SYNTHESIS OF 3-ALKYL-5,6-DIPHENYL-PYRIMIDINE-2,4-DIONES FROM N-CARbamoylsulfilimines AND DIPHENYLCYCLOPROPENONE

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Abstract - 3-Alkyl-5,6-diphenylpyrimidine-2,4-diones (uracil derivatives) have been prepared in moderate to good yields from N-carbamoylsulfilimines and diphenylcyclopropenone in one step. The alkyl group was regioselectively introduced into 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 (RS=N=CR'=CR'2R';)2 N-imidoylsulfilimines (RS=N=CR'=NR2);3 N-acylsulfilimines (RS=N=CR'=O),4 and N-thioacylsulfilimines (RS=N=CR'=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-carbamoylsulfilimines (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.\(^1\)

\[
\begin{align*}
\text{Ph}_2S=\text{NH} & \overset{\text{R-NCO}}{\underset{\text{CHCl}_3, \text{rt}}{\rightleftharpoons}} \text{Ph}_2S=\text{N-CO-NH-R} \\
\text{Ph} & \overset{\text{4}}{\underset{\text{toluene, reflux}}{\rightleftharpoons}} \text{Ph}
\end{align*}
\]

Scheme 1

Treatment of sulfilimine (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, R=H) was prepared using trimethylsilyl isocyanate. The reaction of 3 with diphenylcyclopropenone (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. 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)

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

**Typical experimental procedure:**

N-Butylcarbamoyl-S,S-diphenylsulfilimine (3d) To a stirred solution of 1 (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),
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 C₁₇H₂₆N₂O₂: C, 74.97; H, 6.29; N, 8.75. Found: C, 74.96; H, 6.36; N, 8.74.

**REFERENCES AND NOTES**


10. *Crystal data for 91260 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), d: C₆H₆N₂O₂, M = 320.39, monoclinic, space group C2/c (#15), a = 18.970 (8), b = 7.159 (7), c = 26.442 (6) Å, β = 104.27 (2)°, V = 3480 (3) Å³, Z = 8, Dc = 1.223 g cm⁻³, μ(MoKα) 0.80 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 CHCl₃ - hexane was used. Data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Mo-Kα radiation , λ = 0.71069 Å. Reflection measured: 4956; number of unique reflections (Rint = 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, Rw = 0.051 for 1645 observed reflections (I>3.0σ(I)).


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