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One-pot directed alkylation/deprotection strategy for the synthesis of substituted pyrrole[3,4-d]pyridazinones

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Abstract

In the course of an SAR study of pyrrole[3,4-d]pyridazinones we optimized conditions for a one pot directed lithiation / alkylation reaction that also promoted *in situ* cleavage of a Boc-protecting group on the pyrrole ring. The efficiency of the process allowed access to a number of substituted analogues of interest as possible antitumor agents.

Keywords

metalation; heterocycles; antitumour agents; fused-ring systems; halogenation; lithiation; protecting groups

Inhibition of the monocarboxylate transporters, particularly isoforms MCT1^[1] and MCT4,^[2] is a promising strategy for thwarting tumour growth,^[3] particularly poorly-treated hypoxic tumours.^{[4],[5]} AstraZeneca's MCT1 inhibitor **1** (Fig. 1) has shown early clinical promise^[6] in tumours having high levels of MCT1 expression.^{[7],[8]} The substituted pyrrole[3,4-d]pyridazin-1-one **2** is also highly potent,^{[9],[10],[11]} as are structurally related compounds from other labs,^[12] including our own.^[13] As part of an effort to study the consequences of MCT1 inhibition we wished to prepare analogues of compound **2** that retain a hydroxyl-containing side chain, shown by us^[13] and by Bantick, et. al. to be essential for activity.^[14]

Recently we reported a Grubbs cross metathesis strategy to prepare the ketoester **6** that is used for the synthesis of the core scaffold of inhibitor **2**, the substituted pyrrole[3,4-d]pyridazin-1-one **9** (Scheme 1).^[15] In that report we also discussed prior synthetic strategies to prepare this fused ring system.^[15]

To the pyrrole ring of this core structure **9**, or to a precursor, we wished to install side chains at N1 and C2, mimicking or duplicating the corresponding side chains of inhibitors **1** and **2**. As an example, *N*-alkylation of ester **8** with bromide **10** (Scheme 2), followed by methylhydrazine-promoted ring closure gave the substituted pyrrole[3,4-d]pyridazin-1-one **12**. To our surprise, however, C2 lithiation of **12** was unsuccessful, resulting instead in

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deprotonation at the benzylic-like carbon to give, after quenching with an excess of the thiotosylate **13**^[16] the dithiane-containing derivative **14**. In the ¹H NMR spectrum of **14** it was apparent that the *N*-CH₂ protons for compound **12**, appearing at 5.85 ppm, were absent and also that five rather than four aromatic protons were present. The protons for the S-CH₂-CH₂-CH₂-OTBDMS side chain were also doubled in number relative to that expected for the desired *N*-alkylated pyrrole[3,4-*d*]pyridazin-1-one **15**. The desilylated diol **16** was readily purified and fully characterized to confirm the assigned structure. The CH₂ deprotonation observed for the fused pyrrole **12** had not been seen when similar reaction conditions were used during the synthesis of the naphthyl-substituted analog **2**. The electron-withdrawing ability of the chloropyridyl group relative to that of a naphthylmethyl group was apparently a complicating factor and required a change in tactics. We felt that an appropriate protecting group at pyrrole *N*1 would direct C2 lithiation^[17] and subsequent alkylation. *N*1 deprotection and alkylation would then be used to install the chloropyridylmethyl group of target pyrrole[3,4-*d*]pyridazin-1-one **15**.

A Boc-group indeed was found to successfully direct *o*-lithiation: Boc-protected pyrrole[3,4-*d*]pyridazin-1-one **17** underwent LDA-promoted metalation, as shown by deuterium incorporation upon quenching with CD₃OD, which was confirmed by analysis of its ¹H NMR spectrum. Surprisingly, however, the Boc group was also cleanly removed during the reaction, or more likely in the work-up. Having established the ability to conduct *o*-lithiation, the sulfur-containing side chain was incorporated using thiotosylate **13**. Once again the Boc group was cleanly removed following a methanol quench, giving the thioether **18**, with an unprotected pyrrole group. Likely in such reactions the CH₃OLi that is formed during workup prompts Boc removal. Though Boc group is normally base-stable, alkoxides have been used for Boc deprotection of pyrroles.^[18] The one-pot alkylation / deprotection method was robust, with good results (yields of 57–63 %) upon scale-up for multigram synthesis of the thioether **18** (Table 1).

Other protecting groups were also effective in directing metalation at C2 of the pyrrole ring, including silylethoxymethyl (SEM) and *p*-methoxybenzyl (PMB) groups, as evidenced by quenching of electrophiles **19–21** with iodine followed by MeOH/NH₄Cl workup (Scheme 4). The facile removal of the Boc protecting group in the process, however, made Boc the preferred pyrrole protecting group in such synthetic efforts. The ready access to C-2 iodinated fused pyrroles **21–23** likely will allow access to a wide range of analogues through transition metal-mediated coupling reactions.

With multigram quantities of the key substituted pyrrole[3,4-*d*]pyridazin-1-one **18** available, the installation of various groups at the pyrrole *N*1 by direct alkylation was of interest. Bromide **10**^[19] was prepared on a multigram scale cleanly but in low yield from 4-methyl-2-chloropyridine **24** using NBS with AIBN/dibenzoyl peroxide as radical initiator in CCl₄ at 80 °C (Scheme 5). Similarly, 5-methyl-2-chloropyridine **25**, 2-methyl-5-chloropyridine **26**, and 4-methyl-2-chloroquinoline **27** gave analogous bromides **28**,^[20] **29**,^[21] and **30**,^[22] respectively, following similar protocols.

Preparation of an isoquinoline analog using the 4-methyl isoquinoline substrate **31**^[23] was more problematic, as the desired bromide **32** was contaminated with much larger amounts of

the dibromide **33**, the tribromide **34**, and unreacted starting material, a mixture that was difficult to separate and thus was undesirable even if the efficiency of the conversion to monobromide **32** could be improved. However, the use of the less commonly-used reagent 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave the monobrominated isoquinoline **32** in 80% yield (Scheme 6).

DBDMH was further used for monobromination of a variety of methyl-substituted quinolines.^[24] The mild conditions and the higher selectivity for monobromination relative to the traditional NBS/AIBN/CCl₄ method makes the use of DBDMH preferable and perhaps generally useful in the monobromination of methyl-substituted pyridines and their ring-fused analogues.

Each of the bromides from Schemes 5 and 6 was then used in the efficient alkylation of pyrrole **18**, using NaH in DMF followed by acidic desilylation (Scheme 7). The resulting products **35–39** were then purified by preparative HPLC. Biological evaluation of these compounds and substituted analogues will be the subject of future reports from our laboratories. We feel that the efficient one pot pyrrole metalation/ alkylation/deprotection and DBDMH-promoted monobromination procedures will be of general use in the preparation and study of related heterocycles.

Experimental Section

General Experimental

All reagents and solvents were obtained from commercial suppliers and were used as supplied. NMR spectra were recorded on a 400 MHz spectrometer (400 MHz ¹H, 100 MHz ¹³C) at 25 °C. Chemical shifts are reported in ppm (δ) referenced to residual NMR solvent, with coupling constants (*J*) in hertz. Flash column chromatography was performed using RediSep® columns (60 Å mesh) on a Combiflash Rf® instrument from Teledyne Isco, Inc. All reactions were monitored using TLC and LCMS (conducted using an HPLC coupled with an ion-trap mass spectrometer system, from Thermo-Fisher, Inc.). All new compounds were characterized using ¹H, ¹³C NMR, IR and HRMS. For known compounds, appropriate references are cited and ¹H NMR spectra are present in the supporting information. FTIR spectra were recorded as a neat oil or solid. HRMS samples were analyzed using a TOF analyzer and an ES ionization method. Wherever necessary, reactions were carried out under argon atmosphere. LDA was freshly prepared before each use. Methyl acrylate, isovaleraldehyde and the TOSMIC acid **7** were obtained from commercial sources, as were compounds **24–27**. Substituted isoquinoline **31** was synthesized following a literature procedure.^[23]

Synthesis of methyl 4-(3-methylbutanoyl)-1H-pyrrole-3-carboxylate (8)—To a dry 500 mL 3-neck flask under argon and cooled to 0 °C, fitted with a condenser and addition funnel and containing a stir bar, was added NaH (14.2 g, 352.5 mmol) and DMF (100 mL). To a separate flask containing DMF (100 mL) was added olefin **6** (30 g, 176 mmol) and TOSMIC acid **7** (35 g, 176 mmol). This solution was added to NaH/DMF solution dropwise using an addition funnel, over a period of 45 min. The reaction was allowed to warm to room temperature overnight. Saturated NH₄Cl was added and the

mixture was extracted with ethyl acetate. The organic layer was washed with water followed by brine, dried over Na₂SO₄ and concentrated to give an oily solid which was purified by flash chromatography (ethyl acetate : hexanes, 2 : 1). The fractions corresponding to desired product were isolated, combined and concentrated to give an orange-brown solid (11 g, 31%). ¹H NMR (CDCl₃, 400 MHz) δ 9.14 (br s, 1H), 7.39 (s, 1H), 7.29 (s, 1H), 3.84 (s, 3H), 2.79 (d, *J* = 7.0 Hz, 2H), 2.28 – 2.20 (m, 1H), 0.97 ppm (d, *J* = 7.0 Hz, 6H).

Synthesis of 4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one

(9)—To a 200 ml round bottom flask with stir bar was added in ethanol (50 mL) and compound **8** (1.48 g, 7.07 mmol). To this mixture was added methyl hydrazine (1.6 g, 1.9 mL, 35.4 mmol) and then the reaction mixture was refluxed for 16 h. After confirming the completion of the reaction by LCMS (*m/z* = 410.8), the solution was cooled to room temperature and quenched by addition of sat. NH₄Cl solution (25 mL). This mixture was extracted with ethyl acetate (3 x 40 mL) and the combined organic layers were washed with water (2 x 50 mL), brine (1 x 50 mL), dried over Na₂SO₄ and concentrated to give **9** as a dark brown solid (1.27 g, 87% yield). ¹H NMR (CDCl₃, 400 MHz) δ 12.25 (br s, 1H), 7.55 (s, 1H), 7.27 (merged with CDCl₃ signal) (s, 1H), 3.79 (s, 3H), 2.63 (d, *J* = 7.4 Hz, 2H), 2.23-2.13 (septet, 1H), 0.98 ppm (d, *J* = 6.6 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 159.5, 145.6, 120.2, 116.5, 115.6, 42.5, 38.0, 28.0, 22.7 ppm; FT-IR (neat, cm⁻¹) 3164.9 (br), 2956.8, 2865.9, 1777.9, 1729.7, 1630.7, 1582.7, 1523.8, 1464.8, 1367.7, 1250.8, 1167.8, 1094.8, 1069.8, 880.9, 763.7, 698.8 cm⁻¹; HRMS (ES-TOF) *m/z*: [M + H]⁺ Calc'd for C₁₁H₁₆N₃O: 206.1293, Found: 206.1286.

Methyl 1-((2-chloropyridin-4-yl)methyl)-4-(3-methylbutanoyl)-1H-pyrrole-3-carboxylate (11)—Pale brown oil; 1.01g; 84%. ¹H NMR (CDCl₃, 400 MHz) δ 8.41 (d, *J* = 3.9 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.07 (br s, 1H), 6.95 (d, *J* = 4.0 Hz, 1H), 5.08 (s, 2H), 3.84 (s, 3H), 2.81 (d, *J* = 6.9 Hz, 2H), 2.26-2.18 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 6H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 197.5, 163.9, 152.6, 150.9, 147.9, 128.3, 127.6, 126.7, 122.2, 120.2, 115.8, 52.2, 51.6, 51.2, 25.3, 22.6 ppm; FT-IR (neat, cm⁻¹) 3155.9, 2956.8, 2870.9, 1724.5, 1667.5, 1594.6, 1551.7, 1535.6, 1466.7, 1438.6, 1385.5, 1366.7, 1292.6, 1249.5, 1212.6, 1169.4, 1123.6, 1087.4, 1002.6, 990.7, 935.6, 874.8, 839.6, 813.6, 764.6, 714.6 cm⁻¹; HRMS (ES-TOF) *m/z*: [M + H]⁺ Calc'd for C₁₇H₂₀N₂O₃Cl: 335.1162, Found: 335.0941.

6-((2-chloropyridin-4-yl)methyl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (12)—White solid; 0.401g; 41%. ¹H NMR (CDCl₃, 400 MHz) δ 8.39 (d, *J* = 4.9 Hz, 1H), 7.53 (d, *J* = 2.5 Hz, 1H), 7.04 (br s, 1H), 7.02 (s, 1H), 6.92 (d, *J* = 4.0 Hz, 1H), 5.31 (s, 2H), 3.75 (s, 3H), 2.59 (d, *J* = 7.4 Hz, 2H), 2.20-2.10 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 6H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 157.9, 152.6, 150.5, 148.1, 143.7, 122.1, 121.6, 120.1, 119.9, 117.3, 115.6, 53.0, 42.4, 37.9, 27.9, 22.7 ppm; FT-IR (neat, cm⁻¹) 3097.9, 3052.9, 2954.8, 1645.6, 1595.8, 1582.8, 1550.8, 1534.8, 1465.8, 1451.8, 1391.8, 1335.8, 1149.9, 1123.8, 1088.8, 996.8, 974.9, 876.8, 828.8, 774.8, 757.8, 719.9, 691.8, 670.8 cm⁻¹; HRMS (ES-TOF) *m/z*: [M + H]⁺ Calc'd for C₁₇H₂₀N₄OCl: 331.1326, Found: 331.1317.

Synthesis of 6-(9-(2-chloropyridin-4-yl)-2,2,3,3,15,15,16,16-octamethyl-4,14-dioxa-8,10-dithia-3,15-disilaheptadecan-9-yl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one and 6-((2-chloropyridin-4-yl)bis((3-hydroxypropyl)thio)methyl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (14 and 16)—To a dry 250 mL round bottom flask with stir bar under argon was added THF (anhydrous; 25 mL), **12** (0.390 g, 1.16 mmol), and thiotosylate **13** (0.840 g, 2.33 mmol). The reaction mixture was then cooled to -78°C . Under positive argon flow, LDA (0.5 M; 4.7 mL; 2.33 mmol) was added over 10 min and the reaction mixture was allowed to stir overnight. After confirming the completion of the reaction by TLC, sat. NH_4Cl solution was added to quench the reaction and this mixture was extracted with ethyl acetate (3 x 25 mL), washed with water (3 x 25 mL), brine (1 x 50 mL), dried over Na_2SO_4 , filtered and concentrated to give a crude oil. This material was purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to give the dithiane bis-TBDMS ether **14** as a brown oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.34 (d, $J = 4.7$ Hz, 1H), 7.68 (s, 1H), 7.20 (s, 1H), 7.08 (s, 1H), 6.94 (d, $J = 5.4$ Hz, 1H), 3.74 (s, 3H), 3.66 (br t, $J = 5.5$ Hz, 2H), 3.57 (t, $J = 6.0$ Hz, 2H), 3.05 (t, $J = 7.3$ Hz, 2H), 2.67-2.54 (m, 4H), 2.20-2.09 (m, 1H), 1.78-1.58 (m, 2H), 1.00 (dd, $J = 3.3, 6.6$ Hz, 6H), 0.86 (s, 9H), 0.84 (s, 9H), 0.03 (s, 6H), 0.00 (s, 6H) ppm. This material was dissolved in THF (5 mL) and to this solution was added HCl (4M in dioxane, 2 mL) and the mixture was allowed to stir for 1h. After confirming the deprotection of silyl groups by TLC and LCMS, the solvents were evaporated and the crude product was purified by preparative HPLC to give the diol product **16** as a brown oil (0.301 g, 53% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 8.30 (d, $J = 8.3$ Hz, 1H), 7.92 (s, 1H), 7.23 (s, 1H), 7.08 (s, 1H), 6.95 (obscured d, 1H), 3.80-3.74 (m, 2H), 3.67 (s, 3H), 3.66-3.62 (obscured m, 2H), 3.06-2.99 (m, 1H), 2.72-2.62 (m, 2H), 2.58 (obscured d, 2H), 2.18-2.08 (m, 1H), 1.84-1.75 (m, 2H), 1.73-1.64 (m, 2H), 0.97 (dd, $J = 6.6, 2.76$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 154.1, 152.2, 145.9, 126.0, 123.7, 123.7, 123.4, 121.9, 117.8, 64.5, 62.6, 61.4, 43.5, 40.0, 37.4, 33.7, 32.7, 31.1, 29.8, 29.6, 24.3, 24.3, 24.2 ppm; FT-IR (neat, cm^{-1}) 3381.8, 2953.8, 2869.8, 1633.5, 1585.5, 1546.7, 1491.7, 1463.7, 1421.7, 1374.6, 1348.5, 1286.7, 1261.7, 1238.7, 1202.5, 1160.6, 1125.7, 1087.7, 1052.5, 998.6, 971.7, 907.7, 881.7, 785.6, 736.6, 719.6, 670.6, 695.6; HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ Calc'd for $\text{C}_{23}\text{H}_{32}\text{N}_4\text{O}_3\text{ClS}_2$: 511.1082, Found: 511.1579.

Synthesis of tert-butyl 4-isobutyl-2-methyl-1-oxo-1,2-dihydro-6H-pyrrolo[3,4-d]pyridazine-6-carboxylate (17)—To a dry 100 mL flask with stir bar was added DCM (20 mL) and **9** (0.129 g, 0.63 mmol). Boc anhydride (0.150 g, 0.69 mmol) and catalytic amount of 4-*N,N*-dimethyl aminopyridine (0.015 g, 0.125 mmol) were added and the mixture was stirred for 30 min. After confirming reaction completion by TLC analysis, the solution was concentrated and the residue was dissolved in ethyl acetate. This solution was washed with sat. NH_4Cl solution, water (2 x 20 mL), brine (1 x 25 mL) and was dried over Na_2SO_4 . After concentration, the crude product was purified by flash chromatography (hexanes : ethyl acetate, 1 : 1) to give the off-white solid, compound **17**, as a pure product (0.185 g, 98% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 8.00 (d, $J = 2.0$ Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 3.70 (s, 3H), 2.56 (d, $J = 7.0$ Hz, 2H), 2.20-2.11 (septet, 1H), 0.97 (d, $J = 6.6$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.9, 148.0, 144.2, 121.3, 118.6, 117.7, 114.3, 86.6, 42.2, 37.8, 27.8, 22.6 ppm; FT-IR (neat, cm^{-1}) 3411.9, 2963.8, 2870.9, 1746.6,

1659.6, 1595.8, 1522.8, 1476.8, 1459.8, 1389.7, 1369.7, 1335.8, 1351.8, 1319.8, 1290.7, 1273.5, 1257.6, 1144.5, 1101.6, 1081.7, 986.6, 840.7, 768.6 cm^{-1} ; HRMS (ES-TOF) m/z : $[M + H]^+$ Calc'd for $\text{C}_{16}\text{H}_{24}\text{N}_3\text{O}_3$: 306.1814, Found: 306.1818.

Synthesis of $\text{d}_2\mathbf{9}$ —To a dry 25 mL flask with stir bar under argon was added anhydrous THF (20 mL) and **17** (0.025 g, 0.087 mmol). The solution was cooled to -78°C and to this was added LDA (0.5 M solution in THF, 0.33 mL) and the mixture was stirred at -78°C for 2 h. The reaction was quenched with CD_3OD (0.3 mL) and the solution was stirred for 30 min, concentrated, and the crude product was analyzed by ^1H NMR. Since this compound was made only to test the ability of LDA to deprotonate **17**, the yield was not determined and characterization included only ^1H NMR and LCMS. ^1H NMR (CD_2Cl_2 , 400 MHz) δ 9.93 (br s, 1H), 7.16 (d, $J = 2.8$ Hz, 1H), 3.65 (s, 1H), 2.56 (d, $J = 7.0$ Hz, 2H), 2.18-2.07 (septet, 1H), 0.94 (d, $J = 6.6$ Hz, 6H) ppm. The disappearance of the aromatic proton and Boc group indicate the incorporation of deuterium and the loss of the Boc group, respectively.

7-((3-((tert-butyldimethylsilyl)oxy)propyl)thio)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (18**)**—To a dry 250 mL flask with stir bar under argon was added anhydrous THF (75 mL), **17** (0.405 g, 1.33 mmol) and **13** (0.955 g, 2.65 mmol). The solution was cooled to -78°C and then was added LDA (0.5 M solution in THF, 8.0 mL, 3 equiv.) dropwise over 10 min. This mixture was kept at -78°C for 4 h at and then warmed to room temperature over 2 h. To the reaction was added MeOH (10 mL). After 30 min saturated NH_4Cl (30 mL) was added and the contents were transferred to a separatory funnel and extracted with ethyl acetate. The organic layer was washed with water (3 x 25 mL), brine (1 x 25 mL), dried over Na_2SO_4 and then concentrated to give a crude solid. Purification by flash chromatography (hexanes : ethyl acetate, 1 : 1) gave compound **18** as a pale brown solid (0.32 g, 63 %). ^1H NMR (CDCl_3 , 400 MHz) δ 10.45 (br s, 1H), 7.05 (d, $J = 2.8$ Hz, 1H), 3.79 (t, $J = 5.8$ Hz, 1H), 3.71 (s, 3H), 3.13 (t, $J = 7.3$ Hz, 2H), 2.55 (d, $J = 7.4$ Hz, 2H), 2.18-2.08 (septet, 1H), 1.80 (pentet, 2H), 0.97 (d, $J = 6.6$ Hz, 6H), 0.90 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 158.4, 144.0, 123.2, 121.8, 115.8, 112.6, 61.1, 42.1, 37.7, 32.9, 32.4, 27.9, 25.9, 22.7, 18.3, -5.2 ppm; FT-IR (neat, cm^{-1}) 3128.8, 2953.7, 2928.7, 2856.7, 1621.5, 1579.6, 1502.7, 1462.7, 1439.8, 1342.6, 1253.7, 1096.5, 1062.7, 1005.7, 939.7, 832.4, 772.4, 697.6 cm^{-1} ; HRMS (ES-TOF) m/z : $[M + H]^+$ Calc'd for $\text{C}_{20}\text{H}_{36}\text{N}_3\text{O}_2\text{SSi}$: 410.2297, Found: 410.2281.

General procedure for NBS-promoted bromination reactions

To a dry round bottom flask with stir bar under argon was added CCl_4 , the methyl-substituted heterocycle (1 equiv.), AIBN (0.03 equiv.) and N-bromosuccinimide (1.1 equiv.). The reaction mixture was refluxed overnight. After confirming full conversion by TLC and LCMS analysis, the mixture was cooled to room temperature. The insoluble solids were filtered off and residual solvent was concentrated to give a crude oil that was purified by flash chromatography (hexane : ethyl acetate 9 : 1) to give desired brominated products which were analyzed by LCMS and ^1H NMR.

4-(bromomethyl)-2-chloropyridine (10)^[19]—dark oil (2.2 g, 21% yield). ¹H NMR (CDCl₃, 400 MHz) δ 8.34 (d, *J* = 5.1 Hz, 1H), 7.34 (s, 1H), 7.22 (d, *J* = 5.1 Hz, 1H), 4.35 (s, 2H) ppm.

5-(bromomethyl)-2-chloropyridine (28)^[20]—light yellow solid (5.1 g, 62% yield). ¹H NMR (CDCl₃, 400 MHz) δ 8.41 (s, 1H), 7.72 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 4.46 (s, 2H) ppm.

2-(bromomethyl)-4-chloropyridine (29)^[21]—buff solid (0.55 g, 76% yield). ¹H NMR (CDCl₃, 400 MHz) δ 8.48 (d, *J* = 5.3 Hz, 1H), 7.47 (s, 1H), 7.24 (dd, *J* = 5.4, 2.0 Hz, 1H), 4.52 (s, 2H) ppm.

4-(bromomethyl)-2-chloroquinoline (30)^[22]—white solid (3.47 g, 60% yield). ¹H NMR (CDCl₃, 400 MHz) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.74 (t, *J* = 8.3 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 7.39 (s, 1H), 4.74 (s, 2H) ppm.

DBDMH-mediated bromination procedure, 4-(bromomethyl)-1-chloroisoquinoline (32)—To a 100 mL dry round bottom flask with stir bar under argon was added CHCl₃ (30 mL) and 1-chloro-4-methyl isoquinoline (**31**), (0.501 g, 2.81 mmol). To this was added DBDMH (0.804 g, 2.81 mmol) and AIBN (0.03 equiv.). The flask was fitted with a reflux condenser. The mixture was stirred at room temperature for 2 h, and then heated to 60 °C for 12h. After confirming the completion of the reaction by TLC and LCMS analysis, the mixture was cooled, filtered, and concentrated to give a crude oil which was purified by flash chromatography (hexane : ethyl acetate, 9 : 1) to give desired product as a white solid (0.58 g, 80% yield). ¹H NMR (CDCl₃, 400 MHz) δ 8.45 (d, *J* = 8.5 Hz, 1H), 8.37 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.95 (t, *J* = 8.3 Hz, 1H), 7.80 (t, *J* = 8.2 Hz, 1H), 4.88 (s, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 138.8, 137.3, 134.2, 131.1, 129.1, 127.4, 126.8, 125.6, 120.7, 69.7 ppm FT-IR (neat, cm⁻¹) 3002.8 (s), 2308.8 (s), 1956.8, 1648.7, 1626.7, 1613.7, 1578.7, 1554.7, 1503.7, 1441.7, 1370.7, 1338.7, 1309.6, 1288.7, 1274.7, 1253.7, 1207.6, 1137.7, 961.5, 913.7, 876.7, 779.6, 761.4, 710.6, 663.6 cm⁻¹; HRMS (ES-TOF) *m/z*: [M + H]⁺ Calc'd for C₁₀H₈NCIBr: 255.9529, Found: 255.9501.

4-isobutyl-2-methyl-6-((2-(trimethylsilyl)ethoxy)methyl)-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (19)—To a dry 100 mL round bottom flask under argon was added anhydrous DMF (40 mL) and NaH (0.293 g, 60%, 7.31 mmol) then the solution was cooled to 0 °C. In a separate flask **9** (1.021 g, 4.87 mmol) was dissolved in DMF (10 mL) and then this solution was added dropwise by cannula to NaH/DMF mixture. The reaction mixture was stirred at 0 °C for 2 h and then 2-(Trimethylsilyl)ethoxymethyl chloride (1.067 g, 6.33 mmol) was added. After 6–10 h LCMS analysis indicated the completion of the reaction. Saturated NH₄Cl solution (10 mL) was added and this mixture was extracted with ethyl acetate. The combined organic layers were washed with water (3 x 25 mL), brine (1 x 25 mL), dried over Na₂SO₄ and then concentrated to give a crude solid which was purified using flash chromatography (hexanes : ethyl acetate, 1 : 1) to give **19** as a light brown solid (1.32 g, 82%). ¹H NMR (CDCl₃, 400 MHz) δ 7.58 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 5.41 (s, 2H), 3.73 (s, 3H), 3.48 (br t, 2H), 2.58 (d, *J* = 7.0 Hz, 2H),

2.20-2.11 (septet, 1H), 0.97 ppm (d, $J = 6.6$ Hz, 6H), 0.92 (br t, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 159.8, 145.6, 122.6, 120.6, 118.1, 116.3, 81.2, 68.4, 43.8, 39.3, 29.4, 24.1, 19.1, 0.0 ppm; FT-IR (neat, cm^{-1}) 3095.9, 2951.7, 2866.8, 1636.4, 1586.7, 1534.7, 1459.8, 1427.8, 1399.8, 1355.7, 1335.8, 1288.9, 1249.6, 1203.7, 1167.8, 1146.7, 1093.4, 1072.6, 1036.8, 1016.8, 997.8, 943.7, 928.7, 943.7, 928.7, 859.5, 833.4, 789.7, 748.6, 710.7, 697.6 cm^{-1} ; HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ Calc'd for $\text{C}_{17}\text{H}_{29}\text{N}_3\text{O}_2\text{Si}$: 336.2101, Found: : 336.2107.

4-isobutyl-6-(4-methoxybenzyl)-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (20)—To a dry 100 mL round bottom flask under argon and cooled to 0 °C was added anhydrous DMF (50 mL), **9** (0.502 g, 2.44 mmol), K_2CO_3 (0.505 g, 3.65 mmol), p-methoxybenzyl chloride (0.575 g, 3.65 mmol), tetrabutyl ammonium iodide (0.089 g, 0.243 mmol). The reaction mixture was allowed to warm to room temperature over 12h, after which time LCMS analysis indicated complete conversion. Saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water (3 x 25 mL), brine (1 x 25 mL), dried over Na_2SO_4 and concentrated to give a crude solid which was purified using flash chromatography (hexanes : ethyl acetate, 1 : 1) to give **20** as a light brown solid (0.69 g, 87%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.48 (d, $J = 2.0$ Hz, 1H), 7.14 (d, $J = 8.7$ Hz, 2H), 6.99 (d, $J = 2.0$ Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 2H), 5.19 (s, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 2.54 (d, $J = 7.0$ Hz, 2H), 2.17-2.07 (septet, 1H), 0.97 (d, $J = 6.6$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 162.2, 159.8, 158.3, 143.9, 129.2, 127.6, 120.9, 119.4, 116.4, 115.2, 114.5, 55.4, 54.4, 42.4, 37.8, 27.9, 22.7 ppm; FT-IR (neat, cm^{-1}) 2955.8, 1634.7, 1581.8, 1535.9, 1515.8, 1464.8, 1347.8, 1306.9, 1285.9, 1243.7, 1209.8, 1178.8, 1151.8, 1075.8, 1041.7, 999.8, 971.9, 936.9, 831.7, 788.8, 755.8, 740.8, 695.8 cm^{-1} ; HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ Calc'd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_2$: 326.1864, Found: : 326.1869.

General procedure for iodination

To a clean dry flask with stir bar under argon was added the protected pyrrole compound (1 equiv.) and I_2 (2 equiv.) in anhydrous THF. The reaction mixture was cooled to -78 °C and LDA (0.5 M solution in THF, 3 equiv.) was added dropwise over 10 min. The mixture kept at -78 °C for 4 h and then was allowed to warm to room temperature over 15 h. MeOH (10 mL) was added and the mixture was stirred for 30 min. Saturated NH_4Cl solution (30 mL) was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water (3 x 25 mL), brine (1 x 25 mL), dried over Na_2SO_4 and concentrated to give a crude solid which was purified using flash chromatography to give the desired iodinated product.

7-iodo-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (21)—In this case the Boc protecting group was found to be removed, giving the product (0.627 g, 62%). ^1H NMR (CDCl_3 , 400 MHz) δ 10.76 (br s, 1H), 7.32 (s, 1H), 3.74 (s, 3H), 2.57 (d, $J = 7.4$ Hz, 2H), 2.18-2.07 (septet, 1H), 0.96 (d, $J = 6.6$ Hz, 6H), 0.93 ppm (obscured t, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 159.0, 144.9, 123.2, 121.2, 120.4, 70.2, 68.3, 43.7, 39.2, 29.3, 24.1, 19.2, 0.0 ppm; FT-IR (neat, cm^{-1}) 2953.8, 1731.9, 1635.5, 1586.8, 1536.9, 1495.8, 1464.8, 1406.8, 1347.7, 1286.8, 1249.7, 1210.7, 1177.8, 1074.6, 1035.7, 1000.7,

973.8, 937.7, 915.8, 855.6, 833.3, 788.7, 758.6, 693.6, 663.7 cm^{-1} ; HRMS (ES-TOF) m/z : $[M + H]^+$ Calc'd for $\text{C}_{11}\text{H}_{14}\text{IN}_3\text{O}$: 332.0264, Found: 332.0260.

7-iodo-4-isobutyl-2-methyl-6-((2-(trimethylsilyl)ethoxy)methyl)-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (22)—(0.728 g, 68%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.42 (s, 1H), 5.47 (s, 2H), 3.69 (s, 3H), 3.54 (br t, 2H), 2.53 (d, $J = 7.0$ Hz, 2H), 2.16-2.06 (septet, 1H), 0.97 ppm (d, $J = 6.6$ Hz, 6H), 0.92 (br t, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 159.8, 145.6, 122.6, 120.6, 118.1, 116.3, 81.2, 68.4, 43.8, 39.3, 29.4, 24.1, 19.1, 0.0 ppm; FT-IR (neat, cm^{-1}) 3095.9, 2951.7, 2866.8, 1636.4, 1586.7, 1534.7, 1459.8, 1427.8, 1399.8, 1355.7, 1335.8, 1288.9, 1249.6, 1203.7, 1167.8, 1146.7, 1093.4, 1072.6, 1036.8, 1016.8, 997.8, 943.7, 928.7, 943.7, 928.7, 859.5, 833.4, 789.7, 748.6, 710.7, 697.6 cm^{-1} ; HRMS (ES-TOF) m/z : $[M + H]^+$ Calc'd for $\text{C}_{17}\text{H}_{28}\text{IN}_3\text{O}_2\text{Si}$: 462.1072, Found: 462.1074.

7-iodo-4-isobutyl-6-(4-methoxybenzyl)-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (23)—(0.451 g, 64%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.24 (s, 1H), 7.08 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 5.26 (s, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 2.49 (d, $J = 7.0$ Hz, 2H), 2.13-2.03 (septet, 1H), 0.95 (d, $J = 6.6$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 159.6, 157.6, 143.4, 128.8, 127.3, 121.8, 119.4, 118.7, 114.4, 55.3, 54.6, 42.2, 37.8, 27.8, 22.6 ppm; FT-IR (neat, cm^{-1}) 2954.7, 2867.8, 1638.3, 1616.5, 1583.6, 1512.4, 1494.5, 1463.6, 1380.7, 1287.7, 1246.3, 1213.5, 1175.4, 1113.7, 1099.7, 1030.5, 997.6, 971.6, 881.8, 822.6, 759.5, 690.5 cm^{-1} ; HRMS (ES-TOF) m/z : $[M + H]^+$ Calc'd for $\text{C}_{19}\text{H}_{23}\text{IN}_3\text{O}_2$: 452.0833, Found: : 452.0835.

General procedure for the alkylation of compound 18

To a dry 100 mL flask with stir bar under argon and cooled to 0 $^{\circ}\text{C}$ was added anhydrous degassed DMF (10 mL), NaH (0.024 g, 0.585 mmol) and **18** (0.200 g, 0.488 mmol dissolved in 5 mL of degassed DMF) (5 mL). The mixture was stirred for 2 h. 2-chloro-4-bromomethyl pyridine (**10**) (0.037 g, 0.150 mmol) dissolved in degassed anhydrous DMF (5 mL) was then added dropwise to the reaction mixture, which was stirred overnight with warming to room temperature. At this time LCMS and TLC analysis indicated full conversion. Addition of NH_4Cl solution, extraction with ethyl acetate, washing with water and brine, drying over Na_2SO_4 , filtration, and concentration gave a crude solid that was purified using preparative HPLC over a gradient combination of (methanol : acetonitrile, 1:1) and (water with 1% TFA) to give pure product.

7-((3-((tert-butyldimethylsilyl)oxy)propyl)thio)-6-((2-chloropyridin-4-yl)methyl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (35)—Light brown oil (0.024 g, 70% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 8.32 (s, 1H), 7.33 (obscured d, 1H), 7.15 (s, 1H), 5.52 (s, 2H), 3.67 (s, 3H), 3.54 (t, $J = 6.1$ Hz, 2H), 2.93 (d, $J = 7.2$ Hz, 2H), 2.60 (d, $J = 7.3$ Hz, 2H), 2.20-2.09 (m, 1H), 1.65-1.58 (m, 2H), 0.96 (d, $J = 6.6$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.7, 152.5, 150.3, 149.0, 143.6, 124.3, 121.8, 121.6, 119.9, 118.6, 117.0, 59.4, 49.8, 46.7, 41.9, 38.3, 35.3, 30.8, 29.7, 27.9, 22.7, 22.7, 14.1, 8.7 ppm; FT-IR (neat, cm^{-1}) 3422.9, 2955.8, 1726.8, 1630.7, 1594.7, 1552.8, 1491.8, 1466.7, 1388.7, 1348.7, 1241.5, 1222.5, 1158.5, 1124.7, 1087.7, 1063.7,

1028.3, 876.8, 832.8, 767.7, 757.8, 716.7, 696.7 cm^{-1} ; HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ Calc'd for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2\text{ClS}$: 421.1465, Found: 421.1454.

7-((3-((tert-butyldimethylsilyl)oxy)propyl)thio)-6-((6-chloropyridin-3-yl)methyl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (36)— ^1H NMR (CDCl_3 , 400 MHz) δ 8.29 (d, $J = 4.7$ Hz, 1H), 7.73 (s, 1H), 7.12 (s, 1H), 6.99 (d, $J = 6.3$ Hz, 1H), 5.65 (s, 2H), 3.94 (t, $J = 6.1$ Hz, 2H), 3.74 (s, 3H), 3.08 (obscured t, 2H), 2.55 (d, $J = 6.6$ Hz, 2H), 2.15-2.08 (m, 1H), 1.83-1.77 (m, 2H), 0.96 (d, $J = 6.6$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.8, 151.5, 148.4, 143.6, 137.4, 131.2, 124.7, 123.8, 121.5, 118.5, 116.7, 59.5, 48.2, 41.9, 38.2, 35.3, 30.9, 27.8, 22.6 ppm; FT-IR (neat, cm^{-1}) 3401.8, 3092.9, 2953.7, 2868.8, 1724.9, 1632.4, 1586.6, 1564.7, 1537.8, 1490.6, 1460.5, 1383.6, 1346.5, 1333.5, 1285.7, 1245.7, 1206.6, 1164.7, 1133.7, 1101.5, 1060.6, 1022.5, 998.6, 968.7, 908.7, 851.7, 832.6, 801.7, 765.6, 691.5 cm^{-1} ; HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ + Calc'd for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2\text{ClS}$: 421.1465, Found: 421.1452.

7-((3-((tert-butyldimethylsilyl)oxy)propyl)thio)-6-((5-chloropyridin-2-yl)methyl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (37)—light brown oil (0.020 g, 62% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 8.49 (d, $J = 6.1$ Hz, 1H), 7.29 (obscured d, 2H), 6.93 (s, 1H), 5.61 (s, 2H), 4.08 (t, $J = 5.8$ Hz, 2H), 3.74 (s, 3H), 3.09 (t, $J = 7.5$ Hz, 2H), 2.57 (d, $J = 8.4$ Hz, 2H), 2.18-2.11 (m, 1H), 1.85-1.78 (m, 2H), 0.97 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.9, 154.1, 148.7, 143.8, 136.9, 131.6, 122.2, 121.3, 118.4, 117.3, 59.5, 52.3, 41.9, 38.2, 35.2, 30.8, 27.8, 22.6 ppm; FT-IR (neat, cm^{-1}) 3377.8, 2927.8, 2868.8, 1723.8, 1632.5, 1580.7, 1534.8, 1491.7, 1467.6, 1367.7, 1348.6, 1286.7, 1256.7, 1211.6, 1164.7, 1108.6, 1060.6, 1013.5, 915.7, 830.7, 768.6, 693.6 cm^{-1} HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ Calc'd for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2\text{ClS}$: 421.1465, Found: 421.1454.

7-((3-((tert-butyldimethylsilyl)oxy)propyl)thio)-6-((2-chloroquinolin-4-yl)methyl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (38)—white solid (0.021 g, 52% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 8.13 (d, $J = 8.1$ Hz, 1H), 7.98 (d, $J = 9.8$ Hz, 1H), 7.85 (t, $J = 7.2$ Hz, 1H), 7.70 (t, $J = 9$ Hz, 1H), 7.18 (s, 1H), 6.41 (s, 1H), 6.01 (s, 2H), 3.90 (t, $J = 6.4$ Hz, 2H), 3.79 (s, 3H), 3.15 (t, $J = 5.1$ Hz, 2H), 2.58 (d, $J = 3.8$ Hz, 2H), 2.18-2.11 (m, 1H), 1.81-1.74 (m, 2H), 0.97 (d, $J = 6.6$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.8, 153.9, 150.7, 148.6, 146.7, 134.1, 132.7, 130.8, 127.4, 126.9, 125.0, 124.7, 122.1, 121.6, 120.3, 62.3, 51.0, 44.9, 41.3, 38.4, 33.8, 30.8, 25.6 ppm; FT-IR (neat, cm^{-1}) 3387.9, 3093.9, 2955.9, 1633.8, 1587.8, 1565.9, 1492.9, 1418.9, 1348.8, 1391.8, 1257.9, 1212.9, 1150.8, 1100.8, 1073.9, 899.9, 852.9, 755.8, 697.8 cm^{-1} ; HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ Calc'd for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_2\text{ClS}$: 471.1621, Found: 471.1604.

7-((3-((tert-butyldimethylsilyl)oxy)propyl)thio)-6-((1-chloroisoquinolin-4-yl)methyl)-4-isobutyl-2-methyl-2,6-dihydro-1H-pyrrolo[3,4-d]pyridazin-1-one (39)—buff solid (0.015 g, 80% yield). ^1H NMR (CDCl_3 , 400 MHz) δ 8.46 (d, $J = 8.4$ Hz, 1H), 7.90 (s, 1H), 7.84-7.81 (m, 2H), 7.77-7.74 (obscured m, 1H), 6.97 (s, 1H), 5.89 (s, 2H), 3.93 (t, $J = 5.6$ Hz, 2H), 3.72 (s, 3H), 3.18 (t, $J = 6.4$ Hz, 2H), 2.43 (d, $J = 7.4$ Hz, 2H), 2.04-1.97 (m, 1H), 1.86-1.80 (m, 2H), 0.97 (d, $J = 6.6$ Hz, 6H) ppm; ^{13}C NMR (CDCl_3 , 100

MHz) δ 156.1, 146.7, 144.0, 138.2, 135.3, 132.0, 130.5, 132.6, 129.6, 128.6, 126.7, 125.4, 124.3, 121.4, 119.7, 49.7, 44.7, 41.2, 38.4, 33.8, 30.7, 25.5 ppm; FT-IR (neat, cm^{-1}) 3387.9, 3093.9, 2955.9, 1633.8, 1587.8, 1565.9, 1492.9, 1418.9, 1348.8, 1391.8, 1257.9, 1212.9, 1150.8, 1100.8, 1073.9, 899.9, 852.9, 755.8, 697.8 cm^{-1} ; HRMS (ES-TOF) m/z : $[\text{M} + \text{H}]^+$ Calc'd for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_2\text{ClS}$: 471.1621, Found: 471.1303.

Supplementary Material

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Figure 1.
Structures of potent AstraZeneca MCT1 inhibitors.

Scheme 1.
Synthesis of ketoester **6** and fused pyrrole **9**.

Scheme 2.

Unexpected difficulties in attempts to introduce the sulphur-containing side chain.

Scheme 3.
Boc-directed metalation to give alkylated pyrrole **18**.

Scheme 4.

Protecting group-directed lithiation / iodination.

Scheme 5.
Pyridyl and quinolyl bromides

Scheme 6.
Isoquinoline bromide **32**.

Scheme 7.
Synthesis of substituted pyrrole[3,4-d]pyridazin-1-ones **35–39**.

Table 1

Reaction scale-independent efficiency of the alkylation-deprotection protocol

Entry	17 (g)	Th. yield (g)	Actual 18 (g)	%yield
1	0.32	0.43	0.24	57
2	0.40	0.54	0.32	59
3	1.35	1.81	1.15	63
4	1.75	2.33	1.40	60
5	2.88	3.86	2.35	59
6	5.00	6.71	3.98	59