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Brønsted acid (HNO_3)-catalyzed tandem reaction of α-ketoesters and arylamines: efficient synthesis of 1,2-dihydroquinoline derivatives

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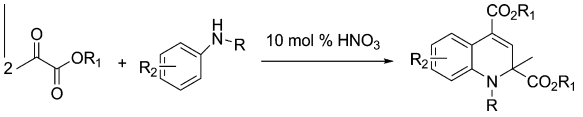
ABSTRACT

A simple and convenient Brønsted acid (HNO_3)-catalyzed tandem reaction of α-ketoesters with primary or secondary aromatic amines for the synthesis of polysubstituted 1,2-dihydroquinolines has been developed via a tandem process, which has the advantages of ready availability of catalyst, operation simplicity, atom efficiency as well as low toxicity. In particular, tricyclic dihydroquinolines, generally prepared with multi-processes, could also be constructed in this one-pot procedure.

One of the great challenges facing chemists this century is to develop simple, efficient, and economic transformations.[1] Nowadays, using micromolecular Brønsted acids as catalysts has attracted much extensive attention for their charming advantages of cheapness, nontoxicity and operation simplicity.[2]

1,2-Dihydroquinoline and their derivatives are ubiquitous in nature, and can serve as important subunits to design tremendous synthetic drug candidates due to their significant pharmacological properties.[3,4] To date, numerous synthetic strategies have been reported for achieving these heterocycles formation,[5] such as modified Skraup reactions,[6] Michael-aldol reaction[7] and tandem reactions of aromatic amines with alkynes.[8] Many of these well developed methods always employed metal salts or large organometallic complexes as catalysts accompanied by the following limitations: heavy atom pollutions, costliness and complex operation. To the best of our knowledge, only one example of Brønsted acid mediated reaction of pyruvic acid with aniline and CH_2N_2 has been reported for the construction of 1,2-dihydroquinoline derivative, in which multi-step procedure and excess of trifluroecetic acid were employed.[9] Herein, we report a simple and convenient Brønsted acid (HNO_3)-catalyzed one-pot tandem reaction of α-ketoesters with primary or secondary aromatic amines for the effective synthesis of polysubstituted 1,2-dihydroquinoline derivatives (Eq. 1). Previously, these compounds could only be prepared by Au/Ag-cocatalyzed procedure (5 mol % and 15 mol %, respectively).[10] It is worth mentioning that complex tricyclic dihydroquinolines, generally prepared with multi-processes,[11] could also be constructed in this one-pot protocol, which demonstrated excellent synthetic efficiency.

Initially, a series of Brønsted acids were applied to the



(1)

transformation of *p*-chloroaniline (**2a**) and methyl pyruvate (**1a**) into 1,2-dihydroquinoline (**3aa**) (Table 1). Among various catalysts examined, nitric acid exhibited the best catalytic activity (entry 7). Hydrochloric acid, trifluoroacetic acid and methanesulfonic acid also gave the desired product in moderate to good yields (entries 2, 6, and 10). While, sulphuric acid, phosphoric acid and boracic acid were not effective for the present transformation (entries 3–5). Under the standard conditions, no reaction was observed in the absence of catalyst, or in the presence of formic acid and acetic acid (entries 1, 8, and 9).

Next, other factors (solvent, temperature and proportion of the substrates) were examined using nitric acid as catalyst (Table 2). Acetonitrile was proved to be the appropriate reaction media while others gave lower yields of the targets (entries 1–6). The reaction could not proceed at room temperature, and the best yield was obtained at 80 °C (entries 1, 7, and 8). In addition, the proportion of substrates also had influence on the efficiency. Compared with entry 1, much excess of **1a** (entry 11) or **2a** (entry 9) would inhibit the transformation.

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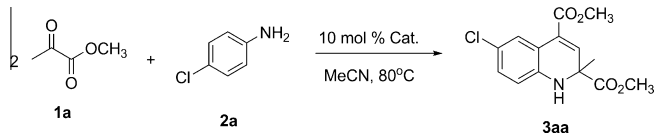
Table 1
Screening of the catalysts[a]



Entry	Catalyst[c]	Yield[b] (%)
1	None	None
2	HCl	83
3	H_2SO_4	13
4	H_3PO_4	Trace
5	H_3BO_3	9
6	CF_3COOH	70
7	**HNO_3**	**88**
8	HCOOH	None
9	CH_3COOH	None
10	CH_3SO_3H	61

[a] Reaction conditions: compound **1a** (1.5 mmol) and **2a** (1 mmol) in CH_3CN (1.5 mL) for 12 h.
[b] Isolated yields based on **1a**.
[c] Concentration of the acids: HCl (34–37.5%), H_2SO_4 (95–98%), H_3PO_4 (85%), HNO_3 (65–70%).

Table 2
Optimization of the reaction[a]

Entry	*T* (°C)	Solvent	**1a** (mmol)	**2a** (mmol)	Yield[b] (%)
1	80	CH_3CN	1.5	1	**88**
2	80	DMF	1.5	1	40
3	80	DMSO	1.5	1	18
4	80	Toluene	1.5	1	23
5	Reflux	THF	1.5	1	23
6	80	1,4-Dioxane	1.5	1	32
7	rt	CH_3CN	1.5	1	None
8	60	CH_3CN	1.5	1	64
9	80	CH_3CN	1	1	61
10	80	CH_3CN	2	1	68
11	80	CH_3CN	1.5	0.5	78[c]

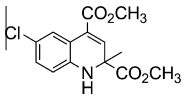
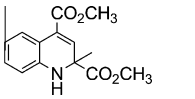
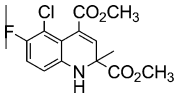
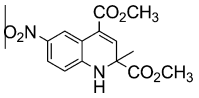
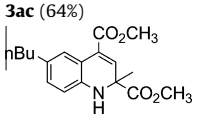
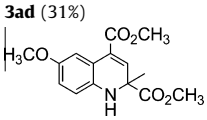
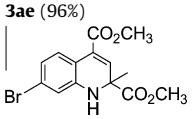
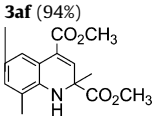
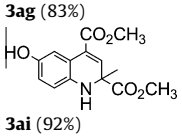
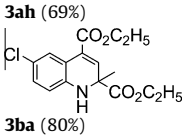
[a] Reaction conditions: HNO_3 (10 mol %), compound **1a** (1.5 mmol), **2a** (1 mmol) in CH_3CN (1.5 mL) for 12 h.
[b] Isolated yields based on **1a**.
[c] Isolated yields based on **2a**.

The scope and generality of this process were explored with respect to various aromatic amines, and a series of 1,2-dihydroquinoline derivatives were obtained in good to excellent yields under the optimized conditions (Table 3). Electronic effect on the aromatic ring of amines had significant influence on the productivity. Those containing electron-donating or neutral groups gave the desired products in good to excellent yields (**3ab**, **3ae**, **3af**, and **3ai**), however, amines bearing electron-withdrawing groups gave the targets in comparatively lower yields (**3aa**, **3ac**, **3ad**, and **3ag**). Ortho-substituted amines also gave relatively lower yields, because of the steric effect (**3ah**).

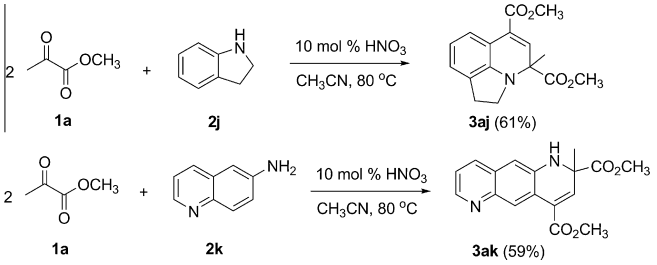
It was worth mentioning that indoline (**2j**) and 3-quinolinamine (**2k**) could also tolerate in this process and produced the tricyclic compounds in moderate yields. Hence, our methodology will provide a convenient route for construction of complex tricyclic dihydroquinolines (Scheme 1, **3aj** and **3ak**), which are usually prepared through multi-step reactions and need cumbersome and laborious procedures.[11]

In order to obtain further insights into this reaction, control experiments were performed as shown in Eq. 2–3.[9] When methyl pyruvate (**1a**) reacted with *p*-methoxyaniline (**2f**) in the absence of catalyst, imine **4af** could be isolated together with a trace amount of enamine isomer (Eq. 2). Furthermore, treatment of **4af** with **1a** under the standard procedure led to the formation of desired product **3af** (Eq. 3). The above results indicated that imine or enamine complex might be the critical intermediate in this tandem reaction.

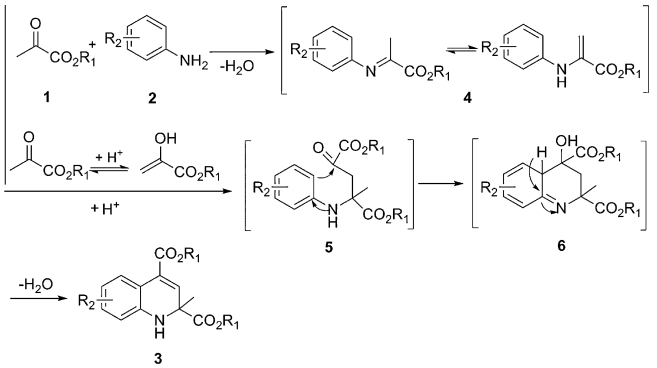
Table 3
Brønsted acid-catalyzed tandem reaction of various α-ketoesters and aromatic amines[a]

Products (Yields[b])	Products (Yields[b])
 **3aa** (88%)	 **3ab** (95%)
 **3ac** (64%)	 **3ad** (31%)
 **3ae** (96%)	 **3af** (94%)
 **3ag** (83%)	 **3ah** (69%)
 **3ai** (92%)	 **3ba** (80%)

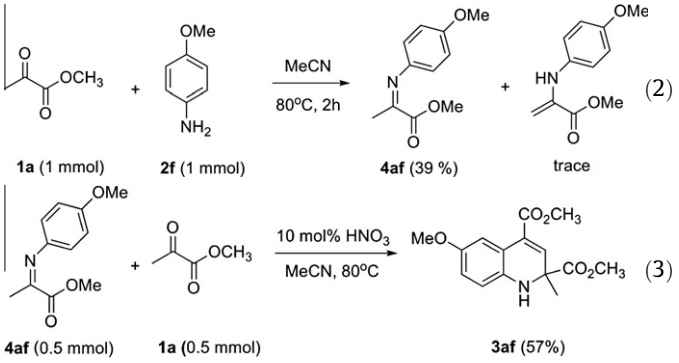
[a] Reaction conditions: HNO_3 (10 mol%), α-ketoester (1.5 mmol) and arylamine (1 mmol) in CH_3CN (1.5 mL) for 8-24 hours.
[b] Isolated yields based on α-ketoester.



Scheme 1. Preparation of tricyclic dihydroquinolines.



Scheme 2. Proposed mechanism.



On the basis of the above results and previous studies,[10] a tentative mechanism was proposed and shown in Scheme 2. Firstly, α-ketoester (**1**) reacts with amine (**2**) to generate the imine or enamine intermediate **4**, which is followed by addition of the enolate (quickly formed from the tautomerization of ketoester), and produces intermediate **5**. Subsequently, the electron-rich benzene ring could add to the keto group to give intermediate **6**. Finally, water elimination and following proton shift would produce the desired 1,2-dihydroquinolines (**3**).[10]

In summary, we have developed a simple and efficient method for the synthesis of polysubstituted 1,2-dihydroquinoline derivatives including tricyclic ones via a one-pot tandem process employing nitric acid as catalyst. Taking into account the combination of desirable features, such as operation simplicity, cheap and readily available catalyst, atom efficiency as well as low toxicity, this catalytic system is expected to provide an expedient access to construct versatile dicyclic and tricyclic 1,2-dihydroquinoline building blocks, which can be used for the synthesis of new drug candidates and other potential biological active molecules. The scope, mechanism, and synthetic application of this reaction are under investigation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.134.

References and notes

1. (a) Anastas, P. T.; Williamson, T. C. Oxford Science Publications, New York, 1998; (b) DeSimone, J. M. *Science* **2002**, *297*, 799.
2. For selected examples, see: (a) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141; (b) Leca, D.; Gaggini, F.; Cassayre, J.; Loiseleur, O. *J. Org. Chem.* **2007**, *72*, 4284; (c) Ramachandran, P. V.; Pratihar, D. *Org. Lett.* **2007**, *9*, 2087; (d) Wu, X. L.; Wang, G. W. *J. Org. Chem.* **2007**, *72*, 9398.
3. (a) Nanteuil de, G.; Duhault, J.; Ravel, D.; Herve, Y. EP 0 528 734A1, 1993; (b) Coughlan, M. J.; Elmore, S. W.; Kort, M. E.; Kym, P. R.; Moore, J. L.; Pratt, J. K.; Wang, A. X.; Edwards, J. P.; Jones, T. K. WO 9 941 256, 1999; (c) Johnson, J. V. *J. Med. Chem.* **1989**, *32*, 1942.
4. (a) Pearce, B. C.; Wright, J. J. U.S. Patent 5 411 969, 1995; (b) Jones, T. K.; Winn, D. T.; Zhi, L.; Hamann, L. G.; Tegley, C. M.; Pooley, C. L. F. U.S. Patent 5 688 808, 1997; (c) Kurata, H.; Kohama, T.; Kono, K.; Kitayama, K.; Hasegawa, T. WO 0 134 570A1, 2001; (d) Jones, T. K.; Goldman, M. E.; Pooley, C. L. F.; Winn, D. T.; Edwards, J. E.; West, S. J.; Tegley, C. M.; Zhi, L.; Hamann, L. G. WO 9 619 458, 1996; (e) Coughlan, M. J.; Elmore, S. W.; Kort, M. E.; Kym, P. R.; Moore, J. L.; Pratt, J. K.; Wang, A. X.; Edwards, J. P.; Jones, T. K. WO 9 941 256, 1999.; (f) Blleau, B.; Martel, R.; Lacasse, G.; Ménard, M.; Weinberg, N. L.; Perron, Y. G. *J. Am. Chem. Soc.* **1968**, *90*, 823; (g) Takahash, H.; Bekkali, Y.; Capolino, A. J.; Gilmore, T.; Goldrick, S. E.; Kaplita, P. V.; Liu, L.; Nelson, R. M.; Terenzio, D.; Wang, J.; Zuvela-Jelaska, L.; Proudfoot, J.; Nabozny, G.; Thomson, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5091.
5. (a) Liu, X. Y.; Che, C. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3805; (b) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029; (c) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2002**, *4*, 4265; (d) Yi, C. S.; Yun, S. Y.; Guzei, I. A. *J. Am. Chem. Soc.* **2005**, *127*, 5782; (e) Lu, G. L.; Portscheller, J. L.; Malinakova, H. C. *Organometallics* **2005**, *24*, 945; (f) Kamakshi, R.; Reddy, B. S. R. *Catalysis Commun.* **2007**, *8*, 825.
6. (a) Kamiguchi, S.; Takahshi, I.; Kurokawa, H.; Miura, H.; Chihara, T. *Appl. Catal., A* **2006**, *309*, 70; (b) Theoclitou, M. E.; Robinson, L. A. *Tetrahedron Lett.* **2002**, *43*, 3907.
7. (a) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813; (b) Makino, K.; Hara, O.; Takiguchi, Y.; Katano, T.; Asakawa, Y.; Hatano, K.; Hamada, Y. *Tetrahedron Lett.* **2003**, *44*, 8925.
8. (a) Luo, Y. M.; Li, Z. G.; Li, C. J. *Org. Lett.* **2005**, *7*, 2675; (b) Liu, X. Y.; Ding, P.; Huang, J. S.; Che, C. M. *Org. Lett.* **2007**, *9*, 2645.
9. Tapia, I.; Alcazar, V.; Grande, M.; Moran, J. R. *Tetrahedron* **1988**, *44*, 5113. This literature reported a multi-step reaction for the synthesis of 1,2-dihydroquinoline from pyruvic acid and aniline, in which self-aldol condensation of pyruvic acid was considered as the key step. However, in our reaction system, when methyl pyruvate (**1a**) was performed separately in the presence of HNO_3, no self-aldol condensation product of methyl pyruvate was detected, suggesting that a different reaction mechanism might be involved in this process.
10. Waldmann, H.; Karunakar, G. V.; Kumar, K. *Org. Lett.* **2008**, *10*, 2159.
11. (a) Cannon, J. G.; Lazaris, S. A.; Wunderlich, T. A. *J. Heterocucli Chem.* **1967**, *4*, 259; (b) Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479; (c) Fillion, E.; Dumas, A. M. *J. Org. Chem.* **2008**, *73*, 2920.