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Synthesis of 2-chloro-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one

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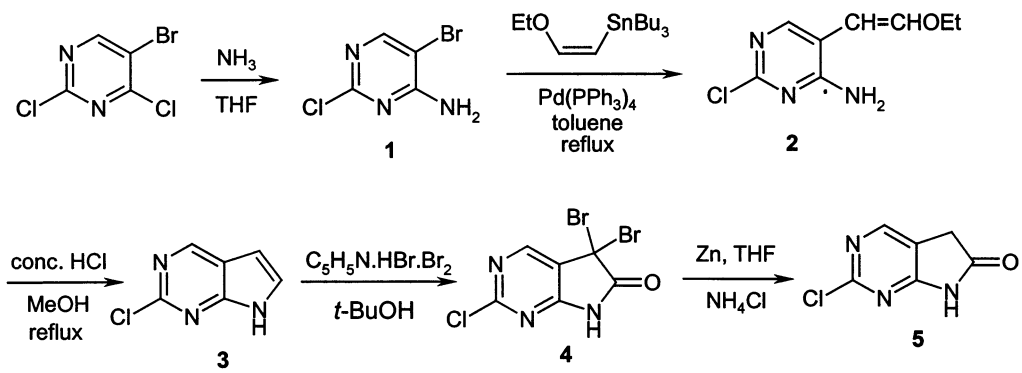
Abstract—1,3-Dihydro-2*H*-indol-2-ones (oxindoles) and 1,3-dihydro-2*H*-pyrrolopyridin-2-ones (azaoxindoles) are useful scaffolds that have been explored for various pharmaceutical uses. Herein we report the synthesis of 2-chloro-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (**5**) and its derivatives, and the application of 5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-ones (diazaoxindoles) as novel scaffold to kinase research areas. © 2001 Elsevier Science Ltd. All rights reserved.

Substituted oxindoles and azaoxindoles have attracted considerable interest in the pharmaceutical industry because of their wide range of biological activities in areas such as inflammation, analgesia, and cancer.[1,2] In an effort to discover novel kinase inhibitors,[3] we explored diazaoxindole as a potential novel template for kinase inhibition. Numerous synthetic efforts on substituted oxindoles and azaoxindoles were reported;[4] however, reports on the synthesis of diazaoxindole have been very limited. In addition, all reports required the construction of 2-substituted-4-chloro-pyrimidine-5-acetate as an intermediate for the synthesis of diazaoxindole, and this limited the substitution modification at the 2-position.[5] In this letter, we report the synthesis of 2-chloro-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (**5**) via its indole precursor **3**, derivatization of **5** to introduce diverse substitution at the 2-chloro position, and application of diazaoxindole as useful scaffold to kinase research areas. We believe that diazaoxindole will be of use to many research programs that have focused on creating biologically useful molecules from oxindoles and azaoxindoles.

As shown in Scheme 1,[6] 4-amino-5-bromo-2-chloropyrimidine (**1**) was obtained in 98% yield by bubbling ammonia gas into a solution of commercially available 5-bromo-2,4-dichloropyrimidine in tetrahydrofuran at room temperature for 1 h. Stille coupling of **1** with (*Z*)-1-ethoxy-2-(tributylstannyl)ethene[7] using a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in refluxing toluene for 16 h afforded a mixture of the (*Z*)- and (*E*)-isomers of alkenylpyrimidine **2** in 51% yield.[8] By using Yamanaka's conditions,[9] alkenylpyrimidine **2** was readily cyclised in the presence of hydrochloric acid in methanol under reflux to give 2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**3**) in 70% yield.[10] Treatment



Scheme 1.

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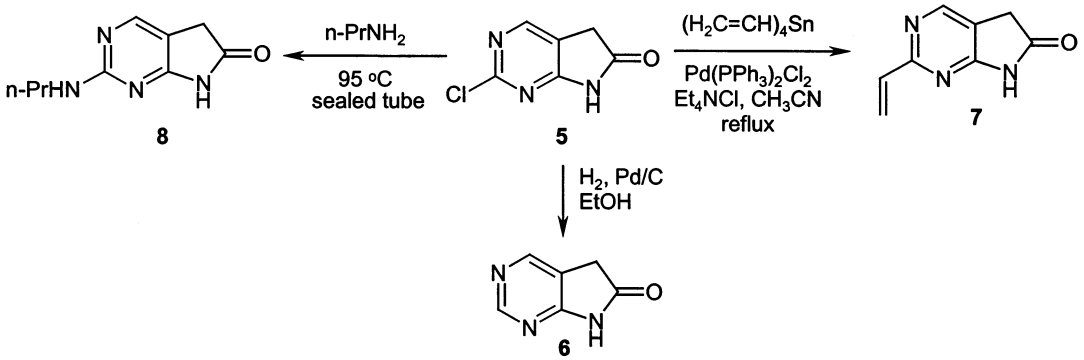
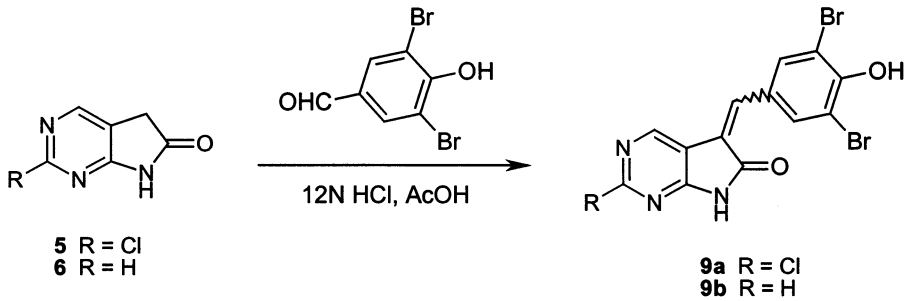


Scheme 2.



Scheme 3.

of compound **3** under Marfat's procedure of using pyridinium tribromide in *tert*-butanol at room temperature provided dibromo derivative **4** in 98% yield.[4e] Dibromo diazaoxindole **4** underwent facile reduction in the presence of excess zinc dust in saturated ammonium chloride and tetrahydrofuran solution at room temperature for 30 min provided 2-chloro-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (**5**) in 80% yield.[11]

Compound **5** can be further manipulated in several ways. Highlighted in Scheme 2 are three examples of introducing substitution at the 2-chloro position of compound **5**. Dechlorination of **5** can be easily achieved by standard hydrogenation conditions [H_2 (50 psi), Pd/C, EtOH] at room temperature to give 5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (**6**). Palladium-catalysed Stille coupling reaction of **5** with tetravinyltin in the presence of $Pd(PPh_3)_2Cl_2$ (0.05 equiv.) and tetraethylammonium chloride (3 equiv.) in acetonitrile under reflux yielded **7** in 40% yield. Treatment of **5** with neat *n*-propylamine at 95°C in a sealed tube afforded amino derivative **8** in 60% yield.

Benzylidine oxindoles and azaoxindoles are known kinase inhibitors.[3,12] In order to examine the biological activity of the diazaoxindoles, we converted **5** and **6** into the corresponding benzylidine derivatives **9a** and **9b** in 50% yield by treatment with 3,5-dibromo-4-hydroxybenzaldehyde in 1:4 ratio of 12N hydrocholoric acid and acetic acid at room temperature (Scheme 3).[13] To our delight, both **9a** and **9b** were potent c-Raf1 kinase inhibitors with IC_{50}'s of 24 nM and 14 nM, respectively.[14]

In conclusion, we have prepared diazaoxindole **5** that not only allows diverse substitution at the 2-chloro position but also is an attractive intermediate for pharmaceutical research areas.

Acknowledgements

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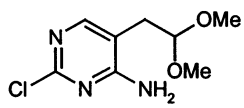
10. Compound **3a** was also isolated from the reaction mixture. It can be converted by **3** by repeating the same cyclization conditions (HCl in MeOH under reflux).



3a

11. Spectroscopicdata for selected compounds are provided. **1**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 5.71(bs, 2H); MS (+ve APCI) m/z (209, M+H). *E* isomer of **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 6.78 (d, $J=12.7$ Hz, 1H), 5.44 (d, $J=12.7$ Hz, 1H), 5.41 (bs, 2H), 3.96 (q, $J=7.1$ Hz, 2H), 1.39 (t, $J=7.1$ Hz, 3H); MS (+ve APCI) m/z (200, M+H). *Z* isomer of **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 6.28 (d, $J=7.1$ Hz, 1H), 5.60 (bs, 2H), 4.93 (d, $J=7.1$ Hz, 1H), 4.00 (q, $J=7.1$ Hz, 2H), 1.31 (t, $J=7.1$ Hz, 3H); MS (+ve APCI) m/z (200, M+H). **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.87 (s, 1H), 8.88 (s, 1H), 7.40 (m, 1H), 6.63 (m, 1H); MS (+ve APCI) m/z (154, M+H). **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 1H), 5.78 (bs, 2H), 4.48 (t, $J=4.8$ Hz, 1H), 3.46 (s, 6H), 2.79 (d, $J=4.8$ Hz, 2H). **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H); MS (-ve APCI) m/z (326, M-H). **5**: ^{1}H NMR (400 MHz, DMSO-*d*6): δ 11.71 (s, 1H), 8.20 (s, 1H), 3.57 (s, 2H); MS (-ve APCI) m/z (168, M-H). **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (s, 1H), 6.81 (m, 1H), 6.58 (d, $J=17.9$ Hz, 1H), 5.76 (d, $J=10$ Hz, 1H), 3.63 (s, 2H); MS (+ve APCI) m/z (162, M-H). **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H), 6.41 (bs, 1H), 3.34 (s, 2H), 3.21 (q, $J=6.7$ Hz, 2H), 1.54 (m, 2H), 0.93 (t, $J=7.5$ Hz, 3H); MS (-ve APCI) m/z (191, M-H). **9a**: ^{1}H NMR (400 MHz, DMSO-*d*6): δ 12.04 (s, 1H), 8.66 (s, 2H), 8.64 (s, 1H), 7.93 (s, 1H); MS (-ve APCI) m/z (430, M-H). **9b**: ^{1}H NMR (400 MHz, DMSO-*d*6): δ 11.64 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.21 (s, 1H), 7.09 (s, 1H), 6.96 (s, 1H); MS (-ve APCI) m/z (396, M-H).
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