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Photosensitized Diels–Alder reactions of *N*-arylimines: synthesis of tetrahydroquinoline derivatives

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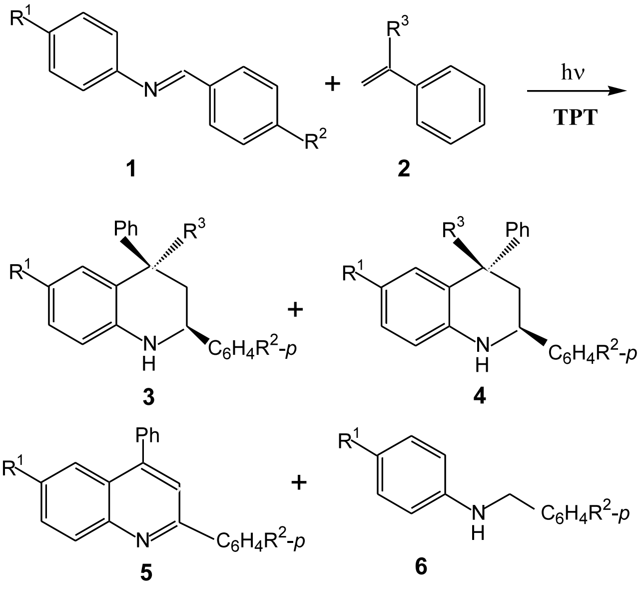
Abstract—Irradiation (λ>345 nm) of catalytic amounts of 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) in a CH_2Cl_2 solution of *N*-aryl imines and α-methylstyrene or styrene produced the corresponding [4+2] cycloaddition products, tetrahydroquinoline derivatives, in good yield. The reaction was controlled by the relative oxidation potentials of the dienophile and the diene. © 2002 Elsevier Science Ltd. All rights reserved.

The tetrahydroquinoline moiety is involved in many biologically active alkaloids, hence a variety of approaches have been developed for synthesis of the tetrahydroquinoline skeleton.[1] The [4+2] Diels–Alder reaction between *N*-arylimines and electron-rich dienophiles is probably the most powerful synthetic tool for constructing *N*-containing six-membered heterocyclic compounds including tetrahydroquinolines.[1b,2] This imino Diels–Alder reaction has been reported to be catalyzed by BF_3Et_2O[2a,b] and other Lewis acids,[2c] transition metal carbonyls,[2d] lanthanide triflates,[2e–i] trifluoroacetic acid[2j] and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ).[2k] Recent progress includes the use of triphenyl phosphonium perchlorate as the catalyst[3] and the one-pot reaction using in situ formed imines from benzaldehyde and amines.[4] To our surprise, however, although photochemically induced Diels–Alder reactions have been well documented,[5] the photosensitized imino Diels–Alder reaction has not been reported previously.[6] As part of our ongoing research program on the synthetic potential of photoinduced electron transfer (PET) reactions[7] we report herein the first PET-catalyzed Diels–Alder reaction of *N*-arylimines with α-methylstyrene and styrene which produces tetrahydroquinoline derivatives in good yields. The PET reaction was initiated by 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) which has been widely used as an electron transfer photosensitizer to induce Diels–Alder reactions.[8] The advantage of using TPT is that it absorbs light in the visible region (λ_{max}=417 and 369 nm in CH_2Cl_2)[8a] and is highly soluble in CH_2Cl_2. Furthermore, since it is a salt, there is no net charge separation associated with the electron transfer step, hence deactivation through back-electron transfer is effectively circumvented.

Irradiation at $\lambda \geq 345$ nm of a deaerated anhydrous CH_2Cl_2 solution (50 ml) of the *N*-arylimine (**1**, 1 mmol), α-methylstyrene (**2a**, 1.5 mmol) and a catalytic amount of 2,4,6-triphenylpyrylium tetrafluoroborate (TPT, 0.05 mmol) at ambient temperature for 16–24



Scheme 1.

Keywords: photoinduced electron transfer; imines; tetrahydroquinolines; cycloaddition.

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hours produced the tetrahydroquinoline derivatives **3** and **4** in good yield as a mixture of two stereoisomers. On the other hand, when styrene (**2b**) was used instead of **2a**, the yield of **3** and **4** was significantly diminished, while the aromatized quinoline **5** and the amine **6** were produced, even as predominant products in some cases (Scheme 1). Careful column chromatography by elution with hexane/acetone (20:1 to 10:1) gave the pure products which were fully identified and the configuration evaluated by 2D NMR spectroscopy.[9] The results are listed in Table 1.

It can be seen from Table 1 that the terminal carbon of **2** added regioselectively to the carbon of the C=N bond of **1** giving exclusively the 4-substituted tetrahydroquinoline derivatives **3** and **4**, and/or the corresponding quinoline derivative **5** in the case of **2b**. The ratio of *syn*/*anti* isomers was approximately 2:1.

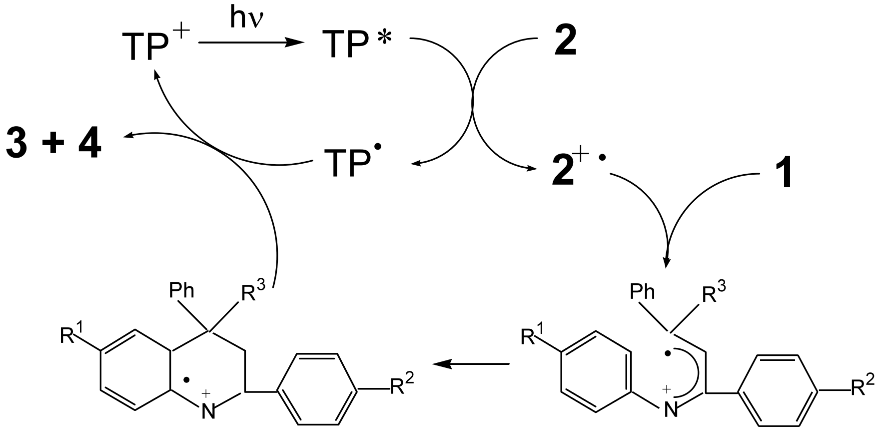
Since no reaction ever took place in the dark even under refluxing conditions or in the absence of TPT under the same experimental conditions with prolonged irradiation, this reaction might be rationalized as a PET-catalyzed non-synchronous cation radical Diels–Alder reaction with **2** acting as the dienophile, similar to the photosensitized cyclodimerization of 1,1-diphenylethene[10a] (Scheme 2). The formation of **5** is easily understood since cation radicals bearing protons are extremely easy to deprotonate due to their high acidity[11] and protonated imines may be easily reduced.[12]

The free energy change, ΔG, for the photoinduced electron transfer between TPT and **2a** and **2b** is calculated to be −0.62 and −0.42 eV, respectively, by using the Rehm–Weller equation,[13,8c] demonstrating that the reaction is thermodynamically feasible. On the other hand, since the oxidation potentials of **1** (1.73, 1.50 and 1.89 V versus SCE for **1a**, **1c** and **1g** respectively[14]) are close to those of **2** (1.67 and 1.87 V versus SCE for **2a** and **2b**, respectively,[8c] electron transfer between photoexcited TPT and **1** should also be possible. However, irradiation of TPT with **1** in the absence of **2** produced nothing but small amounts of aldehydes and amines from the decomposition of **1**. It is seen from Table 1 that substitution of the electron withdrawing nitro group in **1** appreciably shortened the reaction time and increased the conversion and yield, while the electron

Table 1. PET-induced reactions of *N*-arylimines (**1**) with styrenes (**2**)

	1		2	*t* (h)	Conv. (%)	Products and yields[a] (%)			
	R^1	R^2	R^3						
1a	H	H	**2a** CH_3	24	60	**3a** 41	**4a** 28		
1b	CH_3	H	**2a** CH_3	24	65	**3b** 45	**4b** 18		
1c	CH_3O	H	**2a** CH_3	24	50	**3c** 40	**4c** 15		
1d	CH_3	CH_3O	**2a** CH_3	24	43	**3d** 36	**4d** 12		
1e	Cl	H	**2a** CH_3	24	85	**3e** 50	**4e** 22		
1f	CH_3	NO_2	**2a** CH_3	16	80	**3f** 55	**4f** 24		
1g	Cl	NO_2	**2a** CH_3	16	88	**3g** 58	**4g** 25		
1h	CH_3O	NO_2	**2a** CH_3	24	45	**3h** 42	**4h** 20		
1a	H	H	**2b** H	24	65	**3a′** 8	**4a′** Trace	**5a** 47	**6a** 28
1b	CH_3	H	**2b** H	24	72	**3b′** 18	**4b′** Trace	**5b** 45	**6b** 10
1f	CH_3	NO_2	**2b** H	16	87	**3f′** 32	**4f′** 15	**5f** 23	**6f** 18
1g	Cl	NO_2	**2b** H	16	90	**3g′** 30	**4g′** 9	**5g** 28	**6g** 20
1h	CH_3O	NO_2	**2b** H	24	55	**3h′** 25	**4h′** 5	**5h** 25	**6h** 16

[a] Yields of isolated products based on conversion of **1**.



Scheme 2.

donating methoxy group decreased the yield. This suggests that preferential photooxidation of **2** as shown in Scheme 2 is necessary for the reaction to take place efficiently. Methoxy substitution in **1** makes its oxidation potential lower than **2** (e.g. 1.50 V versus SCE for **1c**[14]) and able to quench the photoexcited TPT preferentially, hence the yield of the cross cycloaddition products decreases.

In conclusion this work provides a convenient photochemical approach to construct tetrahydroquinoline and quinoline skeletons which can presumably be extended to other systems. Since the reaction might be modulated by alternating the relative oxidation potentials of the dienophile and the diene, and the reduction potential of the photosensitizer as well, more general synthetic utility is expected.

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9. Representative spectral data of the products. Compound **3a**: colorless needles, mp: 128–129°C (uncor.). HR-ESI-MS: 300.1744 (calcd. for $C_{22}H_{21}N+H^+$, 300.1747). ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.67$ (s, 3H, CH_3), 2.0 (dd, $J=2.8$, 13.2 Hz, 1H, H-3e), 2.34 (dd, $J=11.7$, 13.2 Hz, 1H, H-3a), 4.64 (dd, $J=2.8$,11.7 Hz, 1H, H-2), 6.63 (dd, $J=7.6$, 7.6 Hz, 1H, H-6), 6.65 (d, $J=7.2$ Hz, 1H, H-8), 6.73 (d, $J=8.0$ Hz, 1H, H-5), 7.04 (dd, $J=8.0$, 8.0 Hz, 1H, H-7), 7.19–7.50 (m, 10H, 2×Ph). ^{13}C NMR (100.08 MHz, $CDCl_3$): $\delta=29.7$ (CH_3), 42.2 (C-4), 49.9 (CH_2), 54.1 (CH), 114.6 (C-8), 117.8 (C-6), 125.8 (C-5), 126.7 (2C, Ph), 126.9 (1C, Ph), 127.3 (2C, Ph), 127.7 (C-7), 128.0 (2C, Ph), 128.6 (2C, Ph), 129.9 (1C, Ph), 139.2 (1C, Ph), 144.1 (1C, Ph), 145.0 (C-10), 150.2 (C-9). Compound **4a**: colorless needles, mp: 109–110°C (uncor.). HR-ESI-MS: 300.1742 (calcd. for $C_{22}H_{21}N+H^+$, 300.1747). ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.80$ (s, 3H, CH_3), 2.21 (dd, $J=12.0$, 13.1 Hz, 1H, H-3a), 2.31(dd, $J=3.2$, 13.1, 1H, H-3e), 4.06 (dd, $J=3.2$, 12.0 Hz, 1H, H-2), 6.65 (d, $J=8.2$ Hz, 1H, H-8), 6.81 (dd, $J=7.0$, 7.0 Hz, 1H, H-6), 7.15 (d, $J=7.0$ Hz, 1H, H-5), 7.24 (dd, $J=7.0$, 8.2 Hz, 1H, H-7), 7.12–7.37 (m, 10H, 2×Ph). ^{13}C NMR (100.08 MHz, $CDCl_3$): $\delta=29.6$ (CH_3), 41.6 (C-4), 47.9 (CH_2), 53.2 (CH), 114.3 (C-8), 117.3 (C-6), 125.8 (C-5), 126.7 (2C, Ph), 127.1 (2C, Ph), 127.6 (2C, Ph),128.2 (2C, Ph), 128.3 (C-7), 128.6 (2C, Ph), 140.5 (1C, Ph), 144.2 (1C, Ph), 144.6 (C-10), 150.4 (C-9). The coupling constants of H-2 suggests its axial conformation in both **3a** and **4a**. The significant low-field shift of H-3e and up-field shift of H-2 of **4a** in comparison with those of **3a** suggests an axial 4-phenyl group in **4a** while an equatorial 4-phenyl group in **3a**. The stereochemistry was confirmed by their NOESY spectra which show a clear cross peak between the 4-methyl and H-2 in **3a**, with no such correlation in **4a**.

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