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SYNTHESIS OF 2*H*-1,2,3-TRIAZOLO [4,5-*d*]PYRIMIDINE-5,7-DIONES FROM URACILS USING CYCLIZATION REACTION OF β-AZO-α,β-UNSATURATED SULFILIMINES

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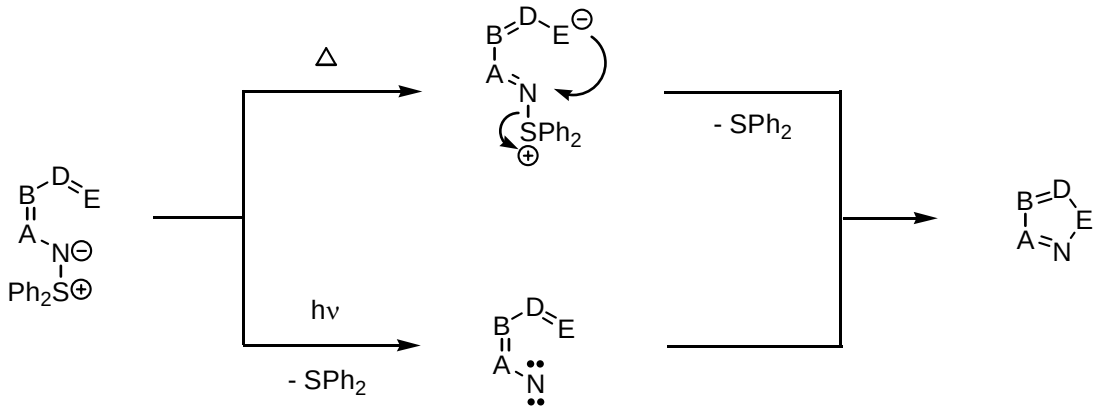
Abstract - *N*-(Uracil-6-yl)-*S*,*S*-diphenylsulfilimine (**1**) prepared from uracils reacted with aryldiazonium salts to give *N*-(5-arylazouracil-6-yl)-*S*,*S*-diphenylsulfilimines (**2**), β-azo-α,β-unsaturated sulfilimines, in good yields. The azo sulfilimines (**2**) were converted on thermolysis into the corresponding 2*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine-5,7-diones (**3**) in good yields.

Sulfilimines ($R^1R^2S{=}NR^3$) are stable sulfur ylides that do not require inert conditions or special handling for use in experiments.[1] One interesting chemical behavior of sulfilimines comes from the nucleophilic nitrogen atom and the good leaving ability of the sulfonium group. This characteristic reactivity has made sulfilimines attractive intermediates in the synthesis of nitrogen-containing heterocycles. In particular, conjugated sulfilimines are valuable as building blocks for the construction of five-membered rings (Scheme 1).[2] We anticipated that five-membered rings (at least one nitrogen atom) fused with a biologically important uracil ring could be easily prepared from uracil derivatives bearing a sulfilimine moiety. In fact, we have synthesized condensed uracil derivatives such as 1,2,5-oxadiazolo[3,4-*d*]-, isoxazolo[3,4-*d*]-, and isothiazolo[3,4-*d*]pyrimidine-4,7-diones from

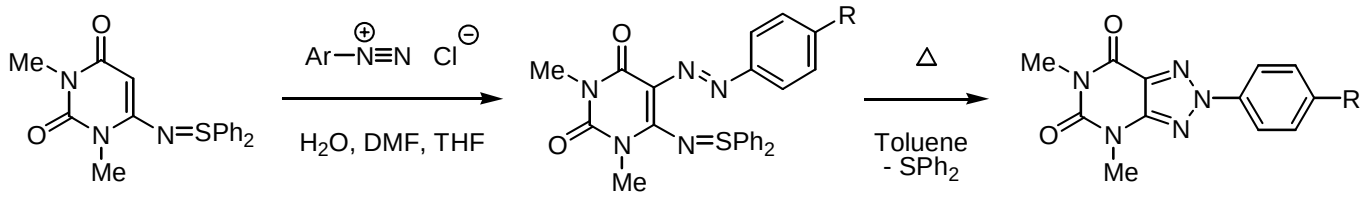


Scheme 1

N-(5-nitroso, 5-acyl, and 5-thiocarbamoyluracil-6-yl)sulfilimines respectively by thermolysis or photolysis.[3]

These successful annulation reactions prompted us to prepare a new conjugated system, β-azo-α,β-unasaturated sulfilimines, and to cyclize them to 2-substituted 1,2,3-triazoles. The synthesis of a 1,2,3-triazole ring by formation of one bond (N^1–N^2) is limited compared with that of two bonds (C^5–N^1 and C^4–N^3 or C^4–C^5 and N^1–N^2).[4] Bis-hydrazones, hydrazone oximes, or hydrazone imines of α-diketones, bis-azides, azo azides, etc. have been used for the synthesis of 2*H*-1,2,3-triazoles by the former method.[5] Recently, the synthesis of 2*H*-1,2,3-triazolo[4,5-*d*]pyrimidines was reviewed, and the cyclization by diazotization of 4,5-diaminopyrimidines, oxidation of 4-amino-5-azopyrimidines, and dehydration of oxime hydrazone on the pyrimidine ring were summarized as the one-bond (N^1-N^2) formation.[6] However, oxidation of 4-amino-5-azopyrimidines needs $CuSO_4 \cdot 5H_2O$, and the availability of arylhydrazines necessary in the preparation of oxime hydrazones is limited. In contrast to these, the present method does not require any heavy metal ions and dehydration reagents, and is applicable to a variety of anilines. Thus, our cyclization of β-azo-α,β-unasaturated sulfilimines to 2*H*-1,2,3-triazoles appears to be a new and useful synthetic route to 2*H*-1,2,3-trialzoles. In order to examine the feasibility of this approach, we studied the preparation of *N*-(5-azouracil-6-yl)sulfilimines (**2**) from *N*-(uracil-6-yl)-*S*,*S*-diphenylsulfilimine (**1**) and their cyclization to 2*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**3**)[4] (Scheme 2).

Reaction of **1**[3] with benzenediazonium chloride in THF/DMF/H_2O at 5°C gave bright red *N*-[1,3-dimethyl-



1 **2** **3**

Scheme 2

5-(phenylazo)uracil-6-yl]-*S*,*S*-diphenylsulfilimine (**2a**), which could be simply isolated by extraction of the reaction mixture in 93% isolated yield. The sulfilimine (**2a**) was a stable solid and storable for months. Its structure was assigned on the basis of elemental analysis, its MS, and IR and ^{1}H-NMR spectra. The signal of the olefinic proton observed at δ 4.91 in the ^{1}H-NMR spectrum of **1** disappeared in that of **2a**, thus indicating that an azo coupling reaction occurred at the C-5 position. Azo coupling appears to be applicable to a variety of diazonium salts. As shown in Table 1, diazonium salts with electron-withdrawing or electron-donating substituents all participated well to give β-azo-α,β-unsaturated sulfilimines (**2b-e**) in 89-98% isolated yields.

Table 1. Synthesis of Compounds (**2**) and (**3**)

Compounds	R	Yield (%)	Compounds	R	Yield (%)
2a	H	93	**3a**	H	92
2b	Me	95	**3b**	Me	93
2c	OMe	89	**3c**	OMe	87
2d	Cl	94	**3d**	Cl	95
2e	NO_2	98	**3e**	NO_2	86

Next, cyclization reactions of β-azo-α,β-unsaturated sulfilimines (**2**) to 1,2,3-triazoles were carried out. A mixture of **2a** and toluene was refluxed, and the characteristic red color of the mixture faded as the reaction proceeded. After 1 h, it was completely converted into 4,6-dimethyl-2-phenyl-4,5,6,7-tetrahydro-2*H*-1,2,3-triazolo-[4,5-*d*]pyrimidine-5,7-dione (**3a**) (92% isolated yield) and diphenyl sulfide. The structure of the product (**3a**) was assigned on the basis of elemental analysis, its MS, and IR and ^{1}H-NMR spectra. Moreover, **3a** was also obtained when a solution of **2a** in acetonitrile was irradiated for 1 h using a high-pressure mercury lamp under

nitrogen atmosphere. However, the *p*-nitro derivative (**2e**) was completely decomposed by UV irradiation for 1 h in acetonitrile, although the corresponding **3e** was obtained in 86% yield on reflux for 1 h in toluene. Therefore, cyclization by heating appears superior to photolysis. As shown in Table 1, nearly complete conversion of **2b-e** to the corresponding **3b-e** was observed when they were heated in toluene under reflux for 1 h. The use and biological properties of 2*H*-1,2,3-triazolo[4,5-*d*]pyridines remain rather undeveloped. A few derivatives are known to show radioactivity protections and activity of fluorescent whitener for synthetic fibers.[6]

In conclusion, we have developed a simple and efficient method for preparation of 2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-diones (**3**) from *N*-(1,3-dimethyl-6-uracilyl)-*S,S*-diphenylsulfilimine (**1**). This method is simple and does not require strict conditions or the use of metal salts.

EXPERIMENTAL

All melting points were determined on a MRK MEL-TEMP II and are uncorrected. IR spectra were recorded on a JASCO FT/IR-420 spectrophotometer. ^{1}H-NMR data were obtained with a JEOL GSX-400 (400 MHz) instrument, and chemical shifts are reported in ppm downfield from TMS. MS spectral data were measured on a JEOL JMS DX-300 spectrometer. Elemental analyses were performed with a YANACO CHN-CODER MT-5.

***N*-[1,3-Dimethyl-5-(phenylazo)uracil-6-yl]-*S,S*-diphenylsulfilimine (2a): typical experimental procedure.** A solution of sodium nitrate (83 mg, 1.2 mmol) in H_2O (2.0 mL) was added dropwise over a period of 20 min to a mixture of aniline (0.11 mL, 1.2 mmol) and concentrated hydrochloric acid (0.2 mL) in H_2O (2.0 mL) at 5°C. After 15 min, a mixture of **1**[3] (339 mg, 1.0 mmol) in DMF/THF (10 mL/5 mL) was added slowly. The mixture was stirred for 1 h at 5°C and for an additional 1 h at rt and then poured into water. After the reaction mixture had been extracted with chloroform, the organic layer was washed with water, dried with magnesium sulfate, and evaporated to afford the crude sulfilimine (**2a**) (412 mg, 93% yield), which was recrystallized from MeOH to give orange needles, mp 145-146°C. IR (KBr): 1687, 1641, 1516, 1473, 1444, 1383, 1232 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.38 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 7.09-7.20 (m, 5H, -N=N-Ph), 7.36-7.48 (m, 10H, -N=SPh_2). MS: m/z (%) 257 (M^+-Ph_2S, 63), 200 (12), 186 (Ph_2S^+, 100), 171 (42), 152 (8). *Anal.* Calcd for $C_{24}H_{21}N_5O_2S \cdot 1/2H_2O$: C,

63.69; H, 4.91; N, 15.48. Found: C, 63.99; H, 5.21; N, 15.20.

***N*-[1,3-Dimethyl-5-(*p*-methylphenylazo)uracil-6-yl]-*S,S*-diphenylsulfilimine (2b):** orange needles, mp 137-138°C (MeOH). IR (KBr): 1693, 1641, 1518, 1471, 1444, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H, C-CH_3), 3.38 (s, 3H, N-CH_3), 3.71 (s, 3H, N-CH_3), 6.98-7.03 (m, 4H, -N=N-C_6H_4-), 7.38-7.51 (m, 10H, -N=SPh_2). MS: m/z (%) 271 (M^+-Ph_2S, 53), 214 (9), 186 (Ph_2S^+, 100), 105 (15), 91 (21). *Anal.* Calcd for $C_{25}H_{23}N_5O_2S \cdot H_2O$: C, 63.13; H, 5.30; N, 14.73. Found: C, 62.92; H, 5.11; N, 14.43.

***N*-[5-(*p*-Methoxyphenylazo)-1,3-dimethyluracil-6-yl]-*S,S*-diphenylsulfilimine (2c):** orange needles, mp 136-137°C (MeOH). IR (KBr): 1689, 1639, 1518, 1442, 1381, 1232 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.38 (s, 3H, N-CH_3), 3.70 (s, 3H, N-CH_3), 3.82 (s, 3H, -OCH_3), 6.71 (d, *J*=8.8 Hz, 2H, -N=N-C_6H_4-), 7.08 (d, *J*=8.8 Hz, 2H, -N=N-C_6H_4-), 7.40-7.52 (m, 10H, -N=SPh_2). MS: m/z (%) 287 (M^+-Ph_2S, 29), 186 (Ph_2S^+, 100), 121 (12), 92 (15), 77 (19). *Anal.* Calcd for $C_{25}H_{23}N_5O_3S \cdot 1/2H_2O$: C, 62.22; H, 5.01; N, 14.51. Found: C, 61.95; H, 4.86; N, 15.49.

***N*-[5-(*p*-Chlorophenylazo)-1,3-dimethyluracil-6-yl]-*S,S*-diphenylsulfilimine (2d):** orange needles, mp 132-133°C (MeOH). IR (KBr): 1697, 1643, 1516, 1469, 1444, 1381, 1363, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.38 (s, 3H, N-CH_3), 3.70 (s, 3H, N-CH_3), 6.99 (d, *J*=8.8 Hz, 2H, -N=N-C_6H_4-), 7.13 (d, *J*=8.8 Hz, 2H, -N=N-C_6H_4-), 7.40-7.50 (m, 10H, -N=SPh_2). MS: m/z (%) 293 (M^++2-Ph_2S, 6), 291 (M^+-Ph_2S, 18), 205 (5), 186 (Ph_2S^+, 100). *Anal.* Calcd for $C_{24}H_{20}N_5O_2ClS \cdot 1/2H_2O$: C, 59.19; H, 4.35; N, 14.38. Found: C, 58.99; H, 4.49; N, 14.45.

***N*-[1,3-Dimethyl-5-(*p*-nitrophenylazo)uracil-6-yl]-*S,S*-diphenylsulfilimine (2e):** red needles, mp 175-176°C (MeOH). IR (KBr): 1701, 1649, 1511, 1442, 1326, 1229, 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.38 (s, 3H, N-CH_3), 3.71 (s, 3H, N-CH_3), 7.11 (d, *J*=8.8 Hz, 2H, -N=N-C_6H_4-), 7.42-7.53 (m, 10H, -N=SPh_2), 8.02 (d, *J*=8.8 Hz, 2H, -N=N-C_6H_4-). MS: m/z (%) 302 (M^+-Ph_2S, 6), 272 (5), 186 (Ph_2S^+, 100), 109 (20), 77 (16). *Anal.* Calcd for $C_{24}H_{20}N_6O_4S \cdot 1/2H_2O$: C, 57.93; H, 4.26; N, 16.90. Found: C, 58.00; H, 4.16; N, 17.15.

4,6-Dimethyl-2-phenyl-4,5,6,7-tetrahydro-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dione (3a): typical experimental procedure. A mixture of **2a** (444 mg, 1.0 mmol) and toluene (10 mL) was heated at reflux for 1 h. The reaction mixture was concentrated under reduced pressure and purified by a silica gel column with chloroform to give **3a** (237 mg, 92% yield) as white powder, mp 208-209°C (MeOH). IR (KBr): 1725, 1675, 1606, 1548, 1490, 1461, 1421, 1349, 1295 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.49 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 7.44-7.54 (m, 3H, ArH), 8.15-8.17 (m, 2H, ArH). MS: m/z (%) 257 (M^+, 100), 200 (16), 171 (42). *Anal.* Calcd for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22. Found: C, 55.75; H, 4.16; N, 26.97.

4,6-Dimethyl-2-(*p*-methylphenyl)-4,5,6,7-tetrahydro-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dione (3b): white powder, mp 192-193°C (MeOH). IR (KBr): 1726, 1678, 1608, 1508, 1425, 1352, 1296, 1059 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H, C-CH_3), 3.49 (s, 3H, N-CH_3), 3.65 (s, 3H, N-CH_3), 7.31 (d, *J*=8.6 Hz, 2H, ArH), 8.03 (d, *J*=8.6 Hz, 2H, ArH). MS: m/z (%) 271 (M^+, 100), 242 (3), 214 (11), 185 (22), 105 (34), 91 (52). *Anal.* Calcd for $C_{13}H_{13}N_5O_2$: C, 57.55; H, 4.83; N, 25.82. Found: C, 57.57; H, 4.74; N, 25.94.

2-(*p*-Methoxyphenyl)-4,6-dimethyl-4,5,6,7-tetrahydro-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dione (3c): white needles, mp 216-217°C (MeOH). IR (KBr): 1716, 1678, 1612, 1512, 1414, 1354, 1300, 1263 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.48 (s, 3H, N-CH_3), 3.64 (s, 3H, N-CH_3), 3.88 (s, 3H, -OCH_3), 7.00 (d, *J*=9.2 Hz, 2H, ArH), 8.07 (d, *J*=9.2 Hz, 2H, ArH). MS: m/z (%) 287 (M^+, 100), 272 (12), 121 (32), 107 (24). *Anal.* Calcd for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.38; H, 4.53; N, 24.33.

2-(*p*-Chlorophenyl)-4,6-dimethyl-4,5,6,7-tetrahydro-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dione (3d): white needles, mp 220-221°C (MeOH). IR (KBr): 1720, 1682, 1608, 1495, 1421, 1352, 1294 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.49 (s, 3H, N-CH_3), 3.65 (s, 3H, N-CH_3), 7.49 (d, *J*=9.0 Hz, 2H, ArH), 8.11 (d, *J*=9.0 Hz, 2H, ArH). MS: m/z (%) 293 (M^++2, 32), 291 (M^+, 100), 234 (16), 205 (29), 125 (26), 111 (35), 67 (30). *Anal.* Calcd for $C_{12}H_{10}N_5O_2Cl$: C, 49.41; H, 3.46; N, 24.01. Found: C, 49.24; H, 3.43; N, 24.02.

4,6-Dimethyl-2-(*p*-nitrophenyl)-4,5,6,7-tetrahydro-2*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-5,7-dione (3e): pale yellow powder, mp 243-245°C (MeOH). IR (KBr): 1728, 1682, 1606, 1589, 1518, 1493, 1425, 1338, 1292 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.51 (s, 3H, N-CH_3), 3.68 (s, 3H, N-CH_3), 8.36 (d, *J*=9.6 Hz, 2H, ArH), 8.41 (d, *J*=9.6 Hz, 2H, ArH). MS: m/z (%) 302 (M^+, 100), 272 (27), 216 (49), 67 (53). *Anal.* Calcd for $C_{12}H_{10}N_6O_4$: C, 47.69; H, 3.33; N, 27.81. Found: C, 47.49; H, 3.36; N, 27.87.

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