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Highly Efficient Synthesis of Polysubstituted 1,2-Dihydroquinolines via Tandem Reaction of α-Ketoesters and Arylamines Catalyzed by Indium Triflate

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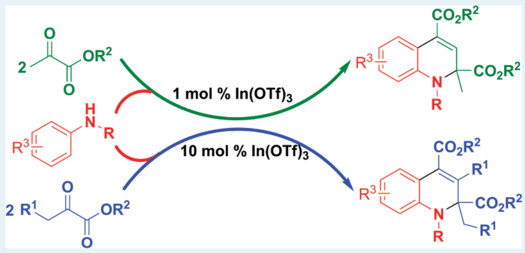
Supporting Information

ABSTRACT: A simple and efficient method for the synthesis of polysubstituted 1,2-dihydroquinolines has been developed via an indium(III)-catalyzed tandem reaction of α-ketoesters with primary or secondary aromatic amines. With respect to the reactions of pyruvates with amines, indium triflate (1 mol %) demonstrated superior catalytic activity and efficiency compared with previously reported $AuCl_3/AgSbF_6$ (5 mol %/ 15 mol %) cocatalyst. The reactions of α-alkyl substituted ketoesters and arylamines, which could not be effectively accomplished by the previous $AuCl_3/AgSbF_6$ and HNO_3 catalytic systems proceeded smoothly in the presence of 10 mol % $In(OTf)_3$ to afford the desired products in moderate to good yields (43%−91%).



KEYWORDS: polysubstituted dihydroquinoline, ketoester, aromatic amine, indium triflate, catalytic synthesis

Dihydroquinoline skeletons are key structural motifs in a variety of natural products,[1−3] pharmaceuticals, and synthetic intermediates. They have attracted attention because of their wide spectrum of biological activities and potential pharmacological applications.[4−9] Various synthetic methods for the preparation of dihydroquinolines have been developed.[10−27] In general, traditional procedures are laborious, low yielding, and require special synthetic precursors.[16] Recently, efficient strategies toward the synthesis of dihydroquinolines have been focused on a catalytic version. For example, transition metals such as palladium,[17] ruthenium,[18,19] silver,[20] and gold[21] catalyzed reactions of anilines with alkynes; scandium triflate,[22] silicotungstic acid,[23] and zeolite[24] catalyzed reactions of anilines with ketones; indium mediated allylation of quinolines;[25] $AuCl_3/AgSbF_6$ (5 mol %/15 mol %) cocatalyzed aldol condensation of pyruvates with arylamines (Scheme 1).[26] Very recently, we reported a convenient approach to the synthesis of polysubstituted 1,2-dihydroquinolines via a Brønsted acid (HNO_3)-catalyzed tandem reaction of pyruvates with primary or secondary aromatic amines.[27] However, this method is not suitable for α-alkyl substituted ketoesters because of the steric effect, which restricts its widespread applications. Herein, we describe a new indium(III)-catalyzed method for the construction of polysubstituted dihydroquinolines from various α-ketoesters and arylamines (Scheme 2). With respect to the reactions of pyruvates with amines, indium triflate (1 mol %) demonstrated superior catalytic activity and efficiency compared with $AuCl_3/AgSbF_6$ (5 mol %/15 mol %) cocatalyst and HNO_3 (10 mol %). The reactions of α-alkyl substituted ketoesters and arylamines, which could not be effectively accomplished by the previous $AuCl_3/AgSbF_6$ and HNO_3 catalytic systems, proceeded smoothly in the presence of 10 mol % $In(OTf)_3$ to afford the desired products in moderate to good yields (43%-91%).

Initially, the reaction of methyl pyruvate (**1a**) with *p*-chloroaniline (**2a**) was performed to examine the catalytic activity of various simple metal complexes such as In, Fe, Sn, Zn, and Cu salts (Table 1, entries 2−9). Among these metal salts (5 mol %) examined, $In(OTf)_3$ was found to be the most effective catalyst and afforded the desired product **3aa** in 95% yield (Table 1, entry 9). No product was observed in the absence of catalyst (Table 1, entry 1). Further optimization suggested that $In(OTf)_3$ still maintained high efficiency even when the catalyst loading was reduced to 1 mol % (Table 1, entries 10 and 11). After an extensive screening of the reaction parameters (Table 1, entries 11−17), the best yield of **3aa** was obtained when reaction was performed in acetonitrile at 80 °C (Table 1, entry 11).

The scope and generality of this reaction were further tested with various combinations of aromatic amines and pyruvates (Table 2). The electronic effect on the aromatic ring of amines has little impact on this transformation; both the electron-rich and the electron-poor amines gave the desired targets in moderate to high yields (**3aa-3ah**). The phenolic hydroxyl

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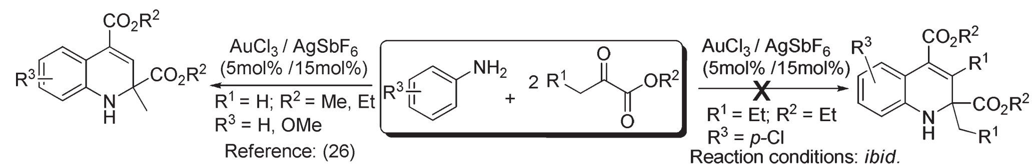
Scheme 1. Au/Ag co-Catalyzed Process



Scheme 2. Indium(III)-Catalyzed Process in This Work

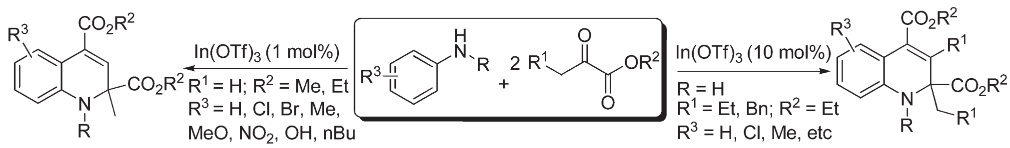
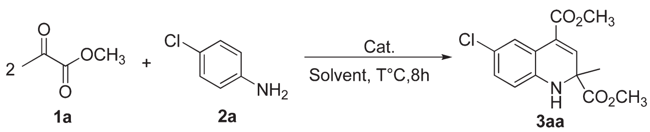


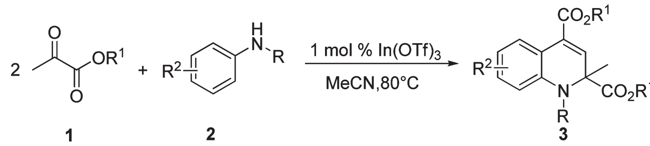
Table 1. Reaction of Methyl Pyruvate (1a) and *p*-Chloroaniline (2a) Under Various Reaction Conditions[a]

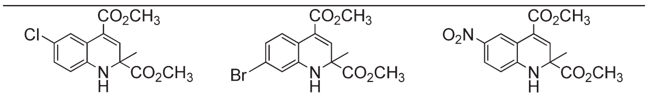


entry	catalyst (mol %)	solvent	T (°C)	yield (%)[b]
1	None	CH_3CN	80	none
2	$InCl_3$ (5)	CH_3CN	80	61
3	$FeCl_3 \cdot 6H_2O$ (5)	CH_3CN	80	56
4	$SnCl_2 \cdot 2H_2O$ (5)	CH_3CN	80	48
5	$ZnBr_2$ (5)	CH_3CN	80	43
6	$Zn(OTf)_2$ (5)	CH_3CN	80	61
7	$Cu(OTf)_2$ (5)	CH_3CN	80	53
8	$CuBr_2$ (5)	CH_3CN	80	93
9	$In(OTf)_3$ (5)	CH_3CN	80	95
10	$CuBr_2$ (1)	CH_3CN	80	77
11	**$In(OTf)_3$ (1)**	**CH_3CN**	**80**	**95**
12	$In(OTf)_3$ (1)	DMF	80	14
13	$In(OTf)_3$ (1)	THF	Rflux	76
14	$In(OTf)_3$ (1)	1,4-dioxane	80	51
15	$In(OTf)_3$ (1)	*n*-hexane	80	65
16	$In(OTf)_3$ (1)	CH_3CN	r. t.	17
17	$In(OTf)_3$ (1)	CH_3CN	60	53

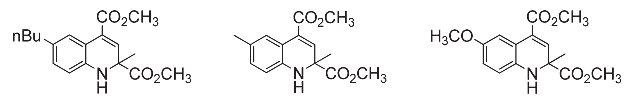
[a] Reaction conditions: compound **1a** (1.5 mmol), **2a** (1 mmol), catalyst (1 or 5 mol %), solvent (1.5 mL), 8 h. [b] Isolated yields based on **1a**.

Table 2. Indium(III)-Catalyzed Tandem Reaction of Various Aromatic Amines and Pyruvates[a,b]

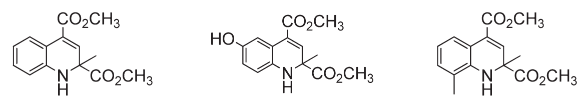




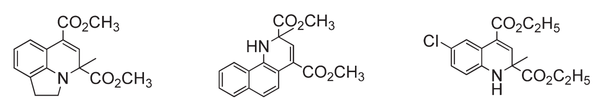
3aa (95%) **3ab** (92%) **3ac** (66%)



3ad (91%) **3ae** (94%) **3af** (93%)



3ag (91%) **3ah** (74%) **3ai** (61%)



3aj (49%) **3ak** (82%) **3ba** (85%)

[a] Reaction conditions: compound **1** (1.5 mmol), **2** (1 mmol), $In(OTf)_3$ (1 mol %), CH_3CN (1.5 mL), 6−24 h. [b] Isolated yields based on **1**.

group was tolerated in this process, and the corresponding product **3ah** was obtained in 74% yield. Substituent at the 2-position of arylamine had significant impact on the yields because of the steric effect (**3ai**). It was noteworthy that when the secondary amine indoline and 1-aminonaphthalene were used, the expected tricyclic compounds **3aj** and **3ak** were afforded in 49% and 82% yields, respectively, which provided a convenient route for the construction of complex tricyclic-dihydroquinolines. In addition, ethyl pyruvate could also give the desired product **3ba** in high yield.

Furthermore, the scope of the α-alkyl substituted ketoesters was also investigated in the presence of 1 mol % $In(OTf)_3$. Nevertheless, none of the expected target was obtained, and

Scheme 3. Reaction of 1c and 2a with 1 mol % $In(OTf)_3$

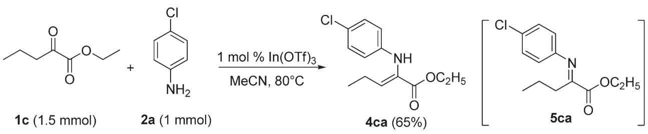
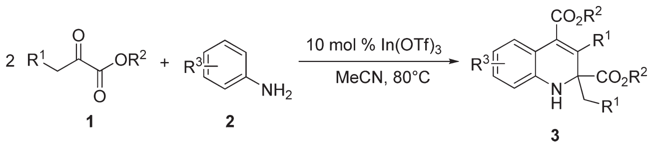
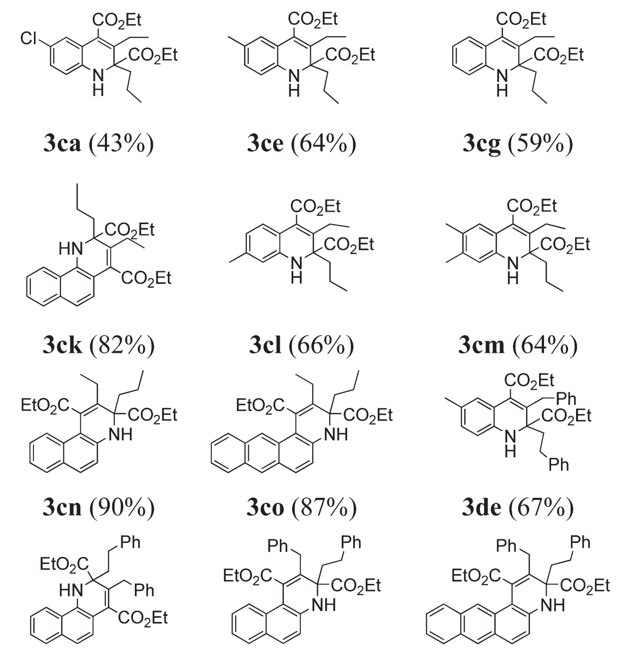


Table 3. Indium(III)-Catalyzed Tandem Reaction of Various Aromatic Amines and α-Alkyl Substituted Ketoesters[a,b]





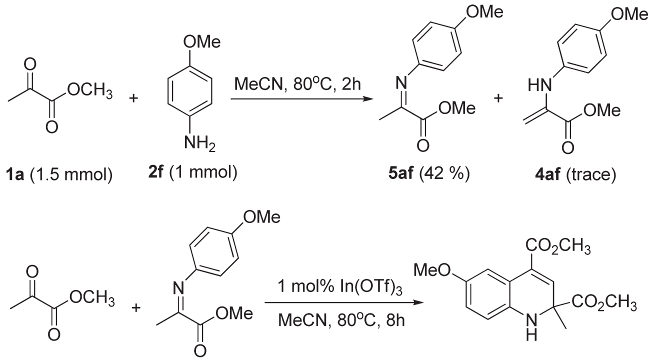
3ca (43%) 3ce (64%) 3cg (59%)
3ck (82%) 3cl (66%) 3cm (64%)
3cn (90%) 3co (87%) 3de (67%)
3dk (89%) 3dn (87%) 3do (91%)

[a] Reaction conditions: compound **1** (1.2 mmol), **2** (0.5 mmol), $In(OTf)_3$ (10 mol %), CH_3CN (1.5 mL), 8−30 h. [b] Isolated yields based on **2**.

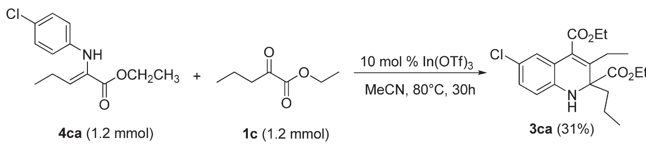
enamine **4ca**, the isomer of the possible intermediate imine **5ca**,[28−30] was the main product, indicating that the presence of the alkyl group inhibited subsequent transformations (Scheme 3).

To our delight, the desired tetra-substituted dihydroquinolines were obtained in moderate to good yields when the catalyst loading was increased to 10 mol % (Table 3). Anilines with different substituent groups provided the polysubstituted dihydroquinolines in moderate yields (**3ca**, **3ce**, **3cg**, **3cl**, **3 cm**, and **3de**). 1-Aminonaphthalene, 2-aminonaphthalene, and 2-aminoanthracene showed excellent reactivity in this procedure and gave the tricyclic or tetracyclic-dihydroquinolines in good yields (**3ck**, **3cn**, **3co**, **3dk**, **3dn**, and **3do**). It was noteworthy that no desired tetra-substituted dihydroquinoline **3ca** was obtained

Scheme 4. Control Experiments of 1a with 2f or 5af



Scheme 5. Control Experiment of 4ca with 1c



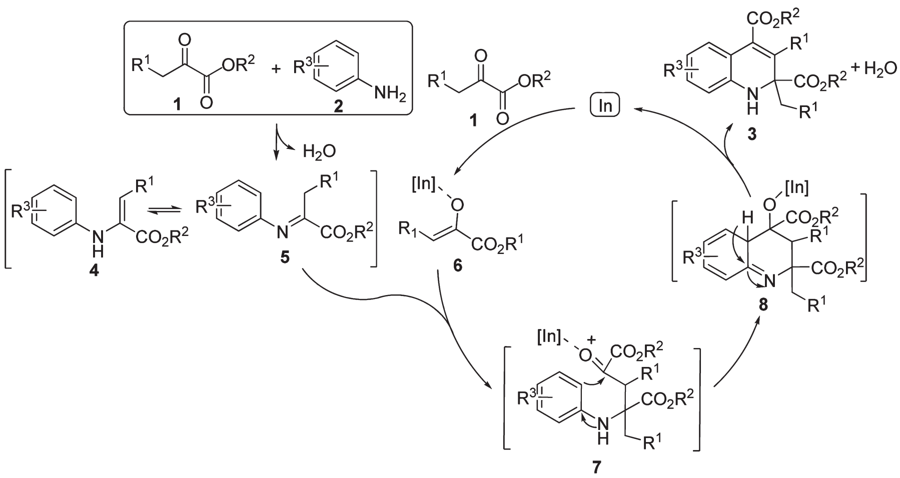
when the reaction of α-alkyl substituted ketoester **1c** with *p*-chloroaniline **2a** was performed in a previously reported system using the Au/Ag cocatalyst.[26] In addition, when changing the reaction conditions to those described in Table 3 while keeping the $AuCl_3/AgSbF_6$ (5 mol %/15 mol %) cocatalyst, the product **3ca** could be achieved with a yield of 24%.

To gain further insights into the reaction, several control experiments were conducted as shown in Schemes 4 and 5. When the reaction of methyl pyruvate (**1a**) and *p*-methoxyaniline (**2f**) was performed in the absence of catalyst, imine **5af** could be isolated together with a trace amount of enamine isomer (Scheme 4). Furthermore, **5af** reacted with **1a** under the standard conditions (1 mol % $In(OTf)_3$) leading to the desired target **3af** in 77% yield (Scheme 4). In addition, the desired product **3ca** was also generated in 31% yields when the reaction of **1c** with isolated enamine **4ca** (the isomer of imine **5ca**[28−30]) was performed in the presence of 10 mol % $In(OTf)_3$ (Scheme 5).

On the basis of the above experimental observations and previous reports,[26,31−34] we proposed a postulated reaction pathway shown in Scheme 6. Initially, the condensation reaction of α-ketoester **1** with amine **2** gave the imine **5** or its isomeric enamine **4**. Subsequently, the $In(OTf)_3$ activated α-ketoester **6**[34] reacted with imine **5** leading to intermediate **7**.[31−33] The electron-rich benzene ring attacked the keto-carbonyl group to form intermediate **8**. Finally, water elimination followed by proton shift would generate the polysubstituted 1,2-dihydroquinoline **3**.

In summary, we have developed a simple and efficient methodology for the construction of polysubstituted 1,2-dihydroquinoline derivatives via a one-pot tandem reaction of α-ketoesters and aromatic amines catalyzed by indium triflate. A series of tri- and tetra-substituted dihydroquinolines were conveniently obtained from simple and readily available starting materials. Application studies of this protocol are ongoing.

Scheme 6. Postulated Reaction Pathway for Indium-Catalyzed Tandem Process



ASSOCIATED CONTENT

Supporting Information. General procedures for the preparation of polysubstituted dihydroquinolines and spectrum details for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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