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Chinese Chemical Letters 22 (2011) 671–674
CHINESE CHEMICAL LETTERS
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# Radical cation salts induced domino reaction of anilines with enol ethers: Synthesis of 1,2,3,4-tetrahydroquinoline derivatives

Xiao Dong Jia [a,b,*], Yan Ren [a], Cong Dde Huo [a], Wen Juan Wang [a], Xiang Ning Chen [a], Qiong Fu [a], Xi Cun Wang [a]

[a] *Key Laboratory of Eco-Environment-Related Polymer Materials, Ministry of Education, Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, China*
[b] *State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

Received 30 September 2010

**Abstract**

A domino reaction of anilines with cyclic and acyclic enol ethers induced by catalytic amounts of $TBPA^{\bullet+}$ (5 mol%) was investigated and a series of 2,4-disubstituted-1,2,3,4-tetrahydroquinolines were synthesized. Different from cyclic enol ethers, when acyclic enol ethers were used in the reaction, they serve as surrogates of acetaldehyde, producing a series of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinolines. A single electron transfer mechanism was proposed to rationalize the products formation.


*Keywords:* Domino reaction; Radical cation salts; 1,2,3,4-Tetrahydroquinoline; Enol ether

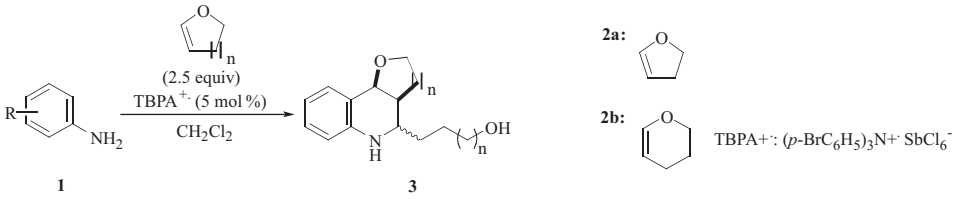
Tetrahydroquinoline scaffold is present in many biologically active alkaloids and many tetrahydroquinoline derivatives represent an important class of organic molecules attracting the interest of many synthetic and medicinal chemists. Development of new approaches for the preparation of a tetrahydroquinoline framework continues to be an active research area [1–3]. Among different strategies for these derivatives, the aza-Diels–Alder reaction between *N*-arylimines and electron-rich dienophiles (Povarov reaction) is probably the most powerful synthetic tool [2–7], due to its efficiency and the ready availability of starting materials. Recently new progress including three-component reaction among aldehydes, anilines, and electron-rich alkenes has been achieved [8–11]. Alternatively, 1:2 coupling of substituted anilines with vinyl ethers or *N*-vinyl lactams followed by tandem cyclization is also an efficient access to 2,4-disubstituted tetrahydroquinolines [12–14]. Although these methods are available, it is necessary to develop simple, convenient and efficient catalysts to synthesize tetrahydroquinolines under mild conditions.

Stable radical cation salt tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{\bullet+}$), which is commercially available, induced reactions have been investigated for decades [15,16]. As part of our ongoing research program on exploring the synthetic potentials of such catalyst [17–21], we recently found that $TBPA^{\bullet+}$ could efficiently induce imino-Diels–Alder reaction to accomplish [4 + 2] cycloaddition of aromatic imines with

* Corresponding author at: Key Laboratory of Eco-Environment-Related Polymer Materials, Ministry of Education, Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, China.
*E-mail address:* jiaxd1975@nwnu.edu.cn (X.D. Jia).

1001-8417/$ – see front matter 
doi:10.1016/j.cclet.2010.12.038

Table 1
Substituent effect on the synthesis of tetrahydroquinolines.

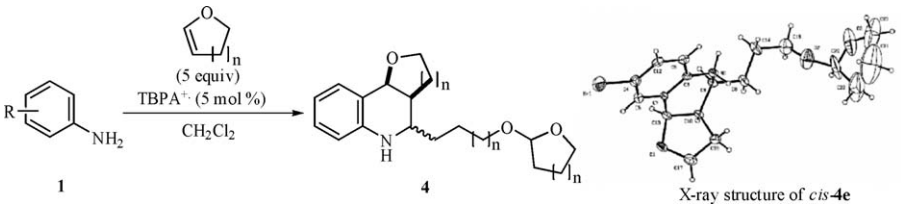



| Entry | R | 2 | 3 | Yield (%)[a] | *trans*:*cis*[b] |
|---|---|---|---|---|---|
| 1 | H | **2a** | **3a** | 92 | 1.2 |
| 2 | H | **2b** | **3b** | 74 | 1.2 |
| 3 | *p*-Cl | **2a** | **3c** | 78 | 0.9 |
| 4 | *p*-Cl | **2b** | **3d** | 71 | 1.0 |
| 5 | *o*-Cl | **2a** | **3e** | 92 | 0.8 |
| 6 | *o*-Cl | **2b** | **3f** | 80 | 1.0 |
| 7 | *p*-Br | **2a** | **3g** | 94 | 0.7 |
| 8 | *p*-Br | **2b** | **3h** | 83 | 1.0 |
| 9 | *p*-$CH_3$ | **2a** | **3i** | 65 | 1.1 |

[a] Isolated yield based on **1**.
[b] Ratio of *trans*-product:*cis*-product which determined by $^1$H NMR.

electron-rich alkenes such as styrene derivatives and *N*-vinyllactams [18–21]. As a continuation of the previous work, we next investigated the domino reaction of anilines with cyclic and acyclic enol ethers. Herein, we describe a highly efficient synthesis of 1,2,3,4-tetrahydroquinolines *via* a tandem cyclization of anilines with enol ethers induced by radical cation salts.

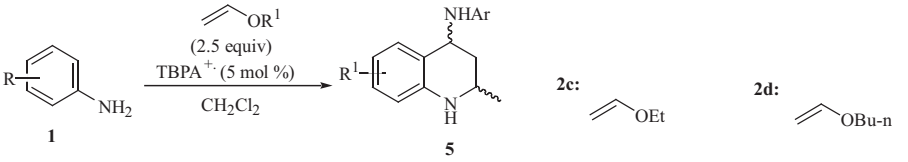
Table 2
Synthesis of protected tetrahydroquinolines[a].




| Entry | R | 3 | 4 | Yield (%)[b] | *trans*:*cis*[c] |
|---|---|---|---|---|---|
| 1 | H | **3a** | **4a** | 65 | 0.4 |
| 2 | H | **3b** | **4b** | 64 | 0.1 |
| 3 | *p*-Cl | **3a** | **4c** | 83 | 0.6 |
| 4 | *p*-Cl | **3b** | **4d** | 75 | 0.1 |
| 5 | *p*-Br | **3a** | **4e** | 89 | 0.8 |
| 6 | *p*-Br | **3b** | **4f** | 83 | <0.1 |
| 7 | *p*-F | **3a** | **4g** | 71 | 0.2 |
| 8 | *p*-F | **3b** | **4h** | 72 | 0.1 |
| 9 | *p*-$CH_3$ | **3a** | **4i** | 90 | 0.5 |
| 10 | *o*-$CH_3$ | **3a** | **4j** | 77 | 0.8 |

[a] *Reaction conditions*: aniline (1 mmol), DHF (5 mmol) or DHP (10 mmol) and $CH_2Cl_2$ (5 mL) at room temperature using $TBPA^{\bullet+}$ (0.05 mmol) for 30 min.
[b] Isolated yield.
[c] Ratio of *trans*-product:*cis*-product which determined by $^1$H NMR.

Table 3
Synthesis of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinolines.




| Entry | R | 2 | 5 | Yield (%)[a] | *trans:cis*[b] |
|---|---|---|---|---|---|
| 1 | H | **2c** | **5a** | 79 | 2.2 |
| 2 | H | **2d** | **5a** | 70 | 2.0 |
| 3 | *p*-Cl | **2c** | **5b** | 71 | 2.4 |
| 4 | *p*-Cl | **2d** | **5b** | 69 | 2.0 |
| 5 | *o*-Cl | **2c** | **5c** | 67 | 1.7 |
| 6 | *o*-Cl | **2d** | **5c** | 66 | 1.7 |
| 7 | *p*-Br | **2c** | **5d** | 72 | 2.6 |
| 8 | *p*-Br | **2d** | **5d** | 65 | 2.2 |

[a] Isolated yield.
[b] Ratio of *trans*-product: *cis*-product which determined by $^1$H NMR.

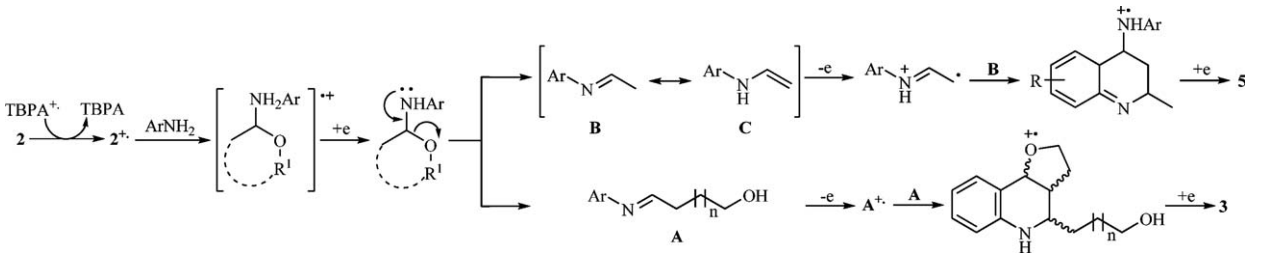
## 1. Results and discussion

Our studies began with the reaction of **1a** and **2a** catalyzed by TBPA$^{\bullet+}$. Initially a solution of **1a** and **2a** was added dropwise to a $CH_2Cl_2$ solution (10 mL) of a catalytic amount of tris(4-bromophenyl)aminium hexachloroantimonate (TBPA$^{\bullet+}$, 5 mol%) at ambient temperature under stirring. After completion detected by TLC, two products were produced as a mixture of stereoisomers. Column chromatographic purification (silica gel, hexane/acetone 40:1) gave products *syn*-**3a** and *anti*-**3a**, which were fully identified by NMR spectroscopy [22].

With these results in hand, we next explore the scope of the reaction by varying the substituents on the aromatic ring of anilines. The results were summarized in Table 1. Generally, most anilines exhibited high reactivity to 2,3-dihydrofuran (DHF), producing the desired products in high yields (entries 1–8). The strong electron-withdrawing group substituted aniline was inactive towards the corresponding enol ethers. We also performed the domino reaction of anilines with 3,4-dihydro-2*H*-pyran (DHP) but the desired products were obtained in lower yield, especially when electron-donating groups were involved.

Interestingly, when 5 equiv. of **2a** was added to the reaction solution, a series of protected adducts were isolated in good yield, in which the free hydroxyl group of **3** was coupled with another molecular of enol ethers (Table 2). The structure and configuration of product *cis*-**4e** were fully identified by X-ray [23]. These compounds were only reported by Batey, formed under dysprosium(III) catalyzed conditions, which is a kind of expensive catalyst and unsuitable to be used widely [13]. These results implied that TBPA$^{\bullet+}$ might act as an efficient catalyst to fulfill protection of hydroxyl groups.

To extend the generality of this reaction, acyclic enol ethers (**2c** and **2d**) were chosen as this tandem cyclization partners to react with anilines and the results are summarized in Table 3. Interestingly, the desired products were only isolated as by-products (<30%). A series of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinolines (**5**) were produced in




Scheme 1. Proposed mechanism of the domino reaction induced by radical cation salts.

moderate yield and *trans*-isomers were preferred [24]. In such process, enol ethers could serve as surrogates of acetaldehyde to participate in the tandem cyclizatioin, avoiding the isolation of the unstable acetaldehyde imines (Scheme 1).

In summary, we have executed an efficient approach in which the tandem cyclization between substituted anilines and enol ethers occurred to achieve the synthesis of a series of tetrahydroquinoline derivatives. We are currently focused on promoting this interesting transformation and further exploring the use in construction of more variable heterocycle compounds. Further research insight into the mechanism of this reaction is also underway in this laboratory.

## Acknowledgments

We thank NSFC (No. 21002079) and Project (No. 20096203120002) supported by the Ministry of Education of the People's Republic of China. We also thank the third Knowledge and Technological Innovation Project (No. NWNU-KJCXGC-03-75 and NWNU-KJCXGC-03-64) of Northwest Normal University for supporting our research.

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[22] Representative spectral data of the products. **3a**: *Cis*-isomer: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.57–1.90 (m, 5H), 2.04 (m, 1H), 2.60–2.67 (m, 1H), 3.43–3.46 (m, 1H), 3.69–3.71 (m, 2H), 3.80–3.82 (m, 2H), 5.12 (d, 1H, $J$ = 8.0 Hz), 6.52 (d, $J$ = 8.0 Hz, 1H), 6.74–6.78 (m, 1H), 7.03–7.07 (m, 1H), 7.30 (d, 1H, $J$ = 7.6 Hz); *trans*-isomer: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.57–1.90 (m, 5H), 2.13–2.26 (m, 1H), 2.80–2.85 (m, 1H), 3.69–3.71 (m, 2H), 3.80–3.82 (m, 2H), 3.94–3.99 (m, 1H), 3.57 (d, 1H, $J$ = 5.6 Hz), 6.63 (d, 1H, $J$ = 8.0 Hz), 6.74–6.78 (m, 1H), 7.08–7.12 (m, 1H), 7.34 (d, 1H, $J$ = 7.6 Hz); EI–MS *m*/*z* (relative intensity, %): 233 (22.1%), 174 (100%), 144 (16.3%), 130 (35.4%).
[23] Representative spectral data of the products. *syn*-**4e**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.57–1.62 (m, 4H), 1.71–1.97 (m, 6H), 2.52–2.58 (m, 1H), 3.34–3.39 (m, 2H), 3.61–3.68 (m, 1H), 3.72–3.75 (m, 2H), 3.78–3.84 (m, 2H), 4.97 (d, 1H, $J$ = 8.0 Hz), 5.05 (d, 1H, $J$ = 4.0 Hz), 6.40 (brs, 1H), 7.05 (d, 1H, $J$ = 8.4 Hz), 7.35 (s, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 23.5, 23.7, 26.3, 31.2, 32.3, 32.4, 42.2, 42.3, 52.0, 66.6, 66.9, 75.2, 110.0, 115.9, 124.6, 130.9, 132.5, 143.8; EI–MS *m*/*z* (relative intensity, %): 383 (1.5%), 381 (1.1%), 254 (16.7%), 252 (18.6%), 210 (3.7%), 208 (2.7%), 143 (3.9%), 71 (100%). Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 790498 for *syn*-**4e**.
[24] Representative spectral data of the products. *trans*-**5d**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.21 (d, 3H, $J$ = 5.6 Hz), 1.50 (t, 1H, $J$ = 10.8 Hz), 2.09 (d, 1H, $J$ = 13.2 Hz), 3.38 (brs, 1H), 3.89 (br, *NH*, 2H), 4.43 (brs, 1H), 6.43 (d, 1H, $J$ = 8.8 Hz), 6.52 (d, 2H, $J$ = 8.4 Hz), 7.13 (d, 1H, $J$ = 7.6 Hz), 7.27 (br, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 21.8, 34.4, 42.3, 48.6, 108.4, 108.8, 114.2, 116.1, 122.4, 131.4, 132.0, 133.0, 143.9, 144.9; EI–MS *m*/*z* (relative intensity, %): 398 (0.7%), 396 (1.5%), 394 (0.8%), 226 (29.0%), 224 (45.5%), 210 (86.9%), 208 (94.4%), 173 (89.5%), 171 (85.1%), 145 (19.4%), 143 (24.8%), 129 (57.9%), 65 (100%); ESI-HRMS: *m*/*z* Calcd. for $C_{16}H_{14}N_2Br_2$ + H: 392.9597, found: 392.9603; *cis*-**5d**: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.22 (d, 3H, $J$ = 6.3 Hz), 1.45 (q, 1H, $J$ = 11.7 Hz), 2.31 (ddd, 1H, $J$ = 2.1, 5.1, 12.9 Hz), 3.58 (ddd, 1H, $J$ = 2.4, 5.7, 11.1 Hz), 3.78 (br, *NH*, 2H), 4.70 (dd, 1H, $J$ = 5.4, 11.1 Hz), 6.38 (d, 1H, $J$ = 9.0 Hz), 6.55 (d, 2H, $J$ = 9.0 Hz), 7.11 (dd, 1H, $J$ = 2.4, 8.4 Hz), 7.25–7.30 (m, 2H), 7.43 (s, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ 22.2, 37.1, 46.9, 50.2, 109.0, 114.7, 115.5, 124.6, 129.6, 130.9, 132.1, 143.8, 146.4, one $^{13}$C siganl lost for overlap; EI-MS *m*/*z* (relative intensity, %): 398 (1.6%), 396 (3.1%), 394 (1.6%), 226 (66.0%), 224 (77.1%), 210 (100%), 208 (91.6%), 173 (82.7%), 171 (85.2%); ESI-HRMS: *m*/*z* Calcd. for $C_{16}H_{14}N_2Br_2$+H: 392.9597, found: 392.9601.