1,2,4-Triazine(VIII): Oxidation of 6-Acetyl-1,2,4-triazine to 1,2,4-Triazin-6-yl-glyoxal and Its Application for the Synthesis of 6,5'- and 6,6'-*bis*-1,2,4-Triazinyls

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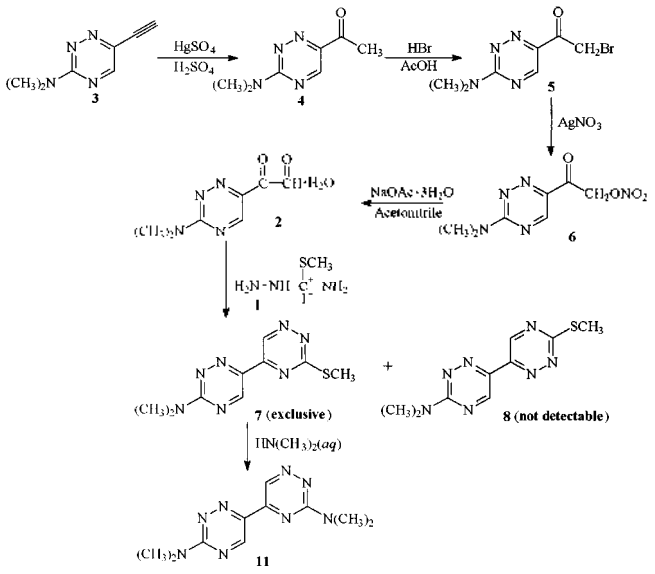
We have reported[1] the synthesis of 6,5'-*bis*-1,2,4-triazinyls and 6,6'-*bis*-1,2,4-triazinyls by the cyclization of 1-hetero-aryl-2-(3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl)-ethandione derivatives with methylthiosemicarbazide hydrogen iodide (**1**), where we assumed that the major product was the 6,5'-*bis*-1,2,4-triazinyls. As extention of our previous research, we attempt to synthesize the 3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl-glyoxal (**2**). We believed that the carbon of aldehyde group is definitely more electrophilic than that of keto, and the reaction with methylthiosemi- carbazide hydrogen iodide (**1**) will produce the 6,5'-*bis*-1,2,4-triazinyls as major product. By comparing ^{1}H NMR of compounds 7 and **8**, we could easily distinguish between 6,5'- (7) and 6,6'-*bis*-1,2,4-triazinyls (**8**). Now we would like to report the synthesis of the first 1,2,4-triazinylglyoxal derivative, which is very important intermediate for the synthesis of 1,2,4-triazines[2] and imid- azoles.[3]

3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl-acetylene (**3**) was hydrated under acidic condition to 6-acetyl-3-*N*,*N*-dimethylamino-1,2,4-triazine (**4**).[4] Since SeO_2 oxidation[5] of acetyl to glyoxal did not work, compound **4** was brominated with HBr/AcOH to give 6-bromoacetyl-3-*N*,*N*-dimethylamino-1,2,4-triazine (**5**)[6] in order to convert to glyoxal by DMSO oxidation.[7] But unfortunately DMSO oxidation of bromoacetyl to glyoxal did not work either. Finally, we try to convert the bromo compound **5** to nitrate ester **6** with $AgNO_3$ and then hydrolyze to 3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl-glyoxal (**2**).[8] This time compound **2** was successfully obtained in yield of 69%. The glyoxal derivative was readily reacted with compound **1** to give 6,5'-*bis*-1,2,4-triazinyl (**7**) exclusively as expected. The corresponding 6,6'-*bis*-1,2,4-triazinyl derivative **8** was not obtained at all (Scheme 1).

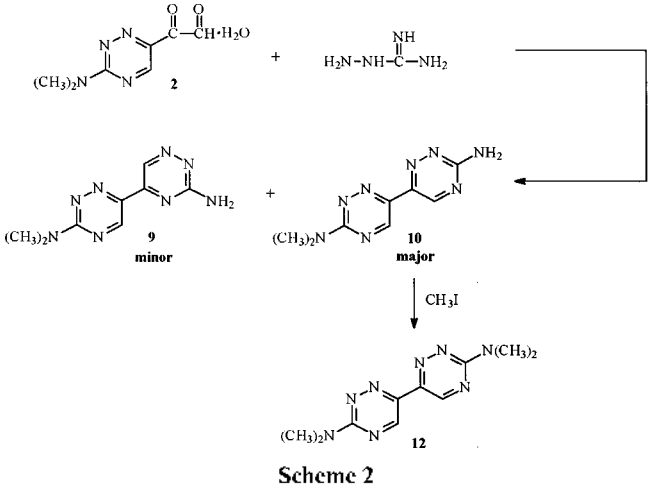
The proton NMR of 6,5'-*bis*-1,2,4-triazinyl 7 showed two protons at δ 9.13 and δ 9.93 respectively. The big difference in chemical shift means that the one at δ 9.13 is 5-H and the other at δ 9.93 is 6'-H. Usually the 6-H of 1,2,4-triazine was shown at lower field than 5-H of 1,2,4-triazine.[9] Compound 7 was further reacted with excess $HN(CH_3)_2$ to give compound **11**, which has *N*,*N*-dimethylamino group on both rings. The proton NMR of compound **11** showed two different peaks at δ 9.11 and δ 9.52 respectively. Definitly one at δ 9.11 is 5-H and the other at δ 9.52 must be 6'-H of 1,2,4-triazine ring. Here again showed quite big difference in chemical shift between 5-H and 6'-H. When the glyoxal **2** was reacted with aminoguanidine, both 6,5'- (**9**) and 6,6'-*bis*-1,2,4-triazinyls (**10**) were produced (Scheme 2).



Scheme 1

In this case, 6,6'-*bis*-1,2,4-triazinyl **10** was the major product. Similar results were observed in other literature too.[10] In order to clarify the structural difference between compound **9** and **10**, they were seperated by column and compound **10** was further reacted with excess methyl iodide to give 6,6'-*bis*-1,2,4-triazinyl (**12**), which is symmetric and has only 5-H proton. Actually compound **12** showed only one peak at δ 9.18 for 5-H. This proves that our stuructural determination of compound **11** was correct.

In summary, 1,2,4-triazine glyoxal (**2**) was first synthesized and used to synthesize the bis-1,2,4-triazinyls. The



Scheme 2

synthesis of imidazole deerivatives by using 1,2,4-triazine glyoxal (**2**) will be published later. Also 3-*N*,*N*-dimethylamino-6-(3-*N*,*N*-dimethylamino-1,2,4-triazin-5-yl)-1,2,4-triazine (**11**) and 3-*N*,*N*-dimethylamino-6-(3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl)-1,2,4-triazine (**12**) were first synthesized in good yields, and they would be checked the possibility to form the "complex with many transition metals as weak ligands." and the experiment of the complex formation is in progress.

Experimetal Section

All chemicals were purchased from Aldrich, and used without further purification. NMR, mass sprectra and elemental analysis were recorded on Varian Unit INOVA 300, Shimadzu Corporation, QP-1000A and Carlo Erba, EA 1108, respectively. Melting points were determined on a Electrothermal melting point apparatus and are uncorrected.

6-Acetyl-3-*N*,*N*-dimethylamino-1,2,4-triazine (4). A mixture of 3-*N*,*N*-dimethylamino-6-ethynyl-1,2,4-triazine (**3**) (0.9 g, 6.1 mmol), mercury(II) sulfate (1.8 g, 6.1 mmol), conc-sulfuric acid (30 mmol) in 70-85% aqueous acetone (150 mL) was refluxed for 2h. After removal of acetone, the residue was made alkaline with aqueous potassium carbonate, and then, extracted with chloroform. The chloroform solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silical gel column chromatography with ethyl acetate/*n*-hexane (1/1) gave 0.61 g (60%) of title compound as a yellow solid: mp 80-81 °C; ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H, CH_3), 3.29 (s, 3H, NCH_3), 3.47 (s, 3H, NCH_3), 8.75 (s, 1H, Tri-H); Mass m/e (rel. intensity) 166 (M^+, 55), 123 (10), 70 (100).

6-Bromoacetyl-3-*N*,*N*-dimethylamino-1,2,4-triazine (5). Bromine (0.057 g, 3.6 mmol) was very slowly added to the solution of 6-acetyl-3-*N*,*N*-dimethylamino-1,2,4-triazine (**4**) (0.6 g, 3.61 mmol) in 30% HBr in AcOH at room temperature. The resulting solution was stirred for 48h at room temperature, and then, poured into water and extracted with ether. The extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silical gel column chromatography with chloroform/*n*-hexane/ethyl acetate (8/4/1) gave 0.70 g (79%) of title compound as a yellow solid: mp 118-119 °C; ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 3H, NCH_3), 3.50 (s, 3H, NCH_3), 4.78 (s, 2H, CH_2Br), 8.77 (s, 1H, Tri-H); Mass m/e (rel. intensity) 246 (M^++2, 10), 244 (M^+, 11), 166 (1), 123 (4), 70 (100).

3-*N*,*N*-Dimethylamino-1,2,4-triazine-6-yl-glyoxal (2). To the solution 6-bromoacetyl-3-*N*,*N*-dimethylamino-1,2,4-triazine (**5**) (0.37 g, 1.5 mmol) in acetonitrile (4 mL) was added silver nitrate (0.39 g, 2.3 mmol) in acetonitrile (4 mL). After stirring for 48h at 40 °C, the mixture was filtered, and the precipitate was thoroughly washed with ether. The combined solvents were evaporated to dryness under reduced pressure. The residue was taken up in ether, washed with water. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford crude product **6**. The crude nitrate ester (0.30 g, 1.3 mmol) in acetonitrile (8 mL) was added to a suspension of sodium acetate trihydrate (0.18 g, 1.3 mmol) in acetonitrile (8 mL). The mixture was vigorously stirred for 2h at room temperature, poured into ice water (16 mL) saturated with sodium chloride, and extracted with ether. The ether solution was washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silical gel column chromatography with ethyl acetate/*n*-hexane (4/1) gave 0.2 g (67%) of title compound as a yellow solid: mp 105-108 °C; ^{1}H NMR (DMSO-d_6) δ 3.21 (s, 3H, NCH_3), 3.39 (s, 3H, NCH_3), 6.10 (t, 1H, CH), 6.62 (d, 2H, $C(OH)_2$), 8.74 (s, 1H, Tri-H); Mass m/e (rel. intensity), 180 (1), 152 (26), 123 (24).

3-*N*,*N*-Dimethylamino-6-(3-methylthio-1,2,4-triazin-5-yl)-1,2,4-triazine (7). A mixture of 3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl-glyoxal (**2**) (0.20 g, 1 mmol) and sodium bicarbonate (0.077 g, 0.92 mmol) in ice water and ethyl alcohol (3 mL : 1 mL) was added to a solution of methylthiosemicabazide hydrogen iodide (0.23 g, 1 mmol) in ice water (2 mL). The mixture was stirred for 1h at room temperature, and then extracted with chloroform. The solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silical gel column chromatography with benzene/ethyl acetate (4/1) followed by recrystallization from ethyl acetate gave 0.23 g (91%) of title compound as a pale yellow solid: mp 205-206 °C; ^{1}H NMR ($CDCl_3$) δ 2.73 (s, 3H, SCH_3), 3.32 (s, 3H, NCH_3), 3.51 (s, 3H, NCH_3), 9.13 (s, 1H, Tri-H), 9.93 (s, 1H, Tri-H), Mass m/e (rel. intensity) 249 (M$^+$, 53), 221 (5), 148 (22), 120 (14); Anal. Calcd. for $C_9H_{11}N_5S$: C, 43.36; H, 4.45; N, 39.33; S, 12.86. Found: C, 43.42; H, 4.17; N, 39.52; S, 12.51.

3-*N*,*N*-Dimethylamino-6-(3-amino-1,2,4-triazin-5-yl)-1,2,4-triazine (9) and 3-*N*,*N*-Dimethylamino-6-(3-amino-1,2,4-triazin-6-yl)-1,2,4-triazine (10). A solution of 3-*N*,*N*-dimethylamino-1,2,4-triazin-6-yl-glyoxal (**2**) (0.1 g, 0.5 mmol) in water and ethyl alcohol (2 mL : 1 mL) was added to a suspension of aminoguanidine bicarbonate (0.095 g, 0.7 mmol) in water (2 mL) at room temperature. After stirred for 2h at room temperature, the solution was extracted with chloroform. The chloroform solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silical gel column chromatography with ethyl acetate/chloroform/*n*-hexane (4/2/1) gave two isomers. Major isomer was 3-*N*,*N*-dimethylamino-6-(3-amino-1,2,4-triazin-6-yl)-1,2,4-triazine (**10**). Further purification by recrystalization from ethyl acetate gave 0.071 g (64%) of compound **10** as a yellow solid: mp 241-242 °C; ^{1}H NMR ($CDCl_3$) δ 3.35 (s, 6H, $N(CH_3)_2$), 5.43 (s, 2H, NH_2), 9.17 (s, 1H, Tri-H), 9.24 (s, 1H, Tri-H); Mass m/e (rel. intensity) 218 (M^+, 85), 190 (20), 120 (97); Anal. Calcd. for $C_8H_{10}N_8$: C, 44.03; H, 4.62; N, 51.39. Found: C, 44.08; H, 4.57; N, 51.60. Minor isomer was 3-*N*,*N*-dimethylamino-6-(3-amino-1,2,4-triazin-5-yl)-1,2,4-triazine. The compound was further purified by recrystallization from methyl alcohol gave 0.02 g (18%) of compound **9** as a yellow solid: mp 288-290 °C; ^{1}H NMR (DMSO-d_6) δ 3.32 (s, 6H, $N(CH_3)_2$), δ 7.32 (s, 2H, NH_2), δ 8.93 (s, 1H, Tri-H), δ 9.32 (s, 1H, Tri-H); Mass m/e (rel. intensity) 218 (M^+, 100), 190 (7), 148 (3), 120 (66).

3-*N,N*-Dimethylamino-6-(3-*N,N*-dimethylamino-1,2,4-triazin-5-yl)-1,2,4-triazine. (11). A mixture of 3-*N,N*-dimethylamino-6-(3-methylthio-1,2,4-triazin-5-yl)-1,2,4-triazine (7) (0.1 g, 0.40 mmol) in 40% dimethylamine (2 mL) was stirred at 60 °C for 12h, and then extracted with chloroform. The chloroform solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silical gel column chromatography with ethyl acetate/*n*-hexane (1/1) followed by recrystallization from ethyl acetate gave 0.089 g (90%) of title compound as a yellow solid: mp 161-162 °C; ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 6H, $N(CH_3)_2$), 3.46 (s, 6H, $N(CH_3)_2$), 9.11 (s, 1H, Tri-H), 9.52 (s, 1H, Tri-H); Mass m/e (rel. intensity) 246 (M^+, 34), 218 (2), 148 (21), 120 (27); Anal. Calcd. for $C_{10}H_{14}N_8$: C, 48.77; H, 5.73; N, 45.50. Found: C, 48.73; H, 5.86; N, 45.46.

3-*N,N*-Dimethylamino-6-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-1,2,4-triazine (12). Iodomethane (0.08 g, 0.56 mmol) was added to DMF solution of 3-*N,N*-dimethylamino-6-(3-amino-1,2,4-triazin-6-yl)-1,2,4-triazine (**10**) (0.061 g, 0.28 mmol) and sodium hydride (0.017 g, 0.71 mmol). The mixture was stirred at room temperature for 30 min. The solvent was evaporated to dryness under reduced pressure. The residue was dissolved in water and extracted with chloroform. The chloroform solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silical gel column chromatography with ethyl acetate/*n*-hexane (2/1) followed by recrystallization from ethyl acetate gave 0.059 g (86%) of **12**: mp 240-241 °C; ^{1}H NMR ($CDCl_3$) δ 3.34 (s, 12H, $2N(CH_3)_2$), 9.18 (s, 2H, Tri-H); Mass m/e (rel. intensity) 246 (M^+, 28), 148 (21), 120 (25); Anal. Calcd. for $C_{10}H_{14}N_8$: C, 48.77; H, 5.73; N, 45.50. Found: C, 48.48; H, 5.86; N, 45.56.

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