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A CAN-initiated aza-Diels–Alder reaction for a facile synthesis of 4-amido-*N*-yl tetrahydroquinolines

Bing Han, Xiao-Dong Jia, Xiao-Ling Jin, Yu-Lu Zhou, Li Yang,
Zhong-Li Liu* and Wei Yu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, China

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Abstract—Cycloaddition of *N*-arylimines with *N*-vinylpyrrolidin-2-one or *N*-methyl-*N*-vinylacetamide was efficiently initiated by cerium(IV) ammonium nitrate (CAN), and produced stereoselectively the corresponding 2,4-*cis*-4-amido-*N*-yl tetrahydroquinoline derivatives in good yields.

Tetrahydroquinoline moiety is present in many biologically active alkaloids and is an important scaffold in making pharmaceutical compounds;[1] hence, a variety of approaches have been developed for the synthesis of tetrahydroquinoline skeleton.[2] The [4+2] cycloaddition between *N*-arylimines and electron-rich dienophiles via the inverse electron demand Diels–Alder (IED–DA) reaction is probably the most powerful synthetic tool for constructing N-containing heterocyclic compounds, including tetrahydroquinolines.[2c,3] This imino Diels–Alder reaction has been reported to be catalyzed by $BF_3{\cdot}OEt_2$[4a] or trifluoroacetic acid.[4b] Recent progress includes the use of milder catalysts such as indium trichloride,[5a] lanthanide triflates,[5b,c] Ti(IV) complex,[5d] or squaric acid.[5e] Benzotriazole-mediated reactions[6] and the one-pot reaction, by using in situ formed imines,[7] were also reported. On our ongoing research program on the synthetic potentials of single electron transfer reactions, we found recently that imino Diels–Alder reactions could take place efficiently via cation radical-mediated chain mechanism.[8] As a logical extension, we were intrigued if cerium ammonium nitrate (CAN) could also initiate similar imino Diels–Alder reactions. CAN has recently emerged as a powerful one-electron oxidant for effecting a wide array of transformations of synthetic importance, including oxidative addition of carbonyl and 1,3-dicarbonyl compounds to alkenes and dienes,[9] dimerization of activated alkenes,[10] intramolecular annulations,[11] oxidative addition of heteroatom-centered radicals to alkenes and alkynes,[9b] as well as a variety of solvent molecule participated reactions.[9c,12] Generally, more than 2 equiv of CAN were required to complete the reaction, while catalytic CAN-induced reactions have scarcely been reported.[13] Therefore, in a recent review of *Acc. Chem. Res.*,[9c] Nair pointed out that making CAN catalytic should be a main focus for the future work of CAN chemistry. Herein, we report a CAN initiated imino Diels–Alder reaction between aryl imines (**1**) and *N*-vinylpyrrolidin-2-one (**2a**) or *N*-methyl-*N*-vinyl-acetamide (**2b**) that produces stereoselectively the corresponding 2,4-*cis*-4-amido-*N*-yl tetrahydroquinoline derivatives in good yields (Scheme 1).

In the procedure, an anhydrous MeCN solution (10 mL) of *N*-arylimine (**1**, 1 mmol) and *N*-vinylpyrrolidin-2-one (**2a**, 1.5 mmol) was added dropwise to a MeCN solution (10 mL) of a catalytic amount of CAN (0.10 mmol) at ambient temperature under stirring. The reaction completed within 1 h as monitored by TLC, affording the tetrahydroquinoline derivatives **3** in good yield (Table 1). Column chromatographic purification (silica gel, hexane/acetone 6:1 to 9:1) gave pure 2,4-*cis*-**3** as a unique product. The structures were fully identified by ^1H, ^{13}C and 2D NMR and HR-MS spectroscopy. As indicated by the large pseudo diaxial couplings (e.g., $J_{H\text{-}2,H\text{-}3} = 9.7$ Hz and $J_{H\text{-}4,H\text{-}3} = 9.6$ Hz for **3b**) in ^1H NMR spectra, the substituents on C-2 and C-4 are both

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Keywords: Cerium(IV) ammonium nitrate; Cycloaddition; Imines; *N*-Vinylamides; Tetrahydroquinolines.

* Corresponding authors. Tel.: +86 931 8912500; fax: +86 931 8625657 (W.Y.); e-mail: yuwei@lzu.edu.cn

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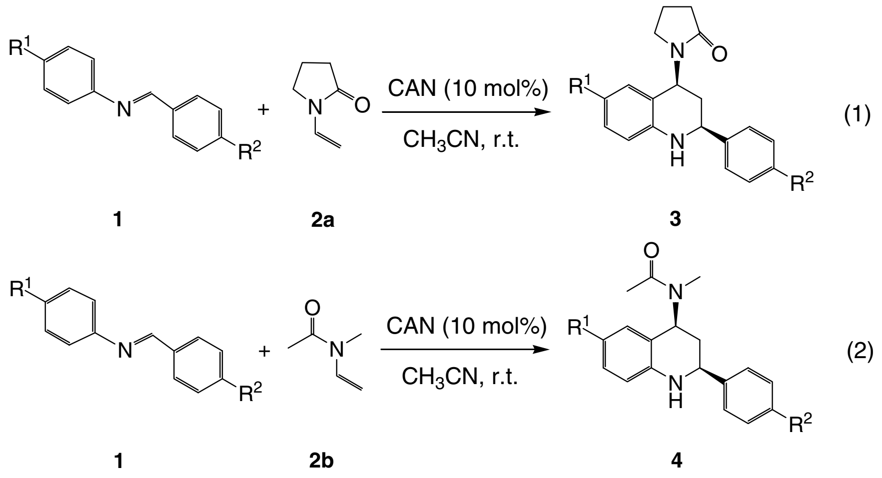


Scheme 1.

Table 1. CAN-initiated cycloaddition of *N*-arylimines (**1**) with *N*-vinylpyrrolidin-2-one (**2a**) or *N*-methyl-*N*-vinyl-acetamide (**2b**)[a]

Entry	Substrates				Product	Yield (%)[b]
		R^1	R^2			
1	**1a**	H	H	**2a**	**3a**	80
2	**1b**	H	Cl	**2a**	**3b**	81
3	**1c**	Br	H	**2a**	**3c**	81
4	**1d**	Cl	NO_2	**2a**	**3d**	85
5	**1e**	H	NO_2	**2a**	**3e**	83
6	**1f**	H	CH_3O	**2a**	**3f**	63
7	**1a**	H	H	**2b**	**4a**	68 (1:2)
8	**1b**	H	Cl	**2b**	**4b**	73 (1:3)
9	**1c**	Br	H	**2b**	**4c**	71 (1:5)
10	**1d**	Cl	NO_2	**2b**	**4d**	77 (1:3)
11	**1e**	H	NO_2	**2b**	**4e**	75 (1:3)
12	**1f**	H	CH_3O	**2b**	**4f**	52 (1:2)

[a] For reaction conditions, see the text.

[b] Isolated yields based on **1**. Values in parentheses indicate the ratio of the two rotamers as determined by ^{1}H NMR.

pseudo-equatorial and located in cis-configuration. This is also confirmed by the clear NOE correlations as exemplified in Figure 1.

The same method was used to the reaction of *N*-arylimines (**1**) with *N*-methyl-*N*-vinylacetamide (**2b**) and produced pure 2,4-*cis*-**4** as a unique product (Table 1). It should be pointed out that the ^{1}H and ^{13}C NMR spectra of **4** show two sets of closely similar signals, demonstrating the existence of two rotamers due to the restricted rotation of the amide bond, as having been reported previously.[14] The ratio of the rotamers was determined from the ^{1}H NMR integration of the H-4a peaks, which were well separated in the spectrum. Reduction of product **4** would give 4-(dialkylamino)-tetrahydroquinolines, which are very useful compounds of therapeutic importance.[1b]

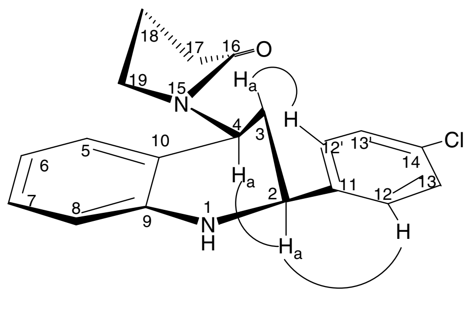
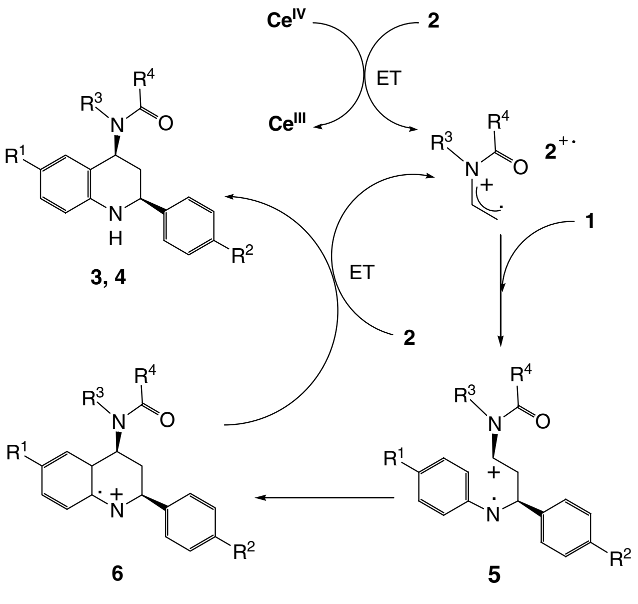


Figure 1. Selective NOE correlations of **3b**.

It is found that no reaction takes place in the absence of CAN. CAN catalyzes the reaction probably by acting as a one-electron oxidant, as expected from the strong oxidizing capacity of CAN, and its facile oxidation of electron-rich alkenes.[9] Indeed, it was observed that Ce^{4+} had been reduced to Ce^{3+} in the reaction. For reactions in which CAN acted as Lewis acid catalyst as reported by Marko et al, no reduction of CAN was detected.[13b] Thus, a cation radical-mediated [4+2] non-synchronous chain cycloaddition as depicted in Scheme 2 was proposed to rationalize the reaction.[8c,16] Since the oxidation potentials of **2a** (1.12 V vs SCE[15]) and **2b** (1.51 V vs SCE[15]) are significantly lower than that of **1** (1.59–



Scheme 2.

1.89 V vs SCE[8c]) except **1f** (1.50 V vs SCE[8c]), enamide **2** shall be preferentially oxidized by CAN, giving the corresponding cation radical $\mathbf{2}^{+\cdot}$. The terminal carbon of $\mathbf{2}^{+\cdot}$ adds regioselectively to the carbon of the C=N bond of **1**, affording cation radical adduct **5**. Ring closure of **5** gives cation radical **6**, which undergoes 1,3-hydrogen shift, and via another electron transfer, is reduced by **2** to give the product **3** or **4**. The second electron transfer produces a new $\mathbf{2}^{+\cdot}$ to propagate the radical chain reaction. This mechanism is supported by the relatively lower yield of **3f** and **4f** because the methoxy substituent in substrate **1f** makes its oxidation potential lower and close to that of **2**; hence, **1f** could also be oxidized by CAN. Since the cation radical of aryl imines is very easy to decompose to the corresponding benzaldehyde and aniline,[8c] the yield was lowered.

In conclusion, this work provides a convenient approach to construct 2,4-*cis*-tetrahydroquinoline skeleton by catalytic amount CAN-initiated cation radical cycloaddition. Extension to other substrates is underway in this laboratory.

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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.2006.03.083.

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