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A Direct Route to 6,6'-Disubstituted-2,2'-Bipyridines by Double Diels-Alder/*retro* Diels-Alder Reaction of 5,5'-bi-1,2,4-Triazines[†]

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[†] Part 29 in 1,2,4-Triazines in Organic Synthesis; for Part 28, see [1]

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Abstract: Inverse electron demand Diels-Alder reaction of functionalized 5,5'-bi-1,2,4-triazines with bicyclo[2.2.1]hepta-2,5-diene in boiling *p*-cymene leads to a range of 6,6'-disubstituted-2,2'-bipyridines in good yield.

Keywords: 5,5'-bi-1,2,4-triazines, norbornadiene, Diels-Alder reaction

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Introduction

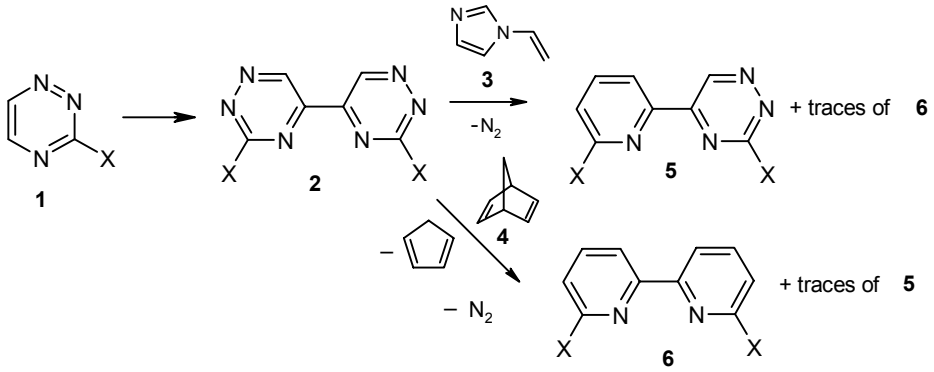
2,2'-Bipyridine is one of the most widely used ligands in coordination and supramolecular chemistry [2]. Particularly interesting and useful are its 5,5'- and 6,6'-disubstituted derivatives in view of their numerous applications in the construction of many larger supramolecular species [3]. The preparation of 6,6'-disubstituted-2,2'-bipyridines is generally allowed by the extension of Ullmann procedure involving Ni- or Pd- catalyzed homo-coupling reactions of the corresponding 6-substituted-2-halopyridines [4]. Despite their efficiency, these methods have been most widely investigated with 2-bromo-6-methylpyridine [5]. Other derivatives bearing different end groups were obtained by the further functionalization of substitutes, i.e., methyl or bromine in the combined pyridine rings [5], by using extrusion procedures involving organophosphorus [6] and organosulfur [7] compounds, or via ring transformation reactions of bis(triazolo)pyridines [8]. More recent approaches employ the intermolecular Diels-Alder/*retro* Diels-Alder (DA-rDA) reaction of 3- or 5-(2-pyridyl)-1,2,4-triazines

[9] or 5,5'-bi-1,2,4-triazines **2** [10]. Previous studies in this laboratory have shown that the latter compounds are excellent substrates for the synthesis of symmetrical cycloalkeno[c]fused 2,2'-bipyridines by the DA-rDA reaction of **2** with cyclic enamines [11]. Now we show that intermolecular DA-rDA reactions of 3,3'-disubstituted-5,5'-bi-1,2,4-triazines **2a-e** with appropriate dienophiles provide ready access to the symmetrical 6,6'-disubstituted-2,2'-bipyridines **6a-e.**

Results and Discussion

The variously substituted 5,5'-bi-1,2,4-triazines **2a-e** were prepared using a modified literature procedure [12], namely the direct dimerization of 3-substituted-1,2,4-triazines **1** (available in multigram quantities by condensation reactions staring from glyoxal and the corresponding carbamidrazones [13] or *N*-alkylthiosemicarbazones [13, 14]), with a 1.5 molar excess of potassium cyanide in water. The highest yields of the 5,5'-bi-1,2,4-triazines **2a-e** were obtained when the reactions were carried out at room temperature for 1 hour. The bitriazines **2a-e** were isolated by extraction with chloroform, and then used in crude form for the synthesis of 2,2'-bipyridines **6a-e** (Scheme 1, Table 1).

Scheme 1



X = SCH_3, $SCH(CH_3)_2$, CH_3, OCH_3, Ph

Table 1. Yields of 5,5'-disubstituted-1,2,4-triazines **2a-e**

Comp.	X	Yield (%)	M.p. (ºC)	Lit. M.p. (ºC)
2a	-SCH_3	94	166-167	168.5-170 [12]
2b	-$SCH(CH_3)_2$	98	173-174	174-175 [15]
2c	-CH_3	67	150-151	151-152 [11]
2d	-OCH_3	95	175-176	175-176.5 [12]
2e	-Ph	93	301-302	-

It has been shown previously that 3,3'-bis(methylsulfanyl)-5,5'-bi-1,2,4-triazine (**2a**, X=SCH_3) undergoes the regiospecific DA-rDA reaction with 1-vinylimidazole (**3**) in boiling bromobenzene to give a single cycloaddition product **5** together with traces of 6,6'-bis(methylsulfanyl)-2,2'-bipyridine

(**6a**) [16]. The reaction took a different course during microwave irradiation of the reaction mixture. Under these conditions the proportion of compound **6a** increased considerably and bipyridine **6a** was obtained in 35% yield when the reaction mixture was irradiated for 4 hrs at 150˚C. Attempts to increase the cycloaddition yields failed, even when longer times are used. In our search for a more effective route to **6a**, we explored the DA-rDA reaction between **2a** and bicyclo[2.2.1]hepta-2,5-diene (**4**), which can be considered as an acetylene equivalent. When this dienophile was used instead of 1-vinylimidazole (**3**), a mixture was obtained that contained compound **6a** as its major component. In order to optimize this step, a variety of solvents were tested under various conditions. The progress of the reaction was followed on TLC after workup of an aliquot. The highest yield of 6,6'-bis(methyl-sulfanyl)-1,2,4-triazine (**6a**), isolated by column chromatography from the reaction mixture, was obtained when the reaction was carried out in *p*-cymene at 170 ˚C. The utility of this reaction was further demonstrated by the one step synthesis of a range of 6,6'-disubstituted 2,2'-bipyridines **6b-e** (Scheme 1).

The treatment of sterically crowded **2b** with **4** under the same reaction conditions affords **6b** in reasonable yield. The extension of this study by using 3,3'-bis(methyl)- (**2c**) and 3,3'-bis(methoxy)- (**2d**) -5,5'-bi-1,2,4-triazines clearly showed the generality of this ring transformation process, since the 2,2'-bipyridines **6c** and **6d** were obtained in good to moderate yields. The formation of 6,6'-bis(methoxy)-2,2'-bipyridine (**6d**) was less favorable, and more time for its completion was required than the reaction which yielded methyl or methylsulfanyl derivatives. 3,3'-Bis(phenyl)-5,5'-bi-1,2,4-triazine (**2e**) also reacted smoothly with **4**, affording 2,2'-bipyridine (**6e**), respectively. Table 2 shows the reaction conditions, yields and melting points of compounds **6a-e**.

Table 2. Reaction times and yields of 6,6'-disubstituted-2,2'-bipyridines **6a-e**

Comp.	X	Reaction time (hrs)	Yield (%)	M.p. (ºC)	Lit. M.p. (ºC)
6a	$-SCH_3$	30	80	130-131	130-131 [17]
6b	$-SCH(CH_3)_2$	26	48	105-106	105-107 [18]
6c	$-CH_3$	25	88	88-89	88-89 [19]
6d	$-OCH_3$	110	59	117-118	118 [20]
6e	-Ph	28	60	175.5-176	176-177 [21]

Conclusions

In summary, we described a new, simple method of gaining access to 6,6'-disubstituted 2,2'-bipyridines **5**, which are valuable components for the construction of larger supramolecular species.

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Experimental

General

Melting points are uncorrected. IR spectra were measured with a Magna IR-760 spectrophotometer. The ^{1}H-NMR spectra were recorded in deuteriochloroform on a Varian-Gemini 200 MHz spectrometer. Mass spectra were measured with an AMD 604 (AMD Intectra GmbH, Germany). Column chromatography was performed on silica gel (230-400 mesh, 60 Merck). All the solvents used were dried and distilled according to standard procedures [22]. Merck $60F_{254}$ plates were used for analytical (TLC) chromatography.

Typical procedure: Preparation of 3,3'-Bis(phenyl)-5,5'-bi-1,2,4-triazine (**2e**)

A solution of 3-phenyl-1,2,4-triazine (0.87g, 5.54 mmol) in water (50 mL) was stirred until complete dissolution. An excess of KCN (0.54 g, 8.31 mmol, 1.5 eq) was then added as a solid in 5 portions. A precipitate (intensively colored) was formed immediately. The reaction mixture was extracted with chloroform (30 x 20 mL). The combined organic extracts were dried over $MgSO_4$, then filtered and concentrated *in vacuo*. The crude product was purified by recrystallization from ethanol to give analytically pure compound **2e** (0.82 g, 95 %) as a yellow solid, m.p. 301-302˚C; ^{1}H-NMR δ: 7.62-7.65 (m, 6 H), 8.68-8.73 (m, 4 H), 10.36 (s, 2 H); Anal. Calcd for $C_{18}H_{12}N_6 \cdot 0.25\ H_2O$: C, 67.96; H, 4.19; N, 26.23. Found: C, 68.25; H, 3.95; N, 26.54.

The synthesis of 6,6'-disubstituted-2,2'-bipyridines **6a-e**. *General procedure*.

The solution of the corresponding 3,3'-disubstituted-5,5'-bi-1,2,4-triazine (1 mmol) in *p*-cymene (10 mL) and bicyclo[2.2.1]hepta-2,5-diene (10 eq) was heated at reflux (for the reaction times see Table 2). The crude products were purified by column chromatography on silica gel (Merck type 60, 230-400 mesh), using a 10:1 hexane-chloroform mixture as eluent, followed by recrystallization from ethanol to give compounds **6a-e** as white solids.

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Sample Availability: Available from the author.