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A NOVEL SYNTHESIS OF A 1,3-DISUBSTITUTED 1,3-DIHYDRO-2*H*-IMIDAZO[4,5-*b*]PYRIDIN-2-ONE. APPLICATION TO GW808990 A CRF$_1$ RECEPTOR ANTAGONIST

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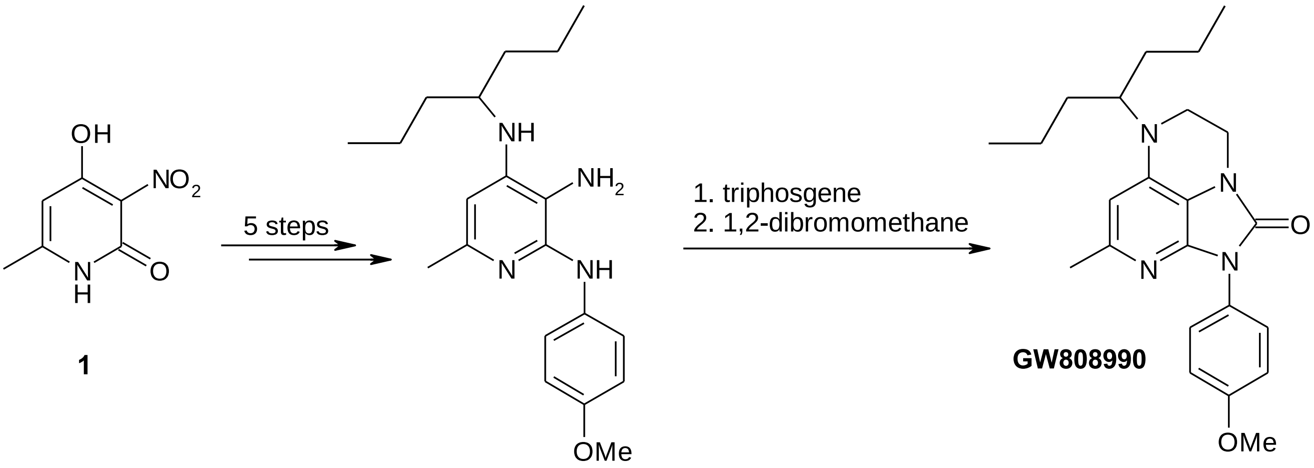
Abstract – A novel synthesis of a 1,3-disubstituted 1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-2-one has been achieved by condensation of iminohydantoin **3** with *t*-butyl acetoacetate in diglyme at 160 °C. Hydrogenation of the product in the presence of 4-heptanone followed by a Buchwald-Hartwig amination afforded GW808990, a CRF$_1$ receptor antagonist.

Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

The corticotrophin release factor (CRF$_1$) antagonist GW808990 was in development as a candidate for the treatment of unipolar depression. The original route is outlined in Scheme 1 and was used to prepare drug substance on a kilogram scale.[1] This chemistry was not developed further into a manufacturing process however due to the use of triphosgene and the genotoxic 1,2-dibromoethane. We have reported an alternative synthesis which also started with the readily available nitropyridone **1** but avoided triphosgene and 1,2-dibromoethane.[2] We report here a novel approach to GW808990 involving the reaction of iminohydantoin **3** with *t*-butyl acetoacetate to generate the core fused pyridyl urea.

RESULTS AND DISCUSSION

Iminohydantoin **3** was prepared as shown (Scheme 2). Iminodiacetonitrile and 4-methoxyphenyl isocyanate were reacted in dichloromethane to give a 4 : 1 mixture of urea **2** and iminohydantoin **3**. This mixture was treated with a catalytic amount of sodium hydride in THF to drive the cyclization to completion. The product exists in the iminohydantoin form as a 3:1 mixture of *E*:*Z* isomers. The structural assignment was made based on ^{1}H and ^{13}C modulated nmr spectroscopy. With the required iminohydantoin in hand we anticipated that it would condense with *t*-butyl acetoacetate to generate an iminoacrylate. These are known to undergo thermal cyclization (240 °C) to 4-hydroxypyridines.[3] In fact when we attempted the reaction of **3** with *t*-butyl acetoacetate in toluene at reflux a 10:1 mixture of 2-hydroxypyridine **5** and 4-hydroxypyridine **4** was obtained. When the solvent was changed to diglyme and the temperature increased to 160 °C, a 1:3 mixture was obtained in favour of the required 4-hydroxypyridine **4**. We had therefore successfully constructed the core 2,3-fused pyridyl urea unit of GW808990 and avoided the need to heat to extreme temperatures. We attempted some optimization of this key reaction exploring the effects of solvent, temperature and added buffers (Table 1).



Scheme 1

Use of polar solvents at greater than 160 °C gave predominantly the desired 4-hydroxy isomer. At less than 115 °C the undesired isomer predominated regardless of solvent polarity. At high temperatures in a non polar solvent the undesired isomer still predominated. Buffering the reaction with triammonium phosphate in diglyme led to an improvement from 3:1 to 5:1 in favour of the required isomer but unexpectedly ammonium acetate buffer gave only an equal mixture of isomers. A further optimised process for the conversion of **2** to **4** without isolation of iminohydantoin **3** was subsequently established.[4]

A possible mechanism for the formation of hydroxypyridines **5** and **4** involves reaction of **3** with acetylketene. This is generated by elimination of t-butanol from *t*-butyl acetoacetate on heating.[5] Acetylketene-acetone adduct (2,2,6-trimethyl-4*H*-1,3-dioxin-4-one) which also generates acetylketene on heating,[6] reacted with **3** in diglyme at 160 °C to give a similar ratio of **4** and **5**. Initial reaction of **3** at nitrogen generates the intermediate **6** which undergoes cyclocondensation to give **5** as the kinetic product.

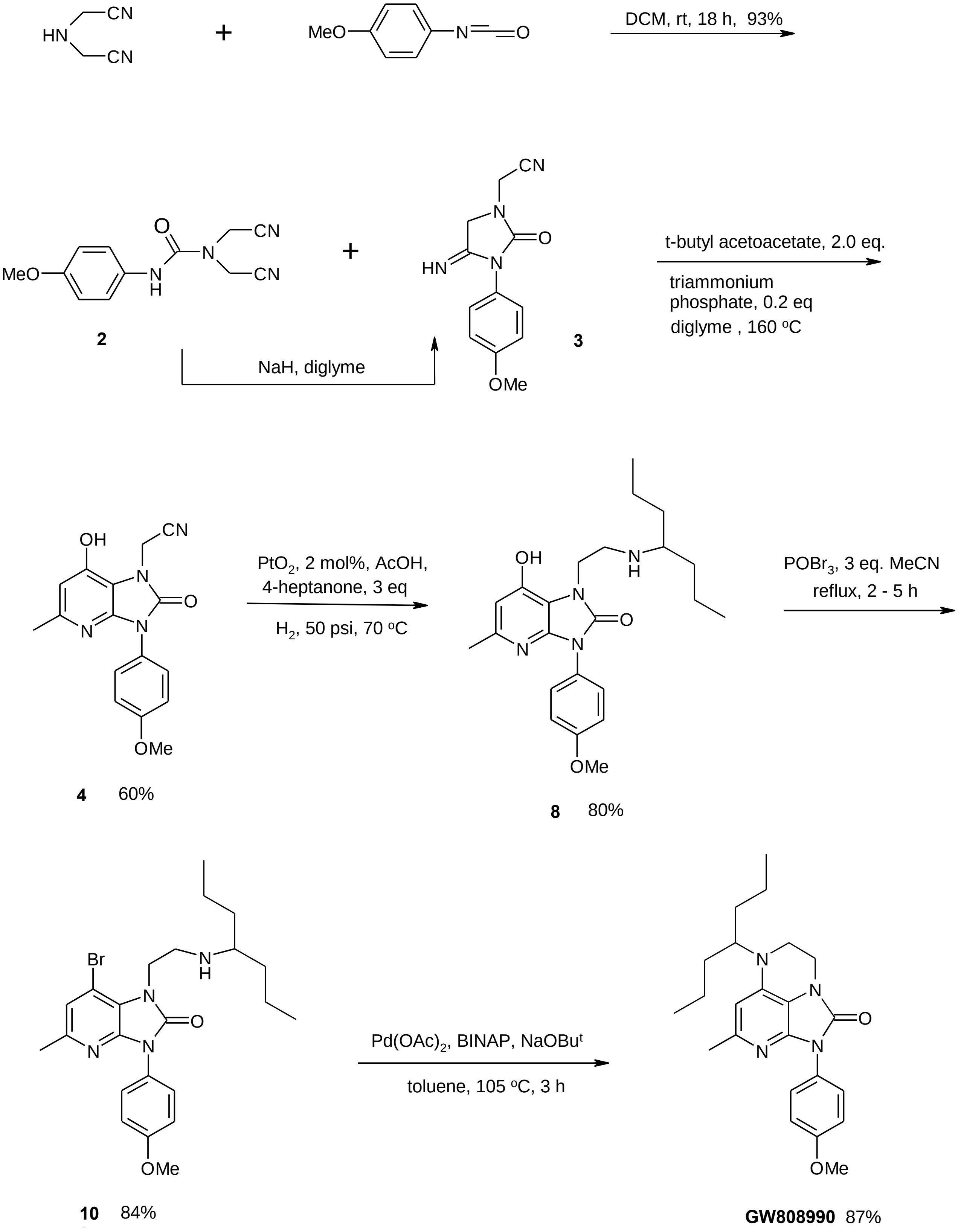
At the higher temperature initial reaction occurs at carbon to generate the thermodynamic product **4** via the intermediate **7** (Scheme 3).

Table 1. Reaction of **3** with *t*-Butyl acetoacetate (2 eq.)

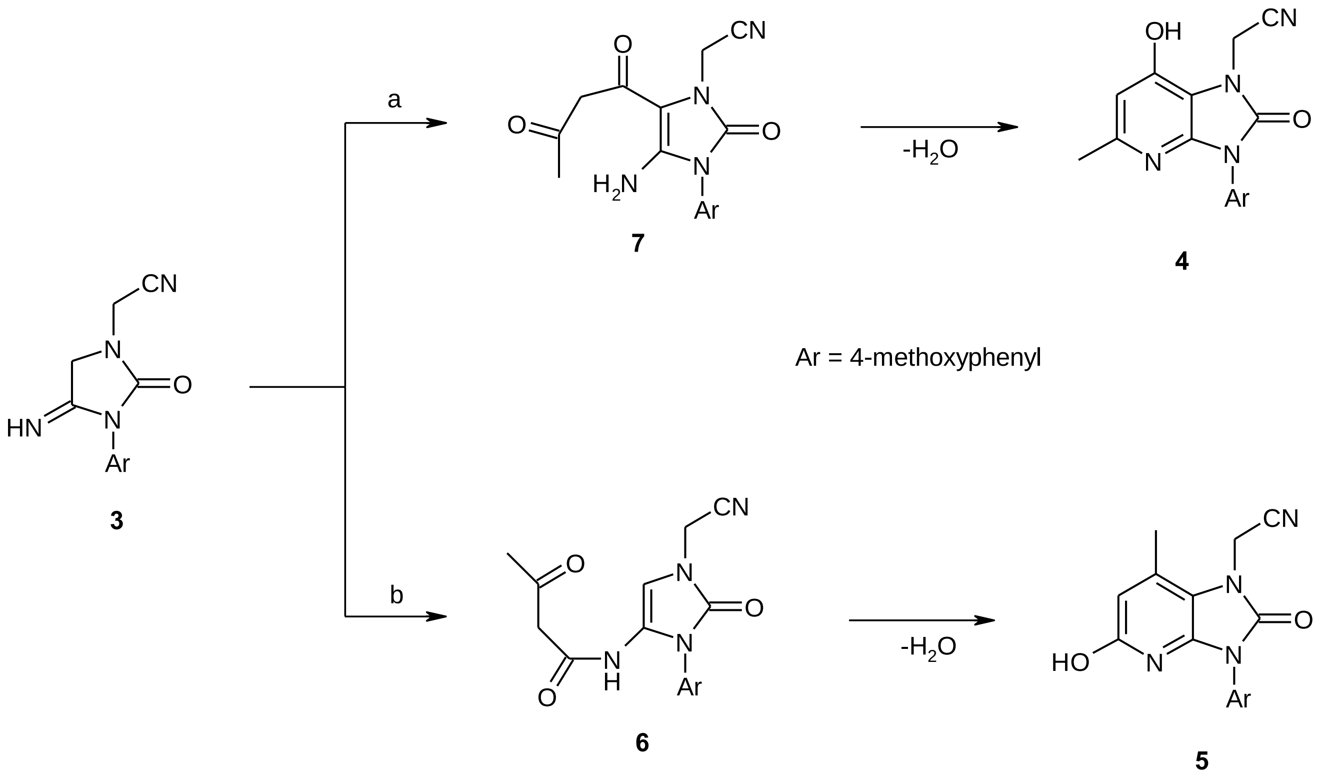
Entry	Solvent	Additive (0.2 eq)	temp (^{o}C)	Product ratio **4**:**5**[a,b]
1	toluene	none	111	1 : 10
2	*o*-xylene	none	140	1 : 1
3	*n*-decane	none	175	1 : 5
4	nmp	none	175	4 : 1
5	anisole	none	154	1 : 1
6	triglyme	none	180	3 : 1
7	triglyme	none	117	1 : 10
8	diglyme	none	160	3 : 1
9	diglyme	ammonium acetate	160	1 : 1
10	diglyme	ammonium citrate	160	7 : 2
11	diglyme	triammonium phosphate	160	**5 : 1**
12	diglyme	triammonium phosphate, sodium methoxide (0.1eq)	160	2 : 3

[a] ratio determined by HPLC.
[b] structural assignments of each isomer made by 2D HMBC spectroscopy.

To complete the synthesis of GW808990 the nitrile group was hydrogenated over platinum oxide in the presence of an excess of 4-heptanone to generate **8** in 70 – 80% yield. Some decyanomethylation[7] (ca 10%) occurred to give **9** as an undesired side product. The product was converted to the bromide **10** in 80% yield using phosphorus oxybromide or to the chloride **11** in 60% yield with phosphorus oxychloride. These halides were readily cyclised to GW808990 using Buchwald type amination conditions (palladium acetate, sodium *tert*-butoxide and phosphine ligand in toluene). Preferred ligands were racemic BINAP for bromide **10** and phosphine **12** for the chloride.[8,9] The product was isolated as the malate salt GW808990B in 50% overall yield from **4** via the bromide **10** (Scheme 2).


HN
CN
CN
+
MeO
N
O
DCM, rt, 18 h, 93%
MeO
O
N
H
N
CN
CN
2
+
CN
N
O
HN
N
OMe
3
NaH, diglyme
t-butyl acetoacetate, 2.0 eq.
triammonium phosphate, 0.2 eq
diglyme , 160 °C
OH
CN
N
O
N
N
OMe
4 60%
PtO2, 2 mol%, AcOH,
4-heptanone, 3 eq
H2, 50 psi, 70 °C
OH
N
H
N
O
N
N
OMe
8 80%
POBr3, 3 eq. MeCN
reflux, 2 - 5 h
Br
N
H
N
O
N
N
OMe
10 84%
Pd(OAc)2, BINAP, NaOBut
toluene, 105 °C, 3 h
N
N
O
N
N
OMe
GW808990 87%

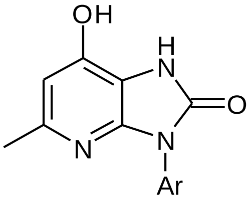
Scheme 2



Conditions: a) *t*-butyl acetoacetate, diglyme 160 °C, b) *t*-butyl acetoacetate, toluene 110 °C

Scheme 3

In summary, a new 5 step synthesis of GW808990 has been developed. The key step involves the reaction of iminohydantoin **3** with an acetylketene precursor in a polar solvent at 160 °C to generate the fused pyridyl urea core. The resultant 4-hydroxypyridine **4** was readily converted to GW808990 with an overall yield of 33% from iminodiacetonitrile.



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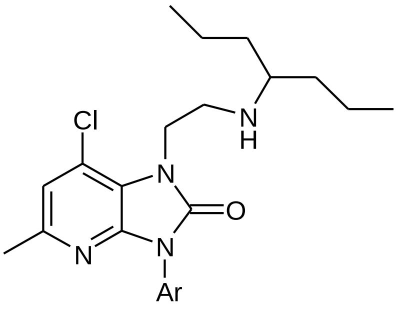
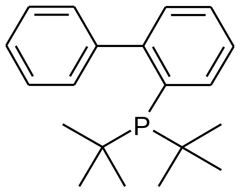


11



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Ar = 4-methoxyphenyl

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4. Experimental procedure for the conversion of **2** to **4**: To a solution of urea **2** (5.00 g, 20.5 mmol) in diglyme (50 mL) was added sodium hydride (5 mg of a 60% w/w suspension in mineral oil, 0.13 mmol). The reaction mixture was stirred at room temperature for 1h. ^{1}H nmr indicated complete conversion to **3**. Mp 116 – 118 °C (from CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO) δ 3.78 (2.25H, s), 3.80 (0.75H, s), 4.17 (1.5H, s), 4.22 (0.5H, s), 4.50 (1.5H, s), 4.52 (0.5H, s), 6.98 (1.5H, d), 7.08 (0.5H, d), 7.20 (0.5H, d), 7.26 (1.5H, d) and 8.31 (1H, s). ^{13}C NMR (400 MHz, DMSO) δ 31.5, (R,R'$\underline{C}H_2$CN), 48.6 (–$\underline{C}H_2N(CH_2CN)$R), 55.3 (O$\underline{C}$H3), 113.8 (Ar), 116.2 ($\underline{C}$N), 122.0 (Ar), 128.6 (Ar), 156.0 ((R,R'N) $\underline{C}$:O (NR'',R''')), 158.0 (Ar) and 159.0 (-$CH_2\underline{C}$:NH(NR,R''). IR (film) 1665, 1509 and 1243 cm^{-1}; m/z 245 (M^++H). After this time citric acid (47 mg, 0.24 mmol) was added. A light precipitate formed. After 1 h further diglyme (50 mL) was added, triammonium phosphate (611 mg, 4.10 mmol) was added and the reaction mixture was heated under reflux. *t*-Butyl acetoacetate (3.4 mL, 20.5 mmol) was added over 2 min. at 158 – 162 °C. *t*-Butanol which formed was distilled off. The reaction mixture was maintained at 162 °C for 45 min after which time further *t*-butyl acetoacetate (3.4 mL, 20.5 mmol) was added. The reaction mixture was stirred at 160 °C for 45 min and after this time the solvent was removed *in vacuo*. The residue was slurried in EtOAc (50 mL) at room temperature for 1 h and at 5 °C for 1 h. The product **4** was filtered, washed with EtOAc (10 mL) and sucked dry. Yield = 3.74g, 59%. Mp 266 – 268 °C (decomp) (from EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 2.29 (3H, s), 3.82 (3H, s), 5.09 (2H, s), 6.54 (1H, s), 7.08 (2H, d, J = 8.9Hz) and 7.47 (2H, d, J = 8.9Hz). ^{13}C NMR (100MHz, DMSO) δ 23.7 ($\underline{C}H_3$Py), 30.7 (-$\underline{C}H_2$CN), 55.4 (O$\underline{C}H_3$), 106.4 (Py), 107.0 (Py), 114.1 (Ar), 114.3 (Ar), 116.4 (-$\underline{C}$N), 126.0 (Ar), 127.8 (Ar), 128.1 (Ar), 144.1 (Py), 148.6 (Py), 151.5 (Py), 151.6 ($\underline{C}$:O) and 158.5 (Ar). IR (film) 3100, 1672, 1647, 1513 and 1254 cm^{-1}; HRMS m/z Calcd for $C_{16}H_{15}N_4O_3$ 311.1144 [M+H], found (311.1144).

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