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Synthesis of pyrrolo[2,3-*d*]pyrimidine-2,4-diones by sunlight photolysis of *N*-(5-vinyluracil-6-yl)sulfilimines

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Abstract—Uracil derivatives having a vinyl group at the C-5 position and a sulfilimine moiety at the C-6 position were prepared and cyclized to 1,3,6-trisubstituted pyrrolo[2,3-*d*]pyrimidine-2,4-diones by sunlight photolysis in good yields.

Sulfilimines are known to be useful building blocks for heterocycles.[1] In the course of our studies on the synthesis of heterocycles using *N*-conjugated sulfilimines, we previously reported a simple method for the preparation of 1,2,5-oxadiazolo[3,4-*d*]-, isoxazolo[3,4-*d*]-, isothiazolo[3,4-*d*]-, and 1,2,3-triazolo[4,5-*d*]pyrimidinediones from uracils having a nitroso-, a carbonyl-, a carbamoyl-, a thiocarbamoyl-,[2] or an azo group[3] at the C-5 position and a sulfilimine moiety at the C-6 position. These cyclization reactions proceeded upon thermolysis or photolysis and resulted in high yields without using oxidizing materials, dehydrating agents, or metal catalysts. In order to expand the scope of this cyclization reaction, we tried to synthesize pyrrolo[2,3-*d*]pyrimidine-2,4-diones from uracils using a new conjugated system, *N*-(5-vinyluracil-6-yl)sulfilimines. Pyrrolo[2,3-*d*]pyrimidine-2,4-diones have been prepared by Michael addition of 6-aminouracils to acetylenedicarboxyate[4] or diacylethylene[5] and by cyclocondensation with glycin derivatives,[6] oxalyl dichloride,[7] chloroacetaldehyde,[8] or diethyl oxalpropionate.[9] Palladium (II)-catalyzed cyclization[10] of 5-allyl-6-aminouracils or 6-(*N*-allyl)aminouracils, photolysis of 6-(1′-triazolyl)uracil,[11] and intramolecular insertion reaction of carbene generated from 6-(*N*-allyl-*N*-methylamino)-5-tosylhydrazonouracil[12] are unique methods for the synthesis of this condensed ring. Since some pyrrolo[2,3-*d*]pyrimidine-2,4-diones show antibacterial, anticancer, or antiviral activity,[13] the development of a method for efficient synthesis of this ring system is desirable. Herein, we report a novel synthesis of pyrrolo[2,3-*d*]pyrimidine-2,4-diones by sunlight photolysis of an *N*-(5-vinyluracil-6-yl) sulfilimines.

The starting materials, *N*-(1,3-dialkyluracil-6-yl)-*S*,*S*-diphenylsulfilimines **1** and *N*-(5-formyl-1,3-dimethyluracil-6-yl)-*S*,*S*-diphenylsulfilimine (**4**) were prepared by the reaction of *N*-unsubstituted *S*,*S*-diphenylsulfilimine with readily available 1,3-dialkyl-6-chlorouracils and 6-chloro-5-formyl-1,3-dimethyluracil, respectively.[2] As outlined in Scheme 1, uracil derivatives **3a** and **b** having a 2-(trifluoroacetyl)vinyl group at the C-5 position were synthesized in 75% and 77% yields, respectively, by the reaction of **1a** and **b** with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**2**)[14] in dichloromethane at room temperature.[15]

On the other hand, the synthetic approach to **3c**–**e** is based on Wittig reaction of **4** with phosphonium salts **5**. A suspension of sulfilimine **4**, benzyltriphenylphosphonium chloride, and sodium hydride in dry THF was refluxed to give *N*-(5-styryluracil-6-yl)sulfilimine (**3c**) in 71% yield.[16] In a similar manner, **3d** and **e** were prepared in 64% and 88% yields, respectively. The structures of the products **3a**–**e** were assigned on the basis of elemental analysis, MS, IR, and ^{1}H NMR spectra. The resulting sulfilimines **3a**–**e** are stable yellow solids and unchanged in a solution in the dark.

Cyclization reactions of **3a**–**e** to pyrrolo[2,3-*d*]pyrimidine-2,4-diones **6a**–**e** were undertaken under various conditions. Thermolysis of **3a** in refluxing toluene for 30 h was unsuccessful. However, sulfilimine **3a** was

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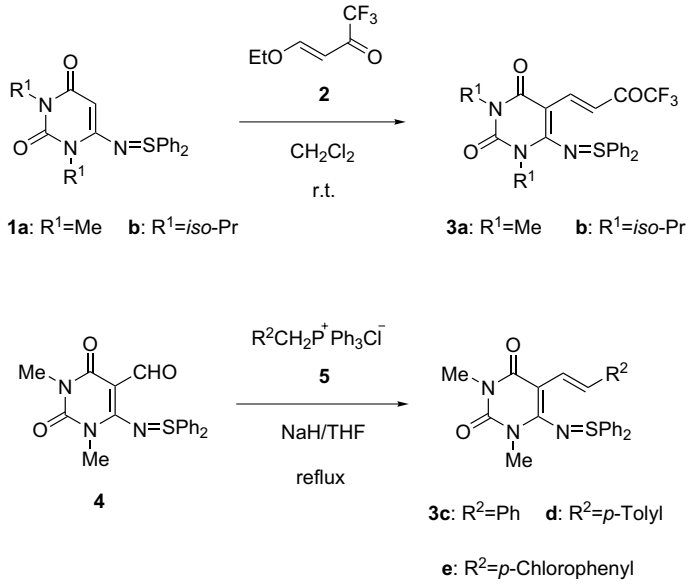
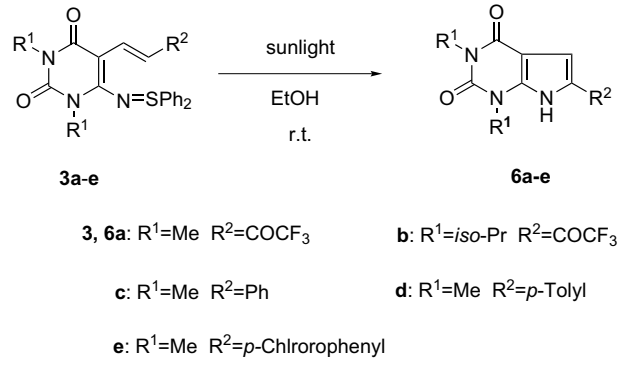


Scheme 1. Preparation of *N*-(5-vinyluracil-1-yl) sulfilimines **3**.

almost completely converted to the corresponding **6a** by UV irradiation using a high-pressure mercury lamp under a nitrogen atmosphere for 10 min in acetonitrile (Scheme 2).

Encouraged by the success of this ring closure reaction, we then applied it to the synthesis of **6c**. However, similar irradiation of **3c** in acetonitrile resulted in decomposition of the starting material with no significant amount of **6c**. Several reaction conditions were examined in order to realize the cyclization to **6c**. As a result, almost quantitative yield of **6c** was obtained, essentially by simple stirring of a solution of **3c** in ethanol for 40 min on exposure to sunlight under aerial atmosphere. The progress of the reaction was easily monitored by color change of the solution from yellow to pink and the products were isolated by a simple procedure. Thus, all the samples **3a**–**e** were subjected to irradiation of sunlight under aerial atmosphere, and they were converted in excellent yields to **6a**–**e** (Table 1).[17] The reaction would proceed through the generation of nitrene intermediates followed by 6π electrocyclization.[1h,18] In the synthetic photochemistry of uracils and related compounds,[19] reactions involving sunlight are scarcely known: autorecycling oxidation of cyclopentanol to cyclopentanone under an oxygen atmosphere using 'doubled 5-deazaflavins' and 'mixed flavins' as catalysts was greatly accelerated by sunlight.[20] It is noteworthy that sunlight was effectively used in our preparation of uracil derivatives.



Scheme 2. Sunlight photolysis of **3** to **6**.

Table 1. Preparation of **6a**–**e** upon sunlight photolysis of **3a**–**e**

Product	Photolysis time	Yield (%)
6a	5.0 h	88
6b	3.5 h	96
6c	40 min	91
6d	40 min	89
6e	40 min	84

In conclusion, we have established a new photochemical method for the preparation of 1,3,6-trisubstituted pyrrolo[2,3-*d*]pyrimidine-2,4-diones **6a**–**e** from uracils **3a**–**e** having a vinyl group at the C-5 position and a sulfilimine moiety at the C-6 position.

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15. A typical experimental procedure. A mixture of **1a**[2] (339 mg, 1.0 mmol) and **2**[14] (504 mg, 3.0 mmol) in CH_2Cl_2 (3 mL) was stirred for 5 days at room temperature. The resulting mixture was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to give *N*-[5-(4,4,4-trifluoro-3-oxo-1-butenyl)-1,3-dimethyluracil-6-yl]-*S*,*S*-diphenylsulfilimine (**3a**) (346 mg, 75%), as light-yellow needles, mp 207–208 °C (MeOH); IR (KBr) 1695, 1641, 1537, 1495, 1439 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (s, 3H), 3.65 (s, 3H), 7.53–7.84 (m, 12H); MS *m*/*z* (%) 275 (M^+-186, 16), 259 (16), 186 (100), 147 (24); UV (MeOH) λ_{max} ($\log\varepsilon$) 206 (4.7), 339 (4.1), 407 (4.3) nm. Anal. Calcd for $C_{22}H_{18}F_3N_3O_3S$: C, 57.26; H, 3.93; N, 9.11. Found: C, 57.29; H, 3.98; N, 9.13. Compound **3b**: 77%, mp 152–153 °C (MeOH); IR (KBr) 1687, 1637, 1547, 1475, 1441, 1254 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 6.8 Hz, 6H), 1.46 (d, J = 6.8 Hz, 6H), 5.20 (qq, J = 6.8 and 6.8 Hz, 1H), 5.63 (qq, J = 6.8 and 6.8 Hz, 1H), 7.26–7.78 (m, 12H); MS *m*/*z* (%) 517 (M^+, 6), 331 (8), 289 (13), 247 (14), 186 (100).
16. A typical experimental procedure. A mixture of **4**[2] (183 mg, 0.50 mmol), benzyltriphenylphosphonium chloride (778 mg, 2.0 mmol), and sodium hydride (60% in oil, 120 mg, 3.0 mmol) in dry THF (10 mL) was refluxed for 20 h. The resulting mixture was dissolved in water (100 mL) and then extracted with CH_2Cl_2 (3×100 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel using AcOEt/CH_2Cl_2 (1/1) as eluent to give *N*-(1,3-dimethyl-5-styryluracil-6-yl)-*S*,*S*-diphenylsulfilimine (**3c**) (157 mg, 71%), as light-yellow needles, mp 154–155 °C (MeOH); IR (KBr) 1684, 1635, 1537, 1442, 1419 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.38 (s, 3H), 3.56 (s, 3H), 6.50 (d, J = 16.0 Hz, 1H), 6.81–6.83 (m, 2H), 7.04–7.06 (m, 3H), 7.26 (d, J = 16.0 Hz, 1H), 7.46–7.55 (m, 6H), 7.69–7.72 (m, 4H); MS *m*/*z* (%) 255 (M^+-186, 10), 186 (100), 92 (10), 77 (25); UV (MeOH) λ_{max} ($\log\varepsilon$) 206 (4.7), 232 (4.5), 307 (4.3). Anal. Calcd for $C_{26}H_{23}N_3O_2S$: C, 70.72; H, 5.25; N, 9.52. Found: C, 70.43; H, 5.27; N, 9.53. Compound **3d**: 64%, mp 171–172 °C (MeOH); IR (KBr) 1683, 1633, 1612, 1545, 1444 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.38 (s, 3H), 3.56 (s, 3H), 6.45 (d, J = 16.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 16 Hz, 1H), 7.47–7.71 (m, 10H); MS *m*/*z* (%) 269 (M^+-186, 17), 212 (15), 186 (100). Compound **3e**: 88%, mp 177–178 °C (MeOH); IR (KBr) 1684, 1633, 1529, 1444 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.38 (s, 3H), 3.55 (s, 3H), 6.45 (d, J = 16.0 Hz, 1H), 6.67–6.70 (m, 2H), 6.98–7.00 (m, 2H), 7.26 (d, J = 16.0 Hz, 1H), 7.48–7.73 (m, 10H); MS *m*/*z* (%) 289 (M^+-186, 26), 232 (22), 186 (100), 175 (21), 109 (19).
17. A typical experimental procedure. Method A. A solution of **3a** (231 mg, 0.50 mmol) in acetonitrile (50 mL) was irradiated for 10 min using a high-pressure mercury lamp under a nitrogen atmosphere. The resulting solution was concentrated under reduced pressure. After the residue had been washed with diethyl ether, the resultant solid was separated by filtration, and recrystallized from methanol to give 6-trifluoroacetyl-1,3-dimethyl-1,2,3,4-tetrahydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6a**) (124 mg, 90%) as white powder, mp 292–293 °C (lit.,[21] mp 281 °C); IR (KBr) 3188, 3113, 1730, 1678, 1645, 1606, 1570, 1421 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (s, 3H), 3.50 (s, 3H), 7.51 (q, J = 2.0 Hz, 1H); MS *m*/*z* (%) 275 (M^+, 65), 218 (35), 206 (24), 149 (97), 66 (100). Anal. Calcd for $C_{10}H_8F_3N_3O_3$: C, 43.65; H, 2.93; N, 15.27. Found: C, 43.59; H, 3.00; N, 15.34. Method B. A solution of **3a** (231 mg, 0.50 mmol) in ethanol (30 mL) was irradiated for 5.0 h using sunlight under aerial atmosphere. The resulting solution was concentrated under reduced pressure. After the residue had been washed with diethyl ether, the resultant solid was separated by filtration, and recrystallized from methanol to give **6a** (121 mg, 88%). Compound **6b**: mp 214–215 °C (MeOH); IR (KBr) 3352, 1722, 1678, 1649, 1597, 1566, 1246, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (d, J = 6.8 Hz, 6H), 1.62 (d, J = 6.8 Hz, 6H), 4.90 (qq, J = 6.8 and 6.8 Hz, 1H), 5.26 (qq, J = 6.8 and 6.8 Hz, 1H), 7.72 (q, J = 2.0 Hz, 1H), 10.20 (br s, 1H); MS *m*/*z* (%) 331 (M^+, 54), 247 (100), 231 (64), 294 (57), 174 (64), 161 (72), 135 (65). Compound **6c**: mp 287–289 °C (MeOH); IR (KBr) 3188, 1687, 1637, 1568 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (s, 3H), 3.54 (s, 3H), 6.84 (s, 1H), 7.23–7.77 (m, 5H), 11.58 (br s, 1H); MS *m*/*z* (%) 255 (M^+, 100), 198 (65), 183 (15), 170 (32), 155 (15), 104 (15). Compound **6d**: mp 330–332 °C (MeOH); IR (KBr) 3273, 1698, 1684, 1641, 1568 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 3.23 (s, 3H), 3.53 (s, 3H), 6.77 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 11.53 (br s, 1H); MS *m*/*z* (%) 269 (100), 212 (76), 185 (73), 169 (32). Compound **6e**: mp 340–342 °C (MeOH); IR (KBr) 3300, 1688, 1633, 1566 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.23 (s,

3H), 3.53 (s, 3H), 6.91 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 11.62 (br s, 1H); MS m/z (%) 291/289 (M^+, 38/100), 232 (73), 217(25), 204 (49), 138 (38), 66 (51).

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