1,2,4-Triazine(VII) : Synthesis of 6,5'-*bis*-1,2,4-triazinyls and 6,6'-*bis*-1,2,4-triazinyls

Jae-Keun Lee*, Heon-Gon Kim, Kyung-Ae Kim†, and Hans Neunhoeffer‡

Department of Chemistry, College of Natural Sciences, Kyungpook National University, Taegu 702-701, Korea
†Specialty Chemical Research Institute, LG Chemical Ltd./Research Park
‡Institut für Organische Chemie der Technischen Hochschule Darmstadt, Petersenstraße 22, W-6100 Darmstadt, Germany
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Out of six possible dimers of 1,2,4-triazine, 3,3'-*bis*-1,2,4-triazinyls and 5,5'-*bis*-1,2,4-triazinyls have been reported.[1-3] When we look at the structure of the dimers, we will find out one or two "ferroin" (-N=C-C=N-) groups in one molecule. The complexation of ferroin groups of our compound is proposed in Scheme 1. But no report about exact structure is not published yet.

Actually, Culbertson and Pan synthesized 3,3'-*bis*-1,2,4-triazinyls for checking the existence of Fe(II) ion in a solution and found that the ferroin group is very sensitive to it. Since 1990, a few groups published Fe,[4] Ru[5] and Mo[6] complexes of 1,2,4-triazine derivatives containing more than one ferroin group. If *N,N*-dimethyl or amino group is substituted at one of 3, 5, or 6 positions, the electron donating effect of amino groups will increase the ability of complexation of 1,2,4-triazines with metals.

Now we wish to report one novel synthesis of 6,5'-*bis*-1,2,4-triazinyls (**7a, 8a**) and 6,6'-*bis*-1,2,4-triazinyls (**7b, 8b**) containing more than one ferroin group. Our synthetic strategy consists of two major steps. The one is the Pd-catalyzed coupling reaction of aromatic acetylene derivatives and the other is oxidation of the resulting triple bond to 1,2-dicarbonyls.

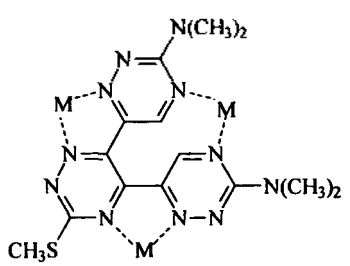
Pd-catalyzed coupling reactions of acetylene derivative on heteroaryl compounds were reported by several research groups.[7-9] The transformation of the acetylene group to 1,2-dicarbonyl is worth for 1,2,4-triazine chemistry because 1,2-dicarbonyl compounds are very important intermediate to form 1,2,4-triazines. Many groups published about transformation of the acetylene group to 1,2-dicarbonyl with various reagents such as metal complex,[10] $KMnO_4$,[11] NBS/DMSO,[12] I_2/DMSO,[13] $PdCl_2$/DMSO.[14] Among these, Yusubov method using $PdCl_2$/DMSO was simple and convenient method to oxidize the aromatic acetylene group to 1,2-dicarbonyl. Thus, we used $PdCl_2$/DMSO to produce 1,2-dicarbonyl compound containing 1,2,4-triazine.

First, 6-ethynyl-3-*N,N*-dimethylamino-1,2,4-triazine (**4**) was synthesized by hydrolysis of 3-*N,N*-dimethylamino-6-trimethylsilylethynyl-1,2,4-triazine (**2**) which was synthesized by the coupling reaction of 6-bromo-3-*N,N*-dimethylamino-1,2,4-triazine (**1**) and trimethylsilylacetylene in the presence of catalytic amount of bis(triphenylphosphine)palladium dichloride-cuprous iodide in triethylamine at 40 °C. Also compound **4** was prepared by the oxidation-decarboxylation of 3-*N,N*-dimethylamino-6-(prop-1-ol-2-yl)-1,2,4-triazine (**3**) using manganese dioxide in the presence of alkaline. Compound **3** was synthesized by the coupling reaction of compound **1** and propagyl alcohol[15] (Scheme 2). The former method has higher productivity, but the latter is more economic.

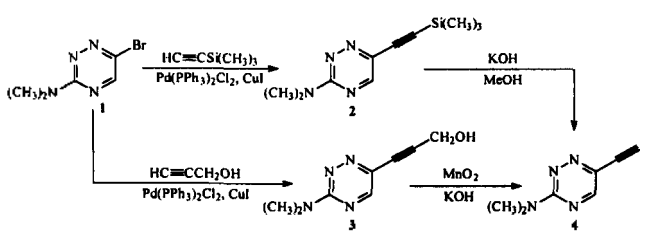
Second, the coupling reaction of 6-ethynyl-3-*N,N*-dimethylamino-1,2,4-triazine (**4**) with 2-bromopyridine was carried out under the same catalyst in DMF at 110 °C to give 1-(pyridin-2-yl)-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (**5b**) with 55% yield. Similarly, the coupling reaction of 6-ethynyl-3-*N,N*-dimethylamino-1,2,4-triazine (**4**) with 6-bromo-3-*N,N*-dimethylamino-1,2,4-triazine (**1**) and 5-bromopyrimidine were also successfully achieved under the same reaction condition to give 1,2-di-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (**5c**) with 45% yield and 1-(pyrimidin-5-yl)-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (**5d**) with 50% yield respectively. But, 1-phenyl-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (**5a**) was prepared by the same method in previous paper (Scheme 3).[9]

But, coupling reaction of 2-chloropyridine and 2-chloropyrimidine were unsuccessful. The starting materials were recovered and a trace amount of dimerization product of 6-ethynyl-3-*N,N*-dimethylamino-1,2,4-triazine (**4**) was obtained.

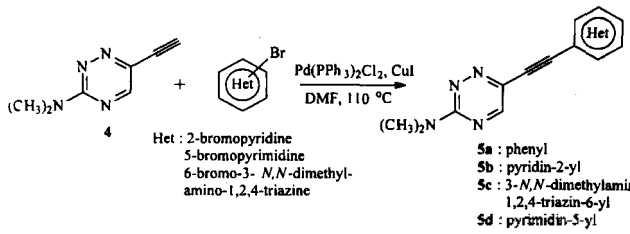
The oxidation of compounds **5a-d** using $KMnO_4$, NBS/DMSO, I_2/DMSO was unsuccessful. But the oxidation using $PdCl_2$/DMSO method was successful to give compounds **6a-c** in moderate to low yields. Our efforts to improve the yield, such as higher reaction temperature and longer reaction time were fruitless (Scheme 4). Strangely, every effort for the oxidation of compound **5d** produced a



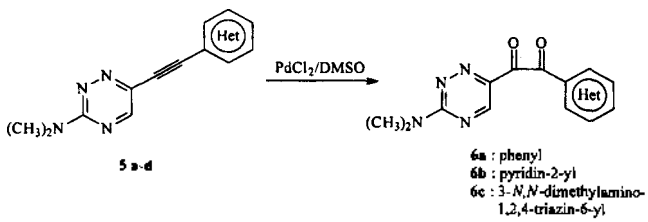
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

trace amount of the desired product and intractable tars.

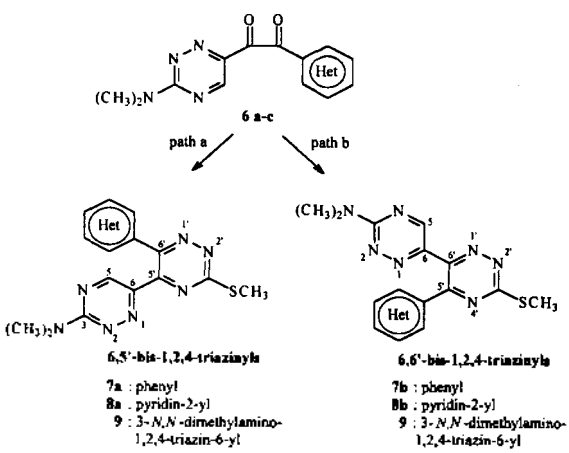
The condensation of S-methylthiosemicarbazide hydrogen iodide with **6a-c** in basic condition readily afforded the 3-methylthio derivatives of 1,2,4-triazines **7, 8, 9** (Scheme 5). But the product was a mixture of 6,5'-*bis*-1,2,4-triazinyls (**7a, 8a**) and 6,6'-*bis*-1,2,4-triazinyls (**7b, 8b**). The ratio of **7a** to **7b** were about 8 : 1 which were determined by ^{1}H NMR.

We temporarily assigned the major product as 6,5'-*bis*-1,2,4-triazinyl. The path a would be much preferred because of the electron donation effect of 3-*N,N*-dimethylamino group in triazine moiety (Scheme 6).

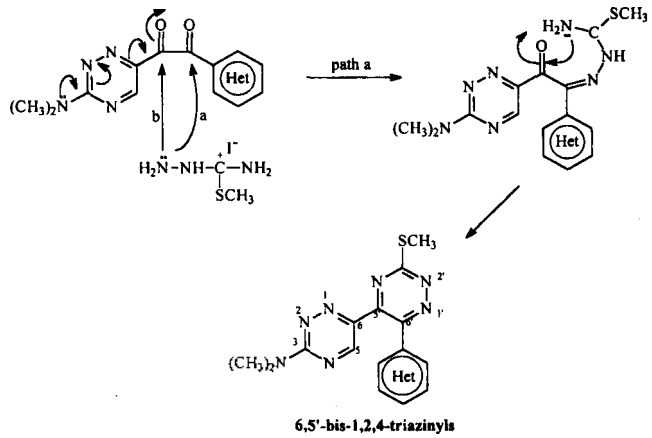
Experimental

All chemicals were purchased from Aldrich, and used without further purification. NMR and mass spectra were recorded on Varian EM-360, General Electric QE-300 and Shimazu GC MS-QP-1000A, respectively. Melting points were determined on a Electrothermal melting point apparatus and are uncorrected.

6-Ethynyl-3-*N,N*-dimethylamino-1,2,4-triazine



Scheme 5.



Scheme 6.

(4) [Method A]. To a mixture of trimethylsilylacetylene (1.18 g, 11.5 mmol) and 6-bromo-3-*N,N*-dimethylamino-1,2,4-triazine (1.95 g, 9.6 mmol) (**1**) in 100 mL of triethylamine were added bis(triphenylphosphine)palladium dichloride (0.202 g, 0.288 mmol) and cuprous iodide (0.183 g, 0.96 mmol). The reaction mixture was stirred at 40 °C for 3 hrs under argon. After filtering off the precipitate, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using hexane/ethyl acetate (4/1) as an eluent to give 3-*N,N*-dimethylamino-6-trimethylsilylethynyl-1,2,4-triazine **2** (1.48 g, 6.7 mmol). yield: 70%, mp 110-112 °C, ^{1}H NMR ($CDCl_3$): δ 0.50 (s, 9H, Si-CH_3), δ 3.50 (s, 6H, $N(CH_3)_2$), δ 8.40 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 220 (M^+, 16), 192 (15), 177 (23).

[Hydrolysis]. A solution of 3-*N,N*-dimethylamino-6-trimethylsilylethynyl-1,2,4-triazine (1.17 g, 5.3 mmol) (**2**) in methanol was added 1 N aqueous potassium hydroxide (50 mL), and the mixture was stirred at room temperature for 2 hrs and extracted with chloroform. The chloroform solution was dried with $MgSO_4$ and evaporated to dryness under reduced pressure after filtering off the $MgSO_4$. The residue was purified by silica gel column chromatography using hexane/ethyl acetate (3/1) as an eluent to give the product **4** (0.67 g, 4.5 mmol). Yield: 85%, mp 70-72 °C, ^{1}H NMR ($CDCl_3$): δ 3.20 (s, 1H, Ace-H), δ 3.50 (s, 6H, $N(CH_3)_2$), δ 8.40 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 148 (M^+, 11), 120 (8), 93 (14).

[Method B]. Bis(triphenylphosphine)palladium dichloride (21 mg, 0.03 mmol), cuprous iodide (11.5 mg, 0.06 mmol) and propagyl alcohol (0.1 g, 1.78 mmol) were added to a solution of 6-bromo-3-*N,N*-dimethylamino-1,2,4-triazine (0.3 g, 1.48 mmol) (**1**) and triethylamine (0.2 mL) in chloroform. The reaction mixture was stirred at 40 °C for 4 hrs and then diluted with hot hexane. A precipitate formed was thoroughly washed with hot hexane. Combined extracts were evaporated under reduced pressure. The residue was purified by silica gel column chromatography using hexane/ethyl acetate (1/2) as an eluent to give 3-*N,N*-dimethylamino-6-(prop-1-ol-2-yl)-1,2,4-triazine **3** (0.19 g, 1.07 mmol). yield: 72%, mp 110-112 °C, ^{1}H NMR ($CDCl_3$): δ 3.20 (s, 6H, $N(CH_3)_2$), δ 4.60 (s, 2H, CH_2OH), δ 8.30 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 178 (M^+, 28), 150 (8),

123 (9).

[Oxidation]. Potassium hydroxide powder (0.11 g, 1.95 mmol) and manganese dioxide (0.34 g, 3.9 mmol) were added to a solution of 6-(prop-1-ol-2-yl)-3-*N,N*-dimethylamino-1,2,4-triazine (0.07 g, 0.39 mmol) (**3**) in benzene. The mixture was stirred at 40 °C for 4 hrs, and the precipitate was filtered and thoroughly washed with ether. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using hexane/ethyl acetate (2/1) as an eluent to give compound **4** (0.02 g, 0.14 mmol). yield : 35%.

1-(Pyridin-2-yl)-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (5b) [General method]. To DMF solution of 2-bromopyridine (0.47 g, 3.0 mmol) and triethylamine (2.1 mL, 15 mmol) were added $Pd(PPh_3)_2Cl_2$ (0.12 g) and CuI (0.032 g) first and then 6-ethynyl-3-*N,N*-dimethylamino-1,2,4-triazine (0.6 g, 3.0 mmol) (**4**) next. After the reaction mixture was heated at reflux for 6 hrs, the solvent was evaporated to the dryness under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate/pet. ether (1/5) as an eluent to give product **5b** (0.37 g, 1.65 mmol) Yield: 55%, mp 154-156 °C, ^{1}H NMR ($CDCl_3$): δ 3.30 (s, 6H, $N(CH_3)_2$), δ 7.50 (m, 2H, Py-H), δ 8.20 (s, 1H, Tri-H), δ 8.40 (m, 2H, Py-H), Mass: m/e (rel. intensity), 225 (M^+, 22), 197 (11), 128 (100).

1,2-Di-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (5c). It was synthesized by the same way as the compound **5b**. Yield: 45%, mp 210-212 °C, ^{1}H NMR ($CDCl_3$): δ 3.50 (s, 12H, $N(CH_3)_2$), δ 8.40 (s, 2H, Tri-H), Mass: m/e (rel. intensity), 270 (M^+, 62), 172 (36), 144 (50).

1-(Pyrimidin-5-yl)-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (5d). It was synthesized by the same way as the compound **5b**. Yield: 50%, mp 184-186 °C, ^{1}H NMR ($CDCl_3$): δ 8.30 (s, 1H, Tri-H), δ 8.90 (s, 2H, Py-H(4,6)), δ 9.20 (s, 1H, Py-H(2)), Mass: m/e (rel. intensity), 226 (M^+, 12), 198 (8).

1-Phenyl-2-(3-*N,N*-Dimethylamino-1,2,4-triazin-6-yl)-ethanedione (6a) [General method]. To a solution of 1-phenyl-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-acetylene (0.12 g, 0.53 mmol) (**5a**) in DMSO (10 mL) was added $PdCl_2$ (19 mg, 0.1 mmol) at room temperature. The reaction mixture was heated at 140 °C for 6 hrs, and then diluted with diethyl ether and thoroughly washed with H_2O and brine successively. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using hexane/ethyl acetate (4/1) as an eluent to give product **6a** (82 mg, 0.32 mmol) Yield: 60%, mp 102-104 °C, ^{1}H NMR ($CDCl_3$): δ 3.30 (s, 3H, N-CH_3), δ 3.45 (s, 3H, N-CH_3), δ 7.2-7.90 (m, 5H, Ph), δ 8.84 (s. 1H, Tri-H), Mass: m/e (rel. intensity), 256 (M^+, 22), 228 (2), 105 (100).

1-(Pyridin-2-yl)-2-(3-*N,N*-Dimethylamino-1,2,4-triazin-6-yl)-ethanedione (6b). It was synthesized by the same way as the compound **6a** Yield: 30%, mp 145-147 °C, ^{1}H NMR ($CDCl_3$): δ 3.29 (s, 3H, N-CH_3), δ 3.42 (s, 3H, N-CH_3), δ 7.48 (t, 1H, Py-H), δ 7.90 (q, 1H, Py-H), δ 8.18 (d, 1H, Py-H), δ 8.60 (d, 1H, Py-H), δ 8.86 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 257 (M^+, 11), 229 (16), 123 (40).

1,2-Di-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-ethanedione (6c). It was synthesized by the same way as the compound **6a**. Yield: 15%, mp 202-204 °C, ^{1}H NMR ($CDCl_3$): δ 3.29 (s, 6H, N-CH_3), δ 3.43 (s, 6H, N-CH_3), δ 8.82 (s, 2H, Tri-H), Mass: m/e (rel. intensity), 302 (M^+, 2), 274 (12), 148 (15).

3-Methylthio-5-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-6-phenyl-1,2,4-triazine (7a) and 3-methylthio-5-phenyl-6-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-1,2,4-triazine (7b) [General method]. A solution of 1-phenyl-2-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-ethanedione (44 mg, 0.17 mmol) (**6a**) and sodium bicarbonate (14.4 mg, 0.17 mmol) in ice water (5 mL) was added to a solution of S-methylthiosemicarbazide hydrogen iodide (47 mg, 0.2 mmol) dissolved in ice water (5 mL). The mixture was stirred for 2 hrs, kept in the refrigerator for 3 hrs, and then extracted with chloroform. The chloroform solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane/ethyl acetate/benzene (1/1/4) to give two major fractions. The first fraction to give greenish yellow solid **7b** (6 mg, 0.018). Yield: 10%, mp 146-147 °C, ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, SCH_3), δ 3.35 (s, 6H, N$(CH_3)_2$), δ 7.40-7.66 (m, 5H, Ph), δ 8.64 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 325 (M^+, 76), 224 (11), 125 (100). The second fraction to give greenish yellow solid **7a** (37 mg, 0.114 mmol). Yield: 68%, mp 143-145 °C, ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 3H, SCH_3), δ 3.31 (s, 6H, $N(CH_3)_2$), δ 7.3-7.6 (m, 5H, Ph), δ 8.8 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 325 (M^+, 76), 224 (11), 125 (100).

3-Methylthio-5-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-6-(pyridin-2-yl)-1,2,4-triaz-ine (8a) and 3-methylthio-5-(pyridin-2-yl)-6-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-1,2,4-triazine (8b). It was synthesized by the same way as the compound **7**. The first fraction to give **8b**. Yield: 15%, mp 168-170 °C, ^{1}H NMR ($CDCl_3$): δ 2.80 (s, 3H, SCH_3), δ 3.33 (s, 6H, $N(CH_3)_2$), δ 7.33 (q, 1H, Py-H), δ 7.92 (m, 1H, Py-H), δ 8.16 (d, 1H, Py-H), δ 8.44 (d, 1H, Py-H), δ 8.91 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 326 (M^+, 2), 297 (5), 283 (10), 225 (100). The second fraction to give **8a**. Yield: 70%, mp 155-157 °C, ^{1}H NMR ($CDCl_3$): δ 2.81 (s, 3H, SCH_3), δ 3.33 (s, 6H, $N(CH_3)_2$), δ 7.38 (m, 1H, Py-H), δ 7.92 (q, 1H, Py-H), δ 8.13 (d, 1H, Py-H), δ 8.43 (d, 1H, Py-H), δ 8.96 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 326 (M^+, 3), 297 (4), 251 (100).

3-Methylthio-5,6-di-(3-*N,N*-dimethylamino-1,2,4-triazin-6-yl)-1,2,4-triazine (9). It was synthesized by the same way as the compound **7**. Yield: 83%, mp 180 °C (dec), ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 3H, SCH_3), δ 3.30 (s, 12H, $N(CH_3)_2$), δ 8.92 (s. 1H, Tri-H), δ 8.96 (s. 1H, Tri-H), Mass: m/e (rel. intensity), 371 (M^+, 39), 357 (11), 328 (12).

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