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Studies on *as*-Triazine Derivatives. IX.¹⁾ Synthesis of 5-Substituted 1,2,4-Triazine Derivatives through an Addition Reaction and Subsequent Oxidation

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The addition reactions of various nucleophiles to 6-methyl-3-phenyl-1,2,4-triazine (**1**) were investigated and a practical preparation of **1** was developed. The reactions showed many similarities to those of quinazoline (at the 4-position) and acridine (at the 9-position). The hitherto unknown compounds 5-cyano- (**3**), 5-carbamoyl- (**5**) and 5-phenacyl-6-methyl-3-phenyl-1,2,4-triazines (**11c**) were synthesized.

Keywords—1,2,4-triazine; nucleophilic addition; aromatization; active methylene compound; catalytic reduction

The most reactive position of a 1,2,4-triazine (*as*-triazine) ring is position 5, where nucleophiles can attack very easily.²⁾ For example, 3,5,6-trichloro-*as*-triazine reacts with 1 mol eq of sodium methoxide to give 3,6-dichloro-5-methoxy-*as*-triazine exclusively.³⁾ Furthermore, the combined electron-attracting effects of three ring nitrogen atoms suggest position 5 to be highly susceptible to nucleophilic addition, when there is no leaving group at this position.⁴⁾ The present paper deals with the synthesis of 5-substituted *as*-triazine derivatives from 6-methyl-3-phenyl-*as*-triazine (**1**).

The reaction of **1** with nucleophiles came up to our expectation, as shown in Chart 1. Compound **1** reacted with sodium bisulfite in methanol to give 6-methyl-3-phenyl-2,5-dihydro-*as*-triazine-5-sulfonic acid (**2**). When a current of sulfur dioxide was bubbled through an aqueous methanolic solution of **1**, the same sulfonic acid (**2**) was obtained. On treatment with sodium cyanide in dimethylformamide (DMF) at room temperature, **2** was converted into 6-methyl-3-phenyl-*as*-triazine-5-carbonitrile (**3**) together with a small amount of **1**. The nitrile (**3**) was alternatively obtained by passing hydrogen cyanide into a solution of **1** in DMF. In this case, air oxidation is considered to be responsible for the direct formation of **3**, although there is no direct evidence for this.

On the other hand, the reaction of **1** with sodium cyanide in DMF resulted in the dimerization of **1**, and the bi-triazine (**4**) was isolated mainly, together with 6-methyl-3-phenyl-*as*-triazine-5-carboxamide (**5**). The by-product (**5**) was identical with an authentic specimen derived from **3** by treatment with hydrogen peroxide in an alkaline medium.

Furthermore, 5-hydrazino-6-methyl-3-phenyl-*as*-triazine (**6**) and 6-methyl-5-oxo-3-phenyl-2,5-dihydro-*as*-triazine (**7**)⁵⁾ were obtained by treatment of **1** with hydrazine and with hydrogen peroxide, respectively. In connection with this result, the addition of hydrazine to quinazoline has been reported to give 4-hydrazinoquinazoline, in which the oxidizing reagent for the aromatization of the intermediate was suggested to be hydrazine itself.⁶⁾

The addition of carbon nucleophiles to **1** was also successful. Namely, methylmagnesium iodide reacted with **1** at room temperature to give 5,6-dimethyl-3-phenyl-2,5-dihydro-*as*-

Chart 1

Chart 2

triazine (**8**), which was smoothly aromatized to 5,6-dimethyl-3-phenyl-*as*-triazine (**9**) by potassium permanganate oxidation. Herein, the 2,5-dihydro-structure is adopted tentatively according to the common practice.⁷⁾

In the presence of sodium hydride, compounds containing an active methylene or methyl group such as ethyl cyanoacetate, phenylacetone nitrile, and acetophenone added smoothly to the 5-position of **1** to give the corresponding adducts (**10a–c**). Although these adducts were too unstable for purification, subsequent oxidation of the crude materials with molecular oxygen gave the aromatic compounds (**11a–c**), as expected.

We also developed a convenient synthesis of **1**. When **7** was treated with phosphoryl chloride and diethylaniline, the reaction proceeded at room temperature, and 5-chloro-6-methyl-3-phenyl-*as*-triazine (**12**) was obtained in good yield. It is possible to control the catalytic reduction of **12** over palladium charcoal to give **1** without concomitant formation of by-products. In connection with these experiments, the following findings should be mentioned.

1) The reaction of methylglyoxal with benzamidrazone has been reported to give a mixture of **1** and 5-methyl-3-phenyl-*as*-triazine, the separation of which was unsuccessful.⁸⁾ In

Chart 3

contrast, the condensation of pyruvic acid with benzamidrazone gave **7** regio-selectively.

2) On heating **7** with phosphoryl chloride alone, the reaction resulted in the recovery of **7**, although the reaction mixture turned dark brown. Therefore the addition of diethylaniline is essential for the dehydroxy-chlorination of **7**.

3) The exhaustive reduction of **12** under these conditions gave 6-methyl-3-phenyl-2,5-dihydro-*as*-triazine (**13**), although the oxidation of **13** with potassium ferricyanide in an alkaline medium afforded **1**.

The present results confirm⁹⁾ that the reactivity of *as*-triazines at the 5-position resembles that of quinazoline (at the 4-position)¹⁰⁾ or acridine (at the 9-position).¹¹⁾

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Mass spectra (MS) were taken with a Hitachi M-52G spectrometer. Proton nuclear magnetic resonance (¹H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad.

Reaction of 1 with NaHSO₃—SO₂ was bubbled into a solution of NaOH (8 g) in H₂O (25 ml) and the resulting precipitate was filtered off. Compound **1** was added to the above filtrate and the mixture was stirred for 10 min at room temperature. The resulting precipitate was collected by filtration and washed with cold H₂O. Recrystallization from H₂O gave 7.35 g (87%) of 6-methyl-3-phenyl-2,5-dihydro-*as*-triazine-5-sulfonic acid monohydrate (**2**), mp 198 °C (dec.), as colorless prisms. ¹H-NMR (DMSO-*d*₆): 2.32 (3H, s), 4.96 (1H, s), 7.7–8.0 (6H, m, exchangeable with D₂O for 1H), 11.0–13.5 (1H, br, exchangeable with D₂O). *Anal.* Calcd for C₁₀H₁₁N₃O₃S·H₂O: C, 44.27; H, 4.83; N, 15.49; S, 11.81. Found: C, 44.37; H, 4.80; N, 15.59; S, 11.92.

Reaction of 1 with SO₂—SO₂ was bubbled into a solution of **1** (5.1 g, 0.03 mol) in 50% aq. MeOH (30 ml). The resulting precipitate was collected by filtration and washed with cold H₂O. Recrystallization from H₂O gave 7.56 g (90%) of **2**, mp 198 °C (dec.), as colorless prisms. This compound was identical with the sample obtained above.

Reaction of 2 with NaCN—A solution of **2** (1.08 g, 0.004 mol) in DMF (5 ml) was added to a solution of NaCN (0.22 g, 0.0044 mol) in DMF (10 ml) and the mixture was stirred for 2 h at room temperature. After removal of the solvent, the residue was chromatographed on a silica gel column. The first fraction, eluted with benzene, gave 6-methyl-3-phenyl-*as*-triazine-5-carbonitrile (**3**), which was recrystallized from cyclohexane to give yellow prisms, mp 134–135 °C (lit.¹⁾ mp 134–135 °C), in 77% yield (0.65 g). The second fraction, eluted with hexane–Et₂O (9:1), gave 6-methyl-3-phenyl-*as*-triazine (**1**), which was recrystallized from hexane–Et₂O to give pale yellow needles, mp 68–69 °C, in 12% yield (0.08 g). These compounds were identical with samples prepared by alternative routes.¹⁾

Reaction of 1 with HCN—An excess of dry HCN was introduced into a solution of **1** (0.43 g, 0.0025 mol) in DMF (20 ml) and the mixture was allowed to stand for 36 h. After removal of the solvent, the residue was purified by silica gel column chromatography using benzene as an eluent. Recrystallization from cyclohexane gave 0.35 g (71%) of **3**, mp 134–135 °C, as yellow prisms.

Reaction of 1 with NaCN—A solution of **1** (0.86 g, 0.005 mol) in DMF (5 ml) was added to a solution of NaCN (2.5 g, 0.05 mol) in DMF (15 ml), and the mixture was stirred for 36 h at room temperature. H₂O (100 ml) was added to the reaction mixture and the separated crystals were collected by filtration, then washed with H₂O.

After air-drying, the crystals were suspended in DMF (20 ml) and O₂ was bubbled into the mixture for 5 min. After removal of the solvent, the residue was purified by silica gel column chromatography. The fraction eluted with hexane–Et₂O (9:1) gave 0.63 g (74%) of 5,5'-bis(6-methyl-3-phenyl-*as*-triazinyl) (**4**), mp 197–199 °C, as orange needles. MS *m/z*: 340 (M⁺). The fraction eluted with CHCl₃ gave 0.05 g (5%) of 6-methyl-3-phenyl-*as*-triazine-5-carboxamide (**5**), mp 222 °C, as yellow needles.

Hydrolysis of 3 with H₂O₂—A mixture of **3** (0.38 g, 0.002 mol), K₂CO₃ (0.15 g), and 30% H₂O₂ (1 ml) in 80% aq. acetone (30 ml) was stirred for 1 h at room temperature. The precipitate was collected by filtration, and washed

with H₂O. Recrystallization from CHCl₃ gave 0.30 g (70%) of **5**, mp 222 °C, as yellow needles.

Reaction of 1 with NH₂NH₂·H₂O—A suspension of **1** (0.86 g, 0.005 mol) in NH₂NH₂·H₂O (20 ml) was refluxed for 6 h. The mixture was concentrated to dryness under reduced pressure. The residue was washed with H₂O and recrystallized from MeOH to give 0.12 g (12%) of 5-hydrazino-6-methyl-3-phenyl-*as*-triazine (**6**), mp 216 °C (dec.) [lit.¹⁾ mp 216 °C (dec.)], as colorless needles. This compound was identical with a sample prepared by an alternative route.¹⁾

Reaction of 1 with H₂O₂ in AcOH—A mixture of **1** (0.34 g, 0.002 mol) and 30% H₂O₂ (1 ml) in AcOH (10 ml) was stirred for 5 h at room temperature. After removal of the solvent, the residue was washed with H₂O and recrystallized from EtOH to give 0.31 g (82%) of 6-methyl-5-oxo-3-phenyl-2,5-dihydro-*as*-triazine (**7**), mp 245—247 °C (dec.) (lit.⁵⁾ mp 245—247 °C), as colorless needles. This compound was identical with a sample prepared by an alternative route.⁵⁾

Reaction of 1 with Methylmagnesium Iodide—A Grignard solution [prepared from 0.24 g (0.01 g atom) of Mg and 1.39 g (0.01 mol) of MeI in dry ether (35 ml)] was added dropwise to a solution of 1.28 g (0.0075 mol) of **1** in dry ether (35 ml) at room temperature under nitrogen and the mixture was stirred for 10 min. Saturated aq. NH₄Cl was added to the reaction mixture and the organic layer was separated, then dried over Na₂SO₄. After removal of the solvent, the residue was recrystallized from hexane–AcOEt to give 1.2 g (86%) of 5,6-dimethyl-3-phenyl-2,5-dihydro-*as*-triazine (**8**), mp 109—111 °C, as colorless needles. ¹H-NMR (CDCl₃): 1.34 (3H, d, *J* = 7 Hz), 2.02 (3H, s), 3.97 (1H, q, *J* = 7 Hz), 7.1—8.0 (5H, m), 8.0—8.9 (1H, br, exchangeable with D₂O). *Anal.* Calcd for C₁₁H₁₃N₃: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.27; H, 6.85; N, 22.22.

Oxidation of 8 with KMnO₄—KMnO₄ (2.37 g, 0.015 mol) was added to a solution of **8** (0.94 g, 0.005 mol) in acetone (100 ml) all at once and the mixture was stirred for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized from hexane to give 0.72 g (77%) of 5,6-dimethyl-3-phenyl-*as*-triazine (**9**), mp 78—80 °C (lit.¹²⁾ mp 82 °C), as pale yellow needles. This compound was identical with a sample prepared by an alternative route.¹²⁾

Reaction of 1 with Ethyl Cyanoacetate—A mixture of ethyl cyanoacetate (1.13 g, 0.01 mol) and NaH (0.48 g, 50% in oil, 0.01 mol) in dry 1,4-dioxane (20 ml) was refluxed for 30 min. A solution of **1** (0.85 g, 0.005 mol) in dry 1,4-dioxane (30 ml) was added thereto, and the mixture was refluxed for 24 h. After removal of the solvent, 3 N HCl (5 ml) and DMF (30 ml) were added to the residue. O₂ was bubbled into the mixture for 5 min. The reaction mixture was concentrated to dryness under reduced pressure, and the residue was purified by silica gel column chromatography using benzene–AcOEt (9 : 1) as an eluent. Recrystallization from AcOEt gave 0.55 g (39%) of ethyl α-cyano-6-methyl-3-phenyl-*as*-triazine-5-acetate (**11a**), mp 193—194 °C (lit.¹⁾ mp 193—194 °C), as yellow prisms. This compound was identical with a sample prepared by an alternative route.¹⁾

Reaction of 1 with Phenylacetonitrile—Following the procedure for the preparation of **11a**, treatment of **1** (0.85 g, 0.005 mol) in dry 1,4-dioxane (50 ml) with NaH (0.48 g, 50% in oil, 0.01 mol) and phenylacetonitrile (1.03 g, 0.01 mol) resulted in the formation of a crude product which was oxidized by oxygen. Recrystallization from MeOH gave 0.42 g (31%) of α-phenyl-6-methyl-3-phenyl-*as*-triazine-5-acetonitrile (**11b**), mp 220—221 °C, as yellow needles.

Reaction of 1 with Acetophenone—Following the procedure for the preparation of **11a**, treatment of **1** (0.85 g, 0.005 mol) in dry 1,4-dioxane (50 ml) with NaH (0.48 g, 50% in oil, 0.01 mol) and acetophenone (1.2 g, 0.01 mol) resulted in the formation of a crude product which was oxidized by oxygen. Recrystallization from AcOEt gave 0.49 g (34%) of 6-methyl-3-phenyl-5-*as*-triazinylmethyl phenyl ketone (**11c**), mp 134—135 °C (lit.¹⁾ mp 134—135 °C), as yellow prisms. This compound was identical with a sample prepared by an alternative route.¹⁾

5-Chloro-6-methyl-3-phenyl-*as*-triazine (12**)**—*N,N*-Diethylaniline (4.5 g, 0.03 mol) was added to a suspension of 6-methyl-5-oxo-3-phenyl-2,5-dihydro-*as*-triazine (**7**)⁵⁾ (5.61 g, 0.03 mol) in POCl₃ (20 ml) and the mixture was stirred at room temperature for 30 min, then diluted with benzene. The benzene solution was washed successively with H₂O, 10% NH₄OH, and sat. aq. NaCl, and dried over Na₂SO₄. After removal of the solvent, the residue was purified by column chromatography on active alumina (Sumitomo, KCG-30) using benzene as an eluent. Recrystallization from hexane–AcOEt gave 5.2 g (84%) of **12**, mp 87—88 °C, as pale yellow prisms.

6-Methyl-3-phenyl-*as*-triazine (1**)**—i) The catalyst, 10% Pd–C (1.0 g), was added to a solution of **12** (4.11 g, 0.02 mol) and Et₃N (4.04 g, 0.04 mol) in benzene (150 ml) and the mixture was shaken under an H₂ stream (1 atm) at room temperature. After absorption of H₂ (1 l, 2 mol eq), the catalyst was removed by filtration. The filtrate was concentrated to dryness and the residue was recrystallized from hexane–AcOEt to give 2.63 g (76%) of 6-methyl-3-phenyl-2,5-dihydro-*as*-triazine (**13**), mp 119—121 °C, as colorless prisms. IR (CHCl₃) cm^{−1}: 3440. ¹H-NMR (CDCl₃): 2.02 (3H, s), 3.96 (2H, s), 7.4—7.6 (3H, m), 7.7—7.9 (2H, m), 8.4—8.9 (1H, br s, exchangeable with D₂O). *Anal.* Calcd for C₁₀H₁₁N₃: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.16; H, 6.25; N, 24.56. A mixture of K₃Fe(CN)₆ (5 g, 0.015 mol) and NaOH (1 g) in H₂O (20 ml) was added to a solution of **13** (1.73 g, 0.01 mol) in benzene (20 ml). The mixture was vigorously stirred for 24 h at room temperature. The benzene layer was separated and dried over K₂CO₃. After removal of the solvent, the residue was purified by silica gel column chromatography using hexane–Et₂O (9 : 1) as an eluent. Recrystallization from hexane–Et₂O gave 1.66 g (97%) of **1**, mp 68—69 °C, as pale yellow needles.

ii) Compound **12** (8.22 g, 0.04 mol) was dissolved in benzene (200 ml), and then 5% Pd–C (0.3 g) and Et₃N

TABLE I. Analytical Data and ^1H -NMR Spectral Data for All Aromatic *as*-Triazines Synthesized

Compd. No.	Formula or lit. mp ($^{\circ}\text{C}$)	Analysis (%)			^1H -NMR δ (CDCl_3 , $J = \text{Hz}$)
		Calcd	(Found)		
		C	H	N	
1	$\text{C}_{10}\text{H}_9\text{N}_3$	70.18 (70.45)	5.21 5.11	24.56 24.56	2.63 (s, 3H), 7.3—7.6 (m, 3H), 8.3—8.7 (m, 3H) ^{a)}
3	134—135 ¹⁾				3.01 (s, 3H), 7.5—7.7 (m, 3H), 8.4—8.7 (m, 2H)
4	$\text{C}_{20}\text{H}_{16}\text{N}_6$	70.57 (70.82)	4.74 4.63	24.69 24.60	2.94 (s), 7.5—7.7 (m), 8.5—8.7 (m), the integrated ratio is 3:3:2
5	$\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}$	61.67 (61.89)	4.71 4.65	26.16 26.43	2.92 (s, 3H), 3.34 (s, 1H, exchangeable with D_2O), 7.6—7.8 (m, 3H), 7.9—8.3 (br, 1H, exchangeable with D_2O), 8.5—8.8 (m, 2H) ^{b)}
6	216 (dec.) ¹⁾				2.27 (s, 3H), 7.0—7.6 (m, 3H), 7.6—8.1 (m, 2H) ^{c)}
9	82 ⁷⁾				2.47 (s, 3H), 2.60 (s, 3H), 7.2—7.6 (m, 3H), 8.2—8.6 (m, 2H) ^{a)}
11a	193—194 ¹⁾				1.41 (t, 3H, $J = 7$), 2.97 (s, 3H), 4.41 (q, 2H, $J = 7$), 7.3—7.8 (m, 3H), 7.9—8.2 (m, 2H), 14.4—14.9 (br, 1H, exchangeable with D_2O)
11b	$\text{C}_{18}\text{H}_{14}\text{N}_4$	75.50 (75.79)	4.93 4.89	19.57 19.63	2.46 (s, 3H), 7.0—7.6 (m, 10H)
11c	134—135 ¹⁾				2.62 (s, 3H), 6.16 (s, 1H), 7.4—7.7 (m, 6H), 7.9—8.1 (m, 2H), 8.2—8.4 (m, 2H), 15.6—16.0 (br, 1H, exchangeable with D_2O)
12	$\text{C}_{10}\text{H}_8\text{ClN}_3$	58.41 (58.18)	3.92 3.73	20.43 20.41	2.42 (s, 3H), 7.3—7.7 (m, 3H), 8.4—8.7 (m, 2H) ^{a)}

a) Measured in CCl_4 . b) Measured in $\text{DMSO}-d_6$. c) Measured in $\text{CF}_3\text{CO}_2\text{H}$.

(8.08 g, 0.08 mol) were added. The mixture was shaken under an H_2 stream (1 atm) at room temperature. After absorption of H_2 (1 l, 1 mol eq), the catalyst was filtered off and washed with benzene (50 ml). The filtrate and washing were combined and concentrated to dryness under reduced pressure. The residue was purified as described above. Recrystallization from hexane– Et_2O gave 6.50 g (95%) of 1, mp 68—69 $^{\circ}\text{C}$, as pale yellow needles. This compound was identical with the sample obtained above.

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