Radical Cation Salts Induced aza-Diels-Alder Reaction: Synthesis of Hexahydrofuro[3,2-c]- quinoline Derivatives

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Abstract: Aza-Diels-Alder reaction between imines and 2,3-dihydrofuran under radical cation induced conditions was achieved and series of hexahydrofuro[3,2-c]quinoline derivatives was prepared. The stereoselectivity was affected by the substituents on imines, which revealed a stepwise mechanism. A radical cation mediated mechanism was proposed to rationalize the formation of the products.

Keywords: Aza-Diels-Alder reaction, Hexahydrofuro[3,2-c]quinolines, radical cation.

INTRODUCTION

Tetrahydroquinoline scaffold is present in various biologically active alkaloids and many tetrahydroquinoline derivatives exhibit numerous biological activities, [1-3] in which furanoquinoline derivatives are an important class of natural products and exhibit a wide spectrum of biological activities, such as antiallergic, anti-inflammatory, antipyretic, analgesic, antiplatelet, psychotropic and estrogenic activity. [4-8] Many biologically active alkaloids, such as teclealbine and flindersiamine, contain furanoquinoline moieties. The probably most powerful method for the construction of tetrahydroquinolines is aza-Diels-Alder reaction between *N*-arylimines and 2,3-dihydrofuran (DHF), due to its efficiency and the ready availability of starting materials. [2, 3, 9-12] Recently, new progress including domino reaction among anilines and DHF has been achieved [13−16], but some shortcomings of this methodology also exist. In most cases, more than stoichiometric amounts of the catalysts are required and furthermore, most of the imines are hygrosopic, unstable at high temperatures and are difficult to purify by distillation or column chromatography. Therefore, it is necessary to develop more simple, convenient and efficient catalysts to synthesize tetrahydroquinolines under mild conditions.

Commercially available, stable radical cation salt tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\cdot}$) induced reactions have been investigated for more than 20 years, and many valuable reactions initiated by such catalyst have been discovered in organic chemistry. [17, 18] As part of our ongoing research program on exploring the synthetic potentials of such catalyst, [19−25] we recently found that $TBPA^{+\cdot}$ could efficiently induce aza-Diels–Alder reaction to accomplish the synthesis of tetrahydroquinolines in good yields and with high selectivity. Herein, we wish to report the synthesis of hexahydrofuro[3,2-c]quinoline derivatives *via* this kind of aza-Diels-Alder reaction induced by radical cation salts.

Our studies began with the reaction of imine **1a** and DHF (**2**) catalyzed by $TBPA^{+\cdot}$. An anhydrous solution of **1a** and **2** in CH_2Cl_2 was added dropwise to a stirred solution of a catalytic amount of $TBPA^{+\cdot}$ suspended in anhydrous dichloromethane at ambient temperature. The reaction completed within 10–15 minutes as detected by TLC, giving exclusively two diasteroisomers of the tetrahydroquinoline derivative **3** and **4** in excellent yield. Column chromatographic purification (silica gel, hexane/acetone 40:1 to 20:1) gave the pure products, which were fully characterised. Based on these results, we chose the reaction of imine **1a** and **2** as a model reaction to optimize the reaction conditions. The results are summarized in Table **1**. [26] Initially, we added the same equivalent of the reactants to the reaction solution and the products **3a** and **4a** were obtained in 82% yield. Higher yield was obtained when the ratio of imine: DHF was raised to 2:1 (entry 2). Addition of more DHF did not improved the yield. We then screened the solvents. $CHCl_3$ and CH_3CN lead to lower yields, probably due to lower solubility of $TBPA^{+\cdot}$. Lower catalysts load also decreased the yields of the desired products.

With the optimized reaction conditions in hand, we then explored the scope of the reaction by varying the substituents on the aromatic ring of the imines. The results are summarized in Table **2**.

Imines **1** with either electron-withdrawing or electron-donating substituents were synthesized to test the generality of this methodology. From Table **1** we can see that all imines reacted with **2a** smoothly giving exclusively the corresponding tetrahydroquinoline derivatives. But the stereoselectivity was affected obviously by the substituents on imines. Electron-withdrawing groups on Ar^1 or electron-donating groups on Ar^2 increased the exo selectivity, giving more trans-products in the products mixture and inverse

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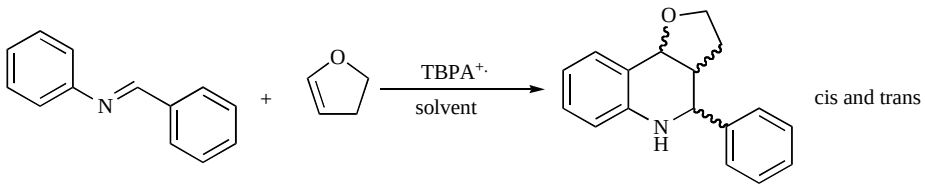
Table 1. Optimization of the Reaction Conditions

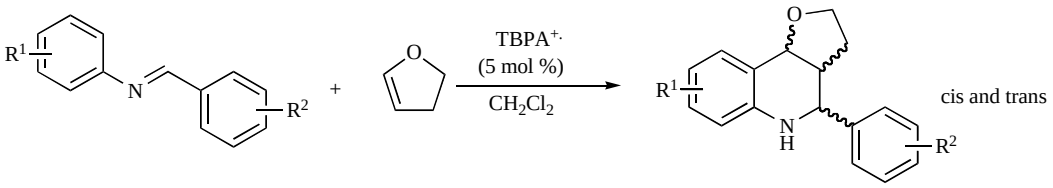


1a **2** **3a** and **4a**

Entry	Solvent	Substrate 1a : 2	Time[a] (h)	Yield[b] (%)	cis : trans (%)
1[c]	CH_2Cl_2	1:1	0.5	82	> 90:10
2[c]	CH_2Cl_2	2:1	0.5	95	> 90:10
3[c]	CH_2Cl_2	3:1	0.5	95	> 90:10
4[c]	$CHCl_3$	2:1	0.5	79	85:15
5[c]	CH_3CN	2:1	0.5	80	83:17
6[d]	CH_2Cl_2	2:1	0.5	85	> 90:10
7[e]	CH_2Cl_2	2:1	0.5	83	> 90:10

[a]Monitored by TLC. [b]Detected by crude ^{1}HNMR. [c]5 mol % $TBPA^{+\cdot}$ was added. [d]2 mol % $TBPA^{+\cdot}$ was added. [e]1 mol % $TBPA^{+\cdot}$ was added.

Table 2. Scope of the Reaction of 1 and 2



1 **2** **3** and **4**

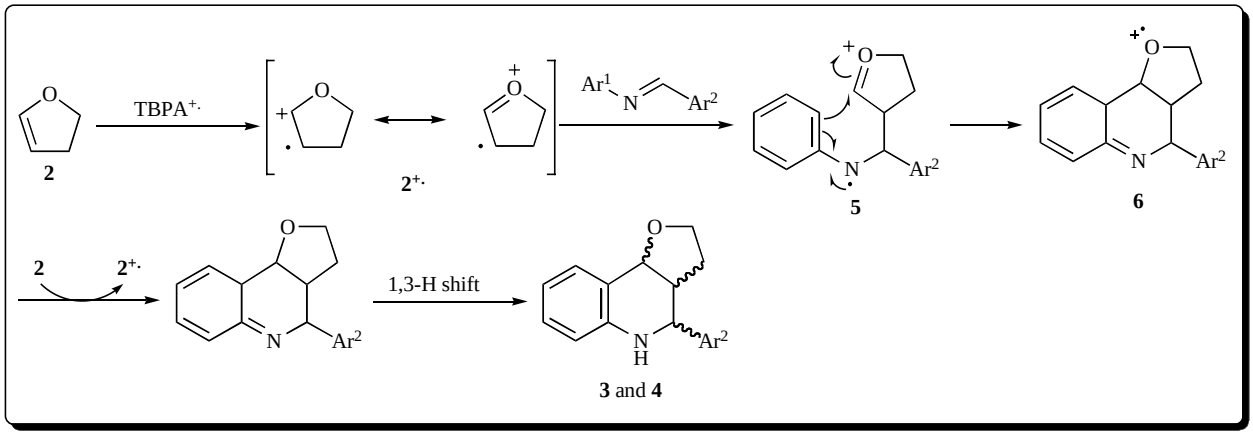
Entry	R^1	R^2	Time[a] (h)	Yield[b] (%)	cis : trans
1	H	H	0.5	93	>90:10 (**3a : 4a**)
2	H	*p*-NO_2	0.5	85	37:63(**3b : 4b**)
3	*p*-OCH_3	*p*-NO_2	0.5	83	<10:90 (**3c : 4c**)
4	*p*-Cl	*p*-NO_2	0.5	77	74:26 (**3d : 4d**)
5	*p*-Br	*p*-NO_2	0.5	75	48:52 (**3e : 4e**)
6	*p*-CH_3	*p*-NO_2	0.5	79	<10:90 (**3f : 4f**)
7	*p*-CH_3	*p*-CN	0.5	87	48:52 (**3g : 4g**)
8	H	*p*-F	0.5	90	48:52 (**3h : 4h**)
9	H	*p*-Cl	0.5	81	>90:10 (**3i : 4i**)
10	*p*-Cl	H	0.5	80	51:49 (**3j : 4j**)
11	*p*-Br	H	0.5	84	50:50 (**3k : 4k**)
12	*p*-CH_3	H	0.5	78	31:69 (**3l : 4l**)

[a]Observed by TLC. [b]Isolated yields. [c]Determined by crude ^{1}HNMR.

electrical property led to lower exo selectivity. However, in the most cases, the stereoselectivity was about 1:1, which implied that a stepwise instead of concerted mechanism was involved in the reaction.

Our previous research have revealed that the oxidation potential of the dienophile must be lower than that of the imine in order for the former to be preferentially oxidized and thus for a successful cation radical aza-Diels–Alder reaction to take place. This criterion was also supported in this reaction. Therefore the following radical cation mechanism was proposed to rationalize the formation of the products.

Firstly, DHF was oxidized by $TBPA^{+\cdot}$, producing its cation radical intermediate 2. This radical cation added to an



imine forming a new cation radical intermediate and intramolecular addition is followed. After the second electron transfer with another DHF to propagate the radical chain reaction and 1,3-H shift, the hexahydrofuro[3,2-c]quinoline derivatives were produced in a stereoselective way.

In summary, we have executed a efficient approach towards the synthesis of hexahydrofuro[3,2-c]quinoline derivatives induced by cation radical salt. We are currently focused on promoting this transformation and further exploring the use in construction of more variable heterocyclic compounds. Further research insight into the mechanism of this reaction is also underway in this laboratory.

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DISCLOSURE

Part of information included in this article has been published in our previous paper (Chinese Chemical Letters Volume 22, Issue 6, June 2011, Pages 671-674).

CONFLICT OF INTEREST

Declared none.

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[26] **Representative Spectral Data of the Products. 3a (*syn*-):** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48-1.56 (m, 1H), 2.16-2.26 (m, 1H), 2.75-2.82 (m, 1H), 3.68-3.74 (m, 1H), 3.79-3.85 (m, 2H), 4.69 (d, J = 2.8 Hz, 1H), 5.27 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.79-6.83 (m, 1H), 7.06-7.11 (m, 1H), 7.29-7.40 (m, 4H), 7.45-7.47 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ24.6, 45.8, 57.5, 66.8, 75.9, 114.9, 119.1, 122.7, 126.5, 127.6, 128.3, 128.6, 130.1, 142.1, 144.9; EI-MS m/z (relative intensity, %): 251 (74.5%), 206 (100%); ESI-HRMS: m/z Calcd for $C_{17}H_{17}NO$+H: 252.1383, found: 252.1389; **4a (*trans*-):** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70-1.74 (m, 1H), 1.99-2.06 (m, 1H), 2.43-2.47 (m, 1H), 3.81-3.90 (m, 3H), 4.05-4.11 (m, 1H), 4.59 (d, J = 5.2 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.81 (dd, J= 1.2, 8.0 Hz, 1H), 7.14 (m, 1H), 7.24-7.44 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ28.6, 43.7, 57.7, 65.2, 76.0, 114.7, 118.2, 120.1, 128.1, 128.4, 128.7, 128.9, 131.2, 141.7, 145.4; EI-MS m/z (relative intensity, %): 251 (65.4%), 206 (100%); ESI-HRMS: m/z Calcd for $C_{17}H_{17}NO$+H: 252.1383, found: 252.1379.