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9-Phenyl-10-methylacridinium: A Highly Efficient and Reusable Organocatalyst for Mild Aromatization of 1,4-Dihydropyridines by Molecular Oxygen

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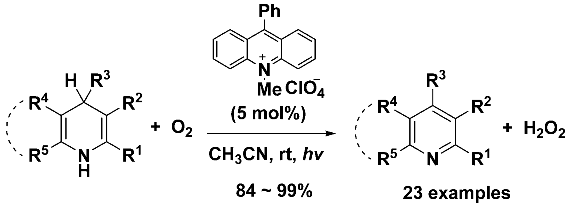

The mild, efficient, and general aerobic aromatization of Hantzsch 1,4-dihydropyridines was realized at room temperature with 5 mol % of 9-phenyl-10-methylacridinium perchlorate as the photocatalyst, which could be easily recovered and reused.

Hantzsch 1,4-dihydropyridines (1,4-DHP) are an important class of drugs for the treatment of cardiovascular diseases such as hypertension and angina pectoris.[1] The reduced nicotinamide adenine dinucleotide (NADH) as a 1,4-DHP derivative acts as the electron source for the reduction of O_2 to H_2O in the respiratory chain.[2] Hantzsch esters (2,6-dialkyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines) have been widely used to model the biological hydride transfer mechanism of coenzyme NADH.[3] In the meantime, 1,4-DHP also serve as important intermediates in the synthesis of multisubstituted pyridine compounds.[4] The oxidative aromatization of 1,4-DHP has thus drawn enormous attention in both synthetic and biomechanistic points of view and continues to be actively pursued. A variety of reagents have been developed for the aromatization.[5−9] These include the use of stoichiometric or excess amount of inorganic oxidants[5] such as $Zr(NO_3)_4$, CAN, CrO_2, HNO_3, MnO_2, $NaIO_4$, and $Mn(OAc)_3$ or organic oxidants[6] such as NO, phenyliodine(III) bis(trifluoroacetate), *S*-nitrosoglutathione, and 4-phenyl-1,2,4-triazole-3,5-dione. To carry out the aromatization in a catalytic way, Tung and Wu et al. reported the elegant photocatalytic aromatization of 1,4-DHP by platinum(II) terpyridyl complexes leading to the generation of H_2.[7] In order to make the aromatization more atom-economical and environmentally benign, the use of molecular oxygen as a clean source of oxidant is, of course, highly desirable. Since oxygen itself does not oxidize 1,4-DHP effectively, the help of an appropriate catalyst is necessary.[8,9] $RuCl_3$, silica gel-supported Co/Mn *p*-aminobenzoate, Pd/C, and ferric perchlorate in acetic acid have thus been developed as catalysts for such a purpose.[10] However, harsh reaction conditions such as high temperature and long reaction time are usually required and the yields of products are sometimes low.[10] More recently, Liu and co-workers reported the photostimulated aerobic aromatization of 1,4-DHP by catalysis of *N*-hydroxyphthalimide.[11] This method is advantageous over the previous ones in terms of organocatalysis. However, it suffers from the low catalytic efficiency (20 mol % of catalyst loading) and the limited scope of application. For example, 4-(nitrophenyl)-substituted 1,4-DHP are inert under such conditions. Besides, the catalyst underwent decomposition under the experimental conditions (CH_3CN, reflux). Therefore, the development of more

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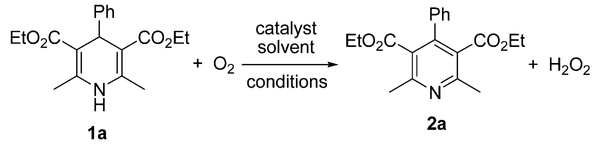
TABLE 1. Optimization of Conditions for Aromatization of 1a

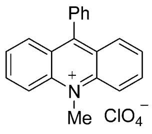


entry	catalyst (mol %)	solvent	conditions	yield[a] (%)
1	**A-1** (10)	CH$_3$CN	reflux, $h\nu$, 10 h	20
2	**A-1** (10)	CH$_3$CN	rt, hv, 12 h	99
3	**A-1** (5)	CH$_3$CN	rt, $h\nu$, 12 h	96
4	none	CH$_3$CN	rt, $h\nu$, 12 h	2
5	**A-1** (5)	CH$_3$CN	rt, 27 h	0
6	**A-1** (5)	CH$_2$Cl$_2$	rt, $h\nu$, 12 h	50
7	**A-2** (5)	CH$_3$CN	rt, $h\nu$, 12 h	77
8	**A-3** (5)	CH$_3$CN	rt, $h\nu$, 12 h	81

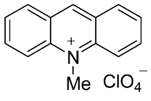
[a] Isolated yield based on **1a**.

efficient, general and catalytic aerobic oxidation of 1,4-DHP remains a challenging task and in turn justifies further research in this area.

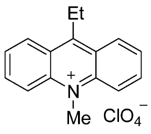
Acridinium salts are a group of mild photo-oxidants with the maximum absorption of $\lambda > 350$ nm.[12,13e] They have recently been shown by Fukuzumi's pioneering works to be effective catalysts in the chemoselective photo-oxidation of xylene, benzyl alcohol and α-methylstyrene with molecular oxygen.[13] Owing to our interest in the reactions and mechanism of coenzyme NADH models,[14] we envisioned that acridinium ions might also be utilized in the oxidation of 1,4-DHP with O$_2$. Thus, we chose 4-phenyl-substituted 1,4-DHP **1a** as the model substrate and 9-phenyl-10-methylacridinium perchlorate (**A-1**), 10-methylacridinium perchlorate (**A-2**) and 9-ethyl-10-methylacridinium perchlorate (**A-3**) as catalysts to explore this possibility. The results are listed in Table 1.



A-1



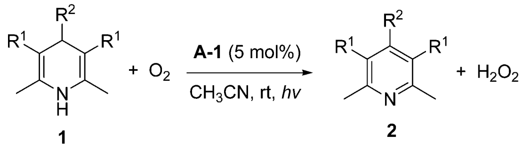
A-2



A-3

Our initial trial used 10 mol % of **A-1** as the catalyst, and the O$_2$-saturated CH$_3$CN solution of **1a** was refluxed under the irradiation of a 150 W high-pressure mercury lamp by cutting off the light of $\lambda < 310$ nm. The expected product **2a** was obtained in only 20% yield (entry 1, Table 1). To our delight, when the reaction was carried out at room temperature (rt), **2a** was produced in quantitative yield (entry 2, Table 1). When the amount of **A-1** was decreased to 5 mol %, the reaction also proceeded smoothly and a 96% yield of **2a** was achieved within the same period of time (entry 3, Table 1). Moreover, ^{1}H NMR of the crude product indicated that the catalyst remained unchanged. Thus, after the evaporation of solvent CH$_3$CN and dissolution of the crude product in anhydrous ether, the acridinium **A-1** precipitated out. By filtration, it was easily recovered and could be directly reused.

TABLE 2. Aromatization of Symmetrical 1,4-DHP



entry	1	R^1	R^2	time (h)	product	yield[a] (%)
1	**1a**	CO$_2$Et	Ph	13	**2a**	98
2	**1b**	CO$_2$Et	*m*-NO$_2$C$_6$H$_4$	7	**2b**	99
3	**1c**	CO$_2$Et	*p*-MeOC$_6$H$_4$	10	**2c**	91
4	**1d**	CO$_2$Et	*o*-BrC$_6$H$_4$	10	**2d**	96
5	**1e**	COMe	Ph	9	**2e**	93
6	**1f**	COMe	*m*-NO$_2$C$_6$H$_4$	10	**2f**	96
7	**1g**	COMe	*p*-MeOC$_6$H$_4$	10	**2g**	91
8	**1h**	CN	*m*-NO$_2$C$_6$H$_4$	10	**2h**	96
9	**1i**	CO$_2$Et	H	1	**2i**	99
10	**1j**	CO$_2$Et	Me	7	**2j**	99
11	**1k**	CO$_2$Et	Et	7	**2k**	77[b]
12	**1l**	CO$_2$Et	*n*-Pr	5	**2l**	90
13	**1m**	CO$_2$Et	Bn	4	**2m**, **2i**	50, 50
14	**1n**	CO$_2$Et	*i*-Pr	3	**2i**	99
15	**1o**	CO$_2$Et	2-furyl	3	**2i**	94

[a] Isolated yield based on **1**. [b] The dealkylation poduct **2i** was isolated in 15% yield.

Our control experiments revealed that both the catalyst and the UV irradiation are essential for the aromatization (entries 4 and 5, Table 1). The reaction had a better performance in CH$_3$CN than in CH$_2$Cl$_2$ (entry 6, Table 1). Acridinium salts **A-2** and **A-3** showed similar catalytic activity, but in a lower efficiency (entries 7 and 8, Table 1). In all the above experiments, the formation of **2a** was always accompanied by the generation of H$_2$O$_2$. This was evidenced by the iodometric titration experiments.[15] When **2a** was obtained in 96% yield (entry 3, Table 1), the amount of H$_2$O$_2$ was titrated to be $\sim$85% yield, implying the approximately 1:1 generation of **2a** and H$_2$O$_2$.

With the optimized conditions (entry 3, Table 1) in hand, we then conducted the aerobic aromatization of a variety of 1,4-DHP (Table 2). In all the cases, the expected products **2** were achieved in excellent yields. 4-Aryl-1,4-DHP containing either an electron-withdrawing group or an electron-donating group all afforded the corresponding products smoothly (entries 1−8, Table 2). 4-Alkyl-1,4-DHP were more reactive, and their aromatization was complete in a shorter period of time (entries 9−14, Table 2).

The above reactions in Table 2 dealt with structurally symmetrical Hantzsch 1,4-DHP. To broaden the scope of application, the oxidation of structurally unsymmetrical 1,4-DHP, which should be of more synthetic value but has never been reported, was carried out for the first time. Thus, 1,4-DHP **3a−g** were prepared and subjected to the treatment with **A-1**/O$_2$ under the optimized conditions (Table 3). Again the aromatization proceeded efficiently under the above optimized conditions.

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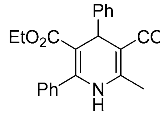
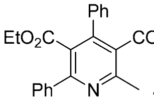
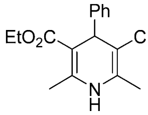
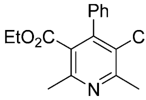
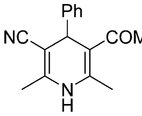
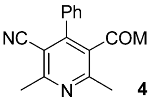
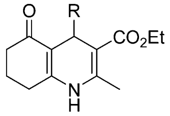
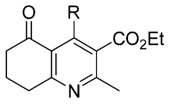
TABLE 3. Aromatization of Unsymmetrical 1,4-DHP

entry	substrate	time (h)	product	yield (%)[a, b]
1	 **3a**	9	 **4a**	99
2	 **3b**	10	 **4b**	98
3	 **3c**	10	 **4c**	92
				
4	**3d** (R = Ph)	13	**4d**	84
5	**3e** (R = p-MeOC$_6$H$_4$)	12	**4e**	86
6	**3f** (R = *o*-BrC$_6$H$_4$)	10	**4f**	90
7	**3g** (R = *m*-NO$_2$C$_6$H$_4$)	10	**4g**	89

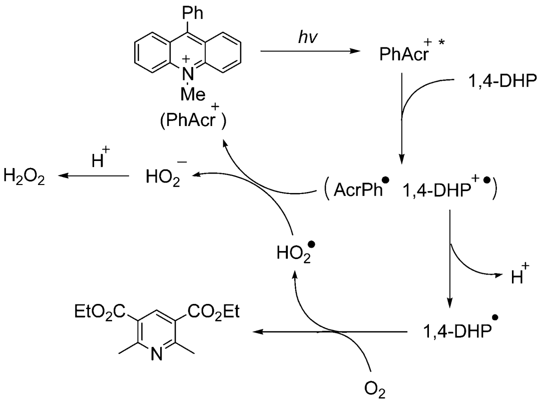
[a] The reaction conditions in Table 2 were used. [b] Isolated yield based on **3**.

By comparison with the literature methods, the catalysis of acridinium salt **A-1** is much superior in view of its high catalytic efficiency, mild reaction conditions, general scope of application, and easy recovery and reuse.

Based on the above results and literature reports,[13e] a plausible mechanism could be drawn for the catalytic aerobic aromatization, as illustrated in Scheme 1. The photoexcitation of 9-phenyl-10-methylacridinium ion (PhAcr$^+$) allows it to abstract an electron from 1,4-DHP to generate the 1,4-DHP cation radical and PhAcr$^•$. The fast deprotonation of 1,4-DHP radical cation gives the 1,4-DHP radical, which reacts with O$_2$ to afford the aromatization product along with the formation of HO$_2^•$. The electron transfer from PhAcr$^•$ to HO$_2^•$ gives HO$_2^-$ and regenerates the catalyst PhAcr$^+$ to complete the catalytic circle.

In summary, we have demonstrated that 9-phenyl-10-methylacridinium serves as an efficient catalyst for the room temperature aromatization of 1,4-DHP by molecular oxygen under metal-free conditions. The easy recovery and reuse of the catalyst make the process more environmental benign and practical.

SCHEME 1. Plausible Mechanism for Catalytic Aromatization



Experimental

Typical Procedure for the Oxidative Aromatization of 1,4-DHP. 9-Phenyl-10-methylacridinium perchlorate (**A-1**, 19 mg, 0.05 mmol) and 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (**1h**, 280 mg, 1.0 mmol) were dissolved in anhydrous CH$_3$CN (10 mL), and the solution was saturated with O$_2$ with the aid of a rubber balloon. The mixture was irradiated at rt with a 150 W high-pressure mercury lamp by cutting off the light of $\lambda <$ 310 nm. After 10 h, TLC monitoring indicated that the starting material **1h** was all consumed. The light was turned off. The resulting solution was concentrated under reduced pressure, and the residue was added into anhydrous ether (10 mL). The ethereal solution was filtered, and the filtrate was concentrated in vacuo. The crude product was then passed through a short gel column with ethyl acetate−hexane (1:1, v:v) as the eluent to give the pure product **2h** as a white solid: yield 290 mg (96%); mp 177−178 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.48−8.41 (2H, m), 7.85−7.81 (2H, m), 2.90 (6H, s); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.5, 154.0, 148.4, 124.5, 130.6, 125.7, 123.9, 114.5, 107.2, 24.7; EIMS *m/z* (rel intensity) 278 (M$^+$, 100), 232 (78), 205 (77), 164 (36), 63 (42), 51 (43), 50 (44), 42 (46). Anal. Calcd for C$_{15}$H$_{10}$N$_4$O$_2$: C, 64.74; H, 3.62; N, 20.13. Found: C, 64.81; H, 3.81; N, 20.10.

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Supporting Information Available: Synthesis and characterizations of **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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