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 Kim¹, and Hans Neunhoeffer²

Department of Chemistry, College of Natural Sciences, Kyungpook National University, Taegu 702-701, Korea
¹Specially Chemical Research Institute, LG Chemical Ltd./Research Park
²Institut 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. When we look at the structure of the dimers, we will find one or two “ferrin” (-N=C-C=N-) groups in one molecule. The complexation of ferrin 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 ferrin group is very sensitive to it. Since 1990, a few groups published Fe₄, Ru₄ and Mo₆ complexes of 1,2,4-triazine derivatives containing more than one ferrin 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 ferrin 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.¹⁹ 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,²⁰ KMnO₄,²¹ NBS/DMSO,²² I₂/DMSO,²³ PdCl₂/DMSO.²⁴ Among these, Yusubov method using PdCl₂/DMSO was simple and convenient to oxidize the aromatic acetylene group to 1,2-dicarbonyl. Thus, we used PdCl₂/DMSO to produce 1,2-dicarbonyl compound containing 1,2,4-triazine.

First, 6-ethyl-3-N,N-dimethylamino-1,2,4-triazine (4) was synthesized by hydrolysis of 3-N,N-dimethylamino-6-trimethylsilyl ethynyl-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-y1-1,2,4-triazine (3) using manganese dioxide in the presence of alkali. Compound 3 was synthesized by the coupling reaction of compound 1 and propargyl alcohol.²⁵ (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-ethyl-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, 2-phenyl-3-[N,N-dimethylamino-1,2,4-triazin-5-yl]-acetylene (5a) was prepared by the same method in previous paper (Scheme 3).

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-ethyl-3,N,N-dimethylamino-1,2,4-triazine (4) was obtained.

The oxidation of compounds 5a-d using KMnO₄, NBS/DMSO, I₂/DMSO was unsuccessful. But the oxidation using PdCl₂/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

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\begin{align*}
\text{Scheme 1.} \\
\text{Scheme 2.}
\end{align*}
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trace amount of the desired product and intractable tar.

The condensation of S-methylthiosemicarbazide hydrogen iodide with 6a-e 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 was about 8:1 which were determined by 1H 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-OP-100QA, respectively. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

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

![Scheme 5](image)

(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 trichloromethane 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-trimethylsilylthethyl-1,2,4-triazine 2 (1.48 g, 67 mmol), yield: 70%, mp 110-112 °C, 1H NMR (CDCl3): δ 0.50 (s, 9H, Si-CH3), δ 3.50 (s, 6H, N(CH3)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-trimethylsilylthethyl-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 MgSO4 and evaporated to dryness under reduced pressure after filtering off the MgSO4. 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, 1H NMR (CDCl3): δ 3.20 (s, 1H, Ace-H), δ 3.50 (s, 6H, N(CH3)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 propargyl 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, 1H NMR (CDCl3): δ 3.20 (s, 6H, N(CH3)2), δ 4.60 (s, 2H, CH2OH), δ 8.30 (s, 1H, Tri-H), Mass: m/e (rel. intensity), 178 (M+, 28), 150 (8),

![Scheme 6](image)

![Scheme 4](image)
[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-([pyridin-2-yl]-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(PPh₃)₄Cl₂ (0.12 g) and CuI (0.032 g) first and then 6-ethyl-3-N,N-di-ethylamino-1,2,4-triazine (0.6 g, 3.0 mmol) (4) next. After the reaction mixture was poured to ice and the potassium carbonate (10 mmol) was added to the reaction mixture. The mixture was stirred for 2 h, kept in the refrigerator for 3 h, 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 to give compound 6a. Yield: 45%, mp 210-212 ºC, 1H NMR (CDCl₃): δ 6.1 (s, 6H, N(CH₃)₂), δ 8.40 (s, 2H, Tri-H), Mass: m/e (rel. intensity), 226 (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 ºC, 1H NMR (CDCl₃): δ 3.50 (s, 12H, N(CH₃)₂), δ 8.40 (s, 2H, Tri-H), Mass: m/e (rel. intensity), 270 (M⁺, 62), 172 (36), 144 (50).

1-[Pyrimdin-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 ºC, 1H NMR (CDCl₃): δ 8.30 (s, 1H, Tri-H), δ 8.90 (s, 2H, Py-H(4,5)), 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 PdCl₂ (19 mg, 0.1 mmol) at room temperature. The reaction mixture was heated at 140 ºC for 6 h, and then diluted with diethyl ether and thoroughly washed with H₂O 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 ºC, 1H NMR (CDCl₃): δ 3.30 (s, 3H, N-CH₃), δ 3.45 (s, 3H, N-CH₃), 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 ºC, 1H NMR (CDCl₃): δ 3.29 (s, 3H, N-CH₃), δ 3.42 (s, 3H, N-CH₃), δ 7.48 (t, 1H, Py-H), δ 7.90 (q, 1H, Py-H), δ 8.18 (d, 1H, Py-H), δ 8.66 (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 ºC, 1H NMR (CDCl₃): δ 3.29 (s, 6H, N-CH₃), δ 3.43 (s, 6H, N-CH₃), 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]. To a solution of 1-phenyl-2-[3-N,N-dimethylamino-1,2,4-triazin-6-yl]-ethanedione (6a) and sodium borohydride (14.4 mg, 0.17 mmol) in water (5 mL) added to a solution of 3-methylthiosemicarbazide hydrogen iodide (47 mg, 0.2 mmol) dissolved in water (5 mL). The mixture was stirred for 2 h, kept in the refrigerator for 3 h, 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 7a (37 mg, 0.114 mmol). Yield: 68%, mp 143-145 ºC, 1H NMR (CDCl₃): δ 2.76 (s, 3H, SCH₃), δ 3.31 (s, 6H, N(CH₃)₂), δ 7.9 (9), (1H, Tri-H), δ 8.9 (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 ºC, 1H NMR (CDCl₃): δ 2.76 (s, 3H, SCH₃), δ 3.31 (s, 6H, N(CH₃)₂), δ 7-7.6 (m, 5H, Ph); δ 8.9 (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-triazine (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 8a. Yield: 15%, mp 168-170 ºC, 1H NMR (CDCl₃): δ 2.80 (s, 3H, SCH₃), δ 3.33 (s, 6H, N(CH₃)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 ºC, 1H NMR (CDCl₃): δ 2.81 (s, 3H, SCH₃), δ 3.33 (s, 6H, N(CH₃)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 ºC (dec), 1H NMR (CDCl₃): δ 2.76 (s, 3H, SCH₃), δ 3.30 (s, 12H, N(CH₃)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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References