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A facile gold(I)-catalysed intramolecular alkyne hydroarylation approach to methyl 5-amino-2*H*-1-benzopyran-8-carboxylate derivatives

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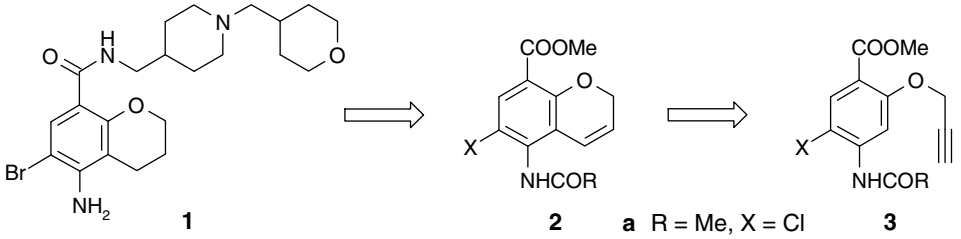
ABSTRACT

A high yielding and selective method for producing methyl 5-amino-2*H*-1-benzopyran-8-carboxylate derivatives via gold(I)-catalysed intramolecular alkyne hydroarylation has been developed.

A key step in the initial synthesis of 5-HT_4 agonist **1** is construction of methyl 5-acetamido-6-chloro-2*H*-1-benzopyran-8-carboxylate (**2a**) via thermal cyclisation of aryl propargyl ether **3a**.[1] Such methodology has been used for related compounds from this therapeutic class.[2–4] However, the high temperature cyclisation of **3a** to **2a** proceeded in only moderate yield due to competing reaction pathways[4,5] and posed significant challenges on scale-up. As part of an investigation into alternative routes[6] to **1**, we were intrigued by the potential utility of metal-catalysed intramolecular alkyne hydroarylation of **3**.



Evaluation of the metal-catalysed cyclisation was carried out in the first instance with platinum(IV) and platinum(II) chloride using aryl propargyl ether **3b**,[4,7] based on the precedent from the groups of Sames[8] and Echavarren.[9] The des-chloro substrate **3b** was chosen for synthetic expediency since in the initial synthesis of **1** the chlorine atom was introduced to facilitate the thermal cyclisation and subsequently removed by hydrogenolysis. Whilst promising results were obtained (Table 1, entries 1–3), the yields of 2*H*-1-benzopyran **2b**[4,7] were limited by competing de-alkylation to phenol **4b**.[7,10] A minor product identified was the methyl ketone **5b**[11] derived from hydration of the alkyne. Unlike the Sames findings,[8] platinum(II) chloride gave a higher yield of **2b** than platinum(IV) chloride. We postulated that dealkylation might be promoted by the presence of chloride ions and considered addition of a silver salt to sequester the chloride. However, platinum(II) chloride with equimolar silver trifluoromethanesulfonate did not significantly improve the yield of **2b**. Interestingly, AgOTf (5 mol %) alone catalysed the reaction (Table 1, entry 4) but gave additional products **6** and **7** characteristic of the high temperature thermal process.[4,12] Thus, benzopyran **2b** was isolated in 46% yield together with benzofuran **6** and indole **7**, in 15% and 8% yields, respectively. It appears that the silver trifluoromethanesulfonate-catalysed reaction proceeded, at least in part, via the Claisen-like [3,3] sigmatropic rearrangement postulated for the thermal process[4] rather than the electrophilic hydroarylation pathway proposed by Sames for the platinum-mediated reaction.[8b]

In recent years, cationic phosphine–gold(I) complexes have emerged as powerful homogeneous catalysts for electrophilic activation of alkynes.[13] Indeed, several examples of 2*H*-1-benzopyran

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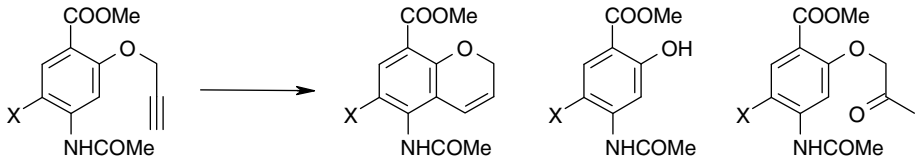
Table 1
Metal-catalysed intramolecular hydroarylation of aryl propargyl ethers **3b** and **3a**



3 **2** **4** **5**

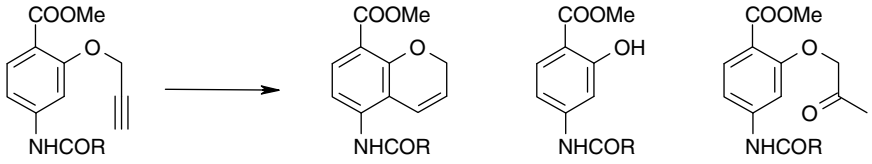
Entry	Catalyst (mol %)	Conditions	HPLC product ratio[a] (%a/a)			Yield[b] (%)
			2	**4**	**5**	**2**
3b: X = H						
1	$PtCl_4$ (5)[c]	Dioxane, 55 °C, O/N	27.8	49.1	4.1	26
2	$PtCl_2$ (5)	Dioxane, 85 °C, O/N	50.2[d]	25.9	2.0	50
3	$PtCl_2$ (5)	2-MeTHF, 70 °C, 24 h	53.4	23.5	1.8	53
4	AgOTf (5)	2-MeTHF, 75 °C, O/N[e]	47.0	8.0	2.7	46
5	(Ph_3P)AuCl/AgOTf (5)	2-MeTHF, 70 °C, 1 h	74.8	7.5	5.0	75
6	(Ph_3P)AuCl/AgOTf (1)	2-MeTHF, 70 °C, 7 h	83.6	9.6	5.2	73[f]
3a: X = Cl						
7	(Ph_3P)AuCl/AgOTf (2)	2-MeTHF, 70 °C, 6 h[g]	10.7	5.5	2.1[h]	–

[a] HPLC peak areas at 220 nm as a percentage of total peaks area.
[b] Isolated yield after silica chromatography, unless noted otherwise.
[c] 5 mol % for 3 h then a further 4 mol % added.
[d] A minor product tentatively assigned as the isomeric 4*H*-benzopyran was also observed (3.5% a/a).
[e] 17.6% a/a of the benzofuran **6** (isolated yield 15%), 15.9% a/a of the indole **7** (isolated yield 8%).[12]
[f] Isolated by crystallisation (with ca. 11% of **2b** in the liquors by HPLC quantitation).
[g] 77.5% a/a **3a** remained.
[h] Methyl ketone product **5a** tentatively assigned.

synthesis via cationic gold(I)-catalysed alkyne hydroarylation have been reported,[9b,14] although only for substrates bearing electron-donating hydroxy or alkoxy substituents. Significantly, application of the cationic gold(I) catalyst generated in situ from chloro(triphenylphospine)gold(I) and silver trifluoromethanesulfonate gave a striking improvement in the rate of reaction, the yield of benzopyran **2b** and the by-product profile due to reduced dealkylation to phenol **4b** (Table 1, entry 5).[15] In addition, a slightly higher amount of methyl ketone **5b** was observed. The catalyst loading was successfully reduced to 1 mol % in situ generated (Ph_3P)AuOTf (Table 1, entry 6). The benzopyran product **2b** was isolated in 73% yield (HPLC purity 98.5%) by crystallisation from 2-methyltetrahydrofuran (2-MeTHF), which purged the by-products **4b** and **5b**, leaving a further ca. 11% of **2b** in the liquors. By comparison, the chloro analogue **3a**[7] was found to be a poor substrate for the gold-catalysed hydroarylation, giving only ca. 10% of **2a** (Table 1, entry 7), suggesting that the aryl group was rendered too electron-poor for facile cyclisation.

The moderate solubility of acetamide **2b** in reaction solvents, notably 2-MeTHF, meant that it crystallised prematurely during the reaction. It was more desirable to have the product remain soluble in hot solvent so that catalyst-derived material could be removed by filtration at the end of the reaction prior to isolation. Hence, further development of the gold(I)-catalysed intramolecular hydroarylation continued with the more soluble pivalamide **3d**[4,6] (Table 2). Aryl propargyl ether **3d** gave a marginally faster reaction

Table 2
Gold(I)-catalysed intramolecular hydroarylation using (Ph_3P)AuNTf$_2$



3 **2** **4** **5**

Entry	Catalyst (mol %)	Conditions	HPLC product ratio[a] (%a/a)			Yield[b] (%)
			2	**4**	**5**	**2**
3d: R = CMe_3						
1	(Ph_3P)AuCl/AgOTf (1)	2-MeTHF, 70 °C, 3 h	79.1	11.6	6.0	80
2	(Ph_3P)AuNTf$_2$ (0.5)	2-MeTHF, 70 °C, 5 h	84.1	7.9	3.7	87
3	(Ph_3P)AuNTf$_2$ (0.5)	$CF_3C_6H_5$, 85 °C, 1 h	90.5	2.8	2.2	88
4	(Ph_3P)AuNTf$_2$ (0.5)	Toluene, 85 °C, 1 h	91.9	2.5	1.5	92
5	(Ph_3P)AuNTf$_2$ (0.1)	Toluene, 85 °C, 2 h	94.0	2.3	0.9	80[c]
3b: R = Me						
6	(Ph_3P)AuNTf$_2$ (0.5)	Toluene, 85 °C, 1 h	92.1	3.1	1.3	92[d]

[a] HPLC peak areas at 220 nm as a percentage of total peaks area (corrected for solvent peak in the case of trifluorotoluene and toluene reactions).
[b] Isolated yield after silica chromatography, unless otherwise noted.
[c] Isolated by crystallisation from toluene, with ca. 10% of **2d** in the liquors by HPLC quantitation.[17]
[d] Isolated by direct crystallisation from the reaction mixture.

in 2-MeTHF with the in situ generated catalyst than **3b**, affording **2d**[4] in 80% yield after flash chromatography (Table 2, entry 1). De-alkylation to phenol **4d**[4] and alkyne hydration to methyl ketone **5d**[11] were again observed at similar levels. However, it should be noted that the tabulated HPLC peak area data somewhat over estimate the levels of **4d** and **5d** due to higher response factors (2.3 and 1.5, respectively) relative to **2d** (1.0) at 220 nm.

The cost of a gold catalyst was likely to be significant on scale up so a major driver was to minimise the catalyst loading. To do this conveniently on a small scale during process development, the isolable catalyst triphenylphosphine gold(I) bis(trifluoromethanesulfonyl)imidate [$(Ph_3P)AuNTf_2$] reported by Gagosz was used.[14,16] This triflimide catalyst (0.5 mol %) gave a slightly higher yield of **2d** (Table 2, entry 2) than the in situ generated $(Ph_3P)AuOTf$ (1 mol %). This may be rationalised by the combination of less dealkylation to phenol **4d**, perhaps due to the absence of any nucleophilic anion or any effect due to a silver salt, and lower alkyne hydration. However, attempts to reduce the catalyst loading to 0.1 or 0.25 mol % in 2-MeTHF resulted in incomplete reactions. A solvent screen was carried out using $(Ph_3P)AuNTf_2$ with the dual aim of reducing the level of minor products and providing scope for reducing catalyst loading. This highlighted α,α,α-trifluorotoluene and toluene as the most promising solvents, giving both a reduction in de-alkylation to **4d** and formation of methyl ketone **5d**. Thus, **2d** was obtained in ca. 90% yield after column chromatography using 0.5 mol % $(Ph_3P)AuNTf_2$ at 85 °C (Table 2, entries 3 and 4). Pleasingly, a lower loading of 0.1 mol % $(Ph_3P)AuNTf_2$ in toluene now gave complete turnover of **3d** to **2d** (Table 2, entry 5). In this case, the benzopyran **2d** was isolated by crystallisation following hot filtration to remove catalyst-derived material.[17] The isolated **2d** contained some residual gold (220 ppm). At this early stage of development metal scavenging was not investigated, although it was anticipated that the gold content would be substantially reduced in the remaining steps required to convert **2d** to the target substance **1**. The acetate **3b** also gave an improved yield of **2b** and less side products with $(Ph_3P)AuNTf_2$ in toluene (Table 2, entry 6).

In summary, a high yielding method for producing methyl 5-amino-2*H*-1-benzopyran-8-carboxylate derivatives **2b** and **2d** via gold(I)-catalysed intramolecular alkyne hydroarylation has been developed. This method provides access to the benzopyran moiety which is a common substructure in pharmaceutical agents. Of the metal catalysts evaluated, cationic gold(I) species were superior and appear to operate via an electrophilic substitution mechanism rather than the Claisen rearrangement manifold of the thermal process.[8b] Low catalyst loading (0.1 mol %) was demonstrated, suggesting that an economic process could be achieved. Further optimisation of solvent, temperature and catalyst loading has yet to be carried out. In addition, other cationic gold(I) catalysts remain to be evaluated.[18,19] The gold-catalysed method avoids the harsh conditions of the corresponding thermal process, which typically requires temperatures of 180–240 °C,[1,4] and in the case of formation of **2b** is much cleaner and higher yielding. A chloro substituent provided selectivity for benzopyran products over alternative isomeric benzofurans for the thermal process,[4] whereas des-chloro substrates proved advantageous in our gold-catalysed benzopyran synthesis, demonstrating some complementarity between the methods.

Acknowledgements

We thank Dr. Klaus Laue (Carbogen Amcis) for initial studies using substrate **3a**. We are grateful to Simon Hayes and Kate Ross for performing screening experiments and Alec Simpson for accurate mass determinations. Dr. Matthew Gray is acknowledged for helpful discussions.

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5. It should be noted that Kakigami et al.[4] reported a modest yield of **2a** from **3a** (29%) in refluxing *N*,*N*-diethylaniline, but saw a significant improvement with the pivaloyl substrate **3c**, giving **2c** in 74% yield. They also found that the *des*-chloro analogues **3b** and **3d** gave poor yields of **2b** and **2d**, respectively, with formation of isomeric benzofurans as the major products. However, our preliminary experiments on thermal cyclisation of **3c** were less selective for **2c** than the literature precedent.
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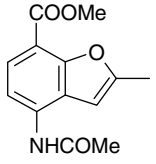
11. Authentic samples of methyl ketones **5b** and **5d** were prepared in poor yields (ca. 20%) by alkylation of phenols **4b** and **4d**, respectively, with chloroacetone in the presence of potassium carbonate in NMP. *Compound* **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (3H, s), 2.38 (3H, s), 3.89 (3H, s), 4.60 (2H, s), 6.90 (1H, dd, *J* 8.5, 1.7 Hz), 7.47 (2H, m), 7.85 (1H, d, *J* 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 27.0, 52.0, 73.6, 104.2, 111.3, 115.3, 133.3, 143.1, 158.5, 165.7, 168.6, 205.4; *m/z* (ES$^+$) 234 ([M+H]$^+$-CH_3OH); HRMS (APCI) calcd for $C_{13}H_{16}NO_5$ ([M+H]$^+$) 266.1023, found 266.1023. *Compound* **5d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (9H, s), 2.39 (3H, s), 3.89 (3H, s), 4.61 (2H, s), 6.89 (1H, dd, *J* 8.5, 1.9 Hz), 7.49 (1H, br s), 7.62 (1H, d, *J* 1.9 Hz), 7.87 (1H, d, *J* 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 27.5, 39.9, 51.9, 73.5, 104.5, 111.7, 115.0, 133.1, 143.5, 158.6, 165.7, 177.3, 205.3; *m/z* (ES$^+$) 308 ([M+H]$^+$), 276 ([M+H]$^+$-CH_3OH); HRMS (APCI) calcd for $C_{16}H_{22}NO_5$ ([M+H]$^+$) 308.1492, found 308.1495.
12. The structures of benzofuran **6** and indole **7** were assigned on the basis of ^{1}H NMR comparison with the literature data.[7]



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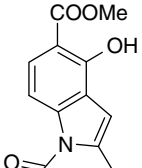

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15. Chloro(triphenylphospine)gold(I) (5 mol %) alone gave no reaction in 2-MeTHF after 1 h at 70 °C.
16. Commercially available from Aldrich as a toluene solvate, $(Ph_3P)AuNTf_2{\cdot}0.5C_7H_8$ cat. no. 677922.
17. A typical experimental procedure for the preparation of **2d** with an unoptimised isolation via crystallisation (cf. Table 2, entry 5) is given. A mixture of aryl propargyl ether **3d** (731.2 mg, 2.53 mmol) and $(Ph_3P)AuNTf_2{\cdot}0.5C_7H_8$ (2.0 mg, 2.5 μmol) in toluene (14.6 ml) was stirred at 85 ± 3 °C under nitrogen for 2 h. The reaction mixture was allowed to cool to 55 °C and filtered, washing the filter paper with toluene (3.6 ml). The filtrate was concentrated in vacuo and the residual solid dissolved in hot toluene (2.9 ml). The solution was allowed to cool and stirred at room temperature overnight. The crystalline solid was collected under suction, washed with toluene (1.5 ml) and dried in vacuo at 45 °C to afford **2d** (584.0 mg, 80%) as an off-white solid; mp 153–155 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (9H, s), 3.87 (3H, s), 4.83 (2H, m), 5.96 (1H, dt, *J* 9.8, 3.9 Hz), 6.38 (1H, m), 7.37 (1H, br s), 7.42 (1H, d, *J* 8.8 Hz), 7.69 (1H, d, *J* 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 39.8, 51.9, 64.9, 115.3, 115.6, 115.9, 118.9, 122.7, 131.4, 136.7, 155.0, 165.8, 176.8; *m/z* (ES$^+$) 290 ([M+H]$^+$); HRMS (APCI) calcd for $C_{16}H_{20}NO_4$ ([M+H]$^+$) 290.1387, found 290.1392. Compound **2d** contained ca. 220 ppm Au and 6 ppm P by ICP. HPLC analysis of the combined filtrate and wash indicated a ca. 10% yield of **2d** was present by comparison with a standard solution.
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