A Palladium-Catalysed Urea Arylation Route to a CRF1 Receptor Antagonist

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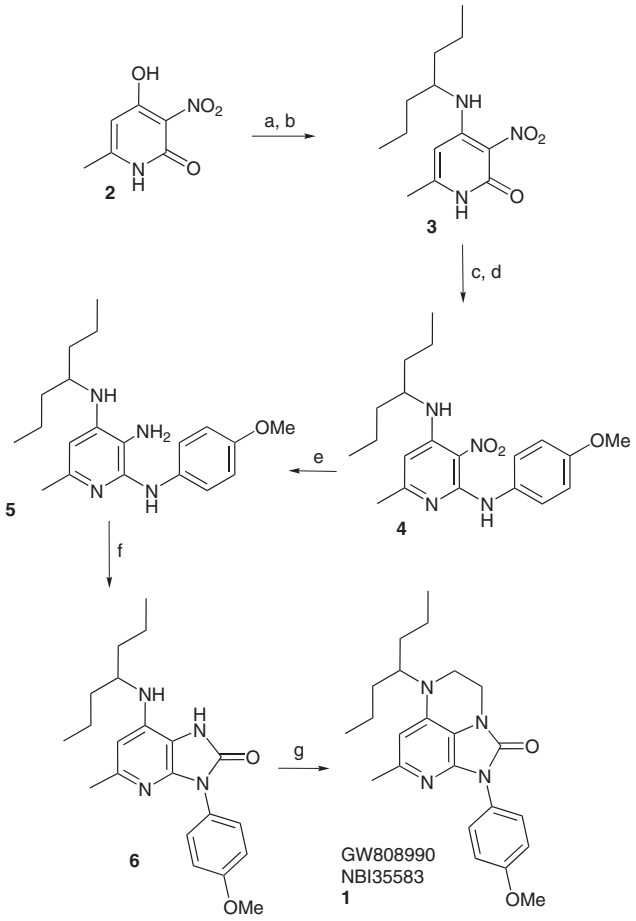
Abstract: A new synthetic approach to a potent CRF antagonist, GW808990 (NBI35583), is reported. The route hinges on the palladium-catalysed intramolecular arylation of a urea with 2-chloropyridine. Spontaneous piperazine ring closure means that a high-yielding bisannulation reaction is the final step.

Key words: CRF antagonist, palladium, catalysis, ligands, urea, arylations

The first corticotrophin release factor (CRF), a 41-amino-acid neurotransmitter was isolated from ovine hypothalmi in 1981.[1] Human CRF has been shown to produce profound alterations in endocrine, nervous and immune system functions. CRF is believed to initiate its biological effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain.[2,3] More recently, numerous small molecule CRF receptor antagonists have been disclosed which could be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.[4]

The 2,3-fused pyridyl urea, GW808990 (also identified as NBI35583), **1** has been developed under a collaborative agreement between GlaxoSmithKline and Neurocrine Biosciences as a promising CRF1 antagonist.[5] The original synthesis is shown in Scheme 1. Other fused pyridyl ureas have been reported as CRF receptor antagonists by Pfizer[6] and DuPont.[7] To date, the reported syntheses of all of these compounds follows the basic structure of the route to **1** as outlined in Scheme 1. Sequential selective substitutions at the 4- and then 2-positions of the readily available nitropyridinone **2** are followed by nitro-reduction of **4** and installation of the urea by reaction of **5** with triphosgene. The final step in the synthesis of **1** is the annulation of the urea **6** with dibromoethane to install the piperazine ring.

At the outset we discovered that the urea installation in triaminopyridine **5** was hampered by poor regioselectivity between the 2- and 4-amino groups. Our initial strategy toward a better synthesis of **1** was designed simultaneously to eliminate this regiochemical issue and avoid the use of genotoxic dibromoethane by exchanging 4-heptylamine for 4-(aminoethyl)heptane (**7**),[8] thus installing the required ethylene functionality from the start.



Scheme 1 *Reagents and conditions*: (a) $PhSO_2Cl$, Et_3N, THF, reflux; (b) 4-heptylamine, Et_3N, 50%, 2 steps; (c) $POCl_3$, MeCN, 50 °C; (d) 4-anisidine, MeCN, 50 °C, 75%, 2 steps; (e) $Na_2S_2O_4$, NaOH, MeCN, H_2O, quant; (f) triphosgene, NaOH, CH_2Cl_2, 80%; (g) dibromoethane, NaOH, CH_2Cl_2, 70%.

2-Chloropyridine **8** was synthesised via an activation/substitution sequence analogous to that described in Scheme 1. Following substitution at the 4-position with **7** the hydroxyl group was acylated and the chloropyridine **8** was then formed in 41% overall yield from **2** (Scheme 2). Although this chemistry could indeed be elaborated to **1** along lines similar to the supply route in Scheme 1, we discovered that the 4-anisidine substitution of the 2-chloropyridine **8** was very difficult. With this in mind we elected to adopt a different approach and we report herein a synthetically distinct route to **1** via a palladium-catalysed bisannulation reaction of the key urea **11**.

Chloropyridine **8** was cleanly reduced by hydrogen at atmospheric pressure with 1% Pt/C catalyst in ethyl acetate

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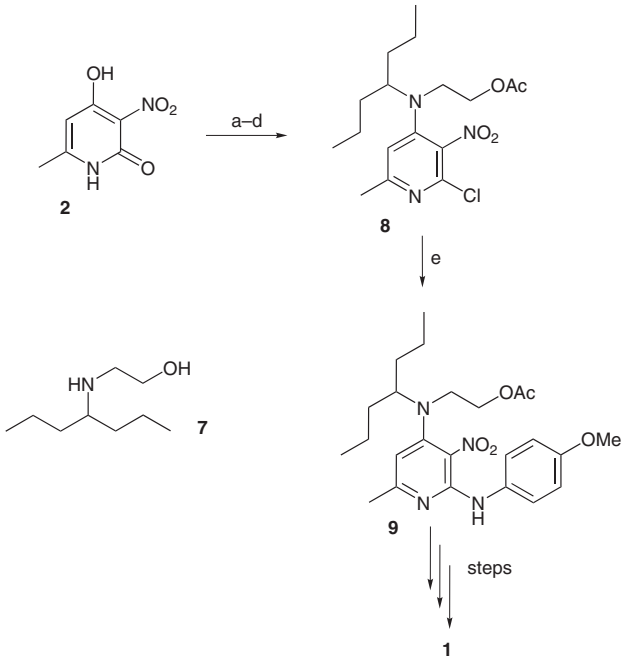
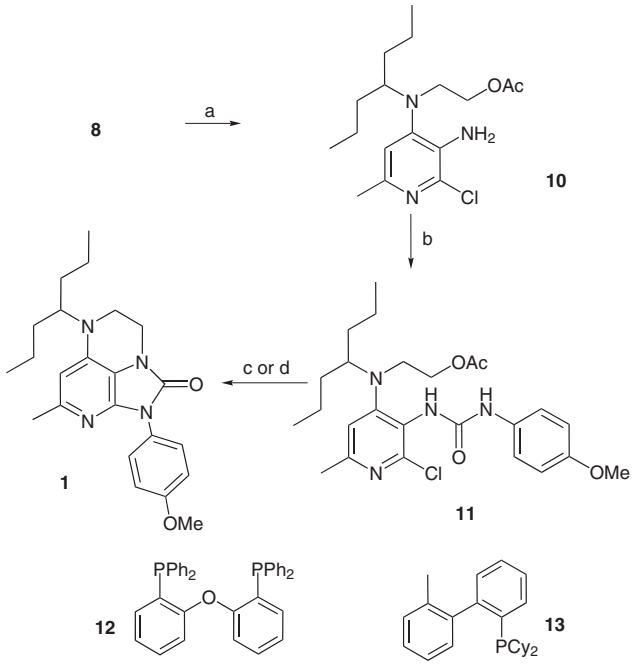


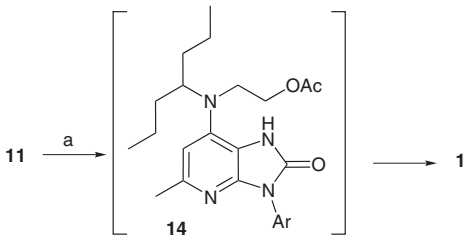
Scheme 2 *Reagents and conditions*: (a) $PhSO_2Cl$, Et_3N, THF, reflux; (b) **7**, Et_3N, 54%, 2 steps; (c) Ac_2O, pyridine, toluene, 85%; (d) $POCl_3$, EtCN, reflux, 90%; (e) 4-anisidine, HCl, MeCN, reflux, 48 h, 25%.

to give **10**, in 74% yield (Scheme 3). After catalyst filtration, the aminopyridine **10**, still in ethyl acetate, can be treated with one equivalent of 4-methoxyphenyl isocyanate[9] to give the crystalline urea **11** in 73% isolated yield.



Scheme 3 *Reagents and conditions*: (a) 1% Pt/C, H_2 (1 atm), AcOH, EtOAc, 74%; (b) 4-methoxyphenyl isocyanate, EtOAc, 73%; (c) $Pd_2(dba)_3$ (3.6 mol%), **12** (7.2 mol%), K_2CO_3 (2.0 equiv), dioxane, reflux, 22 h, 50%; or (d) $Pd_2(dba)_3$ (3.6 mol%), **13** (9 mol%), K_2CO_3 (2.2 equiv), dioxane, reflux, 20 h, 86%.

Various conditions were investigated in an attempt to effect the key N–aryl bond-forming step and, indeed, a few reports of urea substitution of 2-halopyridines are present in the literature.[10–12] Our successful final step to **1** however uses the urea analogue of a Buchwald–Hartwig-type palladium-catalysed aryl–N coupling. This reaction has recently been popularised by Beletskaya who has shown that palladium–dibenzylideneacetone complexes and Xantphos ligands will N-arylate a wide range of ureas with aryl bromides and iodides.[13,14] We explored the possibility of using the related commercial ligand **12**, which did indeed achieve the desired N–aryl bond formation and the subsequent closure of the pyridylpiperazine ring system in 50% yield. In our hands however, better results were observed using Buchwald's catalyst–ligand system as applied to the coupling of amines with 2-chloropyridines.[15] To this end the use of methylbiphenyldicyclohexyl phosphine **13** (9 mol%) and $Pd_2(dba)_3$ (3.6 mol%) with potassium carbonate (2.2 equiv) in refluxing dioxane gave **1** in 86% yield after 18 hours. Chromatographic purification gave **1** in 58% isolated yield. This bisannulation reaction of **11** can be followed by HPLC–MS and it is clear that under the reaction conditions the palladium-catalysed N–aryl bond formation is the faster step (Scheme 4). A related palladium-catalysed intramolecular arylation of ureas has recently been reported.[16]



Scheme 4 *Reagents and conditions*: (a) $Pd_2(dba)_3$ (3.6 mol%), **13** (9 mol%), K_2CO_3 (2.2 equiv), dioxane, reflux, 20 h, 86%.

In summary, a new six-step route to the CRF receptor antagonist GW808990 **1** has been developed. The unoptimised route employs a palladium-catalysed bisannulation–arylation of urea **11**[17] as the key step and allows for the synthesis of **1** in 17% overall yield from **2**.[18]

References and Notes

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(17) Data for **10**: mp 128–129 °C (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.1 Hz, 2 H), 6.80 (d, *J* = 9.1 Hz, 2 H), 6.70 (br s, 1 H), 6.67 (s, 1 H), 6.36 (br s, 1 H), 4.04 (t, *J* = 6.1 Hz, 2 H), 3.75 (s, 3 H), 3.74–3.78 (m, 1 H), 3.46 (t, *J* = 6.1 Hz, 2 H), 2.44 (s, 3 H), 1.89 (s, 3 H), 1.44–1.50 (m, 4 H), 1.21–1.28 (m, 4 H), 0.83 (t, *J* = 7.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 157.1, 156.7, 156.4, 154.2, 152.7, 130.8, 123.2, 118.3, 114.2, 112.4, 91.4, 61.9, 61.7, 41.1, 35.7, 24.3, 20.6, 20.2, 14.2. IR (ATR mode): 1735, 1584, 1510, 1244, 1027, 986, 934, 836 cm^{-1}. HRMS (ES): *m*/*z* [MH$^+$] calcd for $C_{25}H_{36}ClN_4O_4$: 491.2425; found: 491.2406.
(18) The urea **10** (300 mg, 0.61 mmol) and K_2CO_3 (190 mg, 1.38 mmol) were suspended in dioxane (6.0 mL). $Pd_2(dba)_3$ (20 mg, 0.022 mmol, 0.036 equiv) and 2-(dicyclohexylphosphino)-2′-methylbiphenyl (20 mg, 0.055 mmol, 0.09 equiv) were added and the reaction vessel was flushed with Ar and the reaction mixture was heated to reflux for 20 h. Solution yield of the product **1** at this point was 86%. The reaction mixture was then evaporated and partitioned between EtOAc (10 mL) and 5% aq $NaHCO_3$ (5 mL). The EtOAc layer was then separated and dried over $MgSO_4$ before being filtered and evaporated to give the crude product **1** which was purified by chromatography (hexane–EtOAc, 1:1) to give pure **1** in 58% yield. Data for **1**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 2.2, 6.8 Hz, 2 H), 7.00 (dd, *J* = 2.2, 6.8 Hz, 2 H), 6.25 (s, 1 H), 3.98 (t, *J* = 5.0 Hz, 2 H), 3.83 (s, 3 H), 3.74 (m, 1 H), 3.38 (t, *J* = 5.0 Hz, 2 H), 2.44 (s, 3 H), 1.55 (m, 4 H), 1.32 (m, 4 H), 0.92 (t, *J* = 7.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 152.0, 151.2, 141.4, 138.3, 127.2, 126.8, 114.4, 106.8, 99.2, 55.7, 55.5, 39.4, 34.7, 34.7, 25.2, 20.0, 14.0. IR (ATR mode): 1712, 1654, 1515, 1246, 1036, 854, 793, 735, 691 cm^{-1}. HRMS (ES): *m*/*z* [MH$^+$] calcd for $C_{23}H_{31}N_4O_2$: 395.2447; found: 395.2441.