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A novel one-pot synthesis of annulated 2,2'-bipyridine ligands by inverse electron demand Diels–Alder reaction of 5,5'-bi-1,2,4-triazines¹

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Abstract

The Diels–Alder reaction of 5,5'-bi-1,2,4-triazines with cyclic enamines in the absence of a solvent leads to a range of symmetrical, annulated 2,2'-bipyridines in good yield. When the reaction is carried out in boiling dioxane only 5-(heteroaryl)1,2,4-triazines are formed. The latter, bearing methylsulfonyl substituents, are oxidized with potassium permanganate to the corresponding methylsulfonyl derivatives, which easily undergo Diels–Alder reactions with different enamines to give unsymmetrical, annulated 2,2'-bipyridines. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: bi-1,2,4-triazines; enamines; Diels–Alder reaction; annulated 2,2'-bipyridines.

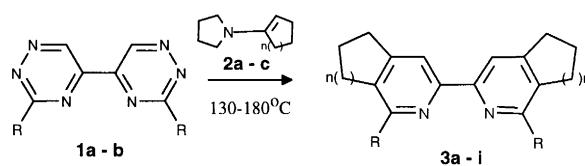
2,2'-Bipyridine ligands are widely used in coordination and supramolecular chemistry.² Their annulated derivatives incorporated into larger macropolycyclic structures are particularly attractive since they form stable luminescent complexes with a variety of lanthanide cations.³ The latter can be used as markers for modern medical applications.⁴ Although there are several methods to synthesize annulated bipyridines with benzo fusion, only a limited number of reports have appeared regarding their analogues with attached cycloalkene rings.⁵ More recent approaches employ cobalt(I)-catalyzed [2+2+2] cycloadditions between 5-hexynenitrile and 1,3-diyne⁶ or the double intramolecular Diels–Alder reaction of α,β -unsaturated hydrazones with 1,3-dialkynes.⁷ This intramolecular Diels–Alder reaction has a broad substrate scope with respect to the unsaturated hydrazones; however, the preparation of the latter compounds requires multistep synthesis. In this communication we present a more straightforward approach to cycloalkenobipyridines which involves the use of intermolecular Diels–Alder reactions of 5,5'-bi-1,2,4-triazines.

Inverse electron demand Diels–Alder reactions of monocyclic 1,2,4-triazines with electron rich dienophiles have become useful tools in the preparation of novel pyridines and bipyridines.⁸ We have applied

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this methodology to the direct synthesis of a range of symmetrical and unsymmetrical, annulated 2,2'-bipyridines from easily available 5,5'-bi-1,2,4-triazines **1a–b**⁹ and cyclic enamines.

Heating 3,3'-bis(methylthio)-5,5'-bi-1,2,4-triazine **1a** with 1-pyrrolidino-1-cyclopentene **2a** in the absence of a solvent at 130°C gives 1,1'-bis(methylthio)-3,3'-bi(cyclopenta[c]pyridine) **3a** in 68% yield. Also, the six- and seven-membered enamines (**2b** and **2c**) react efficiently with **1a** at a higher temperature giving directly **3b** and **3c** in 56 and 70% yields, respectively. Oxidation of 2,2'-bipyridines **3a–c** with potassium permanganate under phase transfer catalysis conditions provides a series of methylsulfonyl derivatives **3d–f** in good yield. The same order of reactivity is observed on treatment of 3,3'-bis(methylthio)-5,5'-bi-1,2,4-triazine **1b** with the cyclic enamines **2a–c**. However, the yield of the bisquinoline derivative **3h** formed in the reaction of **1b** with **2b** is much lower than those of bipyridines **3g** and **3i** (Scheme 1, Table 1).



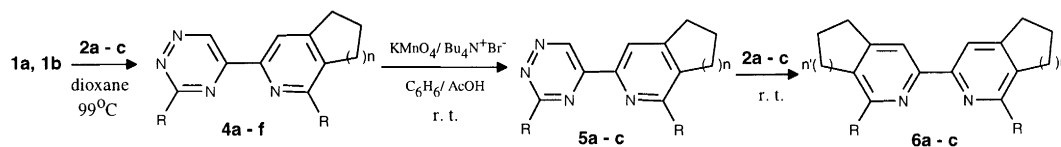
Scheme 1.

Table 1
Yields^a and melting points^b of compounds **3–6**

	n	R	Yield [%]	m. p. [°C]		n	n'	R	Yield [%]	m. p. [°C]
3a	1	SMe	68	272-273	4a	1		SMe	70	181-182
3b	2	SMe	56	226-227	4b	2		SMe	89	189-190
3c	3	SMe	70	265-266	4c	3		SMe	95	182-182
3d	1	SO ₂ Me	62	443-444	4d	1		Me	66	118-119
3e	2	SO ₂ Me	73	344-345	4e	2		Me	60	105-106
3f	3	SO ₂ Me	80	354-355	4f	3		Me	70	136-137
3g	1	Me	68	237-238	5a	1		SO ₂ Me	64	242-243
3h	2	Me	39	231-232	5b	2		SO ₂ Me	79	305-307
3i	3	Me	70	202-203	5c	3		SO ₂ Me	93	243-244
					6a	1	2	SO ₂ Me	58	334-335
					6b	1	3	SO ₂ Me	87	326-327
					6c	2	3	SO ₂ Me	58	346-347

^a Yields are not optimized; ^b m. p. are uncorrected

It has been found that 5,5'-bi-1,2,4-triazines **1a–b** undergo [4+2] cycloadditions with cyclic enamines by a different pathway if the reactions are carried out in an appropriate solvent. When **1a** and **1b** are reacted with **2a–c** in boiling dioxane only 5-(heteroaryl)-1,2,4-triazines **4a–f** are formed in excellent yield. The compounds **4a–c** bearing a methylsulfonyl substituent are oxidized easily with potassium permanganate to the corresponding methylsulfonyl derivatives **5a–c**. The reaction of these compounds with different enamines is completed within 1 hour at room temperature leading to unsymmetrical, annulated 2,2'-bipyridines **6a–c** (Scheme 2, Table 1).



Scheme 2.

In summary, we have described a new, simple method to gain access to annulated 2,2'-bipyridines with cycloalkene rings.

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