Tetrahedron Letters 51 (2010) 6779–6782

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Radical cation salt induced tandem cyclization between anilines and *N*-vinyl amides: synthesis of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinoline derivatives

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ARTICLE INFO

Article history:
Received 11 August 2010
Revised 13 October 2010
Accepted 22 October 2010
Available online 28 October 2010

ABSTRACT

A tandem cyclization of imines with *N*-vinyllactams induced by $TBPA^{+\cdot}$ was investigated, and a series of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinolines were synthesized based on a domino process in which *N*-vinyllactams serve as an acetaldehyde surrogate. A single electron transfer mechanism was proposed and radical cation salt acts as both a Lewis acid and one electron oxidant to induce such transformation.

1. Introduction

Tetrahydroquinoline scaffold is present in various biologically active alkaloids and many tetrahydroquinoline derivatives exhibit numerous biological activities. Among those efficient protocols towards the synthesis of tetrahydroquinoline derivatives, the aza-Diels–Alder reaction between *N*-arylimines and electron-rich dienophiles is probably a most powerful synthetic tool for the construction of nitrogen-containing heterocyclic compounds including tetrahydroquinolines,[1,2] due to its efficiency and the ready availability of starting materials. Recently, new progress including three-component reaction among aldehydes, anilines and alkenes based on one-pot procedure has been achieved.[2] However, some shortcomings based on such methodology also exist. In most cases, more than stoichiometric amounts of the catalysts are required and furthermore, most of the imines are hygroscopic, unstable at high temperatures and are difficult to purify by distillation or column chromatography. It is necessary to develop more simple, convenient and efficient catalysts to synthesize tetrahydroquinolines under mild conditions.

According to Batey and other groups' research, tetrahydroquinoline skeleton can be built via 1:2 coupling of substituted anilines with vinyl ethers (such as dihydrofuran, **ABB** pattern, see Fig. 1).[3] Batey and co-workers also reported such reaction could occur between *N*-vinyllactams (such as dihydropyrrole) and substituted anilines. It is well-known that enamines are tautomer of imines

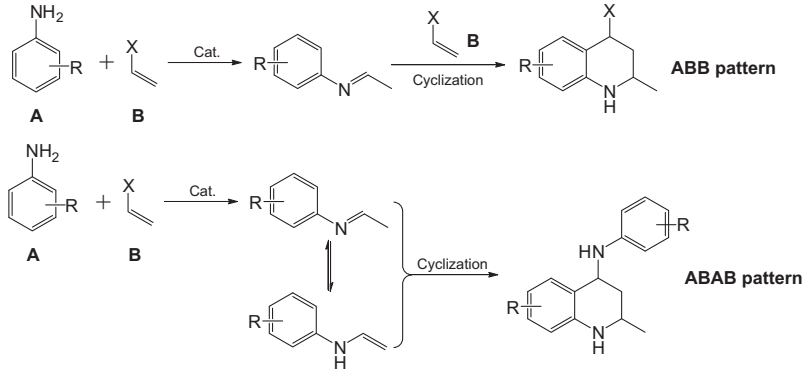

Figure 1. Routes to tetrahydroquinolines via different patterns.

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0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.10.106

when there is α-H in imines, and enamines are also good dienophiles which can participate in construction of tetrahydroquinolines. So we wondered if substituted anilines could react with *N*-vinyllactams producing imines intermediates which react with its enamine tautomers via **ABAB** pattern to achieve the synthesis of 4-anilino-tetrahydroquinoline skeleton (Fig. 1).[4] If our hypothesis is feasible, the *N*-vinyllactams can serve as acetaldehyde equivalent participating in such domino coupling reaction to synthesize tetrahydroquinolines avoiding the isolation of the unstable acetaldehyde imines.

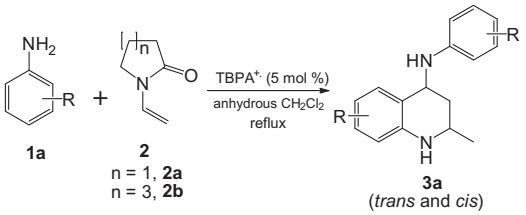
Commercially available, stable radical cation salt tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\cdot}$) induced reactions have been investigated for more than 20 years, and many valuable reactions initiated by such catalyst have been discovered to accomplish kinds of interesting transformations in organic chemistry.[5] As part of our ongoing research program on exploring the synthetic potentials of such catalyst,[6] we recently found that imino-Diels–Alder reaction could be efficiently induced by $TBPA^{+\cdot}$ to accomplish [4+2] cycloaddition of aromatic imines with electron-rich alkenes such as styrene derivatives and *N*-vinyllactams.[6b,c] Herein, we wish to report a novel synthesis of 2-methyl-4-anilino-1,2,3,4-tetrahydroquinoline derivatives via a tandem cyclization of imine with its enamine isomer induced by radical cation salts.

2. Results and discussion

Our studies began with the reaction of aniline **1a** and *N*-vinylpyrrolidinone (**2a**) catalysed by $TBPA^{+\cdot}$. Initially, a solution of **1a** (1 mmol) and **2a** (1 mmol) was added dropwise to a CH_2Cl_2 solution (10 mL) of a catalytic amount of tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\cdot}\ SbCl_6^-$, 0.05 mmol, 5 mol %) at ambient temperature under stirring. Unfortunately, no cycloaddition products were isolated. Next we performed this reaction under refluxing. After column chromatographic purification, a novel 2-methyl-4-anilino-1,2,3,4-tetrahydroquinoline derivative **3a** was isolated in good yield as a mixture of two stereoisomers that were fully identified and the configuration was evaluated by ^1H NMR spectroscopy.[7] With these results in hand, we then conducted a brief optimization of reaction conditions and the results are summarized in Table 1.

Initially, we added same amounts of the reactants to the reaction solution, but the yield was moderate (entry 1). Higher yield was obtained when the ratio of aniline: *N*-vinyllactam was raised to 2:1 (entry 2). Next, a solvent screening was performed to identify the best reaction conditions. From Table 1 we also can see, a remarkable solvent effect was found to exist in $TBPA^{+\cdot}$ initiated cycloaddition. The best result was obtained with CH_2Cl_2 as solvent while $CHCl_3$, CH_2ClCH_2Cl and CH_3CN resulted in lower yields of the desired products (entries 3–5). We also tried the reaction in the presence of one molar excess of DBP (2,6-di-*tert*-butylpyridine) as acid scavenger and the efficiency of the reaction did not change obviously (entry 6). Furthermore, *N*-vinylcaprolactam can also participate in this transformation (entries 7 and 8). Based on such results, in our later experiments, CH_2Cl_2 was chosen as the organic solvent to conduct the radical cation induced reactions.

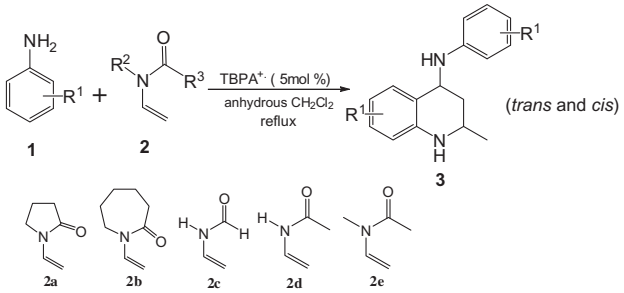
Table 1
Optimization of the reaction conditions



Entry	Solvent	Substrates	Time[a] (h)	Yield[b] (%)
1	CH_2Cl_2	1:1 (**2a**)	1	53
2	**CH_2Cl_2**	**2:1 (2a)**	**1**	**85**
3	$CHCl_3$	2:1 (**2a**)	1	82
4	CH_2ClCH_2Cl	2:1 (**2a**)	1	80
5	CH_3CN	2:1 (**2a**)	1	33
6[c]	CH_2Cl_2	2:1 (**2a**)	1	79
7	CH_2Cl_2	1:1 (**2b**)	0.5	61
8	CH_2Cl_2	2:1 (**2b**)	0.5	87

[a] Monitored by TLC.
[b] Detected by chromatography.
[c] DBP (10 mol %) was added as acid scavenger.

Table 2
Substituent effect on the synthesis of tetrahydroquinolines



Entry	R^1	2	Time (min)	Product	Yield[a] (%)	*trans:cis* [b]
1	H	**2a**	60	**3a**	85	2.1
2		**2b**	30		87	2.0
3		**2c**	60		56	3.5
4		**2d**	60		71	1.7
5		**2e**	30		93	1.9
6	*p*-Cl	**2a**	60	**3b**	70	2.6
7		**2b**	30		68	2.6
8		**2c**	60		90	1.8
9		**2d**	60		90	2.3
10		**2e**	30		98	3.3
11	*o*-Cl	**2a**	60	**3c**	97	1.9
12		**2b**	60		64	1.8
13		**2c**	60		NR	NR
14		**2d**	60		97	1.0
15		**2e**	30		98	1.8
16	*p*-Br	**2a**	60	**3d**	47	1.7
17		**2b**	30		73	3.3
18		**2c**	60		82	2.6
19		**2d**	60		87	1.9
20		**2e**	30		95	1.2
21	*p*-CH_3	**2a**	60	**3e**	NR	NR
22		**2b**	30		72	2.0
23		**2c**	60		NR	NR
24		**2d**	60		39	1.9
25		**2e**	30		74	2.2
26	*p*-CO_2CH_3	**2a**	60	**3f**	25	2.4
27		**2b**	30		25	1.2
28		**2c**	60		69	2.2
29		**2d**	60		65	1.4
30		**2e**	30		73	4.2
31	*p*-F	**2a**	60	**3g**	NR	NR
32		**2b**	30		81	1.3
33		**2c**	60		NR	NR
34		**2d**	60		NR	NR
35		**2e**	30		80	1.7
36	*p*-NO_2	**2a**	360	**3h**	No reaction	
37		**2b**				
38		**2c**				
39		**2d**				
40		**2e**				

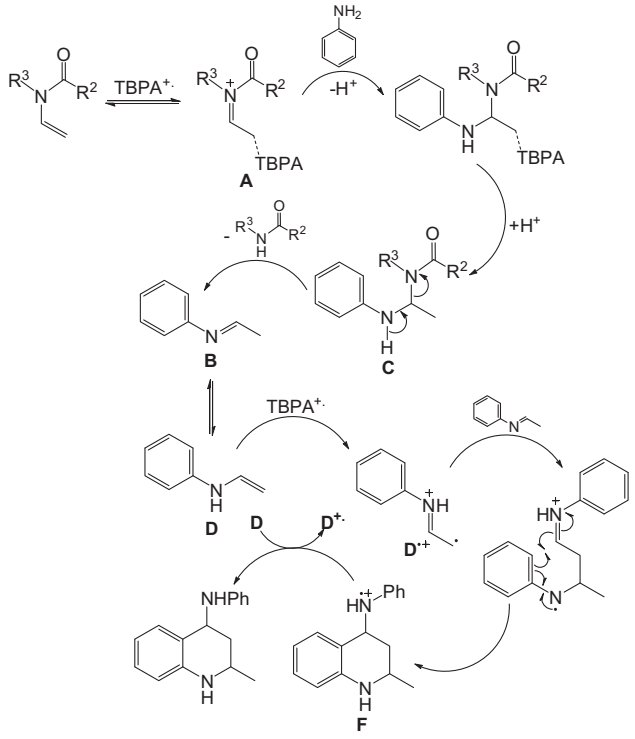
[a] Detected by chromatography.
[b] Determined by ^1H NMR.

We then examined the scope of aniline substrates by varying the substituents on the aromatic ring to explore the generality of this tandem cyclization. The results are summarized in Table 2.

As it can be seen from Table 2, the substituents of **1** exert remarkable effect on the reaction. Most of the anilines acted well in this reaction producing the desired tetrahydroquinolines in good yields (entries 1–20). But when anilines bearing strong electron-donating or electron-withdrawing groups, the reaction did not proceed smoothly and the yields of tetrahydroquinolines decreased. It is easy to know that when those strong electron-withdrawing groups are connected on anilines (entries 26–40), the nucleophilicity of anilines decreases, resulting in the difficulty of the formation of intermediate **C** (Scheme 1). Among our previous Letters, the oxidation potential of the dienophiles must be low enough to be preferentially oxidized.[6b] This criterion is also supported in the reaction. While bearing strong electron-donating groups (such as CH_3 and OCH_3), anilines are more easier to be oxidized by $TBPA^{+\cdot}$, thus the reaction was fully inhibited (entries 21 and 23). We also tried the reaction between *p*-methoxylaniline with all the five *N*-vinyl amides, no desired reaction occurred except for the oxidation of *p*-methoxylaniline.

According to the structure of the products, *N*-vinyl amides serve as acetaldehyde equivalents involved in this reaction. So we chose five different *N*-vinyl amides (**2a**–**e**) to test the influence of the surrogates of acetaldehyde. From Table 2 we can see that the best yields were obtained when *N*-methyl-*N*-vinyl-acetamide **2e** was used as an acetaldehyde equivalent. To confirm the reaction process, we also directly performed the reaction of aniline (**2a**) with acetaldehyde under the standard condition but the desired product **3a** was isolated in lower yield (34%), which implied that it is necessary to use *N*-vinyl amides as surrogates of acetaldehyde.

It is well-known that $TBPA^{+\cdot}$ can also induce acid-catalysed reactions, and in some cases the role of aminium salts was ascertained as a latent source of $SbCl_5$ (to rule out the possible process induced by $SbCl_5$, we also tried the reaction under $SbCl_5$-catalysed conditions, but no any reaction occurred).[8] Generally, addition of DBP can inhibit $SbCl_5$-catalysed reactions (from Table 1, entry 6, we can see addition of DBP does not affect the efficiency of this reaction)[8,9] but Lewis acidity of $TBPA^{+\cdot}$ cannot be inhibited completely. So a possible mechanism was proposed in which $TBPA^{+\cdot}$ acts as both Lewis acid and one electron oxidant to induce such transformation (Scheme 1).



Scheme 1. Proposed mechanism of tandem cyclization.

Firstly, $TBPA^{+\cdot}$ as a Lewis acid was added to the double bond of *N*-vinylamides to form transition substrate **A** that was attacked by aniline. After subsequent elimination of the corresponding amide, Schiff base **B** was generated which underwent enamine tautomerism forming enamine **D**. Enamine **D** was further oxidized by $TBPA^{+\cdot}$ producing its radical cation, followed by addition to another Schiff base **B**. After cyclization and back electron transfer (**D** lost an electron to **F**, producing $\mathbf{D}^{+\cdot}$.) to propagate the chain reaction, 2-methyl-4-anilino-1,2,3,4-tetrahydroquinoline was produced in a stereoselective way.

Different from most literatures' results, the products 2-methyl-4-lactam-1,2,3,4-tetrahydroquinolines (via **ABB** pattern) were **not** isolated. The main reason lies in that in the presence of single electron oxidant, enamine **D** prefers to be oxidized by $TBPA^{+\cdot}$ than the corresponding *N*-vinyllactams (the anilino group in enamine **D** is stronger electron-donating substituent than amide), which is the critical factor resulting in the formation of the products via ABAB pattern.[10]

In summary, we have executed a novel approach in which the tandem cyclization between substituted anilines and *N*-vinyllactams occurred via **ABAB** pattern to achieve the synthesis of a series of tetrahydroquinoline derivatives. We are currently focused on promoting this novel transformation and further exploring the use in construction of more variable heterocycle compounds. Further investigations in the mechanism of this reaction are also underway in this laboratory.

Acknowledgements

We thank Project 20096203120002 supported by the Ministry of Education of the People's Republic of China and the third Knowledge and Technological Innovation Project (NWNU-KJCXGC-03-75 and NWNU-KJCXGC-03-64) of Northwest Normal University for supporting our research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.106.

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7. *Representative spectral data of the products*. *trans*-**3d:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, J = 5.6 Hz, 3H), 1.50 (t, J = 10.8 Hz, 1H), 2.09 (d, J = 13.2 Hz, 1H), 3.38 (br s, 1H), 3.89 (br, *NH*, 2H), 4.43 (br s, 1H), 6.43 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.27 (br, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 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. *syn*-**3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, J = 6.3 Hz, 3H), 1.45 (q, J = 11.7 Hz, 1H), 2.31 (ddd, J = 2.1, 5.1, 12.9 Hz, 1H), 3.58 (ddd, J = 2.4, 5.7, 11.1 Hz, 1H), 3.78 (br, *NH*, 2H), 4.70 (dd, J = 5.4, 11.1 Hz, 1H), 6.38 (d, J = 9.0 Hz, 1H), 6.55 (d, J = 9.0 Hz, 2H), 7.11 (dd, J = 2.4, 8.4 Hz, 1H), 7.25–7.30 (m, 2H), 7.43 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 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 signal 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.
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10. During the course of reaction, Ar_3N, the reduction product of $TBPA^{+\cdot}$, was produced, which suggested that redox reactions occurred.