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Synthesis of ethyl 4-oxo-3,4-dihydro[1]benzofuro[3,2-*d*]-pyrimidine-2-carboxylate and its derivatives

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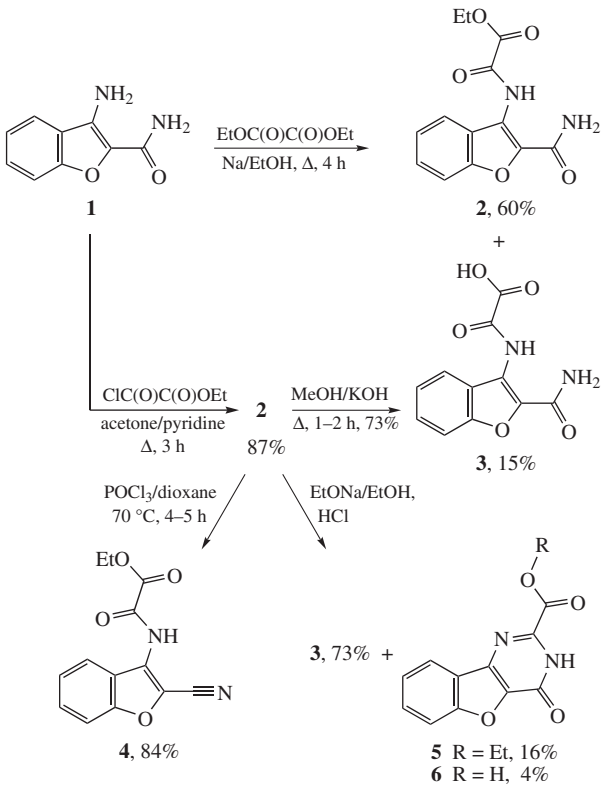
The synthesis of ethyl 4-oxo-3,4-dihydro[1]benzofuro[3,2-*d*]pyrimidine-2-carboxylates was developed to modify the benzofuro-[3,2-*d*]pyrimidine heterocyclic system.

Methods for the synthesis of 4-oxo-3,4-dihydrobenzofuro[3,2-*d*]-pyrimidine system by the intramolecular cyclization were described.[1,2] However, these methods suffer from the lack of versatility, and there is a need for a facile procedure that can incorporate a number of points of structural diversity and a variety of substitution patterns into the target benzofuro[3,2-*d*]-pyrimidine heterocyclic scaffold. Here, we report a convenient synthesis of new 3,4-dihydrobenzofuro[3,2-*d*]pyrimidines.

First, we explored synthetic ways to assemble the desired 4-oxo-3,4-dihydrobenzofuro[3,2-*d*]pyrimidine heterocycle starting from 3-amino-1-benzofuran-2-carboxamide **1**. Compound **1** was obtained using a previously described synthetic approach.[3,4] Our attempts to obtain the desired 4-oxo-3,4-dihydrobenzofuro-[3,2-*d*]pyrimidine heterocyclic system by the reaction of **1** with diethyl oxalate in the presence of EtONa (Scheme 1) gave only products **2** and **3**, with no cyclization product traces.

We have observed that the most convenient synthetic approach to compound **2** is the reaction of **1** with ethyl chloro(oxo)-acetate in a mixture of acetone and pyridine. The reaction smoothly leads to desired product **2** in good yield.† Compound **2** represents a promising starting point for the synthesis of diverse heterocyclic-fused benzofurans. An important feature of compound **2** is the presence of three electron-withdrawing carbonyl groups, as well as exceptionally good leaving ethoxy group in the 3-position and a carboxamide group in the 2-position of the benzofuran ring. We used this compound to investigate cyclization pathways to the target 4-oxo-3,4-dihydrobenzofuro-[3,2-*d*]pyrimidine skeleton.[1,5]



Scheme 1 Synthesis and chemical transformations of intermediate **2**.

Thus, thieno[2,3-*d*]pyrimidin-4(3*H*)-ones were synthesised by the pyrolysis of 4,5-substituted ethyl {[3-(aminocarbonyl)-thien-2-yl]amino}(oxo)acetates.[5] However, we found that compound **2** was destructed by pyrolysis, and only traces of the desired cyclization products and a corresponding decarboxylated product (not shown in Scheme 1) were formed.

We also performed the treatment of compound **2** with a solution of phosphorus oxychloride in dioxane (analogously to Hassan *et al.*[6]). The major product of this reaction was ethyl [(2-cyano-1-benzofuran-3-yl)amino](oxo)acetate **4** (Scheme 1)‡ rather than the target benzofuro[3,2-*d*]pyrimidine. Unequivocal structural assignment for compound **4** was obtained using ^{13}C NMR and ^{1}H–^{1}H NOESY spectroscopic data.

A synthetic route to 2-aryl substituted benzofuro[3,2-*d*]-pyrimidin-4(3*H*)-ones was described by Vaidya *et al.*[1] 2-Phenyl-benzofuro[3,2-*d*]pyrimidin-4(3*H*)-ones were obtained *via* the intramolecular cyclization of 3-(benzoylamino)-1-benzofuran-2-carboxamides. By analogy, we treated compound **2** with KOH in dry methanol and aqueous methanol. Based on LCMS data, several products were formed including major product **3**.

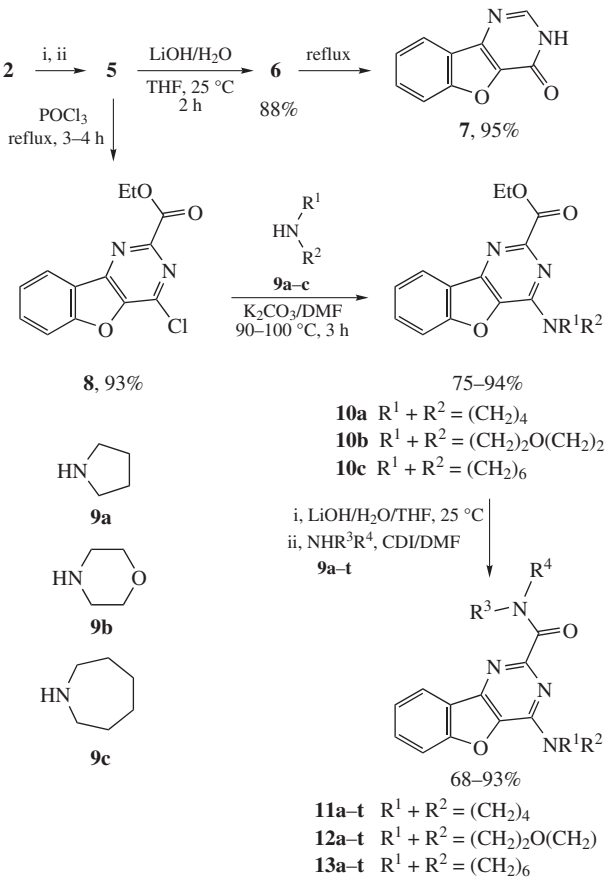
† Melting points were measured with a Buchi B-520 melting point apparatus and are not corrected. ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer in [^{2}H$_6$]DMSO using TMS as an internal standard.

Ethyl {[2-(aminocarbonyl)-1-benzofuran-3-yl]amino}(oxo)acetate **2**. Pure pyridine (5 ml) was added to a solution of **1** (35.2 g, 0.2 mol) in dry acetone (200 ml). Ethyl chloro(oxo)acetate (27.3 g, 0.2 mol) in dry acetone (200 ml) was added dropwise to the solution with vigorous stirring; then, the reaction mixture was heated in a boiling water bath for 3 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). The reaction mixture was cooled to room temperature; the formed precipitate was filtered off and washed with acetone to give the desired product in 87% yield; mp 210–212 °C. ^{1}H NMR ([^{2}H$_6$]DMSO, 400 MHz) δ: 11.57 (s, 1H, NH), 8.32 (d, 1H, Ar-H, *J* 8.4 Hz), 8.28–7.98 (br. d, 2H, NH_2), 7.62 (d, 1H, Ar-H, *J* 8.4 Hz), 7.54 (t, 1H, *J* 8.4 Hz), 7.35 (t, 1H, Ar-H, *J* 8.4 Hz), 4.34 (q, 2H, OCH_2, *J* 6.8 Hz), 1.34 (t, 3H, Me, *J* 6.8 Hz). Found (%): C, 56.47; H, 4.35; N, 10.19. Calc. for $C_{13}H_{12}N_2O_5$ (%): C, 56.52; H, 4.38; N, 10.14.

We found that the reaction of **2** with EtONa in dry ethanol at 45 °C led to ethyl 4-oxo-3,4-dihydro[1]benzofuro[3,2-*d*]pyrimidine-2-carboxylate **5** as the major product (Scheme 2).§ Upon the complete conversion of the initial reactant, the mixture was acidified by glacial acetic acid to pH 5–6, and the precipitate was filtered off to give desired product **5**. Better results were obtained in *tert*-butanol rather than ethanol; in this case, final ester **5** was formed in 79% yield. If the reaction was acidified by HCl, a mixture of compounds **3**, **5**, **6** was formed (Scheme 1).

As an alternative synthetic route toward compound **5**, we explored the reaction in 1,2-dichloroethane (DCE) in the presence of Et_3N and Me_3SiCl (TMSCl) by analogy with the method described by Fuwa *et al.*[7] In this case, the cyclization proceeded smoothly to afford the desired product in 60% yield. The mild alkali hydrolysis of ester **5** afforded acid **6** (yield 88%). Acid **6** could be easily converted to the corresponding benzofuro[3,2-*d*]-pyrimidine **7** by decarboxylation (Scheme 2).¶

The 4-position of the benzofuro[3,2-*d*]pyrimidine system is a useful site for introduction of an additional diversity point to the test heterocyclic system. The assembly of 4-amino substituted benzofuro[3,2-*d*]pyrimidine-2-carboxamides **11a–t**, **12a–t** and **13a–t** is depicted in Scheme 2. According to Sangapure *et al.*[8] ester **5** was readily converted to 4-chloro-benzofuro[3,2-*d*]pyrimidine **8**†† upon treatment with phosphorus oxychloride (yield 93%). Resulting chloride **8** was easily converted to corresponding amines **10a–c** by reactions with



Scheme 2 Synthesis and chemical transformations of ethyl 4-oxo-3,4-dihydro[1]benzofuro[3,2-*d*]pyrimidine-2-carboxylate **5**. *Reagents and conditions*: i, EtONa/EtOH/AcOH, 45 °C, 3–4 h, 66%; ii, DCE, Et_3N, TMSCl, reflux, 16 h, 60%. For R^3 and R^4 substituents see Online Supplementary Materials.

‡ *Ethyl [(2-cyano-1-benzofuran-3-yl)amino](oxo)acetate* **4**. Compound **2** (2.8 g, 0.01 mol) was added to a solution of $POCl_3$ (1.1 ml, 0.01 mol) in pure dioxane (20 ml). The reaction mixture was heated up to 70 °C in boiling water bath for 4–5 h under stirring. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). The solvent was evaporated under reduced pressure. The resulting residue was slowly poured into crushed ice with vigorous stirring. The formed precipitate was filtered off, washed with water and hexane to give compound **4** in 74% yield; mp 135–137 °C. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 11.76 (s, 1H, NH), 7.96 (d, 1H, Ar-H, *J* 8.2 Hz), 7.72 (d, 1H, Ar-H, *J* 8.2 Hz), 7.63 (t, 1H, Ar-H, *J* 8.2 Hz), 7.43 (t, 1H, Ar-H, *J* 8.2 Hz), 4.36 (q, 2H, OCH_2, *J* 6.8 Hz), 1.35 (t, 3H, Me, *J* 6.8 Hz). ^{13}C NMR ([$^2H_6$]DMSO, 75 MHz) δ: 13.8 (Me), 62.8 (OCH_2), 111.5 (CN), 112.0 (C-7), 119.3 (C-5), 121.1 (C-4), 122.3 (C-3a), 124.2 (C-2), 128.0 (C-6), 129.3 (C-3), 153.7 (C-7a), 155.9 [C(O)NH], 159.4 (COOEt). Found (%): C, 60.42; H, 3.96; N, 10.81. Calc. for $C_{13}H_{10}N_2O_4$ (%): C, 60.47; H, 3.90; N, 10.85.

§ *Ethyl 4-oxo-3,4-dihydro[1]benzofuro[3,2-*d*]pyrimidine-2-carboxylate* **5**.

Method A. Compound **2** (30 g, 0.1 mol) was dissolved in absolute ethanol or *tert*-butanol (500 ml). Then, dry NaOEt was added dropwise under stirring at room temperature. The reaction mixture was heated at 45 °C for 3–4 h. After the solution was cooled to room temperature, the solvent (about 500 ml) was evaporated under reduced pressure and acetic acid was added to the resulting residue (pH 5–6). The formed precipitate was filtered off and washed with ethanol, water and hexane. Desired product **5** was obtained in good yield (66 or 79%).

Method B. Triethylamine (92.9 g, 0.92 mol) and TMSCl (32.5 g, 0.3 mol) were added to a solution of compound **2** (5.5 g, 0.02 mol) in DCE (500 ml) in an argon atmosphere. The reaction mixture was stirred under reflux for 16 h. The process was followed by LCMS. After cooling to room temperature, ethyl acetate was added (500 ml), and the solution was washed with 1 M aqueous HCl and a saturated solution of K_2CO_3. The organic fraction was dried over $MgSO_4$ and the crude product was purified by column chromatography on silica gel. The solvent was evaporated under reduced pressure. The residue was triturated with diethyl ether and then filtered off. Target compound **5** was obtained in 60% yield; mp 240–242 °C. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 8.09 (d, 1H, Ar-H, *J* 8.1 Hz), 7.80 (d, 1H, Ar-H, *J* 8.1 Hz), 7.67 (t, 1H, Ar-H, *J* 8.1 Hz), 7.51 (t, 1H, Ar-H, *J* 8.1 Hz), 4.42 (q, 2H, OCH_2, *J* 7.0 Hz), 1.42 (t, 3H, Me, *J* 7.0 Hz). ^{13}C NMR ([$^2H_6$]DMSO, 75 MHz) δ: 14.4 (Me), 63.2 (CH_2), 113.5 (C-6), 121.9 (C-9a), 122.6 (C-8), 125.1 (C-9), 130.5 (C-9b), 140.9 (C-7), 142.8 (C-4a), 145.7 (C-4), 153.4 (C-5a), 156.7 (C-2), 160.4 (COOEt). Found (%): C, 60.53; H, 3.95; N, 10.83. Calc. for $C_{13}H_{10}N_2O_4$ (%): C, 60.47; H, 3.90; N, 10.85.

¶ *4-Oxo-3,4-dihydro[1]benzofuro[3,2-*d*]pyrimidine-2-carboxylic acid* **6** *and benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one* **7**. LiOH (0.06 g, 2.44 mmol) dissolved in the minimum amount of water was added to a solution of compound **5** (0.5 g, 1.94 mmol) in pure THF (5 ml). The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, cold water (10 ml) was added and the solution was acidified by HCl to pH 2. The formed precipitate was filtered off, washed with water, cold ethanol and hexane to give desired acid **6** in 88% yield; mp 291–293 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 8.09 (d, 1H, Ar-H, *J* 7.9 Hz), 7.87 (d, 1H, Ar-H, *J* 7.9 Hz), 7.71 (t, 1H, Ar-H, *J* 7.9 Hz), 7.54 (t, 1H, Ar-H, *J* 7.9 Hz). Found (%): C, 57.43; H, 2.67; N, 12.22. Calc. for $C_{11}H_6N_2O_4$ (%): C, 57.40; H, 2.63; N, 12.17.

Subsequent refluxing of compound **6** in DMSO led to the corresponding decarboxylated product **7** (95%); mp 274–276 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 12.94 (s, 1H, NH), 8.23 (s, 1H, C-H), 8.04 (d, 1H, Ar-H, *J* 7.9 Hz), 7.83 (d, 1H, Ar-H, *J* 7.9 Hz), 7.67 (t, 1H, Ar-H, *J* 7.9 Hz), 7.50 (t, 1H, Ar-H, *J* 7.9 Hz). Found (%): C, 64.54; H, 3.29; N, 15.01. Calc. for $C_{10}H_6N_2O_2$ (%): C, 64.52; H, 3.25; N, 15.05.

†† *Ethyl 4-chlorobenzofuro[3,2-*d*]pyrimidine-2-carboxylate* **8**. Compound **5** (23.8 g, 0.09 mol) was added dropwise to phosphorus oxychloride (240 ml). The resulting suspension was stirred at reflux for 3–4 h. The reaction was followed by TLC (5% MeOH in CH_2Cl_2). The solution was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in dry $CHCl_3$, washed with cold water, 5% $NaHCO_3$ and water again. The solution was dried over anhydrous $MgSO_4$ and purified by flash chromatography on a silica gel/aluminium oxide column (eluent, benzene). The solvent was evaporated *in vacuo*. The residue was triturated with hexane and then filtered off. Corresponding chloride **8** was obtained in 93% yield; mp 158–160 °C. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 8.29 (d, 1H, Ar-H, *J* 7.7 Hz), 7.96–7.85 (m, 2H, Ar-H), 7.63 (t, 1H, Ar-H, *J* 7.7 Hz), 4.46 (q, 2H, OCH_2, *J* 7.1 Hz), 1.44 (t, 3H, Me, *J* 7.1 Hz). Found (%): C, 56.48; H, 3.32; N, 10.08. Calc. for $C_{13}H_9ClN_2O_3$ (%): C, 56.43; H, 3.28; N, 10.12.

secondary amines **9a–c**. Resulting products **10a–c** were isolated as colourless crystals in 75–94% yields.[‡‡] Finally, esters **10a–c** were readily hydrolysed by LiOH dissolved in a mixture of THF and water to furnish corresponding acids, which then were easily transformed to the medium-sized library of 4-amino substituted benzofuro[3,2-*d*]pyrimidine-2-carboxamides **11a–t**, **12a–t**, **13a–t** by reactions with primary and secondary amines **9a–t** (see Online Supplementary Materials).[§§]

Online Supplementary Materials

Supplementary data associated with this article can be found in the electronic version at doi:10.1016/j.mencom.2008.07.018.

[‡‡] *Synthesis of ethyl 4-amino substituted benzofuro[3,2-*d*]pyrimidine-2-carboxylates* **10a–c**. Anhydrous K_2CO_3 (14.4 g, 0.1 mol) and corresponding amine **9a–c** were added to a solution of chloride **8** (22.3 g, 0.08 mol) in dry DMF (100 ml). The reaction mixture was stirred at 90–100 °C for 3 h. After cooling to room temperature, the mixture was poured into cold water and the formed precipitate was filtered off. Amines **10a–c** were obtained in good yield (75–94%).

*Ethyl 4-pyrrolidin-1-ylbenzofuro[3,2-*d*]pyrimidine-2-carboxylate* **10a**. Yield, 91%; mp 144–146 °C. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 8.10 (d, 1H, Ar-H, *J* 7.6 Hz), 7.77 (d, 1H, Ar-H, *J* 7.6 Hz), 7.68 (t, 1H, Ar-H, *J* 7.6 Hz), 7.49 (t, 1H, Ar-H, *J* 7.6 Hz), 4.35 (q, 2H, CH_2, *J* 7.1 Hz), 4.05–3.65 [m, 4H, $N(CH_2)_2$], 2.04–1.94 (m, 4H, CH_2CH_2), 1.34 (t, 3H, Me, *J* 7.1 Hz). Found (%): C, 65.54; H, 5.58; N, 13.28. Calc. for $C_{17}H_{17}N_3O_3$ (%): C, 65.58; H, 5.50; N, 13.50.

*Ethyl 4-morpholin-4-ylbenzofuro[3,2-*d*]pyrimidine-2-carboxylate* **10b**. Yield, 94%; mp 146–148 °C. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 8.14 (d, 1H, Ar-H, *J* 7.7 Hz), 7.83 (d, 1H, Ar-H, *J* 7.7 Hz), 7.73 (t, 1H, Ar-H, *J* 7.7 Hz), 7.52 (t, 1H, Ar-H, *J* 7.7 Hz), 4.37 (q, 2H, CH_2, *J* 7.0 Hz), 4.08–4.02 [m, 4H, $O(CH_2)_2$], 3.84–3.78 [m, 4H, $N(CH_2)_2$], 1.35 (t, 3H, Me, *J* 7.0 Hz). Found (%): C, 62.30; H, 5.14; N, 12.92. Calc. for $C_{17}H_{17}N_3O_4$ (%): C, 62.38; H, 5.23; N, 12.84.

*Ethyl 4-azepan-1-ylbenzofuro[3,2-*d*]pyrimidine-2-carboxylate* **10c**. Yield, 75%; mp 112–114 °C. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 8.11 (d, 1H, Ar-H, *J* 6.6 Hz), 7.74–7.62 (m, 2H, Ar-H), 7.47 (t, 1H, Ar-H, *J* 6.6 Hz), 4.36 (q, 2H, CH_2, *J* 6.5 Hz), 4.10–3.95 [m, 4H, $N(CH_2)_2$], 1.94–1.83 [m, 4H, $(CH_2)_2$], 1.61–1.53 [m, 4H, $(CH_2)_2$], 1.40 (t, 3H, Me, *J* 6.5 Hz). Found (%): C, 67.18; H, 6.34; N, 12.45. Calc. for $C_{19}H_{21}N_3O_3$ (%): C, 67.24; H, 6.24; N, 12.38.

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[§§] *General procedure for preparation of 4-amino substituted benzofuro[3,2-*d*]pyrimidine-2-carboxamides* **11–13**. The hydrolysis of esters **10a–c** was carried out using the synthetic procedure previously described for compound **6**. Corresponding acid **10a–c** (1 mmol) was added to a solution of carbonyldiimidazole (CDI) (1 mmol) in dry DMF (5 ml). The reaction mixture was stirred at 60–80 °C for 2–4 h. After an equimolar amount of amine **9a–t** (1 mmol) was added, the reaction mixture was heated up to 80–90 °C and stirred for 2–4 h. The resulting mixture was cooled to room temperature; then, an aqueous solution of sodium bicarbonate (25 ml, 2.5%) was added. The formed precipitate was filtered off and washed with water. Recrystallization from ethanol gave corresponding carboxamides **11a–t**, **12a–t** and **13a–t** in good yields (68–93%). The ^{1}H NMR spectra were obtained for all the synthesised carboxamides.

*4-(4-Morpholinyl)-*N*-(3-pyridinylmethyl)benzofuro[3,2-*d*]pyrimidine-2-carboxamide* **12o**. This compound was obtained in 70% yield. ^{1}H NMR ([$^2H_6$]DMSO, 400 MHz) δ: 9.28 (t, 1H, NH, *J* 6.3 Hz), 8.57 (d, 1H, Ar-H, *J* 1.4 Hz), 8.43 (d, 1H, Ar-H, *J* 3.1 Hz), 8.15 (d, 1H, Ar-H, *J* 7.5 Hz), 7.82–7.68 (m, 3H, Ar-H), 7.53 (t, 1H, Ar-H, *J* 7.5 Hz), 7.33 (dd, 1H, Ar-H, *J* 7.9 Hz, *J* 5.4 Hz), 4.54 (d, 2H, CH_2, *J* 6.2 Hz), 4.16–4.11 [m, 4H, $O(CH_2)_2$], 3.85–3.79 [m, 4H, $N(CH_2)_2$]. Found (%): C, 64.74; H, 4.97; N, 18.02. Calc. for $C_{21}H_{19}N_5O_3$ (%): C, 64.77; H, 4.92; N, 17.98. Also see Online Supplementary Materials.