Efficient Synthesis of 5-Substituted-4,5-dihydro-1,2,4-triazin-6-ones and 5-Substituted-1,2,4-triazin-6-ones

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Treatment of methyl α-(dimethylaminomethyleneamino)carboxylates **1** (from α-amino acids and dimethylformamide dimethylacetal) with hydrazine gives 5-substituted-4,5-dihydro-1,2,4-triazin-6-ones **2**, which are smoothly dehydrogenated to 5-substituted-1,2,4-triazin-6-ones **3** with potassium permanganate in acetone/acetic acid.

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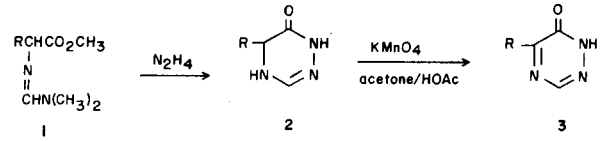
The synthesis, chemistry, and utility of 1,2,4-triazines have been extensively studied and reviewed [2]. Among the derivatives of this ring system which have received the greatest attention are the 1,2,4-triazin-3-ones and the isomeric 1,2,4-triazin-5-ones; by contrast, however, there are only a few scattered reports of 1,2,4-triazin-6-ones or of their potential precursors,4,5-dihydro-1,2,4-triazin-6-ones.

The first synthesis of a 4,5-dihydro-1,2,4-triazin-6-one was reported in 1893 from the reaction of 1-(α-phenylglycyl)phenylhydrazine with formic acid [3]. Sixty years later, several 3-benzyl-4,5-dihydro-1,2,4-triazin-6-ones were prepared by the reaction of methyl and ethyl α-(1-ethoxy-2-phenylethylideneamino)carboxylates with hydrazine [4], but no further examples of this reaction appeared subsequently. Further derivatives of the 4,5-dihydro-1,2,4-triazin-6-one system have been reported from the reaction of hydrazine with 2-carboxamido-2,3-diaryl-3*H*-azirines [5], esters of α-isocyanocarboxylic acids [6], or ethyl α-(thioacyl)aminocarboxylates [7]. A few 4,5-dihydro-1,2,4-triazin-6-ones have also been prepared by the reaction of α-amino acid hydrazines with *t*-butyl isocyanide [8]. With the single exception of the above cited route from ethyl α-(thioacyl)-aminocarboxylates, none of the above procedures is general and most proceed in poor yield.

Curiously, there are no reports on the conversion of these dihydro-1,2,4-triazin-6-ones to their dehydro (aromatic) derivatives. In fact, there are only three methods of preparation of 1,2,4-triazin-6-ones, and none of these is general or efficient. Various 3-aryl-5-benzyl derivatives can be prepared from the reaction of azlactones with hydrazine [9]; 3,5-diphenyl-1,2,4-triazin-6-one has been prepared by alkaline hydrolysis of the corresponding 6-amino derivative [10], and trace amounts of 1-methyl-1,2,4-triazin-6-ones have been isolated from the addition of alkali to 1-methyl-1,2,4-triazinium iodides followed by oxidation of the resulting pseudobases [11].

We report in this paper a new and efficient general synthesis of 5-substituted-4,5-dihydro-1,2,4-triazin-6-ones, as well as a simple procedure for their oxidation to 5-substituted 1,2,4-triazin-6-ones.

Heating a variety of α-amino acids with dimethylformamide dimethylacetal, followed by evaporation of the reaction mixture and vacuum distillation of the residue, results both in esterification and in functionalization of the amino group to give a series of methyl α-(dimethylaminomethyleneamino)carboxylates **1** [12]. Treatment of the latter with slightly more than one equivalent of hydrazine hydrate then gave a series of 5-substituted 4,5-dihydro-1,2,4-triazin-6-ones **2**. This two-step sequence has been carried out with glycine, alanine, valine, phenylglycine and methionine. The dihydrotriazin-6-one usually precipitated directly from the cooled reaction mixture in analytically pure form. This reaction sequence is readily amenable to larger reaction scales (*i.e.* 1-2 moles). It should be noted that 5-methyl-4,5-dihydro-1,2,4-triazin-6-one can also be prepared in somewhat lower yield by reaction of alanine hydrazide with dimethylformamide dimethylacetal.



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It proved to be more difficult than anticipated to effect dehydrogenation of these 4,5-dihydro-1,2,4-triazin-6-ones to the aromatic 1,2,4-triazin-6-ones **3** (a previously unreported transformation). A number of different reagents and conditions were employed including potassium permanganate in acetone, bromine in methanol followed by addition of base, DDQ, and manganese dioxide in refluxing dioxane, but none of these procedures resulted in the formation of the desired 1,2,4-triazin-6-one. 5-Methyl-4,5-dihydro-1,2,4-triazin-6-one could be converted into 5-methyl-1,2,4-triazin-6-one with aqueous potassium permanganate, or with aqueous sodium hypochlorite, but yields were inconsistent, and isolation and purification of the desired product from the oxidation mixture proved to be difficult. A major contributor to these failures was then uncovered

with the discovery that 5-methyl-1,2,4-triazin-6-one was extremely sensitive to base in the presence of oxidizing agents. We therefore treated 5-methyl-4,5-dihydro-1,2,4-triazin-6-one with potassium permanganate in an acetone/acetic acid solution and were gratified to obtain the desired oxidation product in consistent yields of 60-70%. This oxidation was applied with equal success to the preparation of 5-isopropyl and 5-phenyl-1,2,4-triazin-6-one. We were not successful, however, in extending this reaction to the formation of 1,2,4-triazin-6-one itself, although efforts are continuing in this direction.

EXPERIMENTAL

The methyl α-(dimethylaminomethyleneamino)carboxylates derived from glycine, phenylglycine and methionine were prepared from the corresponding amino acid and dimethylformamide dimethylacetal according to the published procedure [12]. The following new compounds were prepared analogously.

Methyl *N*-(Dimethylaminomethylene)alaninate.

This compound was obtained in a yield of 65%, bp 66-67° at 1 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.36 (s, 1H), 3.85 (q, J = 6.83 Hz, 1H), 3.66 (s, 3H), 2.86 (s, 6H), 1.34 (d, J = 6.83 Hz, 3H).

Anal. Calcd. for $C_7H_{15}N_2O_2$: C, 53.15; H, 8.92; N, 17.71. Found: C, 52.97; H, 8.88; N, 17.61.

Methyl *N*-(Dimethylaminomethylene)valinate.

This compound was obtained in a yield of 76%, bp 79-83° at 0.5 mm Hg; ^{1}H nmr (deuteriochloroform): δ 7.26 (s, 1H), 3.70 (s, 3H), 3.31 (d, J = 7.91 Hz, 1H), 2.87 (s, 6H), 2.32-1.92 (m, 1H), 0.88 (d, J = 6.81 Hz, 3H), 0.86 (d, J = 6.81 Hz, 3H).

Anal. Calcd. for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 57.88; H, 9.57; N, 14.91.

Formation of 4,5-Dihydro-1,2,4-triazin-6-ones. General Procedure.

A solution of the methyl α-(dimethylaminomethyleneamino)carboxylate (0.10 mole) and 85% hydrazine hydrate (0.11 mole) in 25 ml of absolute ethanol was heated under reflux for 3 hours under nitrogen. The resulting solution was chilled to −20° and the colorless precipitate which had separated was collected by filtration and (when necessary) recrystallized from absolute ethanol. Further product could then be obtained by concentration of the mother liquors. The following compounds were prepared in this manner.

4,5-Dihydro-1,2,4-triazin-6-one.

This compound was obtained in a yield of 53%, mp 181-183° (lit [6] mp 176-178°). Spectral properties for this compound were in accord with published data.

Anal. Calcd. for $C_3H_5N_3O$: C, 36.36; H, 5.09; N, 42.41. Found: C, 36.62; H, 4.87; N, 42.57.

5-Methyl-4,5-dihydro-1,2,4-triazin-6-one.

This compound was obtained in a yield of 84%, mp 147-150° (lit [6] mp 143-146°). Spectral data were in accord with published data.

Anal. Calcd. for $C_4H_7N_3O$: C, 42.47; H, 6.24; N, 37.15. Found: C, 42.26; H, 6.17; N, 36.93.

This compound could also be prepared as follows. To a stirred solution of 6.34 g (0.0615 mol) of alanine hydrazide in 40 ml of dimethylformamide at 0°, 9.0 ml (0.0677 mole) of dimethylformamide dimethylacetal was added dropwise. The resulting solution was heated at 70° under nitrogen for 2 hours. DMF was then removed from the resulting clear dark solution by evaporation under reduced pressure, and the residual dark red oil was crystallized from 30 ml of boiling acetone. The resulting dark brown solid was then recrystallized from 30 ml of absolute methanol to give 4.57 g (66%) of 5-methyl-4,5-dihydro-1,2,4-triazin-6-one as a pale yellow solid, mp 147-150°, identical in all respects with the material prepared as described above.

5-Isopropyl-4,5-dihydro-1,2,4-triazin-6-one.

This compound was obtained in a yield of 86%, mp 138-140°; ir (potassium bromide): 1660, 1620, 1550 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.04 (br s, 1H), 6.98 (br m, 1H), 6.82 (d, J = 3.94 Hz, 1H), 3.71 (dd, J_1 = 2.97 Hz, J_2 = 1.65 Hz, 1H), 2.23-1.80 (m, 1H), 0.88 (d, J = 6.92 Hz, 3H), 0.82 (d, J = 6.60 Hz, 3H); ^{13}C nmr (DMSO-d_6): δ 162.2, 137.5, 57.6, 31.8, 18.0, 16.6.

Anal. Calcd. for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.77. Found: C, 50.85; H, 7.85; N, 29.64.

5-Phenyl-4,5-dihydro-1,2,4-triazin-6-one.

This compound was obtained in a yield of 73%. In this instance, evaporation of the reaction mixture gave a residual oil which did not crystallize directly. The oil was therefore dissolved in ether and the solution filtered twice through silica gel. Evaporation of the combined filtrates and cooling of the semi-solid residue then gave the desired product in crystalline form, mp 131-132°; ir (potassium bromide): 1670-1635, 1595 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.28 (br s, 1H), 7.55 (br m, 1H), 7.33 (s, 5H), 7.01 (d, J = 3.95 Hz, 1H), 4.91 (d, J = 1.54 Hz, 1H); ^{13}C nmr (DMSO-d_6): δ 160.9, 140.2, 136.6, 127.9, 127.4, 126.3, 35.9.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.62; H, 5.15; N, 23.75.

5-(2-Methylthioethyl)-4,5-dihydro-1,2,4-triazin-6-one.

This compound was obtained in a yield of 83%, mp 124.5-125.5°; ir (potassium bromide): 1675-1625, 1525 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 10.09 (br s, 1H), 7.09 (br m, 1H), 6.82 (d, J = 3.96 Hz, 1H), 3.93 (dt, J_1 = 5.61 Hz, J_2 = 1.31 Hz, 1H), 2.62-2.44 (m, 2H), 2.04 (s, 3H), 2.04-1.71 (m, 2H); ^{13}C nmr (DMSO-d_6): δ 162.6, 137.3, 51.1, 32.7, 28.6, 14.5.

Anal. Calcd. for $C_6H_{11}N_3OS$: C, 41.60; H, 6.40; N, 24.26; S, 18.51. Found: C, 41.59; H, 6.47; N, 24.16; S, 18.70.

5-Methyl-1,2,4-triazin-6-one.

To a stirred suspension of 7.44 g (65.8 mmoles) of 5-methyl-4,5-dihydro-1,2,4-triazin-6-one and 5.30 ml (92.6 mmoles) of glacial acetic acid in 350 ml of anhydrous acetone at 0° was added 6.93 g (43.9 mmoles) of potassium permanganate all at once. The resulting mixture was stirred at 0° under nitrogen for 2.5 hours and then at room temperature for 2.5 hours under nitrogen. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residual yellow solid was taken up in 100 ml of methylene chloride, and the resulting cloudy solution filtered through Celite. Evaporation of the filtrate under reduced pressure and chromatography of the residual yellow solid over silica gel (ether/petroleum ether 1:1) gave 4.71 g (65%) of 5-methyl-1,2,4-triazin-6-one as a colorless crystalline solid, mp 109-111°; ir (potassium bromide): 1675, 1630, 1575, 1520 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 12.65 (br s, 1H), 8.20 (s, 1H), 2.57 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 170.4, 156.8, 141.9, 20.2.

Anal. Calcd. for $C_4H_5N_3O$: C, 43.24; H, 4.53; N, 37.82. Found: C, 43.67; H, 4.49; N, 37.89.

5-Isopropyl-1,2,4-triazin-6-one.

To a stirred suspension of 5.65 g (40.02 mmoles) of 5-isopropyl-4,5-dihydro-1,2,4-triazin-6-one and 3.20 ml (55.90 mmoles) of glacial acetic acid in 200 ml of anhydrous acetone at 0° was added 4.22 g (26.70 mmoles) of potassium permanganate all at once. The resulting reaction mixture was stirred at 0° under nitrogen for 2.5 hours and then at room temperature under nitrogen for 1 hour. The mixture was filtered and the filtrate concentrated under reduced pressure to yield a residual solid which was chromatographed over silica gel (ether:petroleum ether 1:1) to yield 4.58 g (82%) of 5-isopropyl-1,2,4-triazin-6-one as a white crystalline solid, mp 86.0-87.5°; ir (potassium bromide): 1670, 1630, 1605, 1585, 1525 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 12.68 (br s, 1H), 8.27 (s, 1H), 3.55 (septet, J = 6.81 Hz, 1H), 1.29 (d, J = 6.81 Hz, 6H); ^{13}C nmr (deuteriochloroform):

δ 176.7, 156.0, 142.0, 30.4, 19.2.

Anal. Calcd. for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.95; H, 6.37; N, 30.16.

5-Phenyl-1,2,4-triazin-6-one.

To a stirred suspension of 7.00 g (39.96 mmoles) of 5-phenyl-4,5-dihydro-1,2,4-triazin-6-one and 3.20 ml (55.90 mmoles) of glacial acetic acid in 200 ml of anhydrous acetone at 0° was added 4.22 g (26.70 mmoles) of potassium permanganate all at once. The resulting mixture was stirred at 0° under nitrogen for 1 hour and the brown reaction mixture was filtered, concentrated under reduced pressure and the residual solid taken up in 200 ml of warm anhydrous ether and filtered through Celite. The filtrate was evaporated under reduced pressure to yield 6.8 g of a residual brown solid which was then recrystallized from ethyl acetate to give 4.54 g (66%) of 5-phenyl-1,2,4-triazin-6-one as pale yellow needles, mp 165-167°. An additional 0.25 g (total yield 69%) was obtained by evaporation of the filtrate under reduced pressure and recrystallization of the residual oil from ethyl acetate; ir (potassium bromide): 1660, 1590, 1570, 1555 cm^{-1}; ^1H nmr (DMSO-d_6): 13.4 (br s, 1H), 8.66-8.48 (m, 2H), 8.48 (s, 1H), 7.77-7.43 (m, 3H); ^{13}C nmr (DMSO-d_6): δ 160.0, 154.5, 140.8, 132.9, 131.6, 128.9, 127.6.

Anal. Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.23; H, 3.86; N, 24.06.

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