ORGANIC LETTERS

2010
Vol. 12, No. 4
732−735

Synthesis of β-Aminoketones and Construction of Highly Substituted 4-Piperidones by Mannich Reaction Induced by Persistent Radical Cation Salts

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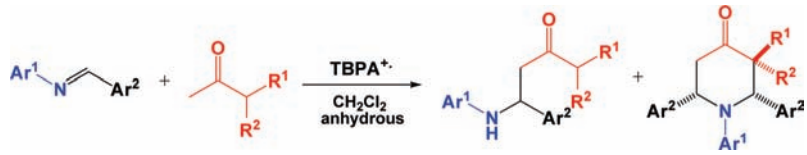
Received December 8, 2009

ABSTRACT



A Mannich reaction of imines and ketones induced by persistent radical cation salts was investigated, and a series of Mannich bases, β-aminoketones, were synthesized. A novel cyclization to form the 4-piperidone skeleton was achieved in a tandem process. The reaction can be rationalized as a radical cation process supported by various evidence.

Since the famous Wurster's Red and Blue salts were prepared in 1879,[1] a great variety of persistent and isolable radical cation salts have been prepared, and many valuable reactions initiated by such salts have been discovered to accomplish many kinds of interesting types of transformations in organic chemistry.[2,3] Among them, aminium radical cation salts, tris(2,4-dibromophenyl)aminium hexachloroantimonate (TDBPA$^{+\bullet}$) and the commercially available tris(4-bromophenyl)aminium hexachloroantimonate (TBPA$^{+\bullet}$), have been widely used as single electron oxidants to achieve selective and highly efficient transformations, such as Diels−Alder reactions, rearrangements, couplings, etc.[3,4] Thereby, from our ongoing research program on the exploration of the synthetic potential of TDBPA$^{+\bullet}$ or TBPA$^{+\bullet}$,[5] we report herein a

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(2) Preparation of various stable and isolable radical cation salts, see: (a) Bell, F. A.; Ledwith, A.; Sherrington, D. C. *J. Chem. Soc. (C)* **1969**, 2719–2720. (b) Boduszek, B.; Shine, H. J. *J. Org. Chem.* **1988**, *53*, 5142–5143. (c) Rathore, R.; Abdelwahed, S. H.; Guzei, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 13582–13583. (d) Debroy, P.; Shukla, R.; Lindeman, S. V.; Rathore, R. *J. Org. Chem.* **2007**, *72*, 1765–1769.

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10.1021/ol9027978
Published on Web 01/20/2010

Mannich reaction initiated by cationic radical salts that produces β-amino ketones and 4-piperidone derivatives.

The Mannich reaction is an important approach in carbon−carbon bond construction and has been widely applied in organic synthesis.[6] In Mannich reactions, the C=N double bond reacts with the enol tautomer of the carbonyl compound to give the β-aminocarbonyl compound, in which the iminium ion is the active species to accelerate the addition (Figure 1). Therefore, the most important point in a Mannich

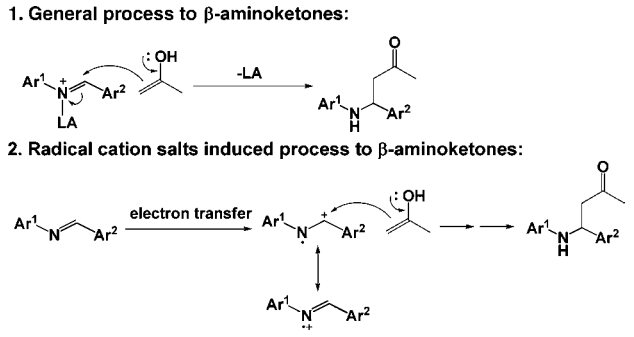


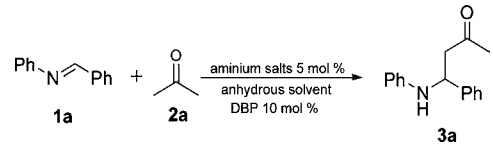
Figure 1. Design for Mannich reaction.

reaction is improving the reactivity of imines toward the enol form of ketones. In most cases, Brønsted acid or Lewis acid was added to prompt the generation of an iminium ion. Alternatively, some activated ketones such as enol silyl ether can also participate in the Mannich addition. However, it would be desirable to use unactivated ketones to achieve this transformation for simplicity. According to our previous research of radical cation chemistry,[5] oxidation of imines to its radical cation may be an alternative choice (Figure 1). If our hypothesis is feasible, the radical cation of imine can serve as an iminium ion equivalent participating in various Mannich or Mannich-type addition reactions.

On the basis of such a hypothesis, our studies began with the addition reaction of imine **1a** and acetone **2a** catalyzed by $TBPA^{+\bullet}$ (5 mol %). In accordance with our mechanistic design, the Mannich-type addition occurred between **1a** and **2a** in the presence of DBP (2,6-di-*tert*-butylpyridine) as an acid scavenger, and the β-amino ketone products were isolated. We then conducted a brief optimization of reaction conditions, and the results were summarized in Table 1.

Initially, we chose DCM as solvent for both **1a** and **2a**. However, most of imine **1a** was recovered, and the yield of **3a** was very low (entries 1−4). Then we used acetone **2a** as the solvent, and a DCM solution of $TBPA^{+\bullet}$ was added slowly to the reaction system. A significant solvent effect was observed: when the reaction was conducted in acetone, the corresponding β-aminoketone was obtained as the major product in good yield (entry 8). It suggests that the concentration of ketone is crucial to generating the corresponding enol form to trap the imine radical cation interrmediate. Other solvents were also tried to dissolve $TBPA^{+\bullet}$, but the yields are lower (entries 5−7). Besides, $TDBPA^{+\bullet}$ can also induce this reaction (entry 9) with a little decreased

Table 1. Optimization of the Reaction Conditions



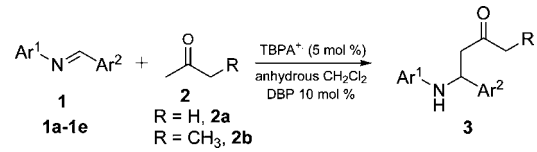
		solvent		time[a]	yield[b]
entry	ratio **1a:2a**	reactants	catalyst	(h)	(%)
1[c]	1:1	CH_2Cl_2	CH_2Cl_2	6	8
2[c]	1:3	CH_2Cl_2	CH_2Cl_2	6	11
3[c]	1:5	CH_2Cl_2	CH_2Cl_2	6	22
4[c]	1:10	CH_2Cl_2	CH_2Cl_2	6	37
5[c]	**2a** as solvent		CH_3CN	6	75
6[c]	**2a** as solvent		$CHCl_3$	6	64
7[c]	**2a** as solvent		$ClCH_2CH_2Cl$	6	71
8[c]	**2a as solvent**		**CH_2Cl_2**	**6**	**82**
9[d]	**2a** as solvent		CH_2Cl_2	6	65

[a] Monitored by TLC. [b] Detected by chromatography. [c] $TBPA^{+\bullet}$ (5 mol %) was added as an initiator. [d] $TDBPA^{+\bullet}$ (5 mol %) was added as an initiator.

yield. We also tried the reaction in the absence of $TBPA^{+\bullet}$, and no reaction was found by TLC.

With the optimized conditions in hand, we then examined the scope of imine substrates by varying the substituents on the aromatic ring to explore the generality of this Mannich reaction. The results were summarized in Table 2.

Table 2. Substituent Effect on the Synthesis of β-Aminoketones



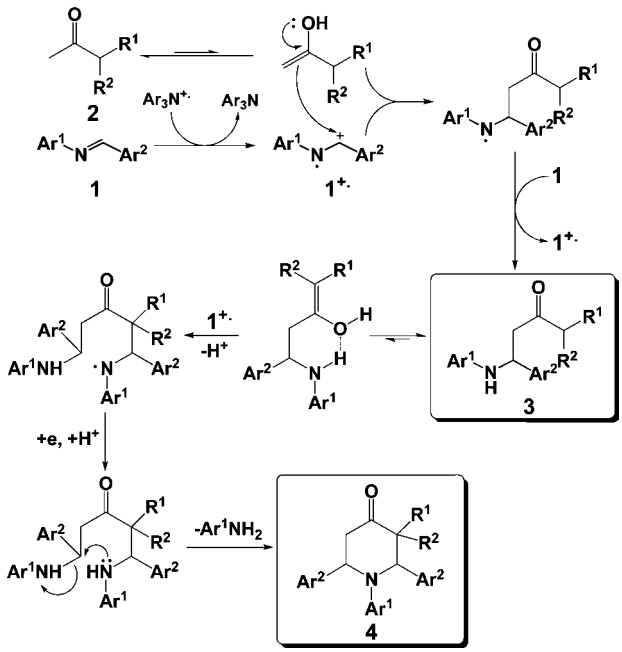
entry	Ar^1	Ar^2	R	time (h)	yield[a] (%)
1	Ph	Ph	H	6	78 (**3a**)
2	Ph	Ph	CH_3	10	64 (**3b**)
3	*p*-ClPh	Ph	H	6	80 (**3c**)
4	*p*-ClPh	Ph	CH_3	10	83 (**3d**)
5	*p*-BrPh	Ph	H	6	65 (**3e**)
6	*p*-BrPh	Ph	CH_3	10	59 (**3f**)
7	Ph	*p*-CH_3 Ph	H	6	72 (**3g**)
8	Ph	*p*-CH_3 Ph	CH_3	10	80 (**3h**)
9	*p*-CH_3Ph	Ph	H	6	86 (**3i**)
10	*p*-CH_3Ph	Ph	CH_3	10	74 (**3j**)

[a] Isolated yield.

No matter what substituent groups were on the aromatic rings on imines, the reactions proceeded smoothly, and the β-amino ketones were isolated in good yields. However, when Ar^1 was changed to benzyl, the reaction became complicated, and most of the starting imine was recovered (not shown in Table 2). It might be because the radical intermediates $\mathbf{1}^{+\bullet}$ (see Scheme 1) underwent proton loss from the benzylic position, causing the reaction to not take place.

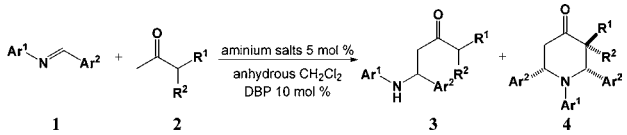
Interestingly, when imines bearing nitro groups (such as *p*-NO_2 and *m*-NO_2) were on the aromatic rings Ar_2, a novel

Scheme 1. Proposed Mechanism for Mannich Addition Induced by Radical Cation



product, 1,2,6-triaryl-4-piperidone, was isolated in moderate yield as a single stereoisomer (Table 3). It is well-known that 4-piperidones are very important building blocks in organic synthesis.[7] In particular, 2,6-disubstituted-4-piperidones are found in the frameworks of many biologically active natural products.[8] So we focused our research on the synthesis of 4-piperidones via addition of ketones to imines mediated by the radical cation procedure (Table 3).

Table 3. Synthesis of 4-Piperidones Induced by Aminium Salts



1 2 3 4

Ar^1 = Ph, Ar^2 = p-NO_2Ph **1f**
Ar^1 = p-ClPh, Ar^2 = p-NO_2Ph **1g**
Ar^1 = p-CH_3Ph, Ar^2 = p-NO_2Ph **1h**
Ar^1 = p-CH_3OPh, Ar^2 = p-NO_2Ph **1i**
Ar^1 = Ph, Ar^2 = m-NO_2Ph **1j**
Ar^1 = p-CH_3Ph, Ar^2 = m-NO_2Ph **1k**

R^1 = H, R^2 = CH_3 **2b**
R^1 = H, R^2 = C_2H_5 **2c**
R^1 = CH_3, R^2 = CH_3 **2d**
R^1 = CH_3, R^2 = C_2H_5 **2e**

entry	1	2	time (h)	3 (%)[a]	4 (%)[a]
1[b]	**1f**	**2b**	6	40 (**3k**)	39 (**4a**)
2[c]	**1f**	**2b**	6	42 (**3k**)	35 (**4a**)
3[b]	**1f**	**2c**	6	46 (**3l**)	22 (**4b**)
4[b]	**1f**	**2d**	18	48 (**3m**)	trace
5[b]	**1f**	**2e**	18	52 (**3n**)	trace
6[b]	**1g**	**2b**	3	39 (**3o**)	27 (**4c**)
7[b]	**1g**	**2c**	3	45 (**3p**)	18 (**4d**)
8[b]	**1h**	**2b**	3	56 (**3q**)	36 (**4e**)
9[b]	**1h**	**2c**	3	40 (**3r**)	28 (**4f**)
10[b]	**1i**	**2b**	3	38 (**3s**)	48 (**4 g**)
11[b]	**1i**	**2c**	3	52 (**3t**)	32 (**4 h**)
12[b]	**1j**	**2b**	6	33 (**3u**)	39 (**4i**)
13[b]	**1j**	**2c**	6	42 (**3v**)	35 (**4j**)
14[b]	**1k**	**2b**	6	34 (**3w**)	38 (**4k**)
15[b]	**1k**	**2c**	6	36 (**3x**)	40 (**4l**)

[a] Isolated yield. [b] $TBPA^{+\bullet}$ (5 mol %) was added as an initiator. [c] $TDBPA^{+\bullet}$ (5 mol %) was added as an initiator.

We varied the ketones reacting with the imine radical cation intermediate and leading to a series of 4-piperidinones. Straight chain ketones acted well in this reaction (entries 1−3 and 6−13). The ketones having more steric bulk (entries 4 and 5) could also be tolerated in the addition process, but only traces of the corresponding 4-piperidones were afforded even after 18 h under the same reaction condition because the cyclization became difficult due to steric hindrance. From the stoichiometric point of view, 2 mol of imines was needed in the cyclization, and we also tried the reaction using **1** in one molar excess; however, the yields of both products **3** and **4** greatly decreased (not shown in Table 3).[9] Futhermore, we also chose $TDBPA^{+\bullet}$ as the catalyst, but the yield of 4-piperidone was decreased (entry 2).

Next, we screened the reaction by varying the imines bearing electron-donating or electron-withdrawing groups on the aromatic ring Ar^2, but no cyclization product was found (only β-amino ketones were isolated), which implies NO_2 on Ar^2 exerts the most important effect on the efficiency of cyclization. We then investigated the substituent effect on Ar^1, but neither electron-donating nor electron-withdrawing groups showed an obvious effect on cyclization to 4-piperidones (entries 6−15). The reason might lie in that when NO_2 was born to Ar^2 the electrophilicity of the corresponding imine radical cation intermediate $\mathbf{1}^{+\bullet}$ was improved dramatically, which made the second addition easier (see Scheme 1). First, the imine loses an electron to form the corresponding radical cation $\mathbf{1}^{+\bullet}$ due to lower oxidation potential (the oxidation potential of imines is about 1.8 V vs SCE,[5a] and the ketones are above 3.0 V vs S.C.E.). $\mathbf{1}^{+\bullet}$ is then trapped by the enol tautomer of ketones. After the elimination of a proton producing a N-centered radical which accepts an electron from another mole of imine to propagate the chain (or from Ar_3N), β-aminoketone is produced. When an imine bearing NO_2 on Ar^2 is involved in this reaction, the electronphilicity of the corresponding imine radical cation $\mathbf{1}^{+\bullet}$ is getting stronger so that it can add to the enol tautomer of β-aminoketone, followed by electron transfer and intramolecular substitution. After the elimination of an aniline, 4-piperidone is generated. In most cases, the decomposition products of imines, benzaldehydes, were isolated as byproduct, which implied the generation of the imine radical cation.

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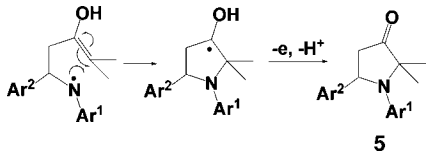
When $TBPA^{+\bullet}$ was added to the solution of imines in the absence of ketones, nearly all of the imines were broken into benzaldehydes. The radical cation mechanism is also greatly supported by the isolation of a minor product **5** (~5%) by the reaction of imine **1f** and methyl *iso*-propyl ketone **2d** (Scheme 2). The N-centered radical added to the double bond, producing a radical intermediate which is further oxidated to a carbocation. After losing a proton, compound **5** was generated.

Scheme 2. Proposed Mechanism for the Generation of Compound **5**



In summary, we have designed and executed a novel approach in which ketones served as carbocation trapping agents to form β-amino ketones and 4-piperidone derivatives under stable radical cation salt induced conditions. We are currently focusing on promoting this novel transformation and further exploring the use in construction of more variable heterocycle compounds. Further mechanism studies of this reaction are also underway in this laboratory.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9027978

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(9) This is because when two moles of imines was added extra solvent must be added to permit sufficient agitation, and the concentration of ketone is too low to efficiently trap the iminium radical cation, producing a greatly reduced yield.