

Thiazolotriazine and Imidazothiadiazine Syntheses

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Received June 12, 1972

Previously, we reported (3) the results of allowing tetrahydro-*as*-triazine-3(2*H*)thiones to react with α,β -difunctional compounds. This paper reports additional syntheses involving triazinethiones and also a method for the synthesis of imidazothiadiazines.

Allowing 1,4,5,6-tetrahydro-1-methyl-*as*-triazine-3(2*H*)-thione (I) to react with 2-bromo-1-indanone in refluxing ethanol yielded, after five minutes, 2,3-dihydro-3-methyl-1*H*,6*H*-indeno[1',2':4,5]thiazolo[2,3-*c*][1,2,4]triazin-10*b*-(5*aH*)ol hydrobromide (II), and after four hours gave 10*b*-ethoxy-2,3,5*a*,10*b*-tetrahydro-3-methyl-1*H*,6*H*-indeno[1',2':4,5]thiazolo[2,3-*c*][1,2,4]triazine (III). This is the first example of the condensation of I with an α -haloketone which gave a hydroxy and an ethoxy containing product. In all other cases (3) only the dehydrated product was obtained. For example, condensation of I with phenacyl bromide and desyl bromide gave 3,4-dihydro-2-methyl-6-phenyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazine hydrobromide (IV) and 3,4-dihydro-2-methyl-6,7-diphenyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazine hydrobromide (V), respectively. Hydroxy compound II is resistant to dehydration because the H at 5*a* and the OH at 10*b* are in a *cis* orientation. This also accounts for prolonged heating resulting in the replacement of hydroxy by ethoxy rather than dehydration.

We have investigated Knoevenagel-type condensations between the active methylene containing heterocycle 3,4-dihydro-2-methyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazin-6(7*H*)one (VI) and various aromatic aldehydes, such as 3,4-dichlorobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, indole-3-carboxaldehyde, and 2-, 3-, and 4-pyridinecarboxaldehyde. In all cases the expected ylidene product (VII*a-f*) was obtained. However, with 3,4-dichlorobenzaldehyde and 3,4,5-trimethoxybenzaldehyde besides the ylidene product, the non-dehydrated α -hydroxybenzyl compound (VIII*a,b*) was also isolated. This difference may be due to the fact that the 3,4-dichlorobenzaldehyde and 3,4,5-trimethoxybenzaldehyde reaction times were much shorter.

The rate of dehydration of the α -hydroxybenzyl compounds is slow due to intramolecular hydrogen bonding, which should be quite strong since the participating

atoms are amide oxygen and hydroxyl and a six-membered ring is formed. α -Hydroxybenzyl compound (VIII*b*) was dehydrated to the ylidene compound VIII*b* in refluxing benzene in the presence of *p*-toluenesulfonic acid.

2-Amino-5,6-dihydro-4,6-dimethyl-4*H*-1,3,4-thiadiazine (IX) is readily prepared by a published procedure (4) consisting essentially of ring opening of propylene sulfide with methylhydrazine to give 1-(1-methylhydrazino)-2-propanethiol which is then treated with cyanogen bromide to give IX. We were interested in determining whether or not aminothiadiazine IX would condense with α,β -difunctional compounds to afford imidazothiadiazines in a manner similar to the condensation of triazinethione I with α,β -difunctional compounds to yield thiazolotriazines. This indeed was the case as evidenced by the fact that allowing aminothiadiazine IX to react with desyl bromide in refluxing ethanol afforded a 24% yield of 3,4-dihydro-2,4-dimethyl-6,7-diphenyl-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine hydrobromide (X).

EXPERIMENTAL

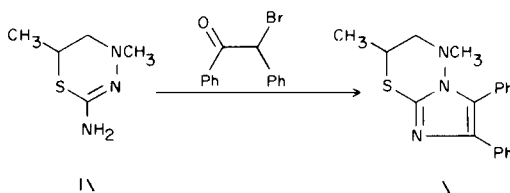
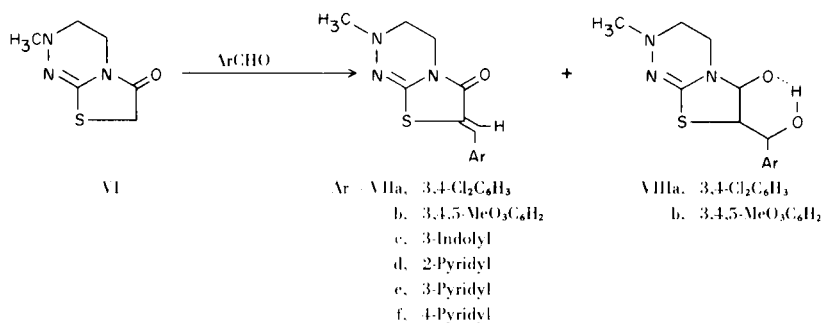
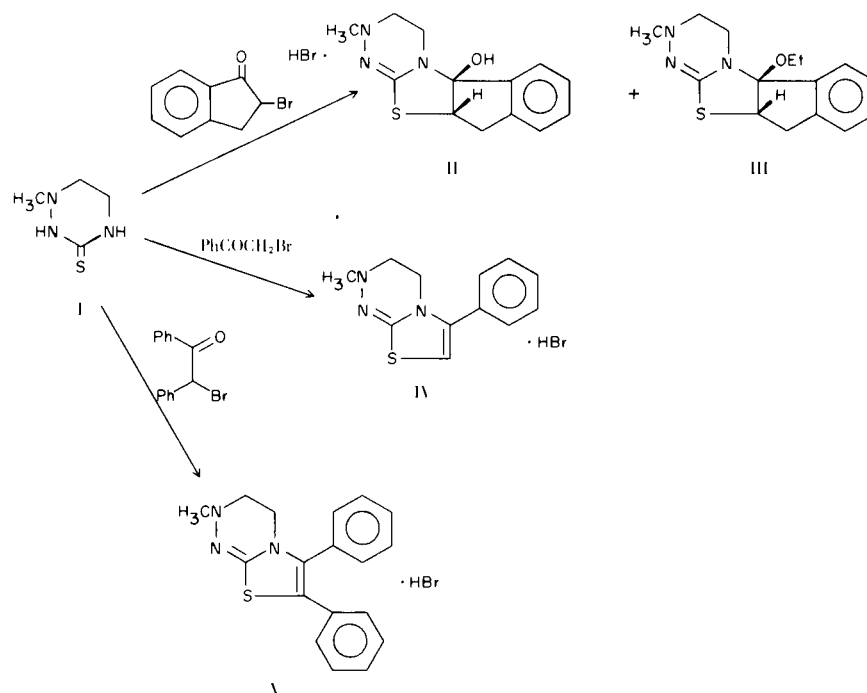
The melting points were obtained in a capillary tube with the Thomas-Hoover Uni-Melt and are uncorrected. The elemental analyses were done by Midwest Microlabs, Inc., Indianapolis, Indiana. The pmr spectra were obtained with a Varian A-60 using TMS as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 337 grating spectrophotometer.

Condensation of Triazinethione I and 2-Bromo-1-indanone.

To a gently refluxing suspension of 23 g. (0.17 mole) triazinethione I in 250 ml. of 95% ethanol was added a warm solution of 37 g. (0.17 mole) 2-bromo-1-indanone. Within 5 minutes the solution turned dark green. One-half of the solution was removed and the remainder was heated under reflux for 4 hours. The aliquot that was removed was evaporated *in vacuo* at 40°. Three recrystallizations of the residual solid from water (followed by a cold acetone wash in each case) gave 11 g. (37%) of 2,3-dihydro-3-methyl-1*H*,6*H*-indeno[1',2':4,5]thiazolo[2,3-*c*][1,2,4]triazin-10*b*-(5*aH*)ol hydrobromide (II) as a white crystalline solid, m.p. 235° dec.; ir (nujol) 3445, 3142, 3028 (OH), 1610 (C=N) cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{OS}\cdot\text{HBr}$: C, 45.62; H, 4.71; Br, 23.35; N, 12.27; S, 9.37. Found: C, 45.33; H, 4.71; Br, 23.65; N, 12.33; S, 9.15.

The remaining one-half of the solution which was heated at reflux for 4 hours was concentrated *in vacuo* and the residue was



treated with sodium carbonate solution and extracted with chloroform. The washed (water) and dried (magnesium sulfate) chloroform extract was evaporated to dryness *in vacuo* to give 27 g. of greenish-blue oil. This oil was chromatographed on 1000 g. of alumina (Baker 0537) using chloroform as eluant to give 13.2 g. of yellow oil which crystallized upon standing. The solid was recrystallized twice from chloroform-*n*-pentane to give 7.2 g. (30%) of 10b-ethoxy-2,3,5a,10b-tetrahydro-3-methyl-1*H*,6*H*-indeno[1',2':4,5]thiazolo[2,3-*c*][1,2,4]triazine (III), m.p. 126-127°; ir (nujol) 1612 (C=N) cm⁻¹; pmr (deuteriochloroform) δ 1.23 (t, J = 7.0 Hz, 3H, CH₃CH₂), 2.7 (s, NCH₃), 2.7-4.25

(multiplets, 9H), 7.1-7.5 (m, 4H).

Anal. Calcd. for C₁₅H₁₉N₃OS: C, 62.25; H, 6.61; N, 14.52; S, 11.07. Found: C, 62.48; H, 6.65; N, 14.81; S, 10.97.

7-(3,4-Dichlorobenzylidene)-3,4-dihydro-2-methyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazin-6(7*H*)one (VIIa) and 3,4-Dihydro-7-(α -hydroxy-3,4-dichlorobenzyl)-2-methyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazin-6(7*H*)one (VIIIa).

A mixture of 10 g. (0.058 mole) of 3,4-dihydro-2-methyl-2*H*-thiazolo[2,3-*c*][1,2,4]triazin-6(7*H*)one (VI), 10 g. (0.058 mole) of 3,4-dichlorobenzaldehyde, 2 ml. of piperidine, and 100 ml. of

95% ethanol was refluxed for 45 minutes, cooled and 4 g. of orange crystals were filtered. Recrystallization (chloroform-ether) afforded 3.4 g. (26%) of benzylidene thiazolotriazinone (VIIa), m.p. 191-192°; ir (nujol) 1680, 1615, 1590 (C=O), C=N, C=C) cm^{-1} ; pmr (deuteriochloroform) δ 2.9 (s, NCH₃), 3.03 (t, 2H, J = 6 Hz), 4.0 (t, 2H, J = 6 Hz), 7.2-7.6 (m, 4H).

Anal. Calcd. for C₁₃H₁₁Cl₂N₃O₂S: C, 47.57; H, 3.37; Cl, 21.60; N, 12.80; S, 9.76. Found: C, 47.74; H, 3.56; Cl, 21.67; N, 13.00; S, 9.94.

The filtrate was evaporated *in vacuo* to give 18 g. of red viscous oil which was chromatographed on 500 g. of alumina (Baker 0537) using chloroform as the eluant to give 4 g. of unreacted thiazolotriazinone VI followed by 7.4 g. of yellow oil which solidified. The solid was recrystallized (chloroform-*n*-pentane) four times to give 3.9 g. (27%) of α -hydroxybenzyl thiazolotriazinone (VIIIa) as white crystals, m.p. 163.5-164.5°; ir (nujol) 3319 (broad, OH), 1712 (C=O), 1600 (C=N) cm^{-1} ; pmr (deuteriochloroform) δ 2.75 (s, NCH₃), 2.83 (t, 2H, J = 6 Hz), 4.37 (d, 1H, J ~ 3 Hz), 5.47 (d, 1H, J ~ 3 Hz), 7.2-7.6 (m, 3H).

Anal. Calcd. for C₁₃H₁₃Cl₂N₃O₂S: C, 45.10; H, 3.78; Cl, 20.48; N, 12.13; S, 9.26. Found: C, 45.07; H, 3.86; Cl, 20.58; N, 11.80; S, 9.11.

3,4-Dihydro-2-methyl-7-(3,4,5-trimethoxybenzylidene)-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIb) and 3,4-Dihydro-7-(α -hydroxy-3,4,5-trimethoxybenzyl)-2-methyl-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIIb).

A mixture of 10 g. (0.058 mole) of thiazolotriazinone VI, 11.5 g. (0.058 mole) of 3,4,5-trimethoxybenzaldehyde, 2 ml. of piperidine, and 100 ml. of 95% ethanol was refluxed for 3 hours, cooled, and 12 g. of yellow-orange crystals (m.p. 177-190°) was filtered. The filtrate was concentrated to give an additional 5.5 g. of yellow crystals, m.p. 170-182°. The two batches of crystals were combined and recrystallized from chloroform-ether to give a mixture of yellow prism clusters and orange needles. A small portion of these was separated "mechanically" with a tweezers and spatula and afforded yellow prisms which melted at 196-197° and orange needles which melted at 187-188°. The entire amount (15 g.) was separated by chromatography on 850 g. of alumina (Baker 0537) using chloroform-ether (1:1) as eluant. The first material eluted weighed 7.3 g. (36%), melted 185-188°, and was assigned structure of 3,4-dihydro-2-methyl-7-(3,4,5-trimethoxybenzylidene)-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIb); ir (potassium bromide) 1680, 1600, 1580, 1570, 1559 cm^{-1} (C=O, C=N, C=C); pmr (deuteriochloroform) δ 2.88 (s, NCH₃), 3.0 (t, J = ~ 5 Hz, CH₂), 3.9 (s, (CH₃O)₃), ~ 3.9 (t, CH₂), 6.73 (s, 2 aromatic H's), 7.55 (s, one vinyl H).

Anal. Calcd. for C₁₆H₁₉N₃O₄S: C, 54.99; H, 5.48; N, 12.03; S, 9.18. Found: C, 54.64; H, 5.41; N, 11.94; S, 9.39.

The second material to be eluted from the column was the light yellow colored compound (4.8 g.) which melted at 195-196.5° and was assigned the structure of 3,4-dihydro-7-(α -hydroxy-3,4,5-trimethoxybenzyl)-2-methyl-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIIb); ir (nujol) 3357 (OH, broad), 1710, 1612, 1579 cm^{-1} (C=O, C=N); pmr (deuteriochloroform) δ 2.8 (s, NCH₃), 2.9 (m, 2H, CH₂), 2.8 (m, 2H, CH₂), 3.87 (s, 3H, CH₃O), 3.90 (s, 6H, (CH₃O)₂), 4.4 (d, J ~ 3 Hz, 1H), 5.5 (d, J ~ 3 Hz, 1H), 6.7 (s, 1 aromatic H), 7.4 (s, 1 aromatic H).

Anal. Calcd. for C₁₆H₂₁N₃O₅S: C, 52.30; H, 5.76; N, 11.43; S, 8.72. Found: C, 52.35; H, 5.93; N, 11.42; S, 9.01.

Conversion of 3,4-Dihydro-7-(α -hydroxy-3,4,5-trimethoxybenzyl)-2-methyl-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIIb) to 3,4-Dihydro-2-methyl-7-(3,4,5-trimethoxybenzylidene)-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIb).

A mixture of 0.5 g. of VIIIb, 50 mg. of *p*-toluenesulfonic acid and 100 ml. of benzene in a flask with a Dean-Stark water separator attached was refluxed for 24 hours, cooled, washed (sodium carbonate-water), dried (magnesium sulfate), and evaporated *in vacuo* to afford a yellow solid which ir and tlc (silica gel-ethyl acetate) indicated was the ylidene compound (VIIb) with a trace of hydroxy compound VIIIb still present (R_f of VIIIb 0.34 and R_f of VIIb 0.56).

3,4-Dihydro-7-(indol-3-ylmethylene)-2-methyl-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIc).

A mixture of 10 g. (0.058 mole) of thiazolotriazinone VI, 8.5 g. (0.058 mole) of indole-3-carboxaldehyde, 2 ml. of piperidine, and 100 ml. of 95% ethanol was allowed to reflux for 24 hours, cooled, and 14 g. (81%) of orange crystals (m.p. 282-286° dec.) was suction filtered. Recrystallization from DMF-ether afforded 12.3 g. of orange-yellow crystals, m.p. 285-287° dec.; ir (nujol) 1680, 1612, 1588 cm^{-1} (C=O, C=N, C=C).

Anal. Calcd. for C₁₅H₁₄N₄O₂S: C, 60.38; H, 4.73; N, 18.78; S, 10.74. Found: C, 60.65; H, 4.96; N, 18.61; S, 10.87.

General Procedure for the Condensation of Thiazolotriazinone VI with 2-, 3-, and 4-Pyridinecarboxaldehydes.

A mixture of 0.5 mole of thiazolotriazinone VI, 0.5 mole of pyridinecarboxaldehyde, 2 ml. of piperidine, and 100 ml. of 95% ethanol was allowed to reflux for 40 hours, cooled, concentrated *in vacuo* to give a solid residue which was recrystallized from an appropriate solvent.

3,4-Dihydro-2-methyl-7-(2-pyridylmethylene)-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIId) was recrystallized from 2-propanol to afford 15.5 g. of orange needles, m.p. 170-171°; ir (nujol) 1715, 1612 cm^{-1} (C=O, C=N); pmr (deuteriochloroform) δ 2.86 (s, NCH₃), 2.96 (t, J = 5 Hz, CH₂), 3.91 (t, J = 5 Hz, CH₂), 7.0-7.8 (m, 4H), 8.72 (d, J = 5 Hz, 1H).

Anal. Calcd. for C₁₂H₁₂N₄O₂S: C, 55.37; H, 4.65; N, 21.52. Found: C, 55.19; H, 4.76; N, 21.45.

3,4-Dihydro-2-methyl-7-(3-pyridylmethylene)-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIe) was recrystallized from 2-propanol to give 9.5 g. of yellow crystals, m.p. 133-134.5°; ir (nujol) 1710, 1612, 1600 (C=O, C=N, C=C); pmr (deuteriochloroform) δ 2.9 (s, NCH₃), 3.02 (t, J = 6 Hz, CH₂), 3.97 (t, J = 6 Hz, CH₂), 7.3-7.8 (m, 4H), 8.7 (broad m, 1H).

Anal. Calcd. for C₁₂H₁₂N₄O₂S: C, 55.37; H, 4.65; N, 21.52. Found: C, 55.52; H, 4.81; N, 21.73.

3,4-Dihydro-2-methyl-7-(3-pyridylmethylene)-2H-thiazolo[2,3-c][1,2,4]triazin-6(7H)one (VIIIf) was recrystallized from 2-propanol to give 8.5 g. of small orange-yellow needles, m.p. 171.5-172.5°; ir (nujol) 1705, 1605, 1579 (C=O, C=N, C=C); pmr (deuteriochloroform) δ 2.9 (s, NCH₃), 3.02 (t, J = 6 Hz, CH₂), 3.95 (t, J = 6 Hz, CH₂), 7.3 (m, 2H), 7.5 (s, 1H, vinyl), 8.7 (m, 2H).

3,4-Dihydro-2,4-dimethyl-6,7-diphenyl-2H-imidazo[2,1-b][1,3,4]-thiadiazine Hydrobromide (X).

A mixture of 5.3 g. (0.036 mole) of 2-amino-5,6-dihydro-4,6-dimethylthiadiazine (IX), 10 g. (0.036 mole) of desyl bromide,

and 150 ml. of ethanol was heated under reflux for 16 hours and then evaporated *in vacuo* to afford 16 g. of semi-crystalline oil. Three recrystallizations from methanol-ether gave 3.8 g. (24%) of yellow crystals, m.p. 275-280° dec.; ir (potassium bromide) 1629, 1604, 1590 (C=N, C=C); pmr (deuteriochloroform) δ 1.36 (d, J = 7 Hz, CH₃CH-), 2.55 (s, NCH₃), 3.1-3.4 (m, 2H, CH₂), 3.5-4.1 (m, 1H, CH₃CH-), 7.1-7.6 (m, 10 aromatic H's).

Anal. Calcd. for C₁₉H₁₉N₃S·HBr: C, 56.72; H, 5.01; Br, 19.86; N, 10.44. Found: C, 57.03; H, 5.22; Br, 20.02; N, 10.78.

REFERENCES

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- (3) Donald L. Trepanier and Paul E. Krieger, *J. Heterocyclic Chem.*, **8**, 621 (1971).
- (4) Donald L. Trepanier, Paul E. Krieger, John H. Mennear, and John N. Eble, *J. Med. Chem.*, **10**, 1085 (1967).