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Ring closure reactions of β-nitroso-, β-acyl-, and β-thiocarbamoyl-α,β-unsaturated sulfilimines. Synthesis of [1,2,5]oxadiazolo[3,4-*d*]-, isoxazolo[3,4-*d*]-, and isothiazolo[3,4-*d*]pyrimidine derivatives from uracils

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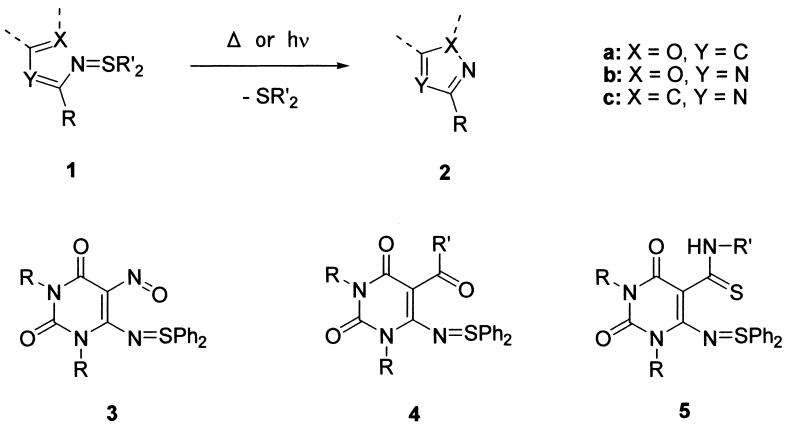
Abstract—1,3-Dialkyl-6-chlorouracils were treated with *S*,*S*-diphenylsulfilimine to give *N*-(1,3-dialkyluracil-6-yl)-*S*,*S*-diphenylsulfilimines. The uracilylsulfilimines were nitrosated, acylated, or thiocarbamoylated to give *N*-(5-nitroso-, 5-acyl-, or 5-thiocarbamoyluracil-6-yl)sulfilimines, respectively. These conjugated sulfilimines were cyclized by thermolysis or photolysis to [1,2,5]oxadiazolo[3,4-*d*], isoxazolo[3,4-*d*], or isothiazolo[3,4-*d*]pyrimidine derivatives. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Sulfilimines ($R^1R^2S{=}NR^3$) are a class of sulfur ylides that occupy an interesting area in sulfur chemistry.[1] One interesting chemical behavior of sulfilimines is based on the nucleophilic nitrogen atom and a good leaving sulfonium group. This characteristic reactivity has made sulfilimines attractive intermediates in the synthesis of heterocyclic compounds, especially when the ylides are conjugated with unsaturated bonds. Conjugated sulfilimine systems such as $N{=}C{-}N{=}SR_2$,[2] $S{=}C{-}N{=}SR_2$,[3] $C{=}C{-}N{=}SR_2$[4] and $O{=}C{-}N{=}SR_2$[5] have been used for the synthesis of heterocycles such as 1,2,4-triazole 2-oxides, 1,2,4-oxadiazoles, condensed imidazolones, isothiazoles, 1,2,4-benzoxadiazines, and oxazolinones. In the course of our studies on synthesis of heterocycles using sulfilimines, we have found a one-step method for synthesizing 3-alkyl-5,6-diphenyluracils from *N*-carbamoylsulfilimines $R{-}NHCON{=}SR_2$ and diphenylcyclopropenone.[6] The preparation of heterocycles using more extended conjugated sulfilimines has also been reported. In an early study on sulfilimines, Tamura et al. succeeded in the formation of isoxazoles (**2a**) from β-acyl-α, β-unsaturated sulfilimine (**1a**) by an intramolecular thermal reaction (Scheme 1).[7] The reaction of the nitrogen analogue (**1b**) similarly proceeded to give 1,2,4-oxadiazoles (**2b**).[8] Benzimidazoles (**2c**) and



Scheme 1.

Keywords: sulfilimine; [1,2,5]oxadiazolo[3,4-*d*]pyrimidine; isoxazolo[3,4-*d*]pyrimidine; isothiazolo[3,4-*d*]pyrimidine; uracil.

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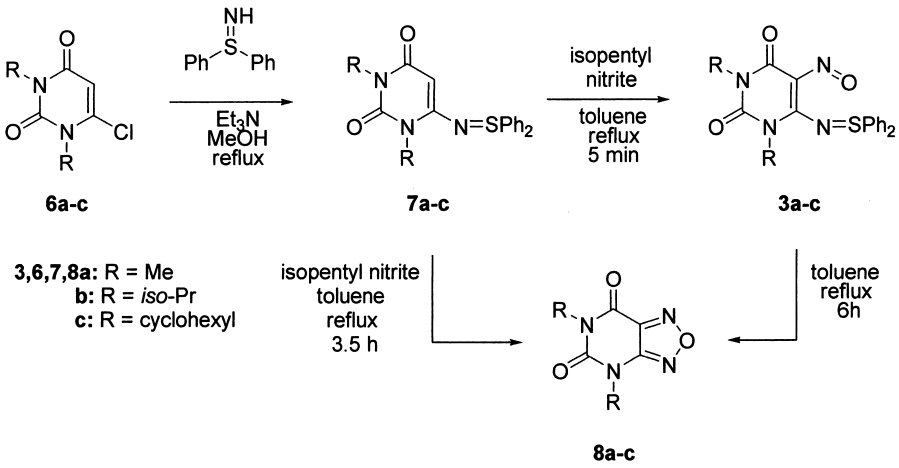


Scheme 2.

other heterocycles were obtained by thermolysis of *N*-(*N*-arylimidoyl)sulfilimines (**1c**).[9] This nature of sulfilimines led us to attempt ring closure reactions of other new conjugated systems of sulfilimines. Use of these conjugated sulfilimines would provide an excellent method for the synthesis of heterocycles containing a C=N double bond without using oxidizing or dehydrating agents for cyclization. Thus, we have prepared useful conjugated systems, β-nitroso-α, β-unsaturated sulfilimines (**3**), β-acyl-α, β-unsaturated sulfilimines (**4**), and β-thiocarbamoyl-α, β-unsaturated sulfilimines (**5**), using uracils and have found a facile cyclization to the corresponding fused [1,2,5]oxadiazoles, isoxazoles, and isothiazoles, respectively.

2. Results and discussion

2.1. Preparation and cyclization of *N*-(5-nitrosouracil-6-yl)sulfilimines (3)

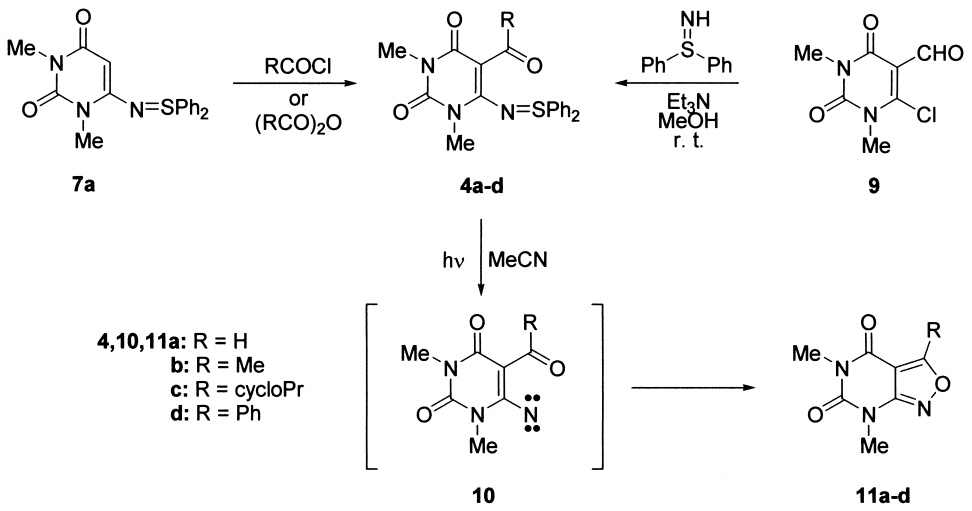
While there are uarcil derivatives that possess ylide structures, such as dimethylsulfoxonium methylides[10] and iminophosphoranes,[11] at the C-6 position, no uracil derivatives bearing a sulfilimine moiety have been reported. We used a simple method for the preparation of uracilyl-sulfilimines, which involves the reaction of 1,3-dialkyl-6-chlorouracils (**6**) with *S*,*S*-diphenylsulfilimine. This *N*-unsubstituted sulfilimine monohydrate can be readily obtained by acidic hydrolysis of *S*,*S*-diphenyl-*N*-*p*-tosyl-sulfilimine.[12] As depicted in Scheme 2, the reaction of **6a**–**c**[13] with *S*,*S*-diphenylsulfilimine monohydrate in the presence of triethylamine in refluxing methanol gave solid sulfilimines (**7a**,**b**) in 85 and 61% yields, respectively. The products were easily isolated by addition of water to the reaction mixture followed by filtration of the resulting precipitates. The sulfilimines (**7a**,**b**) are stable solids and storable for months. However, **7c** (89% crude yield) is an unstable solid, which was used in the next step without further purification.

6-Aminouracils behave as enamines, and their nitrosation occurs readily to give 6-amino-5-nitrosouracil derivatives, which have been used as starting materials for condensed uracil derivatives.[14] Thus, treatment of **7** with isopentyl nitrite in refluxing toluene for 5 min yielded β-nitroso-α, β-unsaturated sulfilimines (**3**), a new conjugated system of sulfilimine, as blue precipitates in 54–86% yields. The signals of the olefinic protons observed in the ^{1}H NMR spectra of **7a**–**c** disappeared in those of **3a**–**c**, thus indicating that nitrosation occurred at the C-5 position.

Classically, 1,2,5-oxadiazoles (furazans) and their derivatives have been prepared[15] by (i) cyclodehydration of the corresponding α-dioximes with thionyl chloride, (ii) oxidation of aromatic nitroso amines with lead tetraacetate, and (iii) deoxygenation of the corresponding furoxans using trialkyl phosphate. However, these methods for the preparation of 1,2,5-oxadiazole require either toxic metals or corrosive dehydrating agents. A new method for synthesizing 1,2,5-oxadiazoles is therefore needed. A mixture of nitroso sulfilimines (**3a**–**c**) in toluene was refluxed for 6 h. The characteristic blue color of the mixture disappeared as the reaction proceeded. The products observed on TLC were the corresponding 1,2,5-oxadiazoles (**8a**–**c**) and diphenyl sulfide, giving good isolated yields (80–98%). The structures of the products **8** were assigned on the basis of elemental analysis and MS, IR and ^{1}H NMR spectra. It is noteworthy that the final fused 1,2,5-oxadiazoles (**8a**–**c**) were prepared in one pot in 53–87% yields from **7a**–**c** without isolation of the nitroso intermediates (**3**); isopentyl nitrite was first added to a mixture of **7** in toluene and the mixture was refluxed for 1.5–3.5 h. The blue color of the nitroso derivatives (**3**) first appeared and then faded, showing the formation of the product. The condensed 1,2,5-oxadiazole (**8a**) was obtained as a by-product of oxidation of 6-amino-1,3-dimethyl-5-nitrosouracil by lead tetraacetate,[16] by deoxygenation of *N*-oxide of **8a**,[17] by treatment of 6-acetoxyimino-1,3-dimethyluracil with sodium nitrite,[18] and recently by oxidation of 6-amino-1,3-dimethyl-5-nitrosouracil with a combination of iodobenzene diacetate and lithium hydride.[19] Thus, we have shown a new route to this biologically important class of heterocycles.[19]

2.2. Preparation and cyclization of *N*-(5-acyluracil-6-yl)sulfilimines (4)

In order to extend the utility of sulfilimine (**7a**) as a building block for preparation of nitrogen-containing heterocycles,



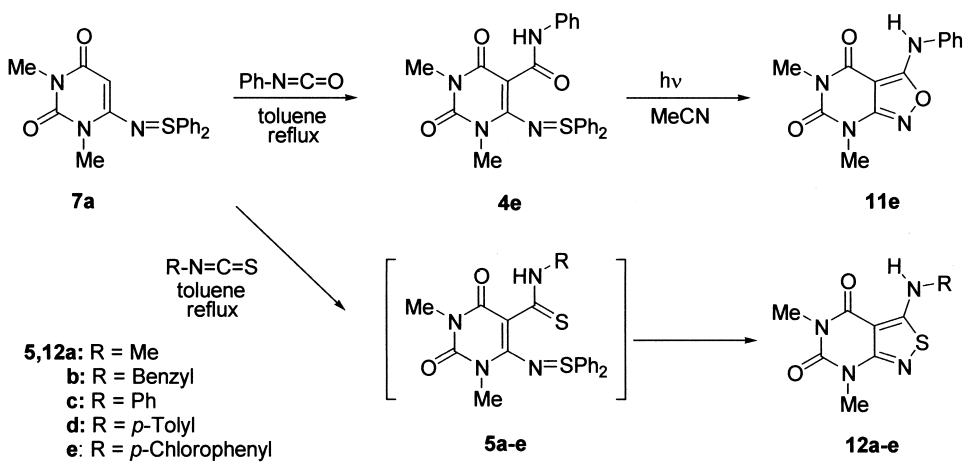
Scheme 3.

we tried to synthesize isoxazolopyrimidines (**11a–d**), which are known to be anti-inflammatory and analgesic agents.[20]

As outlined in Scheme 3, β-acyl-α, β-unsaturated sulfilimines (**4c** and **d**) were prepared by the reaction of **7a** with carboxylic acid chloride in dichloromethane in the presence of triethylamine at room temperature (75–76%), while **7a** was converted to **4b** by heating in acetic anhydride (72%). The formyl derivative (**4a**) was obtained from 6-chloro-5-formyluracil (**9**) and *S*,*S*-diphenylsulfilimine in methanol in the presence of triethylamine without heating (89%). Although a solution of β-acyl-α, β-unsaturated sulfilimines (**4a–d**) in toluene was refluxed for 20 h, they were recovered unchanged. However, it was found that sulfilimines (**4a–d**) were almost completely converted to the expected isoxazolopyrimidines (**11a–d**) by UV irradiation for 3–4 h in acetonitrle (54–91%). It has been reported that some conjugated sulfilimines are cyclized to the same products by thermolysis or photolysis, indicating the involvement of nitrene intermediates.[9] Thus, it seems to be easier to generate the nitrene intermediate (**10**) by UV irradiation than by heating in this case. Thermolysis of β-azido-α, β-unsaturated ketones and esters is also known to give isoxazole derivatives *via* a nitrene or nitrene/azirine intermediate.[21] Stadlbauer et al.[22] recently reported that thermolysis of 6-azidouracils in the presence of polyphosphoric acid led either to the formation of oxazolo[5,4-*d*]pyrimidine-5,7-diones (by reaction with benzoic acid) via the nitrene/azirine intermediate or to the formation of isomeric isoxazolo[3,4-*d*]pyrimidine-4,6-diones (by reaction with aliphatic carboxylic acids) via the nitrene intermediates. However, the use of our method provided only isoxazolo[3,4-*d*]pyrimidine-4,6-diones in good yields.

2.3. Preparation and cyclization of *N*-(5-thiocarbamoyluracil-6-yl)sulfilimines (5)

The successful cyclization of **4a–d** prompted us to use an analogous conjugated system, β-carbamoyl-α, β-unsaturated sulfilimines (**4e**), and a new conjugated system, β-thiocarbamoyl-α, β-unsaturated sulfilimines (**5a–e**), which can readily be prepared by reacting the ylide (**7a**) with isocyanate or isothiocyanates (Scheme 4). Although *N*-[1,3-dimethyl-5-(*N*-phenylcarbamoyl)-6-uracilyl] sulfilimine (**4e**) was isolated (88%) and cyclized by photolysis to the corresponding isoxazolo[3,4-*d*]pyrimidine (**11e**) (18%), the corresponding thiocarbamoyl derivatives (**5a–e**) were difficult to isolate. Interestingly, however, the treatment of **7a** with a variety of isothiocyanates in refluxing toluene yielded isothiazolo[3,4-*d*]pyrimidine-



Scheme 4.

4,6(5*H*,7*H*)-diones (**12a**–**e**) in one step (52–76%) without isolation of the intermediates (**5**). This method has an advantage over the two-step synthesis of isothiazolo[3,4-*d*]pyrimidine-4,6-diones by dithiocarboxylation[23] or thiocarbamoylation[24] of 6-aminouracils followed by oxidation.

3. Conclusion

In conclusion, we have developed a simple and efficient method for preparation of [1,2,5]oxadiazolo[3,4-*d*]-, isoxazolo[3,4-*d*]-, and isothiazolo[3,4-*d*]pyrimidine derivatives using uracil derivatives bearing sulfilimine (**7**). The methods are operationally simple and do not require strict conditions such as the use of anhydrous solvents or the use of oxidizing or dehydrating agents.

4. Experimental

4.1. General

All Melting points were determined on a MRK MEL-TEMP II and are uncorrected. Infrared spectra were recorded on a JASCO A-102 and JASCO FT/IR-420 spectrophotometers. ^{1}H NMR data were obtained with a JEOL GSX-400 (400 MHz) instrument and chemical shifts are reported in ppm downfield from TMS. Mass spectral data were measured on a JEOL JMS DX-300 spectrometer. Elemental analyses were performed with YANACO CHN-CODER MT-5.

4.1.1. *N*-(1,3-Dimethyl-6-uracilyl)-*S*,*S*-diphenylsulfilimine (7a): typical procedure. A mixture of 6-chloro-1,3-dimethyluracil[13] (1.92 g, 11 mmol), *S*,*S*-diphenylsulfilimine monohydrate (4.42 g, 20 mmol) and triethylamine (2.22 g, 22 mmol) in methanol (10 mL) was refluxed for 5 h and then cooled to room temperature. After water (20 mL) was added, the white precipitate was separated by filtration. The resultant solid was purified by recrystallization from methanol to give **7a** (3.17 g, 85%) as colorless plates, mp 232–233°C. IR (KBr): 3049, 1675, 1626, 1560, 1476, 1442, 1286, 1238 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.30 (s, 3H, N–Me), 3.60 (s, 3H, N–Me), 4.91 (s, 1H, C=CH), 7.52–7.74 (m, 10H, ArH). MS: *m*/*z* (%) 339 (M^+, 7), 186 (Ph_2S^+, 100). Anal. calcd for $C_{18}H_{17}N_3O_2S$ (339.41): C, 63.70; H, 5.05; N, 12.38. Found: C, 63.72; H, 5.12; N, 12.40.

4.1.2. *N*-(1,3-Diisopropyl-6-uracilyl)-*S*,*S*-diphenylsulfilimine (7b). Yield 61%, colorless plates, mp 193–194°C (MeOH). IR (KBr): 2967, 1685, 1627, 1560, 1475, 1442, 1272 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.43 (d, *J*=7.2 Hz, 6H, Me), 1.56 (d, *J*=7.2 Hz, 6H, Me), 4.79 (s, 1H, C=CH), 5.15–5.19 (m, 1H, N–CH), 5.60 (br s, 1H, N–CH), 7.50–7.70 (m, 10H, ArH). MS: *m*/*z* (%) 395 (M^+, 10), 286 (30), 244 (10), 201 (10), 186 (Ph_2S^+, 100), 152 (8), 109 (9). Anal. calcd for $C_{22}H_{25}N_3O_2S$ (395.53): C, 66.81; H, 6.37; N, 10.62. Found: C, 66.69; H, 6.36; N, 10.84.

4.1.3. *N*-(1,3-Dimethyl-5-nitroso-6-uracilyl)-*S*,*S*-diphenylsulfilimine (3a): typical procedure. A mixture of **7a** (678 mg, 2.0 mmol) and isopentyl nitrite (281 mg, 2.4 mmol) in toluene (10 mL) was refluxed for 5 min and then cooled to room temperature. After the blue precipitate was separated by filtration, the resultant solid was purified by recrystallization from chloroform–hexane to give **3a** (633 mg, 86%) as blue needles, mp 181–182°C. IR (KBr): 3055, 1711, 1662, 1580, 1511, 1475, 1443, 1377, 1352, 1231 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.26 (s, 3H, N–Me), 3.85 (s, 3H, N–Me), 7.47–7.74 (m, 10H, ArH). MS: *m*/*z* (%) 186 (Ph_2S^+, 100), 182 (33), 152 (12). Anal. calcd for $C_{18}H_{16}N_4O_3S$ (368.41): C, 58.68; H, 4.38; N, 15.21. Found: C, 58.58; H, 4.46; N, 15.19.

4.1.4. *N*-(1,3-Diisopropyl-5-nitroso-6-uracilyl)-*S*,*S*-diphenylsulfilimine (3b). Yield 54%, blue plates, mp 150–151°C (chloroform-hexane). IR (KBr): 2973, 1718, 1670, 1579, 1509, 1444, 1338, 1220 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40 (d, *J*=6.8 Hz, 6H, Me), 1.69 (d, *J*=6.8 Hz, 6H, Me), 5.04–5.08 (m, 1H, N–CH), 5.77–5.81 (m, 1H, N–CH), 7.45–7.70 (m, 10H, ArH). MS: *m*/*z* (%) 238 (M^+−186, 12), 197 (13), 186 (Ph_2S^+, 100), 181 (18), 155 (19), 138 (8). Anal. calcd for $C_{22}H_{24}N_4O_3S$ (424.53): C, 62.24; H, 5.70; N, 13.20. Found: C, 61.79; H, 5.67; N, 13.58.

4.1.5. *N*-(1,3-Dicyclohexyl-5-nitroso-6-uracilyl)-*S*,*S*-diphenylsulfilimine (3c). Yield 60%, blue powder, mp 178–179°C (chloroform–hexane). IR (KBr): 3062, 2933, 2850, 1706, 1662, 1579, 1517, 1473, 1444 cm^{-1}. ^{1}HNMR ($CDCl_3$): δ 1.16–1.98 (m, 16H, $-CH_2-$), 2.28–2.37 (m, 2H, $-CH_2-$), 2.61–2.64 (m, 2H, $-CH_2-$), 4.61–4.67 (m, 1H, N–CH), 5.39 (br s, 1H, N–CH), 7.26–7.72 (m, 10H, Ar). MS: *m*/*z* (%) 237 (M^+−267, 59), 186 (Ph_2S^+, 100), 155 (82), 83 (27). Anal. calcd for $C_{28}H_{32}N_4O_3S$ (504.66): C, 66.64; H, 6.39; N, 11.10. Found: C, 66.33; H, 6.34; N, 11.52.

4.1.6. 4,6-Dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (8a): typical procedure. *Method A*. A mixture of **3a** (368 mg, 1.0 mmol) in toluene (15 mL) was refluxed for 6 h and then the solvent was removed under reduced pressure. After the residue was washed with diethyl ether, the resultant solid was separated by filtration and recrystallized from methanol to give **8a** (166 mg, 91%) as colorless plates, mp 222–223°C (lit.[16] mp 225–226°C).

Method B. A mixture of **7a** (339 mg, 1.0 mmol) and isopentyl nitrite (140 mg, 1.2 mmol) in toluene (10 mL) was refluxed for 3.5 h and then the solvent was removed under reduced pressure. After the residue was washed with diethyl ether, the resultant solid was separated by filtration and recrystallized from methanol to give **8a** (158 mg, 87%).

4.1.7. 4,6-Diisopropyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (8b). Yield 80% (Method A) or 54% (Method B), colorless plates, mp 82–83°C (MeOH). IR (KBr): 2979, 2940, 2879, 1693, 1617, 1540, 1455, 1375, 1351, 1274, 1216 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.52 (d, *J*=6.8 Hz, 6H, Me), 1.55 (s, *J*=6.8 Hz, 6H, Me), 5.09–5.16 (m, 1H, N–CH), 5.21–5.24 (m, 1H, N–CH). MS: *m*/*z* (%) 238 (M^+, 46), 197 (48), 181 (95), 155 (100), 138 (37). Anal. calcd for $C_{10}H_{14}N_4O_3$ (238.25): C, 50.41; H, 5.92; N, 23.52. Found: C, 50.16; H, 5.82; N, 23.27.

4.1.8. 4,6-Dicyclohexyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (8c). Yield 98% (Method A) or

53% (Method B), white plates, mp 153–154°C (MeOH). IR (KBr): 2940, 2863, 1729, 1683, 1614, 1538, 1452, 1272, 1187, 1135 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23–1.94 (m, 16H, $-CH_2-$), 2.23–2.43 (m, 4H, $-CH_2-$), 4.67–4.73 (m, 1H, N–CH), 4.78–4.84 (m, 1H, N–CH). MS: *m/z* (%) 318 (M^+, 1), 237 (36), 155 (59), 55 (100). Anal. calcd for $C_{16}H_{22}N_4O_3$ (318.38): C, 60.36; H, 6.97; N, 17.60. Found: C, 60.36; H, 6.91; N, 17.39.

4.1.9. *N*-(5-Formyl-1,3-dimethyl-6-uracilyl)-*S*,*S*-diphenylsulfilimine (4a). A mixture of **9**[25] (1.01 g, 5.0 mmol), *S*,*S*-diphenylsulfilimine monohydrate (1.31 g, 6.0 mmol), and triethylamine (1.01 g, 10.0 mmol) in methanol (10 mL) was stirred for 1 h and then the precipitate was separated by filtration. The precipitates were purified by recrystallization from methanol to give **4a** (1.63 g, 89%) as colorless plates, mp 202–203°C. IR (KBr): 3056, 1702, 1623, 1492, 1440, 1367, 1301, 1213, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.33 (s, 3H, N–Me), 3.56 (s, 3H, N–Me), 7.49–7.74 (m, 15H, ArH), 9.71 (s, 1H, CHO). MS: *m/z* (%) 367 (M^+, 1), 258 (12), 186 (Ph_2S^+, 100). Anal. calcd for $C_{19}H_{17}N_3O_3S$ (367.42): C, 62.11; H, 4.66; N, 11.44. Found: C, 62.11; H, 4.75; N, 11.35.

4.1.10. *N*-(5-Acetyl-1,3-dimethyl-6-uracilyl)-*S*,*S*-diphenylsulfilimine (4b). A mixture of **7a** (678 mg, 2.0 mmol) and acetic anhydride (10 mL) was refluxed for 1 h and then the solvent was removed under reduced pressure. After the residue was washed with methanol, the resultant solid was separated by filtration and recrystallized from methanol to give **4b** (547 mg, 72%) as colorless plates, mp 189–190°C. IR (KBr): 3054, 2944, 1693, 1633, 1596, 1430, 1224, 1160 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H, –CO–Me), 3.32 (s, 3H, N–Me), 3.58 (s, 3H, N–Me), 7.38–7.71 (m, 10H, ArH). MS: *m/z* (%) 381 (M^+, 1), 339 (6), 195 (19), 186 (Ph_2S^+, 100). Anal. calcd for $C_{20}H_{19}N_3O_3S$ (381.45): C, 62.97; H, 5.02; N, 11.02. Found: C, 62.81; H, 5.08; N, 11.01.

4.1.11. *N*-(5-Benzoyl-1,3-dimethyl-6-uracilyl)-*S*,*S*-diphenylsulfilimine (4d). A mixture of **7a** (678 mg, 2.0 mmol), benzoyl chloride (322 mg, 2.3 mmol), and triethylamine (303 mg, 3.0 mmol) in dichloromethane (10 mL) was stirred for 20 h and then the solvent was removed under reduced pressure. The resultant residue was chromatographed (silica gel, $CHCl_3$ as eluent) to give **4d** (665 mg, 75%), white needles, mp 126–127°C (MeOH). IR (KBr): 3052, 1687, 1623, 1573, 1502, 1430, 1386 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.25 (s, 3H, N–Me), 3.71 (s, 3H, N–Me), 7.22–7.59 (m, 15H, ArH). MS: *m/z* (%) 443 (M^+, 5), 257 (8), 186 (Ph_2S^+, 65), 105 (100). Anal. calcd for $C_{25}H_{21}N_3O_3S\cdot 1/2H_2O$ (452.53): C, 66.35; H, 4.90; N, 9.33. Found: C, 66.80; H, 4.98; N, 9.28.

4.1.12. *N*-(5-Cyclopropyl-1,3-dimethyl-6-uracilyl)-*S*,*S*-diphenylsulfilimine (4c). This compound was prepared in the similar manner as **4d**. Yield 76%, white plates, mp 163–164°C (MeOH). IR (KBr): 3000, 1691, 1639, 1596, 1479, 1430, 1390, 1278, 1209 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.73–0.77 (m, 2H, CH_2), 0.87–0.91 (m, 2H, CH_2), 3.07–3.11 (m, 1H, C–CH–C), 3.34 (s, 3H, N–Me), 3.59 (s, 3H, N–Me), 7.37–7.67 (m, 10H, ArH). MS: *m/z* (%) 407 (M^+, 2), 339 (18), 186 (Ph_2S^+, 100). Anal. calcd for $C_{22}H_{21}N_3O_3S$ (407.49): C, 64.85; H, 5.19; N, 10.31. Found: C, 64.69; H, 5.23; N, 10.34.

4.1.13. *N*-[1,3-Dimethyl-5-(*N*-phenylcarbamoyl)-6-uracilyl]-*S*,*S*-diphenylsulfilimine (4e). A mixture of **7a** (339 mg, 1.0 mmol) and phenyl isocyanate (413 mg, 3.4 mmol) in toluene (5 mL) was refluxed for 20 h and then the solvent was removed under reduced pressure. After the residue was washed with diethyl ether, the resultant solid was separated by filtration and recrystallized from methanol to give **4e** (403 mg, 88% yield) as white needles, mp 180–181°C. IR (KBr): 3056, 1693, 1648, 1585, 1538, 1442, 1359, 1213, 1166 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.36 (s, 3H, N–Me), 3.65 (s, 3H, N–Me), 6.98–7.75 (m, 15H, ArH), 11.57 (s, 1H, NH). MS: *m/z* (%) 458 (M^+, 1), 366 (13), 339 (9), 186 (Ph_2S^+, 100), 119 (24). Anal. calcd for $C_{25}H_{22}N_4O_3S$ (458.53): C, 65.48; H, 4.84; N, 12.22. Found: C, 65.19; H, 4.95; N, 12.05.

4.1.14. 5,7-Dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (11a): typical procedure. A solution of **4a** (367 mg, 1.0 mmol) in acetonitrile (60 mL) was irradiated for 3 h using a high-pressure mercury lamp under nitrogen atmosphere and then the solvent was removed under reduced pressure. The resultant residue was chromatographed (silica gel, $CHCl_3$–AcOEt=1:1 as eluent) to give **11a** (165 mg, 91%) as white plates, mp 167–168°C (MeOH). IR (KBr): 3079, 1679, 1552, 1465, 1428, 1367, 1284, 1126, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.39 (s, 3H, N–Me), 3.54 (s, 3H, N–Me), 8.98 (s, 1H, –C=CH–O–). MS: *m/z* (%) 181 (M^+, 85), 124 (66), 96 (100). Anal. calcd for $C_7H_7N_3O_3$ (181.15): C, 46.41; H, 3.89; N, 23.20. Found: C, 46.23; H, 3.91; N, 23.14.

4.1.15. 3,5,7-Trimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (11b). Yield 88%, white needles, mp 200–201°C (MeOH) (lit.[22] mp 200–202°C). IR (KBr): 2956, 1725, 1679, 1650, 1560, 1508, 1427, 1361, 1297, 1272, 1234 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.75 (s, 3H, C–Me), 3.36 (s, 3H, N–Me), 3.48 (s, 3H, N–Me). ^{13}C NMR ($CDCl_3$): δ 13.2, 28.0, 30.3, 99.8, 151.0, 157.5, 157.9, 174.6.

4.1.16. 3-Cyclopropyl -5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (11c). Yield 54%, white needles, mp120–121°C (MeOH). IR (KBr): 1727, 1691, 1639, 1519, 1427, 1280, 1020 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29–1.33 (m, 2H, CH_2), 1.42–1.45 (m, 2H, CH_2), 2.67–2.71 (m, 1H, C–CH–C), 3.36 (s, 3H, N–Me), 3.46 (s, 3H, N–Me). MS: *m/z* (%) 221 (M^+, 70), 164 (14), 136 (8), 107 (8), 69 (100). Anal. calcd for $C_{10}H_{11}N_3O_3$ (221.21): C, 54.29; H, 5.01; N, 19.00. Found: C, 54.17; H, 4.98; N, 18.95.

4.1.17. 5,7-Dimethyl-3-phenylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (11d). Yield 78%, yellow needles, mp 197–198°C (MeOH) (lit.[22] mp 197–198°C). IR (KBr): 3062, 1716, 1671, 1616, 1475, 1425, 1371, 1056 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.43 (s, 3H, N–Me), 3.55 (s, 3H, N–Me), 7.53–7.59 (m, 3H, ArH), 8.49–8.51 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 28.6, 30.5, 98.2, 125.5, 128.5, 128.6, 128.9, 132.8, 150.7, 157.2, 158.7, 172.4.

4.1.18. 5,7-Dimethyl-3-(phenylamino)isoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (11e). Yield. 18%, yellow

powder, mp 235–236°C (MeOH). IR (KBr): 3355, 2927, 1714, 1644, 1596, 1548, 1486, 1446, 1361, 1290 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.34 (s, 3H, N–Me), 3.43 (s, 3H, N–Me), 7.20–7.42 (m, 5H, ArH), 8.19 (s, 1H, NH) MS: *m/z* (%) 272 (M^+, 100), 243 (6), 215 (18). Anal. calcd for $C_{13}H_{12}N_4O_3$ (272.26): C, 57.35; H, 4.44; N, 20.58. Found: C, 57.15; H, 4.53; N, 20.15.

4.1.19. 5,7-Dimethyl-3-(methylamino)isothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (12a): typical procedure. A mixture of **7a** (339 mg, 1.0 mmol) and methyl isothiocyanate (220 mg, 3.0 mmol) in toluene (3 mL) was refluxed for 14 h and then the solvent was removed under reduced pressure. The resultant residue was chromatographed (silica gel, $CHCl_3$–AcOEt=1:1 as eluent) to give **12a** (133 mg, 59%), mp 196–197°C (MeOH). IR (KBr): 3342, 2950, 1702, 1646, 1592, 1544, 1508, 1452, 1417, 1268 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.06 (d, *J*=5.2 Hz, 3H, NH–Me), 3.34 (s, 3H, N–Me), 3.52 (s, 3H, N–Me), 7.40 (br s, 1H, NH) MS: *m/z* (%) 226 (M^+,100), 198 (24), 169 (8), 141 (16), 112 (18). Anal. calcd for $C_8H_{10}N_4O_2S$ (226.26): C, 42.47; H, 4.45; N, 24.76. Found: C, 42.27; H, 4.39; N, 24.89.

4.1.20. 3-Benzylamino-5,7-dimethylisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (12b). Yield 52%, white needles, mp 170–171°C (MeOH). IR (KBr): 3338, 1695, 1643, 1592, 1542, 1509, 1446, 1243, 1105, 1066 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.33 (s, 3H, N–Me), 3.50 (s, 3H, N–Me), 4.43 (d, *J*=5.6 Hz, 2H, N–CH_2–), 7.26–7.48 (m, 5H, ArH), 7.89 (br s, 1H, N–H). MS: *m/z* (%) 302 (M^+, 23), 224 (4), 91 (100). Anal. calcd for $C_{14}H_{14}N_4O_2S$ (302.35): C, 55.61; H, 4.67; N, 18.53. Found: C, 55.71; H, 4.65; N, 18.60.

4.1.21. 5,7-Dimethyl-3-(phenylamino)isothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (12c). Yield 76%, white needles, mp 180–181°C (MeOH). IR (KBr): 3280, 1698, 1643, 1571, 1519, 1461, 1442, 1349, 1276 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.39 (s, 3H, N–Me), 3.56 (s, 3H, N–Me), 7.13–7.46 (m, 5H, ArH), 9.90 (s, 1H, N–H). MS: *m/z* (%) 288 (M^+, 100), 230 (34), 202 (9), 174 (8), 144 (20). Anal. calcd for $C_{13}H_{12}N_4O_2S$ (288.33): C, 54.15; H, 4.19; N, 19.43. Found: C, 54.31; H, 4.21; N, 19.53.

4.1.22. 5,7-Dimethyl-3-(*p*-tolylamino)isothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (12d). Yield 70%, white powder, mp 192–193°C (MeOH). IR (KBr): 3264, 2921, 1700, 1650, 1600, 1577, 1513, 1459, 1344, 1276 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.36 (s, 3H, Me), 3.39 (s, 3H, N–Me), 3.55 (s, 3H, N–Me), 7.05 (d, *J*=8.8 Hz, 2H, ArH), 7.24 (d, *J*=8.8 Hz, 2H, ArH), 9.78 (s, 1H, NH). MS: *m/z* (%) 302 (M^+, 100), 274 (4), 244 (18), 216 (12), 91 (24). Anal. calcd for $C_{14}H_{14}N_4O_2S$ (302.35): C, 55.61; H, 4.67; N, 18.53. Found: C, 55.69; H, 4.87; N, 18.66.

4.1.23. 3-(*p*-Chlorophenyl)amino-5,7-dimethylisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (12e). Yield 73%, white powder, mp 251–252°C (MeOH). IR (KBr): 3261, 1706, 1656, 1600, 1577, 1515, 1455, 1272, 1099 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.23 (s, 3H, N–Me), 3.39 (s, 3H, N–Me), 7.41 (d, *J*=9.2 Hz, 2H, ArH), 7.52 (d, *J*=9.2 Hz, 2H, ArH), 10.19 (s, 1H, NH). MS: *m/z* (%) 324 (M^++2, 36), 322 (M^+, 100), 264 (17), 236 (6), 208 (6), 178 (8), 111 (11). Anal. calcd for $C_{13}H_{11}ClN_4O_2S$ (322.77): C, 48.37; H, 3.44; N, 17.36. Found: C, 48.30; H, 3.66; N, 17.48.

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