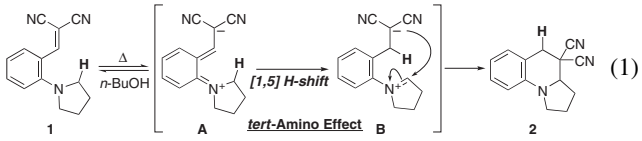
Expeditious Construction of Quinazolines via Brønsted Acid-induced C–H Activation: Further Extension of "*tert*-Amino Effect"

Keiji Mori, Yoshitaka Ohshima, Kensuke Ehara, and Takahiko Akiyama*
Department of Chemistry, Faculty of Science, Gakushuin University, Mejiro, Toshima-ku, Tokyo 171-8558

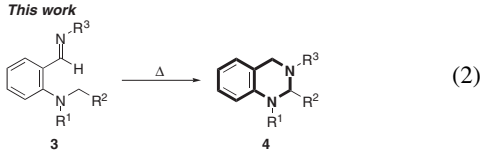
(Received March 10, 2009; CL-090246; E-mail: takahiko.akiyama@gakushuin.ac.jp)

A simple method for the synthesis of quinazolines was developed by exploiting the "*tert*-amino effect." A catalytic amount of Brønsted acid ($TsOH\cdot H_2O$) worked as an effective activator for the concise construction of a quinazoline framework from *o*-formylaniline and amine.

The term "*tert*-amino effect" is used to describe various thermal ring-closure reactions of *N*,*N*-dialkyl-substituted anilines with an unsaturated ortho substituent to afford fused azaring systems.[1,2] A representative example of this process is illustrated in eq 1. When **1** was heated in refluxing *n*-BuOH, [1,5] hydrogen shift from intermediate **A** and 6-endo-cyclization occurred simultaneously to give tetrahydroquinoline derivative **2** in good yield.[2a] A notable step in this reaction is the replacement of a C–H bond α to the tertiary amine nitrogen with a C–C bond, which could be recognized as a kind of sp^3 C–H activation without transition metals.[3] Although these internal redox processes would be a viable method for the construction of various heterocycles, conjugated substrates (such as **1**) were mostly used as the starting material and the use of imine analog **3** for the formation of quinazoline **4** (eq 2) had been overlooked until quite recently except for one report.[4] These features encouraged us to investigate imine analogs. Herein we report a catalytic approach to the synthesis of quinazolines by exploiting the *tert*-amino effect.



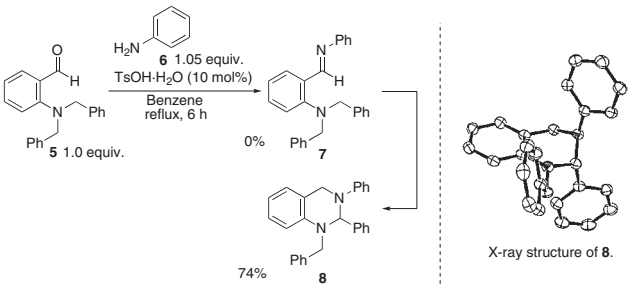
(1)



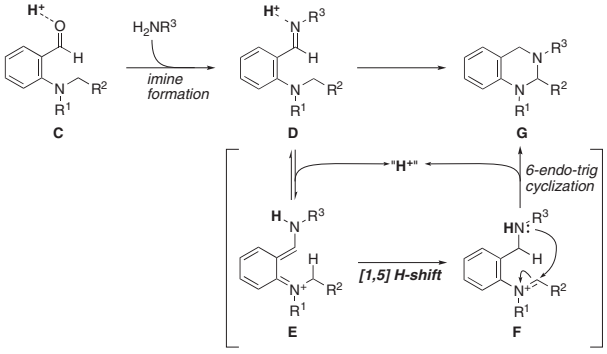
(2)

Firstly, to synthesize the imine **7** for the proposed reaction, the reaction of *o*-formylaniline **5** (1.0 equiv) with aniline (**6**) was conducted in the presence of 10 mol % $TsOH\cdot H_2O$ (Scheme 1). Judging from the TLC results, aldehyde **5** was completely consumed within 6 h in refluxing benzene and a new spot was observed. Interestingly, the resulting product was not imine **7** but quinazoline derivative **8** (74%). Thus, the imine formation and the [1,5] hydrogen shift followed by 6-endo cyclization occurred sequentially in a one-pot glass vessel. The structure of **8** was unambiguously established by single-crystal X-ray analysis.[5]

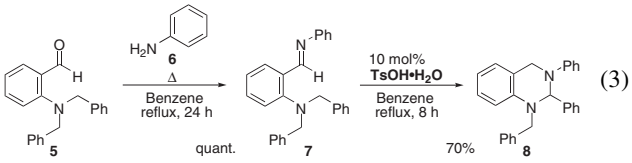
In most cases, processes exploiting the *tert*-amino effect have been triggered by thermal conditions.[1,2] To confirm whether this reaction was promoted by heat or acid catalyst, we conducted the following reaction (eq 3): a mixture of aldehyde **5** and aniline (**6**) was heated in refluxing benzene without an acid catalyst. Corresponding imine **7** was obtained as the sole product and the formation of quinazoline **8** was not observed even after 24 h. The desired cyclization proceeded by the addition of $TsOH\cdot H_2O$ (10 mol %) to imine **7**, suggesting that an acid catalyst was indispensable for this process.



Scheme 1. One-pot synthesis of quinazoline **8**.



Scheme 2. Supposed mechanism of this catalytic process.

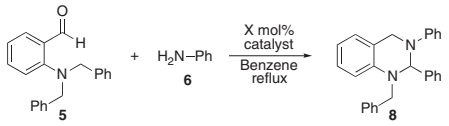


(3)

Scheme 2 illustrates the supposed mechanism of this reaction. The acid catalyst plays two roles in this process: 1) promotion of imine formation and 2) acceleration of the hydrogen shift process. Activation of the corresponding imine nitrogen in **D** by Brønsted acid facilitated the equilibrium between **D** and quinone methide **E**, and consequently, the [1,5] hydrogen shift proceeded rapidly.

Table 1 illustrates the results of investigation of the reaction conditions. Gratifyingly, even in 5 mol % $TsOH\cdot H_2O$, the desired product was obtained in high yield (73%, Entry 2). In the case of 2.5 mol % $TsOH\cdot H_2O$, the yield of **8** was slightly low (59%, Entry 3). Other acids (TfOH, Tf_2NH, TFA, and AcOH)

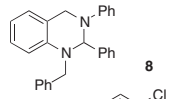
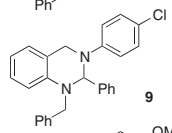
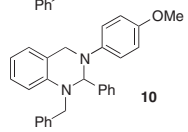
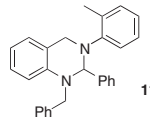
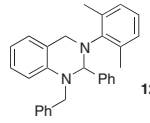
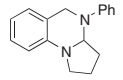
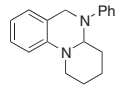
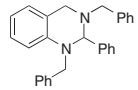
Table 1. Examination of the reaction conditions



Entry	Catalyst	X/mol %	Time/h	Yield/%
1	$TsOH\cdot H_2O$	10	5.5	74
2	$TsOH\cdot H_2O$	5	8	73
3	$TsOH\cdot H_2O$	2.5	12	59
4	TfOH	5	8	22
5	Tf_2NH	5	5	12
6	TFA	5	23	19
7	AcOH	5	9	0
8[a]	$TsOH\cdot H_2O$	5	8	0
9[b]	$TsOH\cdot H_2O$	5	10	70
10[c]	$TsOH\cdot H_2O$	5	9	66

[a]The reaction was conducted at 60 °C. [b]In the presence of MS3A. [c]In the presence of MS5A.

Table 2. Scope and limitations

Entry	Product	Time/h	Yield/%
1	 **8**	8	73
2	 **9**	4.5	88
3	 **10**	6.5	66
4	 **11**	5.5	40
5	 **12**	13	—
6[a]	 **13**	11.5	92
7[a]	 **14**	11.5	34
8[a,b]	 **15**	6	92

[a]In toluene. [b]Excess amount of aldehyde (1.1 mol equiv vs. amine) was used.

gave inferior results (Entries 4–7). At lower temperature (60 °C), the reaction was suppressed completely, giving only imine (Entry 8). Some dehydrating agents (MS3A and MS5A) were insufficient to improve the chemical yield (70 and 66%, respectively, Entries 9 and 10). From the above investigations, we decided that 5 mol % $TsOH\cdot H_2O$ in refluxing benzene provided the optimal conditions.

Next, the scope and limitations of this reaction were examined (Table 2). The electronic environment on the aniline-aromatic-ring group was of no concern in this reaction; both electron-deficient and electron-rich aniline gave desired products **9** and **10** in good yields (88 and 66%, respectively, Entries 2 and 3). On the other hand, the sterically encumbered anilines suppressed the reaction dramatically; *o*-methylaniline gave **11** in only 40% yield (Entry 4), and no product was obtained when 2,6-dimethylaniline was used as the starting material (Entry 5). Polycyclic analogs **13** and **14**[6] were also obtained, although an elevated temperature was required (in refluxing toluene) possibly owing to the decreased hydride donor capabilities of these substrates.

Aliphatic amines also participated in this reaction but special caution was needed (Entry 8). In contrast to aromatic amines, not only an elevated temperature (in refluxing toluene) but also the in situ generation of imine before the addition of $TsOH\cdot H_2O$ and the use of a slight excess of aldehyde (1.1 equiv vs. amine) were required; due to its strong basicity compared with aromatic amine, TsOH was probably deprotonated by the remnant amine that did not participate in the formation of the corresponding imine, and consequently, the acid could not work as a catalyst.[7]

In summary, we have developed a promising catalytic approach to the quinazoline skeleton by Brønsted acid-induced C–H functionalization. This method is applicable to various *o*-formyl *N*,*N*-dialkyl-substituted anilines and amines (aromatic and aliphatic). Further work on related reactions is in progress to synthesize various heterocycles.

References and Notes

1 For reviews, see: a) O. Meth-Cohn, H. Suschitzky, *Adv. Heterocycl. Chem.* **1972**, *14*, 211. b) J. M. Quintela, *Recent Res. Dev. Org. Chem.* **2003**, *7*, 259. c) P. Matyus, O. Elias, P. Tapolcsanyi, A. Polonka-Balint, B. Halasz-Dajka, *Synthesis* **2006**, 2625.

2 a) W. Verboom, D. N. Reinhoudt, R. Visser, S. Harkema, *J. Org. Chem.* **1984**, *49*, 269. b) W. H. N. Nijhuis, W. Verboom, D. N. Reinhoudt, *Synthesis* **1987**, 641. c) W. H. N. Nijhuis, W. Verboom, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1987**, *109*, 3136. d) W. H. N. Nijhuis, W. Verboom, A. A. El-Fadl, S. Harkema, D. N. Reinhoudt, *J. Org. Chem.* **1989**, *54*, 199. e) W. H. N. Nijhuis, W. Verboom, A. A. El-Fadl, G. J. van Hummel, D. N. Reinhoudt, *J. Org. Chem.* **1989**, *54*, 209. f) A. Polonka-Balint, C. Saraceno, K. Ludanyi, A. Benyei, P. Matyus, *Synlett* **2008**, 2846. g) C. Zhang, C. K. De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416.

3 For reviews on C-H functionalization, see: a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731. b) K. Godula, D. Sames, *Science* **2006**, *312*, 67. c) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013.

4 a) W. Verboom, M. R. J. Hamzink, D. N. Reinhoudt, R. Visser, *Tetrahedron Lett.* **1984**, *25*, 4309. b) X. Che, L. Zheng, Q. Dang, X. Bai, *Synlett* **2008**, 2373. During the preparation of our manuscript, Seidel reported similar redox process promoted by TfOH, see: c) C. Zhang, S. Murarka, D. Seidel, *J. Org. Chem.* **2009**, *74*, 419.

5 Crystallographic data reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-717617.

6 The corresponding starting aldehydes were prepared as reported in ref. 2d.

7 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) April 25, 2009; doi:10.1246/cl.2009.524