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A novel one-pot and efficient procedure for the synthesis of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraones

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ABSTRACT

A novel and practical one-pot procedure is described for the preparation of several new of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraones based on the addition reaction of ninhydrin and 6-aminouracils followed by oxidative cleavage of their corresponding dihydroxyindenopyrrolopyr imidines.

Oxygen- and nitrogen-containing heterocycles are important in the area of pharmaceuticals and agrochemicals.[1] Substituted phthalides [isobenzofuran-1(3*H*)-ones)] represent an important class of natural products that possess interesting biological properties.[1] In particular, 3-substituted phthalides are vital heterocyclic motifs in many bioactive compounds, such as isocoumarins, anthraquinones, anthracyclines, and several alkaloids.[2] Their notable characteristics include anti-bacterial, anti-convulsant, anti-HIV, anti-asthmatic, anti-tumor and anti-platelet activities, anesthesia prolongation, and PGF2α inhibitory properties.[3] The chemistry of isobenzofurans is important as they represent 10π electron systems with quinoid nature, which makes them attractive as a building units for oligomeric and polymeric π-conjugated compounds.[4,5]

Pyrrolo[2,3-*d*]pyrimidines are reported to possess biological activities such as anti-HCV, anti-HIV type 1, anti-HSV, adenosine kinase inhibition, Aurora-A kinase inhibition, and cAMP phosphodiesterase inhibition. Many naturally occurring compounds, such as mycalisine A, cadeguomycin, and 2-deoxycadeguomycin possess a pyrrolo[2,3-*d*]pyrimidine moiety.[6,7]

In continuation of our programs to develop more efficient processes for the synthesis of biologically important oxygen- and nitrogen-containing heterocycles,[8] herein, we describe a novel and practical one-pot procedure for the preparation of several new 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraones **2**. We found that addition of lead tetraacetate to a solution of dihydroxyindenopyrrolopyrimidine **1a** in acetic acid at room temperature resulted in the formation of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′(1′*H*,3′*H*,7′*H*)-tetraone (**2a**) in excellent yield (Scheme 1).

To explore the scope and versatility of this method, and in order to optimize the reaction conditions, various solvents and temperatures were investigated for the synthesis of **2a**. We found that using acetic acid (AcOH) as the solvent gave the best result. To further optimize the conditions, the same reaction was carried out in AcOH at temperatures ranging from 25 to 65 °C, at 10 °C intervals. The reaction time was shortened slightly as the temperature increased from 25 to 45 °C. However, further increasing the temperature to 65 °C failed to decrease the reaction time further, however, the amount of by-products were increased. Therefore, a reaction temperature of 25 °C was chosen for all further AcOH-mediated reactions.

As the synthesis of dihydroxyindenopyrrolopyrimidine **1a**, from the addition reaction of ninhydrin (**3**) and aminouracil **4a**,[9] is fast and quantitative, we decided to study the one-pot synthesis of **2a**. We found that the one-pot reaction of ninhydrin (**3**), aminouracil **4a** and lead tetraacetate in acetic acid at room temperature gave product **2a** in a 92% yield, which was comparable to the above described two-step procedure (Scheme 1). In addition, the separation and purification steps for **1a** were eliminated.

The optimized one-pot conditions were applied to the synthesis of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraones **2a–l**[10] starting from ninhydrin (**3**) and aminouracils **4a–l**,[11] (Scheme 2). The results shown in Table 1 indicate that all

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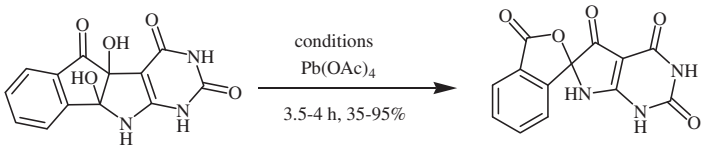
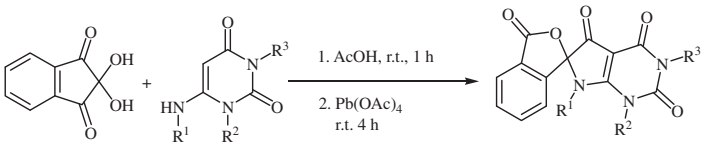


1a 2a

Scheme 1. Optimization of the reaction conditions for the synthesis of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraone (2a).



3 4a-l 2a-l

Scheme 2. One-pot synthesis of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraones **2a–j**.

Table 1
Synthesis of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraones **2a–l**

Entry	Aminouracil[a]	Product	Yield[b] (%)
1	**4a**	**2a**	72
2	**4b**	**2b**	89
3	**4c**	**2c**	88
4	**4d**	**2d**	95
5	**4e**	**2e**	90
6	**4f**	**2f**	83
7	**4g**	**2g**	85
8	**4h**	**2h**	86

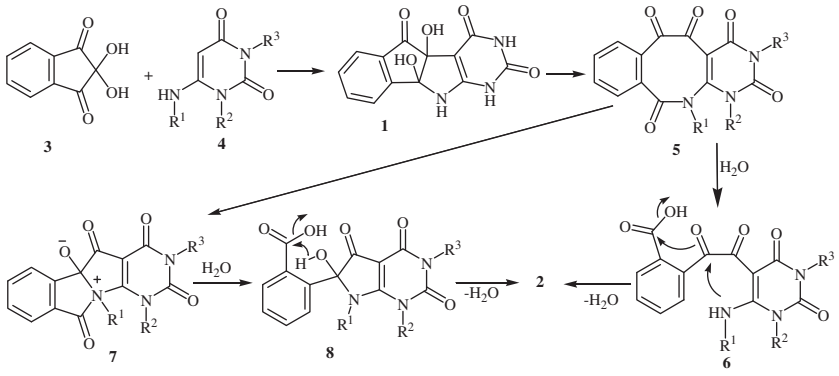
Table 1 (*continued*)

Entry	Aminouracil[a]	Product	Yield[b] (%)
9	**4i**	**2i**	94
10	**4j**	**2j**	92
11	**4k**	**2k**	92
12	**4l**	**2l**	96

[a] 6-Aminouracils **4a** and **4e** were purchased from Merck and used without further purification. 6-Aminouracil derivatives **4b–d** and **4l**,[11a] and **4f–k**,[11b–e] were prepared according to published procedures.
[b] Isolated yields.

the substituted aminouracils undergo effectively the addition and oxidation reactions. Even with sterically hindered aminouracils **4g–k** there was no significant increase in the reaction time or decrease in the yield.

The structures of the products were established by spectroscopic and analytical techniques.[12] The ^{1}H NMR spectrum of **2e** exhibited two sharp singlets at δ 3.12 and 3.67 due to the methyl protons, along with multiplets at δ 7.69–7.87 for the aromatic protons. A singlet at δ 8.30 was identified as the N–H proton. On the other hand, the N–H proton signal for product **2i** was not observed, while two diastereotopic benzylic protons resonated as two distinct doublets at δ 4.58 and 5.00 (J = 18.6 Hz). The ^{1}H decoupled ^{13}C NMR spectrum of **2e** showed 15 distinct resonances, in agreement with the proposed structure. The signal at δ 94.6 or 99.1 was consistent with the presence of a spiro carbon.[8a]



Scheme 3. Mechanism proposed for the one-pot synthesis of 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-tetraones **2a–l**.

A plausible mechanism involving oxidative cleavage of dihydroxyindenopyrrolopyrimidine **1** to pyrimidobenzazocine **5** is proposed in Scheme 3. Intermediate **5** rearranges to the product **2**, by hydrolysis to 2-[(2-(6-amino-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)-2-oxoacetyl)]benzoic acid **6** followed by cyclization. However, it is also reasonable to propose that pyrimidobenzazocine **5** undergoes an intramolecular reaction to give reactive intermediates, **7**,[8a] which subsequently convert into product **2** via rapid hydrolysis to 2-(6-hydroxy-1*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)benzoic acid **8** followed by intramolecular cyclization.

In summary, we have reported a new, one-pot procedure involving the addition reaction of ninhydrin and 6-aminouracils, which leads to dihydroxyindenopyrrolopyrimidines, and their subsequent rearrangement into 3*H*-spiro[isobenzofuran-1,6′-pyrrolo[2,3-*d*]pyrimidine]-2′,3,4′,5′-tetraones in the presence of lead(IV) acetate. The combination of generality, high yields, short reaction times, and mild conditions makes this method a useful procedure.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.113.

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12. *Spectroscopic and analysis data for some selected products*: *3H-Spiro[isobenzofuran-1,6′-pyrrolo[2,3-d]pyrimidine]-2′,3,4′,5′(1′H,3′H,7′H)-tetraone* (**2a**): mp >300 °C; IR (KBr): 3298, 3213, 3086, 1770, 1705, 1562; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.64 (t, J = 6.6 Hz, 1H, arom), 7.71 (d, J = 16.4 Hz, 1H, arom), 7.82 (m, 2H, arom), 8.11 (s, 1H, NH), 11.20 (s, 1H, NH), 12.90 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 93.1, 97.0, 125.3, 125.9, 130.6, 132.2, 136.7, 144.3, 151.0, 158.6, 165.9, 167.6, 186.2; MS (70 eV): m/z (%) = 285 (M+, 75), 257 (100), 229 (97), 186 (65), 105 (55). Anal. Calcd for $C_{13}H_7N_3O_5$: C, 54.74; H, 2.47; N, 14.73. Found: C, 54.81; H, 2.39; N, 14.70. *3H-1′,3′-Dimethyl-spiro[isobenzofuran-1,6′-pyrrolo[2,3-d]pyrimidine]-2′,3,4′,5′(1′H,3′H,7′H)-tetraone* (**2e**): mp >300 °C; IR (KBr): 3379, 1764, 1743, 1666, 1601, 1520; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.12 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 7.69 (dt, J_1 = 7.5 Hz, J_2 = 1 Hz, 1H, arom), 7.80 (t, J = 7.2 Hz, 2H, arom), 7.87 (dt, J_1 = 7.5 Hz, J_2 = 1 Hz, 1H, arom), 8.30 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.4, 37.6, 94.6, 99.1, 125.4, 125.9, 130.5, 132.4, 136.8, 143.2, 151.8, 157.2, 166.4, 168.1, 186.4; MS (70 eV): m/z (%) = 313 (M^+, 55), 285 (100), 257 (98), 200 (84), 105 (80). Anal. Calcd for $C_{15}H_{11}N_3O_5$: C, 57.51; H, 3.54; N, 13.41. Found: C, 57.62; H, 3.54; N, 13.36. *3H-7′-Benzyl-1′,3′-dimethyl-spiro[isobenzofuran-1,6′-pyrrolo[2,3-d]pyrimidine]-2′,3,4′,5′(1′H,3′H,7′H)-tetraone* (**2i**): mp 204–206 °C; IR (KBr): 3401, 1772, 1720, 1706, 1678, 1581; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.20 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 4.58 (d, J = 18.6 Hz, 1H, CH_2), 5.00 (d, J = 18.6 Hz, 1H, CH_2), 7.24–7.29 (m, 5H, arom), 7.71 (m, 1H, arom), 7.80 (m, 2H, arom), 7.91 (m, 1H, arom); ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.4, 33.3, 48.6, 91.2, 97.7, 124.3, 126.4, 126.8, 128.3, 129.5, 130.5, 132.7, 136.4, 137.5, 142.8, 152.0, 156.5, 167.4, 169.2, 182.6; MS (70 eV): m/z (%) = 403 (M^+, 5), 346 (63), 288 (95), 199 (100), 105 (52). Anal. Calcd for $C_{22}H_{17}N_3O_5$: C, 65.50; H, 4.25; N, 10.42. Found: C, 65.39; H, 4.20; N, 10.31.