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Synthesis of 2-amino-3-hydroxy-4-substituted pyridines via regioselective metalation of 3-(1-ethylpropyl)-[1,3]oxazolo[4,5-*b*]pyridin-2(3*H*)-one and application to corticotropin releasing factor$_1$ receptor ligands

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Abstract—An efficient route to the preparation of 2-amino-3-hydroxy-4-substituted pyridines is described. The key step involves the regioselective metalation and subsequent alkylation of the [1,3]oxazolo[4,5-*b*]pyridin-2(3*H*)-one ring system. Base hydrolysis provides access to a variety of 4-substituted pyridines. This chemistry is proved to be useful for the synthesis of corticotropin releasing factor$_1$ receptor ligands.

During the course of our investigation to identify novel ligands for corticotropin releasing factor$_1$ (CRF$_1$) receptors[1] we sought an efficient method for the preparation of 4-substituted pyridines. We were particularly interested in a synthetic route that would be readily amenable to the preparation of compounds bearing a phenyl substituent at the 4-position of the pyridine ring.

Directed *ortho* metalation has been widely used for the regioselective alkylation and arylation of aryl and heteroaryl ring systems.[2] Our synthetic plan began with commercially available 2-amino-3-hydroxy pyridine. It was anticipated that installation of the substituent at the 4-position could be carried out by a directed *ortho* metalation reaction whereby the oxygen at the 3-position would serve as a directing group. This plan was bolstered by the previously reported regioselective metalation of related heterocyclic ring systems.[3,4] The 2-amino and 3-hydroxy groups could be protected as an oxazolidinone, which would be ideal since it could be easily hydrolyzed to regenerate the amino and hydroxy groups later in the synthetic route.

The synthesis begins with alkylation of the amino group of 2-amino-3-hydroxy pyridine (**1**) with 3-pentanone via reductive amination (Scheme 1). Subsequent treatment with triphosgene resulted in the formation of the [1,3]oxazolo[4,5-*b*]pyridin-2(3*H*)-one ring system (**3**). An attempt to directly couple **3** with bromobenzene via a Negishi coupling reaction resulted in a low yield of desired product (Table 1, compound **11**). Regioselective metalation with *t*-BuLi resulted in the formation of a mixture of the desired lithium anion at the 4-position of the pyridine ring as well as addition of *t*-BuLi to the oxazolidinone carbonyl group resulting in the formation of 2,2-dimethylpropionic acid 2-(1-ethyl-propylamino)-pyridin-3-yl ester **16** as the major product in 62% yield (Fig. 1).[5] Cleavage of the C–N bond rather than the C–O bond is likely a result of the enhanced leaving group ability of this nitrogen due to resonance stabilization of the resulting charge into the neighboring pyridine nitrogen. Within several minutes of isolation, the product turned blue in color, which was likely due to trace amounts of air oxidation.

Formation of this undesired byproduct was circumvented by using a two-step procedure to install the

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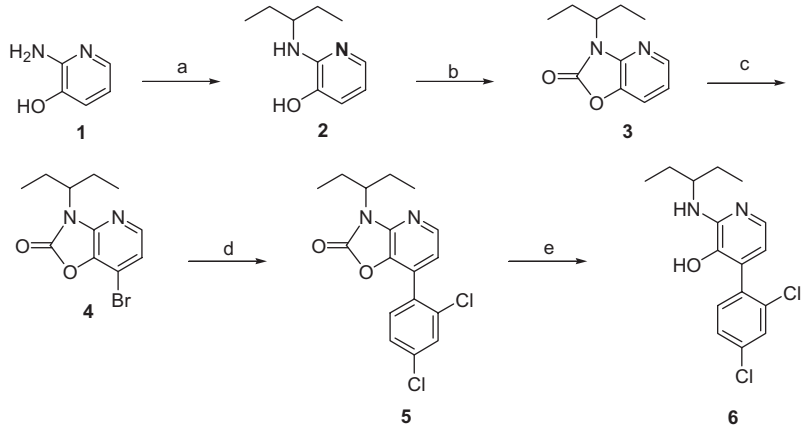
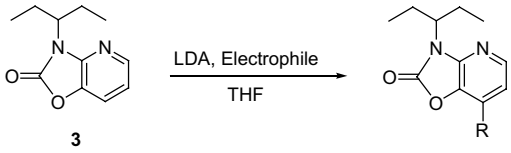
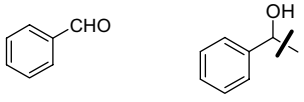
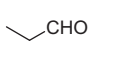
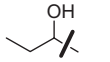
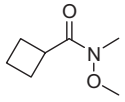
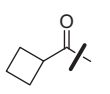


Scheme 1. Reagents and conditions: (a) 3-pentanone, $NaBH_3CN$, THF, 62%; (b) triphosgene, Et_3N, THF 70%; (c) LDA, $BrCH_2CH_2Br$, THF, 65%; (d) $Ba(OH)_2{\cdot}8H_2O$, $Pd(PPh_3)_2Cl_2$, 2,4-dichlorobenzeneboronic acid, DME, H_2O, 80%; (e) KOH, EtOH, 87%.

Table 1.



Compds	Electrophile	R	Yield (%)
4	$BrCH_2CH_2Br$	Br	65
7	MeI	Me	78
8			89
9			73
10			76
11[a]	PhBr	Ph	11

[a] Compound **11** was prepared by a Negishi coupling reaction (*t*-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, PhBr).

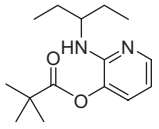
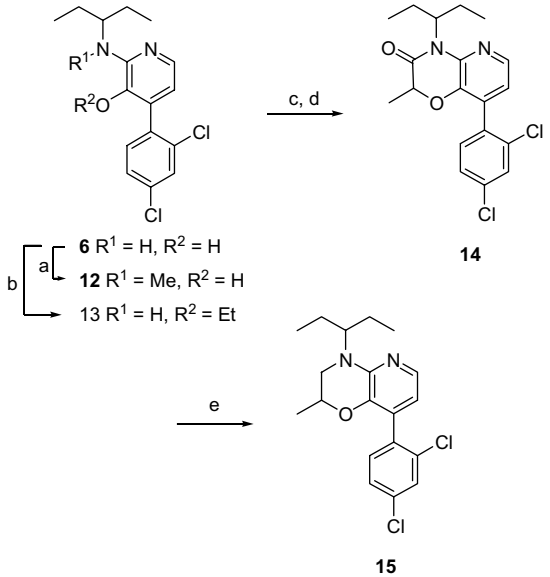


Figure 1. Structure of compound **16**.

phenyl group. Deprotonation with LDA[6] followed by the addition of dibromoethane[3] cleanly afforded desired bromide **4** in 65% yield. Compound **4** was then subjected to Suzuki coupling conditions to furnish biaryl intermediate **5** in good yield. Treatment with NaOH resulted in hydrolysis of the oxazolidinone to form a 2-amino-3-hydroxy-4-substituted pyridine (**6**).

Having successfully completed the synthesis of the desired 4-substituted pyridyl ring system (**6**) we were interested in studying the directed metalation of **3** in more detail. The intermediate lithium anion was subjected to additional electrophiles as shown in Table 1. Addition of methyl iodide, several aldehydes, and a Weinreb amide each proceeded in good yield. Not unexpectedly, treatment with ethyl iodide resulted only in recovery of protonated starting material due to competing elimination.

With 2-amino-3-hydroxy-4-substituted pyridine **6** in hand, it was elaborated further to the desired products (Scheme 2) which were tested for CRF_1 receptor binding affinity. Compound **6** was selectively alkylated on either the amine or hydroxyl groups depending upon the choice of reaction conditions. Subjection of **6** to formaldehyde under reductive amination conditions resulted in the selective formation of **12**; whereas, treatment of **6**



Scheme 2. Reagents and conditions: (a) HCHO, $ZnCl_2$, $NaBH_3CN$, MeOH, 60 °C, 34%; (b) K_2CO_3, EtI, acetone, 81%; (c) K_2CO_3, methyl 2-bromopropionate, 2-butanone, 74%; (d) *p*-TsOH·H_2O (cat), toluene, 4 days, 96%; (e) $BH_3{\cdot}SMe_2$, THF, 84%.

with K_2CO_3 and ethyl iodide resulted in the selective alkylation of the phenol oxygen to form **13**. It was also possible to prepare bicyclic compounds by taking advantage of the differential reactivity of the amine and phenol groups on the pyridine ring. Treatment of **6** with 2-bromomethylpropionate[7] followed by heating in toluene in the presence of *p*-TsOH (4 days) resulted in the formation of **14**. The amide was then reduced with $BH_3{\cdot}SMe_2$ to form **15** in good yield.[8]

Compounds **12**, **13**, and **15** were tested for their binding affinity to the CRF_1 receptor. Compounds **12** and **13** were found to be inactive (K_i > 10,000 nM); however, compound **15** showed moderately potent binding affinity (K_i = 111 ± 10 nM, n = 4) for the CRF_1 receptor. Binding affinities were determined in a CRF_1 receptor binding titration assay using rat frontal cortex homogenate, in which inhibition of specific binding of [^{125}I]ovine–CRF by our test compounds was measured to determine their receptor binding affinity.[9,10]

In conclusion, the preparation of 2-amino-3-hydroxy-4-substituted pyridines was carried out by the regioselective metalation of the [1,3]oxazolo[4,5-*b*]pyridin-2(3*H*)-one ring system (**3**) as a key step. Suzuki coupling followed by base hydrolysis furnished the 4-substituted pyridine intermediate, which was subsequently converted to the desired products. This method appears to be general, allowing ready access to a variety of 2-amino-3-hydroxy-4-substituted pyridines, and was also directly applicable to our investigation of CRF_1 receptor ligands.

Acknowledgements

We thank Ge Zhang and Anne Marshall for the rat CRF receptor binding data for compounds **12**, **13**, and **15**.

References and notes

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5. The structure of compound **16** was confirmed by a COSY experiment in addition to the following characterization data for this compound: blue oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 5.1, 1.5 Hz, 1H), 7.17 (dd, J = 7.5, 1.5 Hz, 1H), 6.51 (dd, J = 7.8, 2.8 Hz, 1H), 4.11 (d, J = 8.1 Hz, 1H), 4.02–3.97 (m, 1H), 1.64–1.55 (m, 2H), 1.54–1.41 (m, 2H), 1.37 (s, 9H), 0.88 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.99, 151.39, 144.62, 132.96, 128.06, 111.37, 52.26, 39.37, 27.20, 26.95, 9.79; IR (thin film) 2965 (s), 2935 (m), 2875 (m), 1758 (s), 1609 (s), 1500 (s), 1169 (s), 1104 (s) cm^{-1}; HRMS (ESI) *m/e* 265.1918 [(M+H)$^+$, calcd for $C_{15}H_{25}N_2O_2$ 265.1916].
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8. Characterization data for compounds **2**–**15** follows: compound **2**: yellow solid; mp 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 5.5 Hz, 1H), 6.81 (d, J = 7.3 Hz, 1H), 6.41–6.37 (m, 1H), 4.95 (br, 1H), 3.94–3.85 (m, 1H), 1.68–1.46 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H); HRMS (ESI) *m/e* 181.1343 [(M + H)$^+$, calcd for $C_{10}H_{17}N_2O$ 181.1341]; **3**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 5.5, 1.5 Hz, 1H), 7.40 (dd, J = 7.7, 1.1 Hz, 1H), 7.03 (dd, J = 7.7, 5.2 Hz, 1H), 4.25–4.15 (m, 1H), 2.26–2.14 (m, 2H), 1.96–1.82 (m, 2H), 0.89 (t, J = 7.3 Hz, 6H); HRMS (ESI) *m/e* 207.1141 [(M+H)$^+$, calcd for $C_{11}H_{15}N_2O_2$ 207.1134]; compound **4**: colorless solid; mp 83.5–84.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 5.5 Hz, 1H), 7.19 (d, J = 5.8 Hz, 1H), 4.21–4.12 (m, 1H), 2.24–2.11 (m, 2H), 1.95–1.81 (m, 2H), 0.89 (t, J = 7.7 Hz, 6H); HRMS (ESI) *m/e* 285.0236 [(M+H)$^+$, calcd for $C_{11}H_{14}N_2O_2Br$ 285.0239]; compound **5**: blue-green solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 5.4 Hz, 1H), 7.57 (d, J = 1.4 Hz, 1H), 7.43–7.36 (m, 2H), 7.09 (d, J = 5.5 Hz, 1H), 4.26–4.18 (m, 1H), 2.29–2.16 (m, 2H), 1.99–1.85 (m, 2H), 0.93 (t, J = 7.3 Hz, 6H); LRMS (APCI) *m/e* 351.1 [(M+H)$^+$, calcd for $C_{17}H_{17}N_2O_2Cl_2$ 351.1]; compound **6**: green amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.34 (dd, J = 8.4, 1.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 6.28 (d, J = 5.1 Hz, 1H), 4.88 (br, 1H), 3.98 (br, 1H), 1.71–1.49 (m, 4H), 0.94 (t, J = 7.3 Hz, 6H); HRMS (ESI) *m/e* 325.0888 [(M+H)$^+$, calcd for $C_{16}H_{19}N_2OCl_2$ 325.0874]; compound **7**: colorless solid; mp 65–66 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J = 5.5 Hz, 1H), 6.86 (d, J = 5.8 Hz, 2H), 4.23–4.13 (m, 1H), 2.39 (s, 3H), 2.28–2.13 (m, 2H), 1.94–1.80 (m, 2H), 0.89 (t, J = 7.3 Hz, 6H); LRMS (APCI) *m/e* 221.1[(M+H)$^+$, calcd for $C_{12}H_{17}N_2O_2$ 221.1]; compound **8**: light yellow solid; mp 115.5–116.5 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 5.5 Hz, 1H), 7.51 (dd, J = 8.4, 1.8 Hz, 2H), 7.42–7.31 (m, 3H), 7.24 (d, J = 5.5 Hz, 1H), 6.15 (s, 1H), 4.21–4.13 (m, 1H), 2.23–2.09 (m, 3H), 1.92–1.83 (m, 2H), 0.88 (t, J = 7.7 Hz, 6H); HRMS (ESI) *m/e* 313.1543 [(M+H)$^+$, calcd for $C_{18}H_{21}N_2O_3$ 313.1552]; **9**: pale blue oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 5.5 Hz, 1H), 7.14 (d, J = 5.5 Hz, 1H), 4.98 (t, J = 6.6 Hz, 1H), 4.23–4.13 (m, H), 2.53 (br, H), 2.23–2.11 (m, H), 1.94–1.80 (m, 4H), 0,99 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 7.4 Hz, 6H); LRMS (APCI) *m/e* 265.0 [(M+H)$^+$, calcd for $C_{14}H_{21}N_2O_3$ 265.2]; compound **10**: pale blue oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 5.5 Hz, 1H), 7.48 (d, J = 5.5 Hz, 1H), 4.28–4.18 (m, 1H), 4.14–4.08 (m, 1H), 2.38 (q, J = 8.0 Hz, 4H), 2.28–2.09 (m, 3H), 1.98–1.83 (m, 1H), 0.89 (t, J = 7.7 Hz, 6H); LRMS (ESI) *m/e* 289.1540 [(M+H)$^+$, calcd for $C_{16}H_{21}N_2O_3$ 289.1540]; compound **11**: blue oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.15 (d, J = 5.8 Hz, 1H), 7.90 (dd, J = 6.6, 2.1 Hz, 2H), 7.58–7.44 (m, 3H), 7.28 (d, J = 5.5 Hz, 1H), 4.29–4.20 (m, 1H), 2.38–2.20 (m, 2H), 2.00–1.82 (m, 2H), 0.94 (t, J = 7.3 Hz, 6H); HRMS (ESI) *m/e* 283.1450 [(M+H)$^+$, calcd for $C_{17}H_{19}N_2O_2$ 283.1447]; **12**: light green solid; mp 72.6–73.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 5.1 Hz, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.36–7.28 (m, 2H), 6.87 (d, J = 5.1 Hz, 1H), 2.99–2.95 (m, 1H), 2.71 (s, 3H), 1.69–1.52 (m, 4H),

0.92 (t, $J = 7.3$ Hz, 6H); HRMS (ESI) *m/e* 339.1024 [$(M+H)^+$, calcd for $C_{17}H_{21}N_2OCl_2$ 339.1031]. Anal. Calcd for $C_{17}H_{20}N_2OCl_2$: C, 60.18; H, 5.94; N, 8.27. Found: C, 60.27; H, 5.90; N, 8.16; compound **13**: dark blue oil; ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.85 (d, $J = 5.5$ Hz, 1H), 7.51 (m, 1H), 7.30 (d, $J = 1.1$ Hz, 2H), 6.35 (d, $J = 5.1$ Hz, 1H), 4.85 (d, $J = 9.2$ Hz, 1H), 4.07–4.00 (m, 1H), 3.53 (q, $J = 6.9$ Hz, 2H), 1.72–1.49 (m, 4H), 1.10 (t, $J = 7.0$ Hz, 3H), 0.95 (t, $J = 7.3$ Hz, 6H); HRMS (ESI) *m/e* 353.1216 [$(M+H)^+$, calcd for $C_{18}H_{23}N_2OCl_2$ 353.1187]. Anal. Calcd for $C_{18}H_{22}N_2OCl_2$: C, 61.20; H, 6.29; N, 7.94. Found: C, 61.06; H, 6.31; N, 7.71; compound **14**: dark oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J = 4.8$ Hz, 1H), 7.52 (d, $J = 2.1$ Hz, 1H), 7.35 (m, 1H), 7.25 (d, $J = 4$ Hz, 1H), 5.1 (m, 1H), 4.66 (q, $J = 6.5$ Hz, 1H), 2.31 (m, 2H), 1.91 (sept, $J = 7.3$ Hz, 2H), 1.51 (d, $J = 7.0$ Hz, 1H), 0.89 (t, $J = 7.4$ Hz, 6H); HRMS (ESI) *m/e* 379.0980 [$(M+H)^+$, calcd for $C_{19}H_{21}Cl_2N_2O_2$ 379.2797]; compound **15**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, $J = 5.1$ Hz, 1H), 7.47 (d, $J = 2.2$ Hz, 1H), 7.30 (m, 2H), 6.32 (d, $J = 5.1$ Hz, 1H), 4.86 (m, 1H), 4.15 (m, 1H), 3.30 (dd, $J = 12.0$, 2.2 Hz, 1H), 3.02 (m, 1H), 1.64 (m, 4H), 1.28 (d, $J = 6.2$ Hz, 3H), 0.93 (t, $J = 7.3$ Hz, 6H); HRMS (ESI) *m/e* 365.1169 [$(M+H)^+$, calcd for $C_{19}H_{23}N_2OCl_2$ 365.2962].

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