Synthesis of Aryl-substituted Quinoline Derivatives via Brønsted Acid-catalyzed [4+2] Aza Diels–Alder Reaction

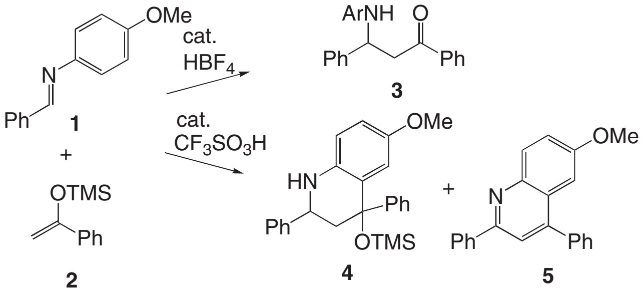
Takahiko Akiyama,* Saeko Nakashima, Koji Yokota, and Kohei Fuchibe
Department of Chemistry, Gakushuin University, Mejiro, Toshima-ku, Tokyo 171-8588

(Received April 27, 2004; CL-040483)

CF_3SO_3H-catalyzed [4+2] aza Diels–Alder reaction of aldimines with silyl enol ethers, and subsequent in situ oxidation furnished quinoline derivatives in good to excellent yields, wherein use of CF_3SO_3H as a Brønsted acid is critical for the cyclization reaction.

The aza Diels–Alder reaction of *N*-aryl aldimine with electron-rich alkene provides useful method for the preparation of quinoline and tetrahydroquinoline derivatives,[1] which are precursors of the nitrogen containing natural products. A number of Lewis acid catalysts such as $InCl_3$,[2] $BiCl_3$,[3] $BF_3{\cdot}OEt_2$,[4] $Yb(OTf)_3$,[5] $LiClO_4$,[6] as well as Brønsted acid catalysts such as CF_3CO_2H,[7] TsOH,[8] PPh_3HClO_4,[9] CF_3CH_2OH,[10] and photochemical conditions[11] have been developed for the aza Diels–Alder reaction.

We already reported that Brønsted acid catalyzed the Mannich-type reaction of silyl enolates with aldimines to give β-amino carbonyl compounds in excellent yields.[12,13] For example, treatment of aldimine **1** with silyl enol ether **2** in the presence of aq HBF_4 (10 mol %) in CH_3CN furnished β-amino ketone **3** in a high yield. In the course of the reaction, we have found that use of CF_3SO_3H in place of HBF_4 dramatically changed the reaction course; aza Diels–Alder reaction took place smoothly to afford a mixture of tetrahydroquinoline **4** and quinoline **5**.[14,15] We wish to report herein intriguing effect of the Brønsted acid on the cyclization reaction and its application to one-pot synthesis of quinoline derivatives.



In the first place, we studied the effect of Brønsted acid in the reaction of **1** and **2** in CH_3CN and the results are shown in Table 1. Aqueous HBF_4 afforded β-amino ketone **3** exclusively (Entry 1). In order to elucidate the effect of H_2O present, anhydrous $HBF_4{\cdot}OEt_2$ was employed but **3** was obtained exclusively (Entry 2). Anhydrous camphor sulfonic acid gave **3** in a high yield (Entry 4). Use of aq HPF_6 resulted in the formation of the mixture of **3** and **4** (Entry 5). Interestingly, use of $HClO_4$ or CF_3SO_3H suppressed the formation of **3**, and gave **4** and **5** in good combined yields (Entries 7, 8).

Next, effect of the solvent was examined by use of 10 mol % of CF_3SO_3H as a Brønsted acid catalyst (Table 2). Use of aprotic solvent afforded a mixture of **4** and **5**,[16] whereas protic solvent furnished **3** exclusively.

Table 1. Effect of Brønsted acid[a]

Entry	Brønsted acid	Yield of **3**/%	Yield of **4**/%	Yield of **5**/%
1	HBF_4[b]	88	0	0
2	$HBF_4{\cdot}OEt_2$	90	0	0
3	CF_3CO_2H	39	0	0
4	CSA	89	0	0
5	HPF_6[c]	70	11	0
6	FSO_3H	25	51	12
7	$HClO_4$[d]	0	53	20
8	CF_3SO_3H	0	26	69

[a] Aldimine **1** (1.0 equiv.) and silyl enol ether **2** (1.5 equiv.) were treated with Brønsted acid (10 mol %) in CH_3CN at room temperature. [b] 50% aq solution, [c] 60% aq solution. [d] 70% aq solution.

Table 2. Effect of solvent[a]

Entry	Solvent	Yield of **3**/%	Yield of **4**/%	Yield of **5**/%
1	CH_2Cl_2	0	11	69
2	Et_2O	62	7	21
3	CH_3CN	0	26	69
4	CH_3CN-H_2O[b]	87	0	0
5	*i*-PrOH	96	0	0

[a] Aldimine **1** (1.0 equiv.) and silyl enol ether **2** (1.5 equiv.) were treated with CF_3SO_3H (10 mol %) at room temperature. [b] 1.5 molar equivalent of H_2O based on imine was added.

Above results are summarized as follows; i) use of stronger Brønsted acid gave cycloadducts **4** and **5** preferentially, ii) use of protic solvent furnished Mannich adduct **3**, iii) addition of excess amount of water gave **3**. Effects of the Brønsted acid and solvent are explained as follows; Brønsted acid-catalyzed addition of silyl enolate **2** with imine **1** generates an intermediate **6** (Figure 1). The nucleophilic attack of some nucleophile in the medium on the silicon atom would give **3**, whereas intramolecular addition of enamine to the oxonium ion furnishes **4**. When weaker Brønsted acid was used, corresponding conjugate base would at-

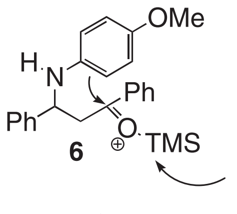


Figure 1.

tack the silicon atom to give **3**. In contrast, conjugate base of stronger Brønsted acid is less nucleophilic and the attack on the silicon atom is suppressed. Water also acted as a nucleophile toward silicon atom, thus interrupting the formation of **4**.[17]

Next, one-pot synthesis of quinoline derivative was examined. Although oxidizing agents such as DDQ, I_2, and CAN were not effective, $Mn(OAc)_3$ turned out to be effective for the synthesis of quinoline derivatives. Treatment of aldimine and silyl enol ether (2.0 equiv.) with CF_3SO_3H (10 mol %) in CH_3CN at room temperature for 3 h, and subsequent oxidation of the mixture with $Mn(OAc)_3$ (2.0 equiv.) in AcOH at room temperature overnight furnished numerous kinds of quinoline derivatives in good to excellent yields (Figure 2).[18]

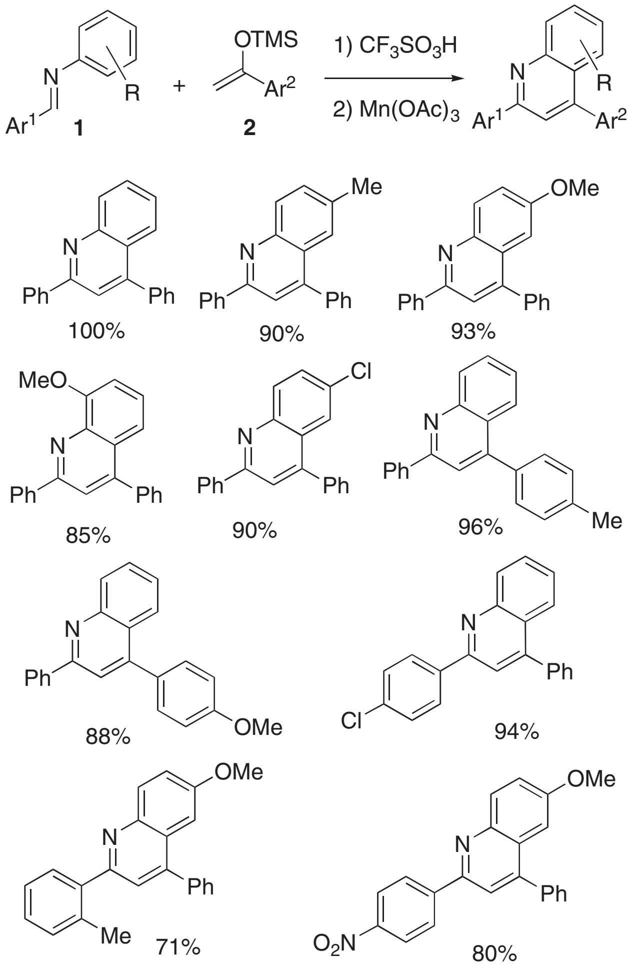


Figure 2. One-pot synthesis of quinolines.

In conclusion, we have found an intriguing effect of the Brønsted acid leading to quinoline derivative by [4+2] cycloaddition reaction of silyl enol ether and aldimines. Subsequent $Mn(OAc)_3$ mediated oxidation in one pot conditions furnished quinoline derivatives in good to excellent yields.

References and Notes

1 D. L. Boger, S. M. Weinreb, "Hetero Diels-Alder Methodology in Organic Synthesis," Academic, San Diego (1987), Chap. 2 and 9; S. M. Weinreb, in "Heterodienophile Additions to Dienes," ed. by B. M. Trost and I. Fleming, Oxford (1991) Vol. 5, p 401; P. Buonora, J.-C. Olsen, and T. Oh, *Tetrahedron*, **57**, 6099 (2001).
2 G. Babu and P. T. Perumal, *Tetrahedron Lett.*, **39**, 3225 (1998).
3 H. Laurent-Robert, B. Garrigues, and J. Dubac, *Synlett*, **2000**, 1160.
4 B. Crousse, J.-P. Bégue, and D. Bonnet-Delpon, *Tetrahedron Lett.*, **39**, 5765 (1998).
5 a) S. Kobayashi, H. Ishitani, and S. Nagayama, *Chem. Lett.*, **1995**, 423. b) Y. Makioka, T. Shindo, Y. Taniguchi, K. Takaki, and Y. Fujiwara, *Synthesis*, **1995**, 801. c) Y. Ma, C. Qian, M. Xie, and J. Sun, *J. Org. Chem.*, **64**, 6462 (1999). d) D. Cheng, J. Zhou, E. Saiah, and G. Beaton, *Org. Lett.*, **4**, 4411 (2002).
6 J. S. Yadav, B. V. S. Reddy, C. V. Rao, and R. Srinivas, *Synlett*, **2002**, 993.
7 P. A. Grieco and A. Bahsas, *Tetrahedron Lett.*, **29**, 5855 (1988).
8 Y. Nomura, M. Kimura, Y. Takeuchi, and S. Tomoda, *Chem. Lett.*, **1978**, 267.
9 R. Nagarajan, S. Chitra, and P. T. Perumal, *Tetrahedron*, **57**, 3419 (2001).
10 M. V. Spanedda, V. D. Hoang, B. Crousse, D. Bonnet-Delpon, and J.-P. Begue, *Tetrahedron Lett.*, **44**, 217 (2003).
11 W. Zhang, X. Jia, L. Yang, and Z.-L. Liu, *Tetrahedron Lett.*, **43**, 9433 (2002).
12 T. Akiyama, J. Takaya, and H. Kagoshima, *Synlett*, **1999**, 1045; T. Akiyama, J. Takaya, and H. Kagoshima, *Tetrahedron Lett.*, **42**, 4025 (2001); T. Akiyama, J. Takaya, and H. Kagoshima, *Adv. Synth. Catal.*, **344**, 338 (2002); T. Akiyama, J. Itoh, and K. Fuchibe, *Synlett*, **2002**, 1269; T. Akiyama, J. Itoh, K. Yokota, and K. Fuchibe, *Angew. Chem., Int. Ed.*, **43**, 1566 (2004).
13 For the Brønsted acid-catalyzed aza Diels–Alder reaction, see; T. Akiyama, J. Takaya, and H. Kagoshima, *Tetrahedron Lett.*, **40**, 7831 (1999).
14 Lewis acid promoted aza Diels-Alder reaction of *N*-aryl aldimine and silyl enol ether has been reported. See, Ref. 5b.
15 For recent examples of the preparation of quinolines, K. Sangu, K. Fuchibe, and T. Akiyama, *Org. Lett.*, **6**, 353 (2004); B. R. McNaughton and B. L. Miller, *Org. Lett.*, **5**, 4257 (2003), and references cited therein.
16 The structure of **5** was determined by comparison of the ^1H NMR spectra with the literature data.[19]
17 pK_a values of Brønsted acids follow; HBF_4 (−0.44),[20] $HClO_4$ (−10).[21]
18 Typical experimental procedure (2,4-diphenylquinoline), To a solution of benzylideneaniline (40.2 mg, 0.222 mmol) and α-trimethylsiloxystyrene (88 μL, 0.444 mmol) in CH_3CN (1 mL) was added a CH_3CN solution of CF_3SO_3H (98 μL, 0.021 mmol) (0.226 mol/L solution of CF_3SO_3H in CH_3CN) at room temperature. After being stirred at the temperature for 3 h, $Mn(OAc)_3{\cdot}2H_2O$ (120.1 mg, 0.448 mmol) and AcOH (3 mL) were added. The mixture was stirred at the temperature for 24 h. After removing the solid by filtration over Celite, the filtrate was neutralized by addition of sat. $NaHCO_3$ solution. The filtrate was extracted with CH_2Cl_2 and the combined extracts were washed with sat. $NaHCO_3$ solution and brine. Removing the solvent in vacuo gave crude material. Purification of the crude material with *p*-TLC (hexane:ethyl acetate = 7:1/v:v) furnished 2,4-diphenylquinoline (62.4 mg, 0.221 mmol) in a quantitative yield.
19 T. Nishio and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1773.
20 T. N. Sudakova and V. V. Krasnoshchekov, *Zh. Neorg. Khim.*, **23**, 1506 (1978).
21 W. N. White, T. Vogelmann, M. Morse, and H. S. White, *J. Org. Chem.*, **42**, 162 (1977).

Published on the web (Advance View) June 21, 2004; DOI 10.1246/cl.2004.922