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Tetrahydroquinoline syntheses induced with catalytic amounts of viologen additives

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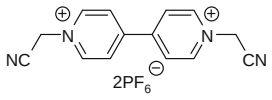
ABSTRACT

The viologen *N,N′*-dicyanomethyl-4,4′-bipyridinium·2PF_6 was found to induce an aza-Diels–Alder reaction of *N*-arylimines with *N*-vinylpyrrolidinone or *N*-vinylcarbazole, producing tetrahydroquinoline derivatives with high cis/trans selectivities and yields.

1,2,3,4-Tetrahydroquinolines have diverse applications including use as pesticides, dyes, and corrosion inhibitors.[1] Further interest in these compounds stems from an array of biological activities where some are used as pharmaceutical agents and others have reasonable potential to become approved for such use.[1] Thus numerous synthetic efforts have been made to develop a manifold of pathways to access this group of heterocycles.[1,2] In the early 1960s, Povarov reported that Lewis acids could catalyze the reaction of *N*-arylimines with ethyl vinyl ether to form tetrahydroquinolines;[3] subsequently, this approach has proven to be one of the most powerful synthetic routes to 1,2,3,4-tetrahydroquinolines,[4] as well as to many quinolines upon aromatization.[5] This reaction of *N*-arylimines with electron-rich dienophiles, often classified as an inverse-electron-demand aza-Diels–Alder reaction, has since been catalyzed by a wide variety of substances including standard Lewis acids,[4a,b] protic acids,[4c] lanthanide triflate,[4d] iodine,[4e] Selectfluor™,[4f] DDQ,[4g] nitrosonium ion (NO^+),[4h] cerium ammonium nitrate (CAN),[4i] and radical cations.[4j–l] Recently and not unrelated, we have found that a series of viologens and pyridinium salts can induce aziridine-forming reactions from π-nucleophiles and imines that are similar to those used in the above-described Povarov reaction.[6] We therefore speculated that the viologens may also be applicable to inducing and thus broadening the scope of tetrahydroquinoline synthesis.

Though they are not commonly employed in mainstream organic synthesis, viologens, that is, *N,N′*-disubstituted-4,4′-bipyridinium salts, are used extensively in biochemistry, electrochemistry, and photochemistry.[7] Due to their ability to undergo one-electron reduction to form the corresponding radical cations, viologens have been generally used as electron mediators and have thus found widespread practical application as active ingredients in herbicides and as components of electrochromic devices.[7] Viologens have also attracted the attention of chemists in the field of supramolecular chemistry since they can be used to construct molecular devices based on electron transfer from electron-rich donor compounds to the electron-deficient viologens.[8] In organic synthesis, viologens have seen moderate use as electron transfer mediators in reactions involving oxidation-reduction processes.[9] However, their use as catalysts for substrate activation remains rare.[10] In this Letter, we report that tetrahydroquinoline-forming reactions, involving *N*-arylimines and either of two *N*-vinyl nucleophiles, can be efficiently induced in the presence of the viologen, *N,N′*-dicyanomethyl-4,4′-bipyridinium·2PF_6 (**1a**).



1a

A series of *N*-arylimines (**2**) was prepared by condensation of substituted anilines and aldehydes. *N*-vinylpyrrolidinone (**3a**) was initially employed as the so-called dienophilic species in this reaction. In a typical procedure, 0.5 mmol *N*-benzylideneaniline (**2a**) and 0.6 mmol *N*-vinylpyrrolidinone (**3a**) were dissolved in 2 mL dry CH_3CN at room temperature, followed by the addition of 1 mol % viologen **1a** to the stirred solution. The reaction was found to be complete after 8 h, as determined by ^1H NMR spectroscopy, thus providing the *cis*-2,4-di-substituted-tetrahydroquinoline **4a** as the predominant product in 85% isolated yield (Scheme 1). The observed cis-selectivity is in accord with the results obtained in similar reactions by use of other types of catalysts.[4h–k]

To probe the reaction scope and mechanism, a progression of electronically diverse *N*-arylimines was explored. Regardless of the imines used (**2a**–**h**), high cis-selectivities were observed and,

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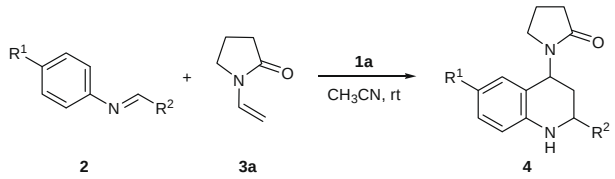


Scheme 1.

in most cases, good to excellent isolated yields were obtained (Table 1). The cis-selectivity was confirmed by X-ray analysis of a single crystal of the major diastereomer of tetrahydroquinoline **4g**, Figure 1.[11] The main differences resulting from the use of the various imines was the amount of reaction time and the quantity of viologen needed to achieve consumption of the imine. The electron-rich imines (**2b**–**d**) were clearly less reactive than all other imines. For example, **2b** and **2c**, bearing a *para*-methoxyphenyl substituent on either side of the imine C═N bond, required more viologen (**1a**) and a longer reaction time (compared with **2a**) to achieve complete consumption of the imine. In the case of **2d**, which has electron-donating substituents on both sides of the imine, 5 mol % **1a** and a reaction time of 48 h were needed to consume the imine. As a result, the yields were lower for these electron-rich tetrahydroquinolines due to imine decomposition and side reactions prior to the desired reaction. In contrast, for imines bearing electron-withdrawing groups, **2e**–**h**, 1 mol % **1a** was sufficient to allow consumption of the imine. Furthermore, lesser reaction time was required for **2f** and **2g** and higher product yields were also obtained. For imine **2h**, a notably shorter reaction time (1 h) was needed to provide an 87% isolated yield of *cis*-**4h**. However, for imine **2e**, which features an *N*-(*para*-nitrophenyl) group, only 37% *cis*-**4e** was isolated and a significant amount of benzaldehyde along with unidentified byproducts was observed, presumably due to the relative instability of imine **2e** under the reaction conditions.

Following an analogous procedure, the use of *N*-vinylcarbazole (**3b**) as the dienophile was also explored (Scheme 2). Compared to the cases employing vinyl species **3a**, for **3b**, only 1 mol % viologen **1a** was needed for most imines to achieve a faster reaction. Although the diastereoselectivity was typically lower in this series, the combined yields[11] of *cis*-**5** and *trans*-**5** were generally excellent (Table 2). Again, electron-rich imine **2d** was the least reactive substrate, requiring the addition of 5 mol % **1a** to achieve completion of the reaction and with the lowest cis/trans selectivity (81:19). The electron-deficient imines **2f**–**h** were readily consumed and converted in 1 h or less. In contrast with the reaction series involving **3a**, we observed that a polymerization of **3b** occurred in every case,[12] especially when the reaction was performed at the standard concentration (ca. 250 mM) and when an electron-deficient *N*-aryl substituent was present. Thus, up to

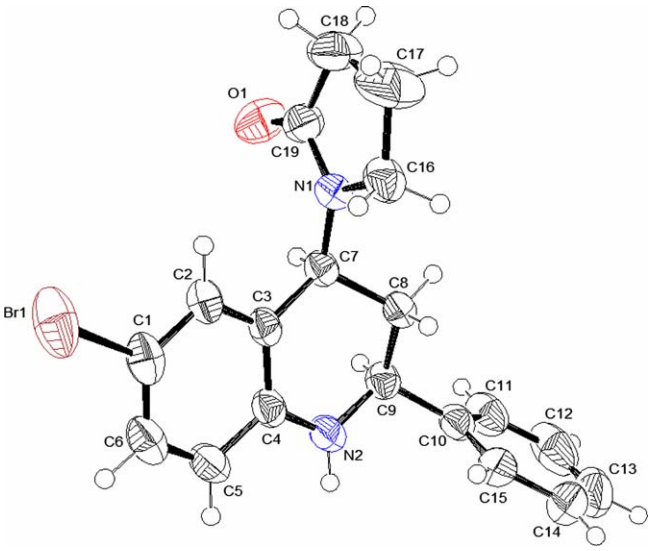
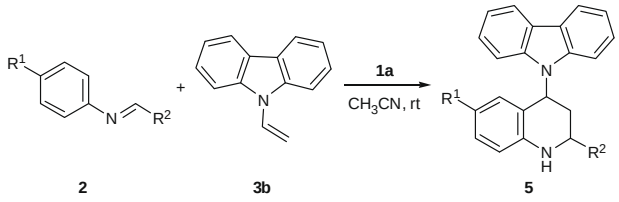


Figure 1. Structure of the major diastereomer of product **4g**.



Scheme 2.

1.5 equiv of **3b** and a more dilute system (100 mM imine) were necessary for the consumption of **2g**. In the extreme case of **2e**, even 1.5 equiv **3b** and a lower concentration only allowed a less than 5% conversion of **2e** to **5e**, whereas over 95% of **3b** was converted to polymeric compounds.

Our efforts to expand the scope of the dienophilic species with imine **2g** were met with limited success. For example, in the presence of 1 mol % **1a**, ethyl vinyl ether proved to be less reactive, that is, after 8 h, only 50% conversion of the imine and a significant amount of byproducts were observed. With an increase of **1a** to 5 mol %, complete conversion of imine occurred within 6 h; however, less than 40% (cis and trans combined) of the corresponding tetrahydroquinoline was isolated. Furthermore, styrene was essentially unreactive under the same reaction conditions wherein only decomposition of the imine was observed.

Regarding plausible mechanisms for the reaction, a radical cation pathway[4h–l] has been commonly proposed when different

Table 1
Viologen-induced aza-Diels–Alder reaction of *N*-arylimines (**2a**–**h**) with *N*-vinylpyrrolidinone (**3a**)[a]

Entry	*N*-Arylimine	R^1	R^2	**1a** (mol %)	Time (h)	cis:trans[b]	Yield *cis*-**4**[c] (%)
1	**2**[a]	H	Ph	1	8	96:4	85
2	**2b**	MeO	Ph	2	24	95:5	81
3	**2c**	H	*p*-MeO-C_6H_4	2	20	95:5	73
4	**2d**	MeO	*p*-MeO-C_6H_4	5	48	93:7	61
5	**2e**	NO_2	Ph	1	8	95:5	37
6	**2f**	H	*p*-NO_2-C_6H_4	1	6	97:3	90
7	**2g**	Br	Ph	1	6	95:5	92
8	**2h**	MeO	CO_2Et	1	1	97:3	87

[a] 1.2 equiv **3a** was used in each case.
[b] Determined from ^1H NMR spectra of the crude products.
[c] Isolated yield of *cis*-**4**.

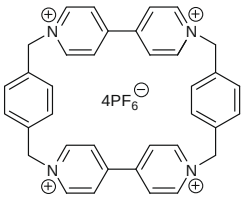
Table 2
Viologen-induced aza-Diels–Alder reaction of *N*-arylimines (**2a–h**) with *N*-vinylcarbazole (**3b**)[a]

Entry	*N*-Arylimine	R^1	R^2	**1a** (mol %)	Time (h)	cis:trans[b]	Yield **5**[c] (%)
1	**2a**	H	Ph	1	1	88:12	95
2	**2b**	*p*-MeO	Ph	1	4	89:11	95
3	**2c**	H	*p*-MeO-C_6H_4	1	3	86:14	89
4	**2d**	*p*-MeO	*p*-MeO-C_6H_4	5	8	81:19	88
5	**2e**[d]	*p*-NO_2	Ph	1	1	—	<5[e]
6	**2f**	H	*p*-NO_2-C_6H_4	1	1	86:14	93
7	**2g**[d]	*p*-Br	Ph	1	1	85:15	92
8	**2h**	*p*-MeO	CO_2Et	1	0.5	82:18	94

[a] 1.2 equiv **3b** was used in each case, except where noted.
[b] Determined from ^1H NMR spectra of the crude products.
[c] Combined isolated yield of *cis*-**5** and *trans*-**5**.
[d] 1.5 equiv **3b** was used and imine concentration was 0.1 M.
[e] Less than 5% **2e** was reacted.

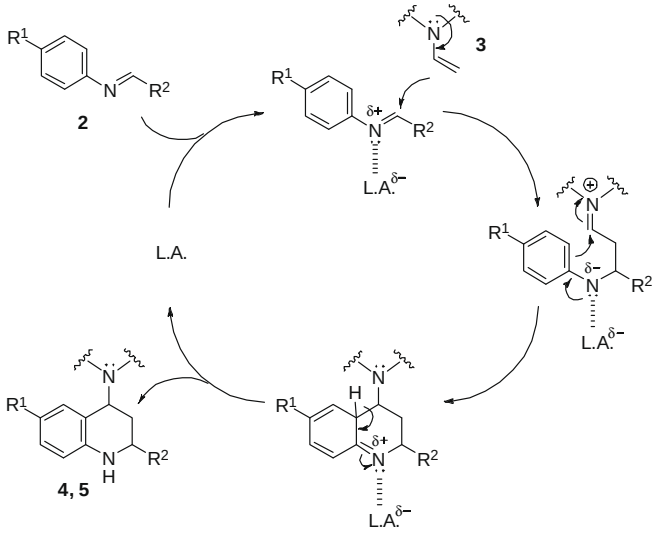
types of oxidants were employed. Such a redox process, however, would be less likely in this case. For example, from the known reduction potentials of **1a** (−180 mV vs SCE[8]), **3a** (1120 mV vs SCE[4k]), **3b** (1300 mV vs SCE[4k]), and **2** (1550–1870 mV vs SCE[4k]), it can be concluded that **1a** is not capable of oxidizing either of the reactants to generate a radical cation intermediate.

To investigate the possible interactions between viologens and reactants, a bis-viologen cyclophane (**1b**) was applied in the reaction of **2a** with **3b**. Interestingly, use of 1 mol % **1b** led to the consumption of **2a** within 2 h. When the more reactive imine **2f** was used, only 1 h was needed for the completion of the reaction. Both reactions gave similar cis/trans selectivities to those obtained with the use of **1a** as the additive. Gratifyingly, the majority of cyclophane **1b** was recovered after the reaction.[11]



1b

Based on the sum of these results and prior work by others, a non-concerted mechanism[4m–o] is proposed here where **1a** essentially functions as a Lewis acid (L.A.) which presumably interacts with the *N*-lone pair electrons of the imine (Scheme 3). Nucleophilic attack of the β-carbon of the vinyl group followed by electrophilic addition to the aniline-derived ring of the imine furnishes the cyclization intermediate. Tautomerization results in the tetrahydroquinoline product. While the exact nature of the interactions between the viologens and the reactants remains to be defined, an exciting possibility exists that a chiral viologen derivative[13] may be capable of inducing an asymmetric aza-Diels–Alder reaction of *N*-arylimines with *N*-vinyl compounds.



Scheme 3.

In summary, we have found that low catalytic loadings of the viologen *N,N′*-dicyanomethyl-4,4′-bipyridinium·$2PF_6$ (**1a**) can readily induce an aza-Diels–Alder reaction of a series of *N*-arylimines with *N*-vinylpyrrolidinone or *N*-vinylcarbazole, producing the corresponding 1,2,3,4-tetrahydroquinolines with high cis/trans selectivities and yields. A reaction mechanism based on imine activation by the viologen was proposed. Detailed studies of the reaction mechanism are currently underway. Development of chiral viologen derivatives and their applications in this and other reactions[6] are also being investigated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.058.

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