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A NOVEL AND CONVENIENT SYNTHESIS OF 1,3,5-TRIAZINE-2,4(*1H,3H*)-DIONES

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Abstract - Several 1,3,5-triazine-2,4(*1H,3H*)-diones (**1** - **5**) were newly synthesized by the reaction of *N*-substituted thiocarboamides with silver cyanate. The structure was confirmed by the X-Ray structure analysis, and the pathway affording them was estimated.

It has been reported that some 1,3,5-triazine-2,4(*1H,3H*)-dione derivatives have some pharmaceutical activities such as 5-HT_2 antagonist,[1] herbicidal,[2,3] and antitumour activity.[4] Since the 1,3,5-triazine-2,4(*1H,3H*)-dione ring is regarded as an aza-analog of uracil, they are expected to have various biofunctionalities further. However, they are exclusively synthesized by the reaction of *N*-substituted amidines with chlorocarbonyl isocyanate,[5] diphenyl iminodicarboxylate,[6] or phenoxycarbonyl isocyanate,[1,7] and so many their derivatives have not been known. Meanwhile, we have been developing the organic synthesis through desulfurization of various thiocarbonyl compounds by silver salt.[8-12] In our serial studies, here we wish to report on the convenient and novel synthetic method of 1,3,5-triazine-2,4(*1H,3H*)-diones through the desulfurization of thiocarboamides, such as 1,3-disubstituted 2-thioureas, trisubstituted thioureas, and *N*-substituted thioamides by silver cyanate.

We at first examined the reaction of 1,3-diphenyl-2-thiourea with silver cyanate under an ambient condition, and obtained product (**1**) in 76% yield with liberating silver sulfide. The structure of **1** was unequivocally established by a single crystal X-Ray diffraction structure analysis.[13] An ORTEP drawing was given as shown in Figure 1, and **1** was identified to be 6-anilino-1-phenyl-1,3,5-triazine-2,4(*1H,3H*)-dione.

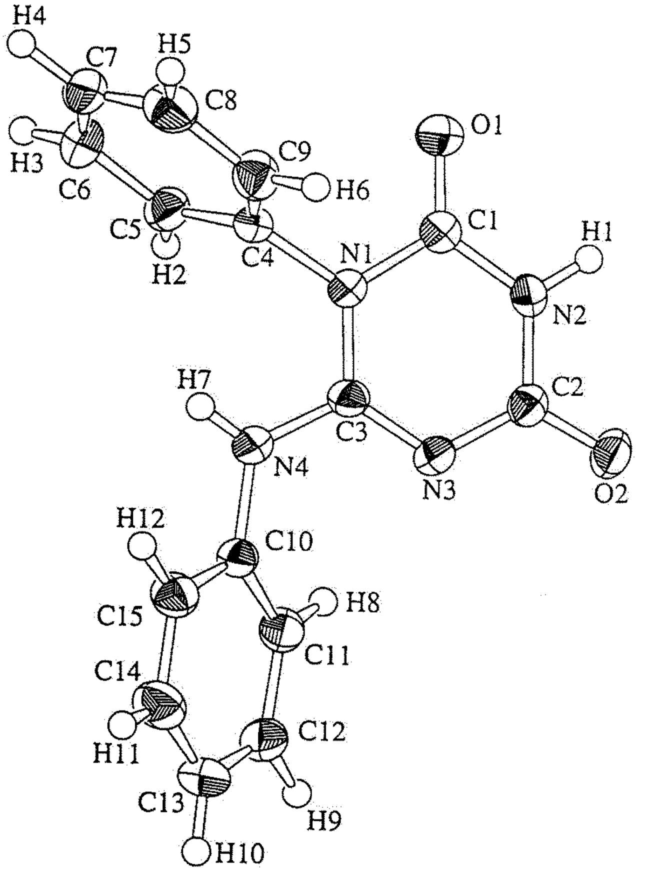
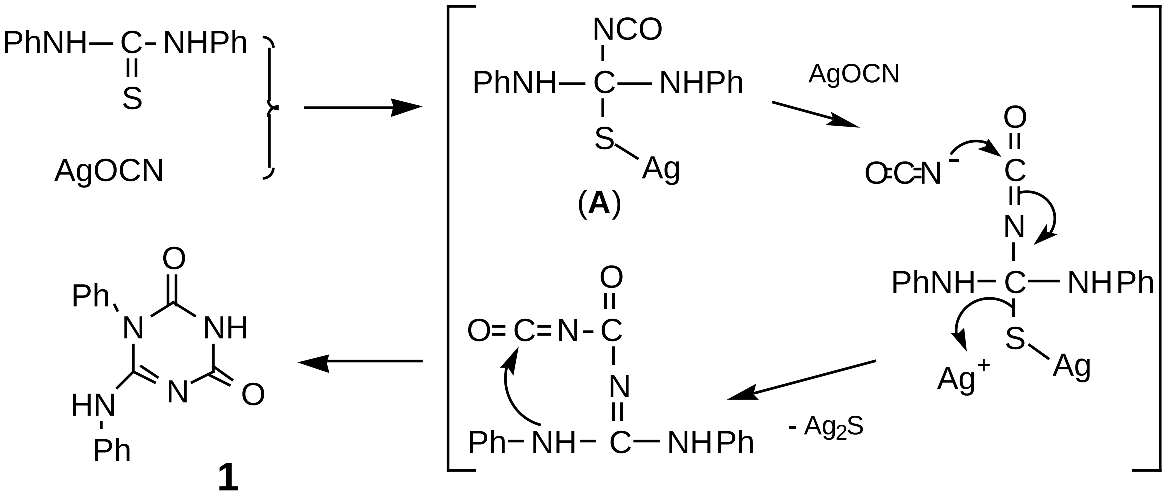


Figure 1. The ORTEP drawing of the molecular structure of **1** as 50% probability ellipsoids.

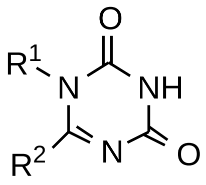
Selected bond length (Å): O(1)-C(1) 1.208(3), O(2)-C(2) 1.226(2), N(1)-C(1) 1.398(3), N(1)-C(3) 1.384(3), N(1)-C(4) 1.448(3), N(2)-C(1) 1.365(3), N(2)-C(2) 1.385(3), N(3)-C(2) 1.358(3), N(3)-C(3) 1.307(3), N(4)-C(3) 1.348(3), N(4)-C(10) 1.426(3).

Selected bond angles (°): C(1)-N(1)-C(3) 120.4(2), C(1)-N(1)-C(4) 116.4(2), C(3)-N(1)-C(4) 123.1(2), C(1)-N(2)-C(2) 124.7(2), C(2)-N(3)-C(3) 118.8(2), C(3)-N(4)-C(10) 124.7(2), O(1)-C(1)-N(1) 121.9(2), O(1)-C(1)-N(2) 124.4(2), N(1)-C(1)-N(2) 113.6(2), O(2)-C(2)-N(2) 118.9(2), O(2)-C(2)-N(3) 122.5(2), N(2)-C(2)-N(3) 118.5(2), N(1)-C(3)-N(3) 123.4(2), N(1)-C(3)-N(4) 116.2(2), N(3)-C(3)-N(4) 120.4(2).



Scheme 1

From the result of the crystallography, a plausible pathway affording **1** is estimated as shown in Scheme 1. 1,3-Diphenyl-2-thiourea and silver cyanate form the 1:1 adduct (**A**). **A** is subjected to attack of another silver cyanate, and cyclizes immediately together with elimination of silver sulfide to give **1**. Various 1,3,5-triazine-2,4(*1H*,*3H*)-diones (**2** - **5**) were similarly obtained in good yields by treatment with the corresponding thiocarboamides.



2〜5

2 : R^1 = Ph, R^2 = Ph
3 : R^1 = Ph, R^2 = $4-ClC_6H_4$
4 : R^1 = $4-ClC_6H_4$, R^2 = Morpholino
5 : R^1 = $4-CH_3C_6H_4$, R^2 = 9-Xanthenyl

It was thus found that through the desulfurization-cyclization of thiocarboamides with silver cyanate a number of 1,3,5-triazine-2,4(*1H*, *3H*)-diones, *so-called* 5-aza uracils, are conveniently synthesized. It is believed that this synthetic method contributes to researching various bioactive functionalities, and an attempt to synthsize *N*-glycosyl derivatives of the aza-uracil is under way.

EXPERIMENTAL

Materials. Silver cyanate, 1,3-diphenylthiourea, and thiobenzanilide were purchased from the usual suppliers. 4-chlorothiobenzanilide and 9-xanthenylthiocarbo-4'-toluide were prepared by treating the corresponding amide with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson Reagent), respectively.[14] 4-Morpholinylthiocarbo-4'-chloroanilide was obtained by the reation of morpholine with 4-chlorophenylisothiocyanate.[15]

General procedure of synthesizing 1,6-disubstituted 1,3,5-triazine-2,4(*1H*,*3H*)-diones.

To a solution of a thiocarboamide (1.2 mmol) and triethylamine (240 mg, 2.4 mmol) in acetonitrile (5 mL) silver cyanate (360 mg, 2.4 mmol) was added by bits with stirring, and the reaction mixture was heated to reflux for 1 h. After removal of silver sulfide by filtration, organic layer was passed through on a silica gel column (Merk silica gel 60, ethyl acetate), and evaporated under reduced pressure. The resulting products were recrystallized from ethanol to give white powder of **1 - 5**. Their yields (based on thiocarboamide), mps, analytical results, and spectral data (IR, ^{1}H and ^{13}C NMR) are shown below.

6-Anilino-1-phenyl-1,3,5-triazine-2,4(*1H*,*3H*)-dione (1).

Yield 76%; mp 246 °C. ^{1}H NMR δ =7.15-7.58 (10H, *m*), 8.27 (1H, *s*), 11.02 (1H, *s*); ^{13}C NMR δ = 125.61, 128.26, 129.79, 129.93, 133.52, 137.26, 150.79, 154.80; IR ν 3244 (N-H), 3155 (N-H), 1732 (C=O), 1698 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.18; H, 4.30; N, 19.93.

1,6-Diphenyl-1,3,5-triazine-2,4(*1H*,*3H*)-dione (2).

Yield 85%; mp 236 °C. ^{1}H NMR δ = 7.19-7.35 (10H, *m*), 11.84 (1H, br *s*); ^{13}C NMR δ = 127.97, 128.74, 128.87, 129.00, 129.77, 130.45, 133. 90, 136.56, 151.05, 155.52, 166.01; IR ν 3045 (N-H), 1747 (C=O), 1699 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.01; H, 4.22; N, 15.75.

6-(4'-Chlorophenyl)-1-phenyl-1,3,5-triazine-2,4(*1H,3H*)-dione (**3**).

Yield 78%; mp 225 °C. ^{1}H NMR δ= 7.28-7.37 (9H, *m*), 11.80 (1H, br *s*); ^{13}C NMR δ = 127.94, 128.91, 129.49, 130.56, 132.52, 135.16, 136.14, 150.72, 155.21, 164.85; IR ν 3173 (N-H), 3052 (N-H), 1736 (C=O), 1694 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_3O_2Cl$: C, 60.11; H, 3.36; N, 14.02. Found: C, 60.02; H, 3.34; N, 13.86.

1-(4'-Chlorophenyl)-6-morpholino-1,3,5-triazine-2,4(*1H,3H*)-dione (**4**).

Yield 89%; mp 227 °C. ^{1}H NMR δ = 3.11-3.15 (4H, *m*), 3.38 - 3.41 (4H, *m*), 7.48 - 759 (4H, *m*); ^{13}C NMR δ = 47.78, 65.14, 129.16, 130.41, 135.62, 151.22, 154.30, 158.73; IR ν 3225 (N-H), 3059 (N-H), 1730 (C=O), 1699 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_4O_3Cl$: C, 50.58; H, 4.24; N, 18.15. Found: C, 50.61; H, 4.21; N, 17.99.

1-(4''-Tolyl)-6-(9'-xanthenyl)-1,3,5-triazine-2,4(*1H,3H*)-dione (**5**).

Yield 46%; mp 248 °C. ^{1}H NMR δ = 2.33 (3H, *s*), 5.67 (1H, *s*), 6.21-7.27 (12H, *m*), 9.11 (1H, br *s*); ^{13}C NMR δ = 21.28, 45.95, 117.19, 117.35, 123.57, 128.17, 128.55, 129.83, 129.96, 130.02, 139.99, 150.98, 154.98, 169.10; IR ν 3140 (N-H), 3032, 2825, 1753 (C=O), 1682 (C=O), 1576, 1261 (C-O) cm^{-1}. Anal. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found; C, 72.10; H, 4.45; N, 10.94.

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13. X-Ray structure analysis of product (**1**). A colorless transparent block crystal with dimensions of 0.60 x 0.43 x 0.27 mm^3 was used. Data collection was carried out using a Nonius CAD4 diffractometer with graphite-monochromated Mo$K\alpha$ radiation. Crystal data: $C_{15}H_{12}N_4O_2$, FW = 280.29, orthorhombic, space group $P2_12_12_1$, a = 7.0840(4), b = 9.881(1), c = 18.843(1) Å, V = 1318.9(2) $Å^3$, Z = 4, D_c = 1.41 gcm^{-3}, μ = 1.0 cm^{-1}. Intensity data $3° \leq 2\theta \leq 60°$ with ω-scans. Corrections for the Lorentz and polarization factors, and an empirical absorption correction using ψ-scans. No decay correction. Of the 2579 collected reflections, 2225 were unique and 1747($I > 1.0\sigma(I)$) were used. The structure was solved by a direct method (SAPI91). All the hydrogen atoms were located using difference Fourier maps. The refinement was carried out by full-matrix least-squares on F with anisotropic thermal parameters for the non-H atoms and isotropic ones for the H-atoms (R = 0.041, Rw = 0.048, $w = 1/[\sigma^2(F_o) + 0.0009F_o^2]$, S = 1.13). All the calculations were performed on a Hewlett Packard 9000-715/100 with Molecular Structure Corporation TEXSAN.
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