figure 1). Contained within many of these alkaloids is a stereogenic centre at the α-position on the ring which is commonly installed, either enantio- or diastereoselectively, via a Pictet-Spengler or Bischler-Napieralski condensations. Ideally, a key synthetic building block for the total synthesis of such targets would be the α-vinyl substituted tetrahydroisoquinoline, since the vinyl group can be readily manipulated (Scheme 1).

Scheme 1. Tetrahydroisoquinoline natural products crispine A (1), quinocarcin (2), korumpensamine (3) and α-vinyl tetrahydroisoquinoline building block (4) and its known conversion to 5 and 6.

However, access to α-vinyl substituted tetrahydroisoquinolines using the Pictet-Spengler or Bischler-Napieralski approaches is somewhat problematic and therefore unsuitable. To overcome this chemical issue a number of approaches have been disclosed, including: (a) vinyl organometallic addition to suitable quinoline substrates, (b) Pd-catalysed addition to allenamides, (c) iridium and palladium catalysed intramolecular allylic amination, and finally, (d) an intramolecular hydroarylation on a masked conjugated N-acyl iminium species (Scheme 2), and it is this last approach that is the focus of this letter.

In 2005 Rutjes reported a synthetically flexible route to α-vinyl substituted tetrahydroisoquinoline building blocks (10) via a Sn(II) or TFA catalysed cyclisation of allylic N,O-acetals (7). This was followed in 2007 by Navarro-Vazquez and Dominguez who elegantly illustrated that allenamides (8) could be cyclised under acidic condition to yield α-vinyl substituted tetrahydroisoquinolines (10) in good yield. While both authors used a masked conjugated N-acyl iminium (9) to generate their α-vinyl tetrahydroisoquinoline substrates (10), it was only the work of Rutjes who investigated any diastereoselectivity in their transformation, which was found to be modest.

Scheme 2. Previous N-acyl iminium approaches to α-vinyl tetrahydroisoquinolines

Recently, we described the Au(I) activation of allenamides and their subsequent reaction with electron rich arenes and arylamines to yield functionalised enamide building blocks (Scheme 3). This approach to allenamide activation, under such mild conditions, led us to consider whether an intramolecular arene cyclisation could be accomplished. Therefore, in this brief letter we would like to disclose a concise and yet highly diastereoselective route to a key α-vinyl substituted tetrahydroisoquinoline building blocks.

Scheme 3.
To test our approach to Au(I)-catalysed intramolecular cyclisation we synthesised allenamide 17 in two steps from the known acid 15 (Scheme 4). Allenamide 17 was then exposed to a variety of cyclisation conditions as shown in Table 1.

Scheme 4. (a) DCC, CH₃Cl, DMAP, N-methylpropargyl amine; (b) THF, KO'Bu [75% over 2-steps].

Table 1. Conditions for the intramolecular cyclisation of 17 to 18.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp.(ºC)</th>
<th>T (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuPPh₃OTf</td>
<td>r.t.</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>AuPPh₃NTf₂</td>
<td>35</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf</td>
<td>r.t.</td>
<td>16</td>
<td>s.m.</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>r.t.</td>
<td>16</td>
<td>decomp.</td>
</tr>
<tr>
<td>5</td>
<td>AuPPh₃OTf</td>
<td>r.t.</td>
<td>16</td>
<td>96</td>
</tr>
</tbody>
</table>

All reactions were performed under an atmosphere of N₂ unless otherwise stated and with 5 mol% catalysts unless otherwise stated. Isolated yield. 20 mol%, 2.5 mol%.

Exposure of 17 to 5 mol% AuPPh₃OTf gave the desired intramolecular cyclisation product in an excellent yield with tlc showing full consumption of the starting material within an hour (entry 1). A switch to the AuPPh₃NTf₂ did give the desired product but the reaction time was extended considerably (entry 2). To show the requirement of Au(I) catalysts the reaction was undertaken with AgOTf which gave only starting material (entry 3), while TFA did catalyse the reaction but gave predominantly decomposition products (entry 4). Finally, we decreased the catalysts loading of AuPPh₃OTf to 2.5mol% which furnished the cyclized product in 96% yield but required an extended reaction time as compared to entry 1.

With result in hand we then investigated the cyclisation the Boc protected allenamide 21 which was synthesised in 3-steps from the known acid 19 (Scheme 5). Unfortunately, exposure of this substrate to our Au(I) catalyzed cyclisation conditions, failed to deliver any of the desired product with only starting material being returned. We believe that this maybe a consequence of the bulky Boc protecting group contained within 21 hampering activation of the allenamide by the Au(I) catalyst.

Consequently, based on our previous investigations on intermolecular allenamide activation we targeted an oxazolidinone protected allenamide 22 as a Boc surrogate.

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Scheme 5. (a) Boc₂O, NEt₃, H₂O, dioxane; (b) MeI, K₂CO₃, DMF; NaH; (c) KO'Bu, propargyl bromide [60% over 3-steps]; (d) AuPPh₃OTf or AuPPh₃NTf₂ (5 mol%), CH₂Cl₂, rt or reflux, 16h.

The synthesis began with conversion of L-DOPA (13) to its Boc protected methyl ester under standard conditions, followed by global methylation with MeI and K₂CO₃ to give 14 in 92% overall yield over the 3-steps. Subsequent LiBH₄ reduction of 14 and treatment of the crude product with thionyl chloride in THF delivered the oxazolidinone 15 in 88% yield over the 2-steps. Finally, 15 was alkylated with propargyl bromide to furnish the alkyne 16 which could then be rearranged under basic conditions to give the desired chiral allenamide 22 in 62% yield. Alternatively, treatment of 15 under modified Heaney/Ley conditions with propargyl bromide directly gave 22 in 60% yield. Allenamide 22 proved to be crystalline and crystals suitable for single crystal X-ray analysis were obtained. The X-ray depiction is shown below in Scheme 6.

Scheme 6. (a) MeOH, SOCl₂; (b) Boc₂O, Et₃N, MeOH; (c) MeI, K₂CO₃, DMF [92% over 3-steps]; (d) LiBH₄, THF; (e) SOCl₂, THF [88% over 2-steps]; (f) NaH, propargyl bromide (80% in hexane); (g) KO'Bu, THF [62% over 2-steps]; (h) KO'Bu, propargyl bromide (80% in hexane), DMSO [60%].

Treatment of 22 with AuPPh₃OTf (5 mol%) in CH₂Cl₂ delivered a single product 23 in quantitative yield. The reaction time was remarkably short, with the reaction completion within minutes of the addition of the Au(I) salt, indicating a very facile reaction. Exhaustive NMR analysis indicated a single product with a δe > 98% and with an
absolute stereochemistry as shown in Scheme 7. The relative stereochemistry of the product was assigned on the basis of a NOESY enhancement between $H_6$ and the vinylic $H_2$ proton.

\[ \text{Scheme 7. Au(I) catalysed cyclisation of 22} \]

Treatment of allenamide 22 with AuPPh$_3$NTf$_2$ (5 mol%) also gave the tetrahydroisoquinoline 23 quantitatively and in excellent de. It must be noted this high diastereoselectivity is in contrast to the moderate de's reported by Rutjes$^5$ for similar cyclisations, and the high yield is a significant improvement over that reported by Navarro-Vázquez and Domínguez$^2$ for their TFA catalysed cyclisations of allenamides.

In summary, a brief, yet high yielding synthesis of a key α-vinyl substituted tetrahydroisoquinoline has been achieved. The key step was an Au(I)-catalysed hydroarylation of a chiral pool derived allenamide delivering the key building block in high diastereoselectivity. Use of this building block and this synthetic approach for the synthesis of alkaloid natural products is currently under investigation.

Supporting Information for this article include $^1$H and $^{13}$C NMR of 22 and 23 and the Crystallographic data for 22.

Acknowledgments

The authors thank Loughborough University for funding and Mark Edgar for NMR analysis.

References and Notes


(13) (S)-4-(3,4-Dimethoxybenzyl)-3-(propa-1,2-diyl) oxazolidin-2-one. To a solution of 15 (0.58 g, 2.45 mmol) in THF (20 mL) at 0°C under a N$_2$ atmosphere was added NaH (0.12 g, 2.93 mmol) and the mixture stirred at room temperature for 2h. After this period propargyl bromide (0.32 mL, 2.88 mmol) was added cautiously and the reaction mixture stirred for a further 24h at room temperature. After this period sat. NH$_4$Cl was added and the resultant aqueous layer extracted with Et$_2$O (x2). The combined organic layers were then washed with brine, dried (Na$_2$SO$_4$), filtered and the solvent removed in vacuo. The crude product was then dissolved in THF (20 mL) and cooled to 0°C followed by addition of BuOK (0.08 g, 0.66 mmol). The reaction mixture was then stirred for 2h at 0°C after which all the starting material had been consumed. The reaction mixture was then diluted with Et$_2$O and washed sequentially with H$_2$O and brine. The combined organic layers were then dried (Na$_2$SO$_4$), filtered and the solvent removed in vacuo. The crude product was then purified by column chromatography (R$_f$ = 0.55, 1:1 ethyl acetate – petroleum ether) yielding the title compound as a colourless solid (0.40 g, 60%), m.p. 118-120°C from CH$_2$Cl$_2$ – petroleum ether; $\nu_{max}$ (solution, CHCl$_3$) 3021, 1752, 1516, 1461, 1262, 1226, 1028 cm$^{-1}$; $\delta_0$ (400 MHz; CDCl$_3$) 6.84 (t, $J$ = 6.8 Hz, 1H), 6.76 – 6.73 (m, 1H), 6.64 – 6.62 (m, 1H), 6.58 (d, $J$ = 1.6 Hz, 1H), 5.51 (dd, $J$ = 6.4, 10.0 Hz), 5.44 (dd, $J$ = 6.4, 10.0 Hz), 4.20 (t, $J$ = 8.4 Hz, 1H), 4.08 (dd, $J$ = 3.6, 8.8 Hz, 1H), 4.05 – 4.00 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.06 (dd, $J$ = 3.2, 14.0 Hz, 1H), 2.65 (dd, $J$ = 8.8, 14.0 Hz, 1H); $\delta_0$ (100 MHz; CDCl$_3$) 201.7(C), 155.0(C), 149.2(C), 148.3(C), 127.9(C), 121.4(CH), 112.4(CH), 111.5(CH), 111.5(CH), 96.0(CH), 87.9(CH), 66.6(CH), 56.0(CH), 55.7(CH), 36.6(CH). HRMS M$^+$, C$_9$H$_7$NO$_3$ found 298.1045, requires M$^+$ 298.1055; $[\alpha]_D^{20} = 2.03$ (c 1.00 CHCl$_3$).


(15) Crystal data for 22: C$_5$H$_3$NO$_2$: $M$ = 275.30, orthorhombic, space group $P$2$_1$$\bar{2}$1$\bar{2}$, $a$ = 7.2379(10), $b$ = 11.5884(15), $c$ = 16.6772(2) A, $V$ = 1398.8(3) A$^3$, $T$ = 150 K, $Z$ = 4, $\mu$(Mo-Ka) = 0.095 mm$^{-1}$, 1422 data measured using a Bruker APEX 2 CCD diffractometer with graphite-monochromated Mo-Ka radiation.
(λ = 0.71073 Å). 2026 data were unique, \( R_{\text{int}} = 0.0329 \); all unique data used in refinement against \( F^2 \) values to give final \( wR_2 = 0.0885 \) (on \( F^2 \) for all data), \( R = 0.0338 \) [for 1831 data with \( F^2 > 2\sigma(F^2) \)], absolute structure could not be determined from the diffraction data; Friedel pairs were merged. \( H \) atoms on C(6) had coordinates freely refined; all other \( H \) atoms were constrained. Programs used were Bruker SMART\(^{(16)}\), SAINT\(^{(16)}\), SHELXTL\(^{(17,18)}\) and local programs. CCDC 838703 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) SMART and SAINT software for CCD diffractometers, Bruker AXS Inc, Madison, WI, 2008.


(19) To our knowledge the only previous example of a single crystal X-ray structure of an unsubstituted chiral allenamide was reported by the group of Hsung (see, Tracey, M. R.; Grebe, T. P. Brennessel, W. W.; Hsung, R. P. Acta Cryst. 2004, C60, o830).

(20) To a solution of 22 (100 mg, 0.36 mmol) in CH\(_2\)Cl\(_2\) (2 mL) at room temperature was added a 5 mol% solution of AuPPh\(_3\)OTf. (NB. The 5 mol% solution of AgPPh\(_3\)OTf was prepared from the addition of AuClPPh\(_3\) (9 mg, 0.018 mmol) to AgOTf (4.7 mg, 0.018 mmol)) in CH\(_2\)Cl\(_2\) (1 mL) and the resultant suspension stirred for 10 min. at room temperature). After 5 min., the starting material was consumed after which the solvent was removed in vacuo. The crude product was then purified by column chromatography (\( R_f = 0.25, 1:1 \) ethyl acetate - petroleum ether) to yield 23 as a colourless oil (98 mg, quantitative); \( \nu_{\text{max}} \) (solution, CHCl\(_3\)) 3020, 2936, 1749, 1613, 1518, 1420, 1226, 1115 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 6.62 (s, 1H), 6.58 (s, 1H), 5.98 – 5.90 (m, 1H), 5.29 – 5.24 (m, 3H), 4.57 – 4.52 (t, \( J = 8.4 \) Hz, 1H), 4.15 – 4.12 (dd, \( J = 8.4, 8.8 \) Hz, 1H), 4.05 – 3.99 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.83 (d, \( J = 7.7 \) Hz, 2H); \( \delta_C \) (100 MHz, CDCl\(_3\)) 156.7 (C), 148.3 (C), 148.0 (C), 136.4 (CH), 125.2 (C), 127.7 (C), 117.5 (CH\(_2\)), 111.6 (C), 110.4 (C), 68.5 (CH\(_2\)), 56.0 (CH\(_2\)), 55.9 (CH\(_3\)), 54.7 (CH\(_2\)), 48.6 (C), 33.8 (CH\(_2\)); HRMS MNa\(^+\), \( C_{15}H_{17}NO_4 \), found 298.1044, requires MNa\(^+\) 298.1055; \([\alpha]_{D}^{21}\) -160.8 (c 1.00 CHCl\(_3\)).
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![Chemical structure diagram]