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SYNTHESIS OF 6-SUBSTITUTED IMIDAZO[4,5-*d*]PYRIDAZIN-7-ONES

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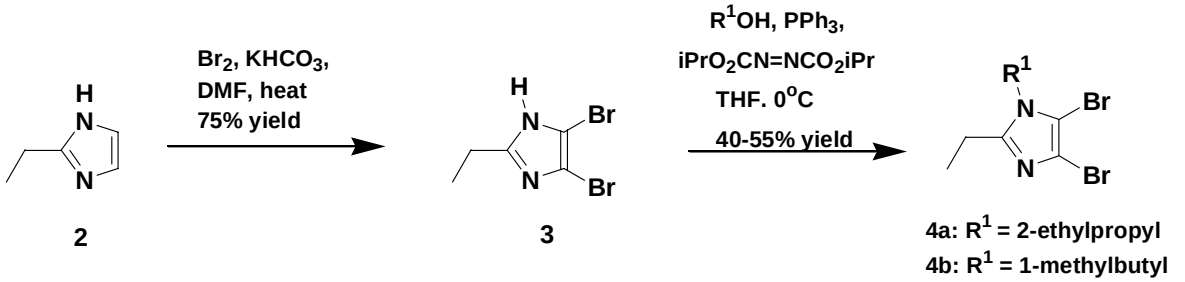
Abstract – A novel synthesis of 6-substituted imidazo[4,5-*d*]pyridazin-7-ones is described, which employs 1,2-disubstituted 4-aroylimidazole-5-carboxylates as key intermediates**.**

The syntheses of pyridazines and their fused derivatives are attracting considerable interest since these compounds are being explored as potential medicinal and agrochemical products.[3] We sought an efficient method of preparation of imidazo[4,5-*d*]pyridazin-7-ones (**1**) as part of a discovery program to identify novel ligands for corticotropin releasing factor (CRF) receptors.[4,5] The details are reported herein.

Our strategy focussed first on the construction of an appropriately substituted imidazole and its subsequent conversion to the bicyclic target (**1**) (Scheme 1). Bromination of 2-ethylimidazole (**2**) in the presence of solid $KHCO_3$ afforded dibromo imidazole (**3**) in 75% yield. Coupling with various alcohols under Mitsunobu conditions generated intermediates (**4**). Regioselective metalation with n-butyllithium[5,6] and treatment with N,N-dimethylformamide (DMF) provided aldehydes (**5**), which were slightly unstable at room temperature. They therefore were usually converted immediately to acetals (**6**) under standard conditions. Treatment of intermediates (**6**) with n-butyllithium, followed by reaction with aroyl chlorides gave ketones (**7**). Substitution of the benzoyl chlorides by the corresponding aldehydes or esters led to inferior yields and/or decomposition. Liberation of the aldehyde was achieved by treatment with aqueous acid. Formation of the cyanohydrin *in situ*, benzylic oxidation with MnO_2 and methanolysis provided methyl esters (**8**). Esters (**8**) were then condensed with anhydrous hydrazine to give imidazopyridazinone (**10a**), which was alkylated exclusively on nitrogen to give the targets (**1**). The presence of the carbonyl group was confirmed by IR spectroscopy ($\nu = 1680 \pm 10$ cm^{-1}, KBr pellet). Alternatively, treatment of esters (**8**) with N-alkylhydrazines gave products (**1**) directly. Scheme 1 illustrates the compounds prepared by the

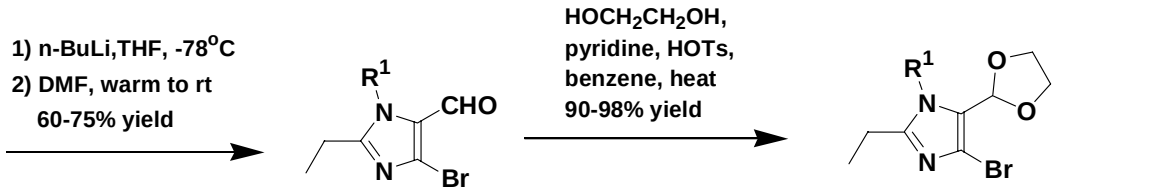
Scheme 1.



2

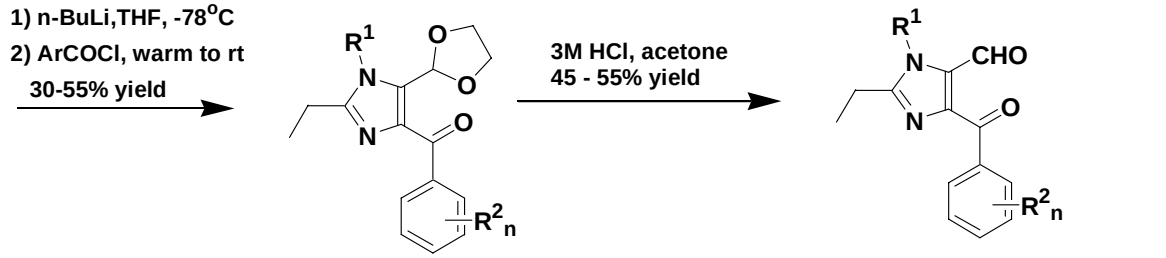
3

4a: R^1 = 2-ethylpropyl
4b: R^1 = 1-methylbutyl



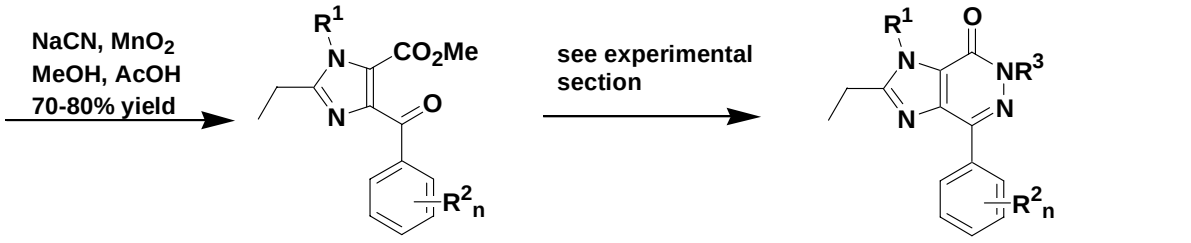
5a: R^1 = 2-ethylpropyl
5b: R^1 = 1-methylbutyl

6a: R^1 = 2-ethylpropyl
6b: R^1 = 1-methylbutyl



7a: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2
7b: R^1 = 1-methylbutyl; R^2_n = 2,4-Cl_2
7c: R^1 = 1-methylbutyl; R^2_n = 2,5-Me_2-4-MeO
7d: R^1 = 2-ethylpropyl; R^2_n = 2,4-$(CF_3)_2$

8a: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2
8b: R^1 = 1-methylbutyl; R^2_n = 2,4-Cl_2
8c: R^1 = 1-methylbutyl; R^2_n = 2,5-Me_2-4-MeO
8d: R^1 = 2-ethylpropyl; R^2_n = 2,4-$(CF_3)_2$



9a: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2
9b: R^1 = 1-methylbutyl; R^2_n = 2,4-Cl_2
9c: R^1 = 1-methylbutyl; R^2_n = 2,5-Me_2-4-MeO
9d: R^1 = 2-ethylpropyl; R^2_n = 2,4-$(CF_3)_2$

10a: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2; R^3 = H
1a: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2; R^3 = Me
1b: R^1 = 1-methylbutyl; R^2_n = 2,4-Cl_2; R^3 = Me
1c: R^1 = 1-methylbutyl; R^2_n = 2,5-Me_2-4-MeO; R^3 = Me
1d: R^1 = 2-ethylpropyl; R^2_n = 2,4-$(CF_3)_2$; R^3 = Me
1e: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2; R^3 = Et
1f: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2; R^3 = Pr
1g: R^1 = 2-ethylpropyl; R^2_n = 2,4-Cl_2; R^3 = CH_2-cyclopropyl

above methods. Substitution on the phenyl ring can be varied widely by these procedures since aroyl chlorides are readily available intermediates.

In summary, an efficient route to imidazo[4,5-*d*]pyridazin-7-ones (**1**) has been devised. Some compounds (**1**) were tested for their binding affinity to rat CRF receptors using cortical homogenates and [^{125}I]-Tyr^{0}-ovine CRF.[7,8] A leading example is compound (**1a**) (rat CRF K_i = 2.2 ±0.4 nM (n=3)).

EXPERIMENTAL

Analytical data were generated using the following procedures. Proton NMR spectra were recorded on an Varian FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in the solvents specified below. MS spectra or HRMS spectra were recorded on a Finnegan MAT 8230 spectrometer using chemi-ionization (CI) with NH_3 as the carrier gas. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Combustion analyses were performed by Quantitative Technologies, Whitehouse, NJ. Reagents were purchased from commercial sources and, when necessary, purified prior to use.[9] Chromatography (TLC or preparative) was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given.

4,5-Dibromo-2-ethylimidazole (3):

To a solution of 2-ethylimidazole (2.32 g, 24.2 mmol) in DMF (30.0 mL) was added $KHCO_3$ (6.1 g, 61 mmol). Bromine (3.12 mL, 61 mmol) was added dropwise over 30 min at rt. The reaction mixture was then stirred at 70 °C for 4 h. The reaction mixture was cooled to 0°C. The inorganic materials were filtered and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give an oil. The oil was treated with water (50.0 mL) and the resulting solid was collected by filtration. Drying *in vacuo* provided the title product (4.59 g, 75%), which was used without further purification because of instability: mp 149-150 °C; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J = 7), 2.75 (q, 2H, J = 7); MS: 255.0.

4,5-Dibromo-2-ethyl-1-(1-ethylpropyl)imidazole (4a):

A mixture of **3** (8.3 g, 33 mmol), triphenylphosphine (9.4 g, 36 mmol) and molecular sieves (10 g) in THF (100 mL) was cooled to 0 to - 5°C. 3-Pentanol (3.4g, 39 mmol) was added under nitrogen atmosphere. The reaction mixture was then stirred at 0 °C for 30 min. Diisopropyl azodicarboxylate (7.2 g, 33 mmol) was added dropwise over 20 min. The mixture was then stirred at 0°C for 2 h, then at rt for 2 days. The reaction mixture was filtered and the collected solid was washed with dichloromethane. Solvent was removed from the filtrate *in vacuo* to afford a yellow liquid. Flash column chromatography ($CHCl_3$) afforded the title product as a colorless oil (4.9 g, 46.5 %): ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 6H, J = 7), 1.33 (t, 3H, J = 7), 2.00

(m, 4H), 2.69 (q, 2H, J = 7), 3.95 (m, 1H); MS: 325.0 (M^+ + H); Anal. Calcd for $C_{10}H_{16}N_2Br_2$: C, 37.06; H, 4.99; N, 8.64. Found: C, 37.20; H, 4.79; N, 8.82.

4,5-Dibromo-2-ethyl-1-(1-methylbutyl)imidazole (4b):

This compound, a clear pale yellow liquid, was prepared like **4a** (4.9 g, 41.5 %): ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 6H, J = 7), 1.23 (d, 3H, J = 7), 2.00 (m, 4H), 2.68 (q, 2H, J = 7), 3.95 (m, 1H); MS: 325.0 (M^+ + H). Anal. Calcd for $C_{10}H_{16}N_2Br_2$: C, 37.06; H, 4.99; N, 8.64. Found: C, 37.21; H, 4.81; N, 8.80.

4-Bromo-2-ethyl-1-(1-ethylpropyl)-imidazole-5-carboxaldehyde (5a):

A solution of **4a** (3.7 g, 11.4 mmol) in THF (40.0 mL) was cooled to - 78 °C under nitrogen atmosphere. A solution of n-butyllithium in hexane (1.6 M, 7.4 mL, 11.9 mmol) added dropwise over 30 min. The mixture was then stirred at -78 °C for 1 h. DMF (2.7 mL, 34.2 mmol) was added dropwise over 15 min. The reaction mixture was stirred at -78 °C for 60 min and then quenched with a saturated NH_4Cl solution (10 mL) at -78 °C. The reaction mixture was extracted with ether (3 X 25 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford a yellow oil. Flash column chromatography ($CHCl_3$) gave a colorless oil (1.97 g, 64 %): ^{1}H NMR ($CDCl_3$): δ 0.78 (t, 6H, J = 7), 1.38 (t, 3H, J = 7), 1.88 (m, 4H), 2.76 (q, 2H, J = 7), 3.95 (m, 1H), 9.67 (s, 1H); MS: 275 (M^+ + 2H). Anal. Calcd for $C_{11}H_{17}N_2OBr$: C, 48.36; H, 6.27; N, 10.25. Found: C, 47.98; H, 6.01; N, 10.17.

4-Bromo-2-ethyl-1-(1-methylbutyl)imidazole-5-carboxaldehyde (5b):

This compound, a colorless oil, was prepared like **5a** (18.5 g, 59 %): ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 7), 1.15 (m, 2H), 1.36 (t, 3H, J = 7), 1.52 (d, 3H, J = 7), 1.90 (m, 2H), 2.78 (q, 2H, J = 7), 4.30 (m, 1H), 9.67 (s, 1H). Anal. Calcd for $C_{11}H_{17}N_2OBr$: C, 48.36; H, 6.27; N, 10.25. Found: C, 48.64; H, 6.01; N, 10.00.

4-Bromo-2-ethyl-1-(1-ethylpropyl)imidazole-5-carboxaldehyde ethylene glycol acetal (6a):

A mixture of **5a** (1.75 g, 6.4 mmol) in benzene (150 mL) was treated with ethylene glycol (1.2 mL, 25 mmol), pyridine (0.28 g, 3.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.67 g, 3.5 mmol). The reaction mixture was stirred at reflux temperature in an apparatus equipped with a Dean-Stark trap for 24 h. The reaction mixture was cooled to rt, diluted with EtOAc (50 mL), washed with saturated sodium bicarbonate solution then brine. Drying over $MgSO_4$, filtration and removal of solvent *in vacuo* provided an oil. Flash column chromatography (1:3=EtOAc:$CHCl_3$) gave a white solid (1.96 g, 97 %): mp 70-71 °C; ^{1}H NMR ($CDCl_3$): δ 0.84 (t, 6H, J = 7), 1.33 (t, 3H, J = 7), 1.84 (m, 4H), 2.72 (q, 2H, J = 7), 4.15 (m, 4H), 4.53 (m, 1H), 5.86 (s, 1H); MS: 317.1 (M^+); Anal. Calcd for $C_{13}H_{21}N_2O_2Br$: C, 49.22; H, 6.67; N, 8.83. Found: C, 49.43; H, 6.61; N, 8.78.

4-Bromo-2-ethyl-1-(1-methylbutyl)imidazole-5-carboxaldehyde ethylene glycol acetal (6b)

This compound, a white solid, was prepared like **6a** (20.7 g, 96 %): mp 69-70°C; ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J = 7), 1.17 (m, 2H), 1.34 (t, 3H, J = 7), 1.44 (d, 3H, J = 7), 1.81 (m, 2H), 2.72 (q, 2H, J = 7), 4.07 (m, 4H), 4.53 (br s, 1H), 5.86 (br s, 1H); MS: 317.1 (M^+); Anal. Calcd for $C_{13}H_{21}N_2O_2Br$: C, 49.22; H, 6.67, N, 8.83. Found: C, 49.38; H, 6.62; N, 8.68.

4-(2,4-Dichlorobenzoyl)-2-ethyl-1-(1-ethylpropyl)imidazole-5-carboxaldehyde (8a)

A solution of **6a** (1.08 g, 3.4 mmol) in THF (20.0 mL) was cooled to -78 °C. A 1.6 M solution of n-butyllithium in hexane (2.4 mL, 4 mmol) was added dropwise over 15 min under nitrogen atmosphere. The reaction mixture was then stirred at -78 °C for 2.5 h. A solution of 2,4-dichlorobenzoyl chloride (0.84 g, 4 mmol) in THF (5.0 mL) was added over 15 min. The mixture was stirred at -78 °C for 6 h then at rt overnight. The mixture was quenched with a saturated NH_4Cl solution (10.0 mL) and extracted with ethyl acetate (3 X 30 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Solvent was removed *in vacuo*. Flash column chromatography (15:85 = EtOAc:hexane) provided the acetal **7a** as a yellow oil (0.61 g, 44 % yield): δ 0.84 (t, 6H, J = 7), 1.33 (t, 3H, J = 7), 1.84 (m, 4H), 2.72 (q, 2H, J = 7), 4.19 (m, 4H) 4.73 (m, 1H), 6.67 (s, 1H), 7.28 (d, 1H, J = 8), 7.42 (s, 1H), 7.51 (d, 1H, J = 8); MS: 411.2 (M^+). The acetal (**7a**) was dissolved in acetone (15.0 mL) and treated with a 3.0 M aqueous HCl solution (30.0 mL) at rt. The reaction mixture was stirred for 24 h at this temperature. The reaction mixture was quenched with brine (50.0 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Solvent was removed *in vacuo*. Flash column chromatography (15:85 = EtOAc:hexane) gave a yellow solid (0.28 g, 51 %): mp 85-86 °C; ^{1}H NMR ($CDCl_3$): δ 0.79 (m, 6H), 1.31 (t, 3H, J = 7), 2.07 (m, 4H), 2.78 (q, 2H, J = 7), 4.02 (m, 1H), 7.36 (d, 1H, J = 8), 7.46 (dd, 1H, J = 8,2), 7.57 (d, 1H, J = 2), 10.1 (s, 1H); MS: 367 (M^+); Anal. Calcd for $C_{18}H_{20}N_2O_2Cl_2$: C, 58.87; H, 5.50; N, 7.64. Found: C, 58.91; H, 5.60; N, 7.44.

4-(2,4-Dichlorobenzoyl)-2-ethyl-1-(1-methylbutyl)imidazole-5-carboxaldehyde (8b)

This compound was prepared like compound (**8a**). The acetal **7b** was isolated after chromatography (15:85 = EtOAc:hexane) as a white solid (2.4 g, 59 %): mp 129-130 °C; ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, J = 7), 1.21 (m, 2H), 1.27 (t, 3H, J = 7), 1.49 (d, 3H, J = 7), 1.77 (m, 2H), 2.74 (m, 2H), 4.19 (m, 4H) 4.73 (m, 1H), 6.67 (s, 1H), 7.28 (d, 1H, J = 8), 7.42 (s, 1H), 7.51 (d, 1H, J = 8); MS: 411 (M^+); Anal. Calcd for $C_{20}H_{24}N_2O_3Cl_2$: C, 58.40; H, 5.88; N, 6.81. Found: C, 58.45; H, 5.95; N, 6.68. The title compound was isolated after chromatography (15:85 = EtOAc:hexane) as a yellow solid (1.46 g, 71%): mp 43-44 °C; ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J = 7), 1.17 (m, 2H), 1.34 (t, 3H, J = 7), 1.44 (d, 3H, J = 7), 1.81 (m, 2H), 2.72 (q, 2H, J = 7), 4.53 (br s, 1H), 7.36 (d, 1H, J = 8), 7.46 (dd, 1H, J = 8,2), 7.57 (d, 1H, J = 2), 10.2 (s, 1H). MS: 367 (M^+);

Anal. Calcd for $C_{18}H_{20}N_2O_2Cl_2$: C, 58.87; H, 5.50; N,7.64. Found: C, 58.96; H, 5.34; N, 7.46.

4-(2,5-dimethyl-4-methoxybenzoyl)-2-ethyl-1-(1-methylbutyl)imidazole-5-carboxaldehyde (8c)

This compound was made like compound (**8a**). The acetal (**7c**) was isolated after chromatography (15:85 = EtOAc:hexane) as a yellow solid (1.53 g, 38 %): mp 160-162°C; ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3H, J = 7), 1.28 (m, 2H), 1.32 (t, 3H, J = 7), 1.50 (d, 3H, J = 7), 1.78 (m, 2H), 2.16 (s, 3H), 2.46 (s, 3H), 2.79 (m, 3H), 3.85 (s, 3H), 4.10 (m, 4H), 4.45 (m, 1H), 6.45 (s, 1H), 6.65 (s, 1H), MS: 401.3 (M^+ + H); Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found; C, 69.05; H, 8.10; N, 6.33. The title compound was isolated after chromatography (15:85 = EtOAc:hexane) as a yellow liquid (0.48 g, 39 %): ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J = 7), 1.20 (m, 2H), 1.34 (t, 3H, J = 7), 1.57 (d, 3H, J = 7), 1.92 (m, 4H), 2.17 (s, 3H), 2.51 (s, 3H), 2.85 (m, 2H), 3.88 (s, 3H), 6.70 (s, 1H), 7.49 (s, 1H), 10.1 (s, 1H). HRMS: Calcd for $C_{21}H_{29}N_2O_3$: 357.2178; Found: 357.2169 (M^+ + H).

4-(2,4-Di-trifluoromethylbenzoyl)-2-ethyl-1-(1-ethylpropyl)imidazole-5-carboxaldehyde (8d)

This compound was prepared like compound (**8a**). The acetal (**7d**) was isolated after chromatography (15:85 = EtOAc:hexane) as white solid (1.53 g, 64%): mp 105-106 °C; ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 6H, J = 7), 1.21 (t, 3H, J = 7), 1.87 (m, 4H), 2.67 (q, 2H, J = 7), 4.12 (m, 4H), 4.47 (m, 1H), 6.76 (s, 1H), 7.68 (d, 1H, J = 8), 7.84 (d, 1H, J = 8), 7.95 (s, 1H); MS: 479.2 (M^+ + H). Anal. Calcd for $C_{22}H_{24}N_2O_3F_6$: C, 55.23; H, 5.07; N, 5.87. Found; C, 54.96; H, 5.09; N, 5.72. The title product was isolated after chromatography (15:85 = EtOAc:hexane) as a yellow liquid (1.03g, 82 %): ^{1}H NMR ($CDCl_3$): δ 0.79 (m, 6H), 1.25 (t, 3H, J = 7), 1.89 (m, 4H), 2.74 (q, 2H, J = 7), 4.15 (m, 1H), 7.72 (d, 1H, J = 8, 7.91 (d 1H, J = 8), 7.99 (s, 1H), 10.5 (s, 1H); MS: 435 (M^+ + H); Anal. Calcd for $C_{20}H_{20}N_2O_2F_6$: C, 55.30; H, 4.64; N, 6.46; Found; C, 55.03; H, 4.45; N, 6.27.

Methyl 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-ethylpropyl)imidazole-5-carboxylate (9a)

A mixture of **8a** (0.367 g, 1 mmol) in methanol (60 mL) was reacted with NaCN (0.245 g, 5 mmol), AcOH (96 mg, 1.6 mmol) and activated MnO_2 (1.24 g, 21 mmol). The resulting mixture was stirred at rt under a nitrogen atmosphere for 18 h. The reaction mixture was filtered through celite and the filter pad was washed with methanol. The filtrate was concentrated *in vacuo*. Flash chromatography (1:100 = MeOH:CH_2Cl_2) and recrystallization from hexane gave a white solid (320 mg, 81 %): mp 73-74 °C; ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 6H, J = 7), 1.33 (t, 3H, J = 7), 1.90 (m, 5H), 2.77 (q, 2H, J = 7), 3.69 (s, 3H), 7.30 (d, 1H, J = 8), 7.45 (s, 1H), 7.56 (d, 1H), J = 8); Anal. Calcd for $C_{19}H_{22}N_2O_3Cl_2$: C, 57.44; H, 5.58; N, 7.05. Found: C, 57.31; H, 5.45; N, 6.85.

Methyl 4-(2,4-dichlorobenzoyl)-2-ethyl-1-(1-methylbutyl)imidazole-5-carboxylate (9b)

This compound, a yellow oil, was made like **9a** (910 mg, 85 %): ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, J = 7), 1.21 (m, 2H), 1.27 (t, 3H, J = 7), 1.49 (d, 3H, J = 7), 1.77 (m, 2H), 2.74 (m, 3H), 3.69 (s, 3H), 7.30 (d, 1H, J = 8), 7.45 (s, 1H), 7.56 (d, 1H, J = 8); MS: 397.2 (M^+); Anal. Calcd for $C_{19}H_{22}N_2O_3Cl_2$: C, 57.44; H, 5.58; N, 7.05. Found: C, 57.25; H, 5.70; N, 6.80.

Methyl 4-(2,5-dimethyl-4-methoxybenzoyl)-2-ethyl-1-(1-methylbutyl)imidazole-5-carboxylate (9c)

This compound, a yellow oil, was made like **9a** (205 mg, 53%): ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J = 7), 1.23 (m, 2H), 1.35 (t, 3H, J = 7), 1.57 (d, 3H, J = 7), 1.95 (m, 2H), 2.13 (s, 3H), 2.52 (s, 3H), 2.83 (m, 2H), 3.56 (s, 3H), 3.86 (s, 3H), 4.12 (m, 1H), 4.65 (m, 1H), 6.67 (s, 1H), 7.34 (s, 1H); HRMS: Calcd for $C_{22}H_{30}N_2O_4$: 386.2205. Found: 387.2264 (M^+ + H).

Methyl 4-(2,4-Di-trifluoromethylbenzoyl)-2-ethyl-1-(1-ethylpropyl)imidazole-5-carboxylate (9d)

This compound, a pale yellow solid, was made like **9a** (350 mg, 75%): mp 57-58 °C; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 6H, J = 7), 1.28 (t, 3H, J = 7), 1.89 (m, 4H), 2.72 (q, 2H, J = 7), 3.79 (s, 3H), 4.13 (m, 1H), 7.71 (d, 1H, J = 8), 7.87 (d, 1H, J = 8), 7.98 (s, 1H); MS: 465.3 (M^+ + H); Anal. Calcd for $C_{21}H_{22}N_2O_3F_6$: C, 54.31; H, 4.79; N, 6.03. Found: C, 53.92; H, 4.68; N, 5.80.

4-(2,4-Dichlorophenyl)-2-ethyl-1-(1-ethylpropyl)imidazo[4,5-*d*]pyridazin-7-one (10a):

A mixture of **9a** (0.100 g, 0.25 mol) in ethanol (10 mL) was treated with hydrazine (0.105 g, 3.3 mol) and refluxed under a nitrogen atmosphere for 48 h. Flash column chromatography (15:85 = EtOAc:hexane, then methanol) and trituration with ether afforded a white solid (70 mg, 74 %): mp 246-247 °C; ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 6H, J = 7), 1.38 (t, 3H, J = 7), 2.08 (m, 2H), 2.39 (m, 2H), 2.92 (q, 2H, J = 7), 4.08 (m, 1H), 7.39 (d, 1H, J = 7), 7.56 (m, 2H), 10.27 (s, 1H). HRMS: Calcd for $C_{18}H_{20}N_4OCl_2$: 379.1092. Found: 379.1070 (M^+ + H).

4-(2,4-Dichlorophenyl)-2-ethyl-1-(1-ethylpropyl)-6-methylimidazo[4,5-*d*]pyridazin-7-one (1a)

Compound (**9a**) (0.100 g, 0.25 mmol) in ethanol (10 mL) was treated with anhydrous methylhydrazine (0.150 g, 3.3 mmol) for 24 h. The solvent was removed *in vacuo*. Flash column chromatography (1:50 = MeOH:CH_2Cl_2) afforded a white solid (30 mg; 31 %): mp 94-95 °C; ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 3H, J = 7), 0.89 (t, 3H, J = 7), 1.36 (t, 3H, J = 7), 2.09 (m, 1H), 2.11 (m, 2H), 2.42 (m, 2H), 2.91 (q, 2H, J = 7), 3.93 (s, 3H), 7.38 (d, 1H, J = 8), 7.54 (m, 2H); HRMS Calcd for $C_{19}H_{22}N_4OCl_2$: 393.1249. Found: 393.1250 (M^+ + H).

4-(2,4-Dichlorophenyl)-2-ethyl-6-methyl-1-(1-methylbutyl)imidazo[4,5-*d*]pyridazin-7-one (1b)

This compound (a white solid recrystallized from hexane) was prepared like **1a** (42 mg, 43 %): mp 89-90 °C; ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, J = 7), 1.28 (m, 2H), 1.25 (t, 3H, J = 7), 1.55 (d, 3H, J = 7), 1.82 (m, 2H), 2.77 (q, 2H, J = 7), 3.72 (s, 3H), 4.52 (m, 1H), 7.30 (d, 1H, J = 7), 7.45 (s, 1H), 7.56 (d, 1H, J = 8); MS: 393.2 (M^+); Anal. Calcd for $C_{19}H_{22}N_4OCl_2$: C, 58.02; H, 5.65; N, 14.24. Found: C, 58.32; H, 5.59; N, 14.14.

4-(2,5-Dimethyl-4-methoxyphenyl)-2-ethyl-6-methyl-1-(1-methylbutyl)imidazo[4,5-*d*]pyridazin-7-one (1c)

This compound, an off-white solid, was prepared like **1a** (43 mg, 43 %): ^{1}H NMR (acetone-d_6): δ 0.85 (t, 3H, J = 7), 1.05 (m, 2H), 1.29 (t, 3H, J = 7), 1.66 (m, 2H), 2.00 (m, 4H), 2.16 (s, 3H), 2.27 (s, 3H), 2.92 (q, 2H, J = 7), 3.79 (s, 3H), 3.86 (s, 3H), 6.84 (s, 1H), 7.26 (s, 1H); HRMS: Calcd for $C_{22}H_{30}N_4O_2$: 383.2447. Found: 383.2433 (M^+ + H).

4-(2,4-Di-trifluoromethylphenyl)-2-ethyl-1-(1-ethylpropyl)-6-methylimidazo[4,5-*d*]pyridazin-7-one (1d)

This compound, a white solid, was made like **1a** (16 mg, 14 %): mp 139-140 °C; ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 6H, J = 7), 1.36 (t, 3H, J = 7), 2.13 (m, 2H), 2.43 (m, 2H), 2.91 (q, 2H, J = 7), 3.92 (s, 3H), 4.09 (m, 1H), 7.90 (m, 2H), 8.08 (s, 1H); HRMS: Calcd for $C_{21}H_{22}N_4OF_6$: 461.1776; Found: 461.1763 (M^+ + H).

4-(2,4-Dichlorophenyl)-2,6-diethyl-1-(1-ethylpropyl)imidazo[4,5-*d*]pyridazin-7-one (1e)

To a solution of **10a** (0.1 g, 26.4 mmol) in benzene (5.0 mL) were added Bu_4NBr (8.5 mg, 26.4 mmol), powdered KOH (15.0 mg, 26.4 mmol) and iodoethane (0.124 g, 79 mmol). The resultant mixture was stirred at rt under nitrogen for 20 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with brine (10 mL). Drying over $MgSO_4$, filtration, removal of solvent *in vacuo* and flash column chromatography (CH_2Cl_2) provided a colorless oil (58 mg, 54 %): ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 6H, J = 7), 1.36 (t, 3H, J = 7), 1.44 (t, 3H, J = 7), 2.14 (m, 2H), 2.42 (m, 2H), 2.92 (q, 2H, J = 7), 4.06 (m, 1H), 4.37 (q, 2H, J = 7), 7.37 (d, 1H, J = 7), 7.56 (m, 2H); HRMS: Calcd for $C_{20}H_{24}N_4OCl_2$: 407.1405. Found: 407.1404 (M^+ + H).

4-(2,4-Dichlorophenyl)-2-ethyl-1-(1-ethylpropyl)-6-propyl-imidazo[4,5-*d*]pyridazin-7-one (1f)

The title compound, a colorless oil, was prepared like **1e** (56 mg, 51 %): ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, J = 7), 0.99 (t, 3H, J = 7), 1.21 (t, 3H, J = 7), 1.36 (t, 3H, J = 7), 1.92 (m, 2H), 2.10 (m, 2H), 2.39 (m, 2H), 3.48 (q, 2H, J = 7), 4.06 (m, 1H), 4.27 (m, 2H), 7.36 (d, 1H, J = 8), 7.56 (m, 2H); Anal. Calcd for $C_{21}H_{26}N_4OCl_2$: C, 59.86; H, 6.23; N, 13.30. Found: C, 59.86 ; H, 6.12 ; N, 13.13.

6-(*N*-Cyclopropylmethyl)-4-(2,4-dichlorophenyl)-2-ethyl-1-(1-ethylpropyl)-imidazo[4,5-*d*]pyridazin-7-one (1g)

The title compound, a colorless oil, was prepared like **1e** (68 mg, 59 %): ^{1}H NMR ($CDCl_3$): δ 0.50 (m, 2H), 0.81 (m, 2H), 0.82 (t, 6H, J = 7), 1.37 (t, 3H, J = 7), 1.39 (m, 1H), 2.36 (m, 2H), 2.41 (m, 2H), 2.92 (q, 2H, J = 7), 4.07 (m, 1H), 4.18 (d, 2H, J = 7), 7.38 (d, 1H, J = 8), 7.57 (m, 2H); HRMS: Calcd for $C_{22}H_{26}N_4OCl_2$: 433.1562. Found: 433.1563 (M^+ + H).

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