

**SYNTHESIS OF 3-ALKYL-5,6-DIPHENYLPYRIMIDINE-2,4-DIONES
FROM *N*-CARBAMOYLSULFILIMINES AND
DIPHENYLCYCLOPROPENONE**

Masahiko Takahashi,* Yuhsuke Kadowaki, Yasuo Uno, and Yoshiharu Nakano†

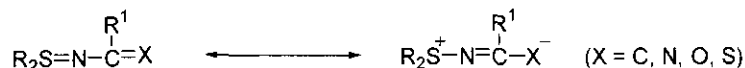
Department of Materials Science, Faculty of Engineering, Ibaraki University, Hitachi,
Ibaraki 316-8511, Japan

E-mail: takamasa@hcs.ibaraki.ac.jp

† Faculty of Science, Ibaraki University, Mito, Ibaraki 310-8512, Japan

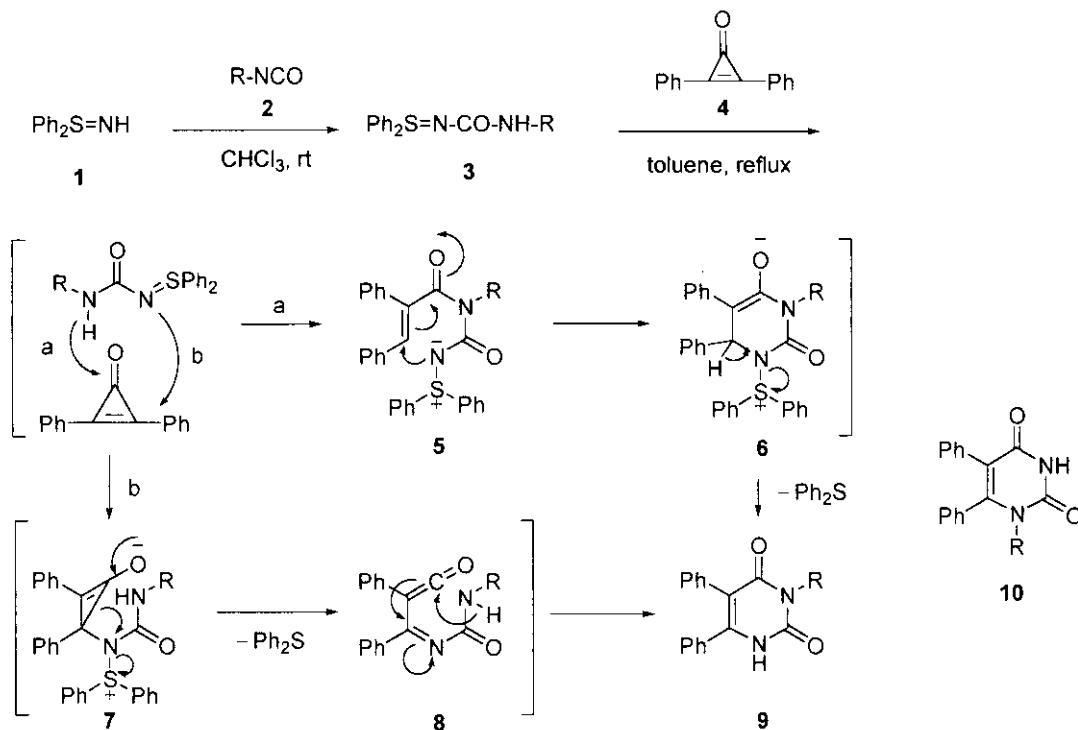
Abstract - 3-Alkyl-5,6-diphenylpyrimidine-2,4-diones (uracil derivatives) have been prepared in moderate to good yields from *N*-carbamoysulfilimines and diphenylcyclopropenone in one step. The alkyl group was regioselectively introduced into to the N-3 position of the pyrimidine ring.

Sulfilimines (or sulfimides) are a well-known class of sulfur ylides,¹ and their *N*-functionalized derivatives are especially useful for the synthesis of heterocycles. These functionalized sulfilimines are classified as *N*-aryl or olefinic sulfilimines ($R_2S=N-CR^1=CR^2R^3$),² *N*-imidoylsulfilimines ($R_2S=N-CR^1=NR^2$),³ *N*-acylsulfilimines ($R_2S=N-CR^1=O$),⁴ and *N*-thioacylsulfilimines ($R_2S=N-CR^1=S$).⁵ These sulfilimines, as shown below, have a nucleophilic center (X) and



a sulfonium group as a good-leaving group. As a result, they serve as a building block for the introduction of the $N=C-X$ moiety into heterocycles. On the other hand, *N*-carbamoysulfilimines (**3**) have two nucleophilic nitrogens and a leaving sulfonium group, suggesting that they are useful reagents for the introduction of a urea unit ($NH-CO-NR$) into heterocycles. Our interest in the synthesis of heterocycles using sulfur ylides⁶ led us to study the reactivities of **3**,

from which we found a new route to pyrimidine-2,4-diones (uracils) (Scheme 1). Uracils are one of the biologically most important class of heterocycles and many synthetic methods have been reported.⁷



Scheme 1

Treatment of sulfilimine⁸ (**1**) with alkyl isocyanates (**2**) in chloroform at room temperature gave *N*-carbamoylsulfilimines (**3**) in 57-92% yields (Table 1). However, the reaction with aryl isocyanates did not proceed smoothly, and the corresponding urea derivatives were sometimes formed. The product (**3a**, $\text{R}=\text{H}$) was prepared using trimethylsilyl isocyanate. The reaction of **3** with diphenylcyclopropanone (**4**)⁹ was carried out in refluxing toluene and, as expected, resulted in the formation of 3-alkyl-5,6-diphenylpyrimidine-2,4-diones (**9**) or isomeric 1-alkyl-5,6-diphenylpyrimidine-2,4-diones (**10**) in 51-94% yields (Table 1). Since it was difficult to distinguish clearly between the two isomeric structures (**9**) and (**10**) on the basis of the spectral data, X-ray structural analysis was performed using the product obtained from **3d**, and the results apparently showed that the condensation product is 3-butylpyrimidine-2,4-dione (**9d**), not 1-butylpyrimidine-2,4-dione (**10d**) (Figure 1).¹⁰ The reaction pathway is considered to be that shown in Scheme 1.¹¹ The nitrogen atom substituted by the alkyl group (R) would attack at the carbonyl group of **4** (path a) to give the ring-opened intermediates (**5**), which is cyclized by Michael addition, giving the second intermediates (**6**). Elimination of diphenyl sulfide from **6** would give the final products (**9**). An alternative

route is also possible, where the ylide nitrogen would attack at the C-2 position of **4** (path b) to give the adduct (**7**). Extrusion of diphenyl sulfide from **7** followed by cyclization of the resulting ketene intermediate (**8**) would form the product (**9**). The regioselective *N*-alkylation of pyrimidine-2,4-diones by alkylating agents was reported to be sometimes troublesome, and also the unambiguous synthesis of *N*-alkylated pyrimidine-2,4-diones from *N*-alkylated starting materials is rather limited.^{7,12} Thus, we have shown a new one-step synthesis of pyrimidine-2,4-dione (uracil) derivatives from *N*-carbamoylsulfilimines (**3**) and diphenylcyclopropenone (**4**), where the alkyl group is regioselectively introduced into the N-3 position.

Table 1. Products (3**) and (**9**)**

R	3	Yield	mp	9	Yield	mp
		(%)	(°C)		(%)	(°C)
H	a	73	232 - 233	a	55	301 - 303
Propyl	b	68	87 - 88	b	51	201 - 202
Isopropyl	c	86	120 - 121	c	83	240 - 242
Butyl	d	57	73 - 74	d	94	181 - 182
Cyclohexyl	e	82	151 - 152	e	71	268 - 269
Benzyl	f	92	158 - 159	f	76	218 - 219

Typical experimental procedure:

N-Butylcarbamoyl-*S,S*-diphenylsulfilimine (**3d**) To a stirred solution of **1**⁸ (1.28 g, 6.4 mmol) in CHCl₃ (10 mL) was added butyl isocyanate (0.74 mL, 6.7 mmol) dropwise. After stirring at rt for 3 h, the solvent was removed to give oil, which was solidified by adding ethyl acetate-hexane. The precipitates were collected by filtration to give **3d** (1.09 g, 57% yield), colorless needles, mp 73-74 °C (ethyl acetate). IR (KBr): 3375, 2950, 1590, 1500, 1260 cm⁻¹. ¹H-NMR (CDCl₃): δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.32 - 1.41 (m, 2H), 1.46 - 1.53 (m, 2H), 3.26 (br s, 2H),

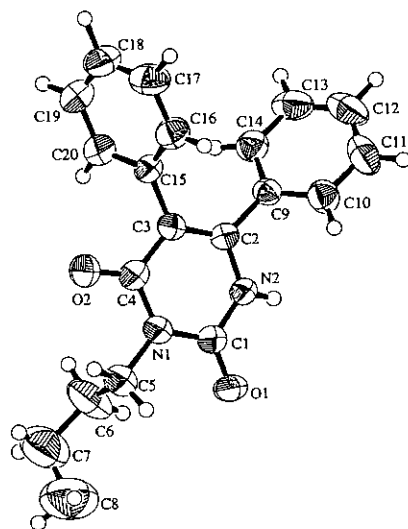


Figure 1

4.95 (br s, 1H), 7.43-7.70 (m, 10 H). MS: m/z (%) 300 (M^+ , 15), 228 (52), 201 (12), 186 (100). Anal. Calcd for $C_{17}H_{20}N_2OS$: C, 67.96; H, 6.71; N, 9.33. Found: C, 68.08; H, 6.77; N, 9.49.

3-Butyl-5,6-diphenyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (9d) A mixture of **3d** (301 mg, 1.0 mmol) and **4** (200 mg, 1.0 mmol) in toluene (5 mL) was refluxed for 13 h. After removal of the solvent, the solid residue was recrystallized from $CHCl_3$ to give **9d** (293 mg, 94% yield), white needles, mp 181-182 °C. IR (KBr): 3100, 2995, 1700, 1640, 1455 cm^{-1} . 1H -NMR ($CDCl_3$): δ 0.94 (t, $J=7.4$ Hz, 3H), 1.32-1.42 (m, 2H), 1.61-1.68 (m, 2H), 3.95 (t, $J=7.6$ Hz, 2H), 7.09-7.36 (m, 10H), 9.53 (br s, 1H). MS: m/z (%) 320 (M^+ , 82), 278 (51), 264 (100), 220 (60), 104 (56). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.75. Found: C, 74.96; H, 6.36; N, 8.74.

REFERENCES AND NOTES

1. A review: I. V. Koval, *Sulfur Reports*, 1993, **14**, 149.
2. Y. Tamura, K. Sumoto, H. Matsushima, H. Taniguchi, and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 4324; T. L. Gilchrist, C. J. Harris, F. D. King, M. E. Peek, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2161.
3. T. L. Gilchrist, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1964; T. L. Gilchrist, C. J. Harris, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1969; T. L. Gilchrist, C. J. Harris, D. G. Hawkins, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2166; T. Fuchigami and

- K. Odo, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1793; Y. Tomimatsu, K. Satoh, and M. Sakamoto, *Heterocycles*, 1977, **8**, 109.
4. D. M. Ketcha, M. Abou-Gharbia, F. X. Smith, and D. Swern, *Tetrahedron Lett.*, 1983, **24**, 2811.
5. H. Yoshida, H. Taketani, T. Ogata, and S. Inokawa, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3124.
6. M. Takahashi and M. Hatazaki, *Heterocycles*, 1995, **41**, 1667; E. C. Taylor, M. Takahashi, and N. Kobayashi, *Heterocycles*, 1996, **43**, 437.
7. D. J. Brown, "Comprehensive Heterocyclic Chemistry," Vol. 3, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Inc., Oxford, 1984, pp. 57 – 155.
8. T. Yoshimura, T. Omote, N. Furukawa, and S. Oae, *J. Org. Chem.*, 1976, **41**, 1728.
9. Synthesis of heterocycles from diphenylcyclopropenone is summarized: N. Abe, T. Murafuji, Y. Sugihara, and A. Kakehi, *Heterocycles*, 1995, **41**, 2289.
10. Crystal data for 91260 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): δ 0.91 (t, $J = 7.4\text{ Hz}$, 3H), 1.32 – 1.41 (m, 2H), 1.46 – 1.53 (m, 2H), 3.26 (br s, 2H), **d**: $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2$, $M = 320.39$, monoclinic, space group C2/c (#15), $a = 18.970$ (8), $b = 7.159$ (7), $c = 26.442$ (6) Å, $\beta = 104.27$ (2)°, $V = 3480$ (3) Å³, $Z = 8$, $D_c = 1.223\text{ g cm}^{-3}$, $\mu(\text{MoK}\alpha) 0.80\text{ cm}^{-1}$, $F(000) = 1360.00$. A colorless prism of dimensions 0.10 x 0.43 x 0.47 mm obtained from a solution of CHCl_3 - hexane was used. Data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo-K α radiation, $\lambda = 0.71069\text{ Å}$. Reflection measured: 4956; number of unique reflections ($R_{\text{int}} = 0.025$): 4838. The structure was solved by direct method and all the non-hydrogen atoms were refined anisotropically by full matrix least squares to give $R = 0.052$, $R_w = 0.051$ for 1645 observed reflections ($I > 3.00\sigma(I)$).
11. Y. Hayasi and H. Nozaki, *Tetrahedron*, 1971, **27**, 3085; T. L. Gilchrist, C. J. Harris, and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1974, 487.
12. D. J. Brown, "The Chemistry of Heterocyclic Compounds," Vol. 16, ed. by A. Weissberger, Interscience Publishers, Inc., New York, 1962, pp. 31-115 and pp. 356-388.

Received, 4th June, 1999