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An efficient one-step synthesis of 2-arylquinolin-4(1*H*)-ones with the aid of a low-valent titanium reagent

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ABSTRACT

A short and facile synthesis of a series of 2-arylquinolin-4(1*H*)-ones was accomplished in good yields via the novel reductive cyclization of 2-nitrochalcones promoted by $TiCl_4$/Zn. This method has the advantages of accessible starting materials, one-step procedure, convenient manipulation, and moderate to high yields.

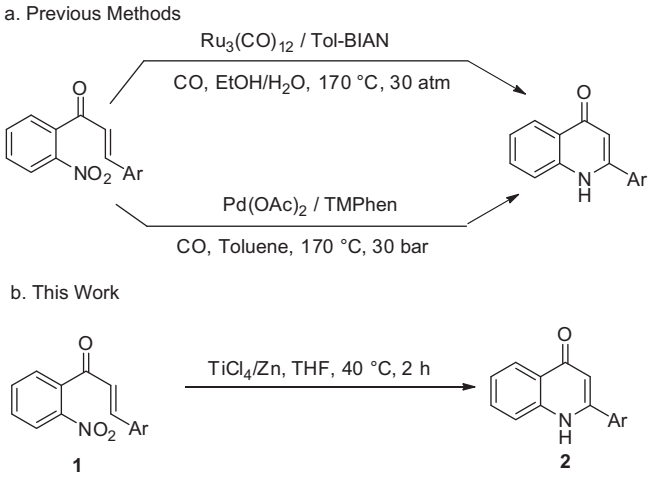
Low-valent titanium reagents have an exceedingly high ability to promote reductive coupling reaction of carbonyl compounds and are attracting increasing interest in organic synthesis.[1] Many other functional groups can also be coupled.[2] Recently, we have focused on the synthesis of heterocyclic compounds using low-valent titanium reagent. We have previously reported the synthesis of quinazolin-4(3*H*)-ones,[3] pyrroles,[4] quinazoline-2,4-diones,[5] indazol-3(2*H*)-ones,[6] and naphtho[1,2-*e*][1,3]oxazine[7] induced by low-valent titanium reagent.

The 2-arylquinolin-4(1*H*)-one core structure represents a highly privileged and biologically relevant molecular scaffold which occurs in many natural products.[8–11] Over the last years, the interest in 2-arylquinolin-4(1*H*)-ones and their analogs has been the subject of extensive study as potential anti-tumor, anti-mitotic, and cytotoxic agents[12] as well as anti-platelet agents.[11] To construct this intriguing 2-aryl-4-quinolone scaffold, several synthesis methods have been developed from different starting materials.[13] Among them, reductive cyclization of 2-nitrochalcones attracts more attention because diverse starting materials are readily available via Aldol condensation of 2-nitroacetophenone with benzaldehyde derivatives. However, the main disadvantage of this method is the use of Ru and Pt catalyst in high temperature (170 °C) and high pressure (30–40 bar of CO) (Scheme 1, a).[14] Here we wish to describe a new method induced by the $TiCl_4$/Zn system for the one-step synthesis of 2-arylquinolin-4(1*H*)-ones using 2-nitrochalcones as the starting material (Scheme 1, b).

In a preliminary study, 1-(2-nitrophenyl)-3-(4-methylphenyl)prop-2-en-1-one **1a** was used to define the reaction conditions for the preparation of 2-(4-methylphenyl)quinolin-4(1*H*)-one **2a**.

First, different types of low-valent titanium systems were investigated as reductive reagent for this reaction (Table 1, entries 1–5). $TiCl_4$/Zn (1:2) gave the best result of synthesis of **2a** (80%) (entry 1). Further optimization of the reaction conditions revealed that the use of 3 equiv of $TiCl_4$/Zn (1:3) at 40 °C (Table 1, entry 10) gave results superior to those under the other reaction conditions (Table 1, entries 6–9 and 11–12).

In order to apply this reaction to library synthesis, various kinds of 2-nitrochalcones were subjected to give the corresponding



Scheme 1. The synthesis of 2-arylquinolin-4(1*H*)-ones from 2-nitrochalcones.

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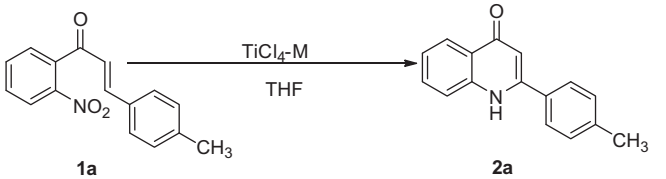
Table 1
Optimization for the synthesis of **2a**

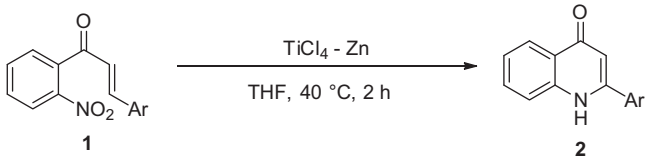


1a **2a**

Entry	$TiCl_4$/M system	Ratio[a]	Temperature (°C)	Isolated yield (%)
1	$TiCl_4$/Zn (1:2)	1:3	rt	80
2	$TiCl_4$/Mg (1:2)	1:3	rt	75
3	$TiCl_4$/Fe (1:2)	1:3	rt	72
4	$TiCl_4$/Al (1:2)	1:3	rt	65
5	$TiCl_4$/Sm (1:2)	1:3	rt	68
6	$TiCl_4$/Zn (1:2)	1:1	rt	55
7	$TiCl_4$/Zn (1:2)	1:2	rt	70
8	$TiCl_4$/Zn (1:2)	1:4	rt	65
9	$TiCl_4$/Zn (1:3)	1:3	rt	84
10	$TiCl_4$/Zn (1:3)	1:3	40	90
11	$TiCl_4$/Zn (1:3)	1:3	60	82
12	$TiCl_4$/Zn (1:3)	1:3	Reflux	78

[a] Ratio of **1a** and $TiCl_4$.

Table 2
Synthesis of compound **2**[15]



1 **2**

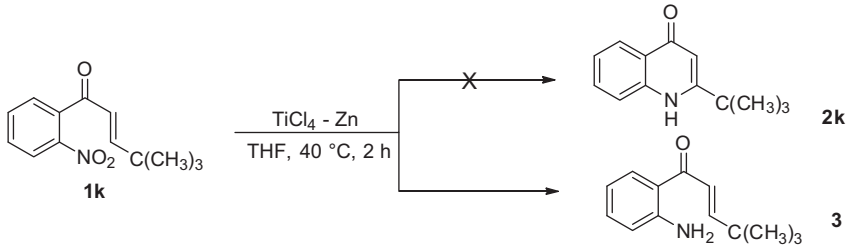
Entry	Ar	Compd	Isolated yield (%)	Mp (°C)	Lit. mp (°C)
1	4-$CH_3C_6H_4$	**2a**	88	287–289	290–292
2	4-$CH_3OC_6H_4$	**2b**	87	290–292	295–297
3	4-FC_6H_4	**2c**	70	>300	322–325
4	4-BrC_6H_4	**2d**	80	>300	318–320
5	3,4-$OCH_2OC_6H_3$	**2e**	89	285–286	288–290
6	Thiophene-2-yl	**2f**	79	270–271	>260
7	4-$N(CH_3)_2C_6H_4$	**2g**	85	>300	>300
8	4-ClC_6H_4	**2h**	86	247–249	252–254
9	3,4-$(CH_3O)_2C_6H_3$	**2i**	85	248–250	241–243
10	3-ClC_6H_4	**2j**	80	278–280	>260

2-arylquinolin-4(1*H*)-ones. The results are summarized in Table 2. All of the 2-nitrochalcones gave the expected products either bearing electron-withdrawing groups (such as halide) or electron-donating groups (such as alkyl group, alkoxyl group) in moderate to good yields under the same reaction conditions. Therefore, we can conclude that the electronic nature of the substituents has no significant effect on this reaction.

In order to demonstrate the efficiency and the applicability of the present method, we performed the reductive cyclization of 4,4-dimethyl-1-(2-nitrophenyl)pent-2-en-1-one (**1k**) under the optimized conditions. However, the desired product 2-(*tert*-butyl) quinolin-4(1*H*)-one (**2k**) can not obtained, 1-(2-aminophenyl)-4,4-dimethylpent-2-en-1-one (**3**) was obtained (Scheme 2). Therefore, this method is not suitable for the preparation of 2-alkylquinolin-4(1*H*)-ones.

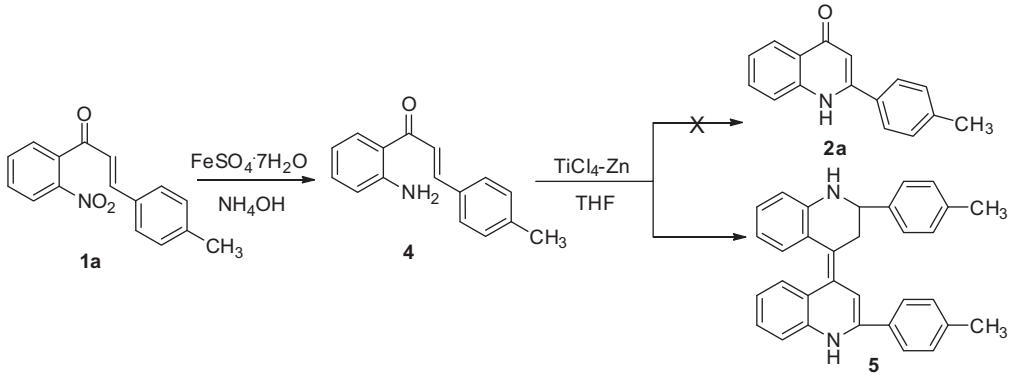
Because the nitro compounds are easy to be reduced to amines by the low-valent titanium reagent,[16] we think this reaction may proceed through the intermediate amine **4**. As shown in Scheme 3, the nitro compound was reduced by the low-valent titanium reagent to generate amine **4**, which was then followed by subsequent Lewis acid promoted Michael addition and dehydrogenation to achieve the product.

To prove this point, we chose **1a** as the starting material. Compound **1a** was firstly reduced to 2′-aminochalcone **4** by $FeSO_4{\cdot}7H_2O$, which was isolated and identified by spectral data. Then intermediate **4** was reacted with the low-valent titanium reagent in THF. To our surprise, 2,2′-di(4-methylphenyl)-2,3,-dihydro-1*H*,1′*H*-4,4′-biquinolinylidene **5** was obtained as our final product (Scheme 3), while the one we desired, **2a**, was not



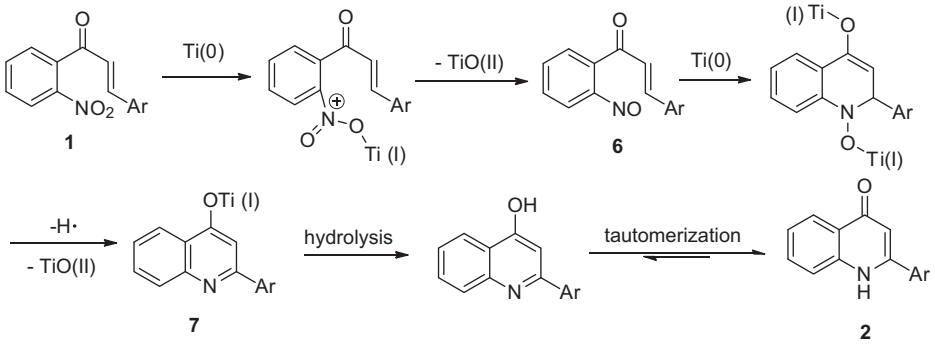
1k **2k** **3**

Scheme 2. The reaction of 4,4-dimethyl-1-(2-nitrophenyl)pent-2-en-1-one induced by $TiCl_4$/Zn.



1a **4** **2a** **5**

Scheme 3. The reaction of 2′-aminochalcone induced by $TiCl_4$/Zn.



Scheme 4. The proposed reaction mechanism.

detected. This indicated that in this reaction the nitro compound was not simply reduced to amines.

According to literature,[17] we suppose the following mechanism to explain this reaction. $TiCl_4$ is reduced by Zn dust to give low-valent titanium species. In the initial step, **1** was reduced by low-valent titanium to nitroso-compound **6**. Then reductive nitroso-compound **6** reacted with α,β-unsaturated ketone and gave the intermediate **7**. Then the product **2** was obtained by hydrolysis and tautomerization (Scheme 4).

In conclusion, a series of 2-arylquinolin-4(1*H*)-ones were synthesized via the reductive cyclization of 2-nitrochalcones induced by low-valent titanium reagent ($TiCl_4$/Zn). Compared to the reported methods, this method has the advantages of easily available starting materials, mild reaction condition, avoiding the use of toxic transition metal, short reaction time, high yields, and convenient manipulation.

Acknowledgments

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.089.

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15. *Typical experimental procedure*: $TiCl_4$ (0.7 mL, 6 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (1.17 g, 18 mmol) in freshly distilled anhydrous THF (10 mL) at room temperature (rt) under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt, and a solution of 2-nitrochalcones **1** (2 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred under the temperature of 40 °C for 2 h. After this period, the thin layer chromatography (TLC) analysis of the mixture showed the completion of this reaction. The mixture was then quenched with 5% HCl (30 mL) and extracted with $CHCl_3$ (3 × 50 mL). The extracts were washed with water (3 × 50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude products were purified by recrystallization from 95% ethanol. *2-(4-Methylphenyl)quinolin-4(1H)-one* ***(2a)***: Light yellow solid; mp 287–289 °C (Lit.[18] 290–292 °C); IR (KBr, cm^{-1}): 3350, 3021, 2919, 1714, 1645, 1614, 1580, 1514, 1361, 819, 750; ^1H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 6.30 (s, 1H, CH), 7.30 (t, *J* = 10.0 Hz, 1H, ArH), 7.37 (d, *J* = 10.0 Hz, 2H, ArH), 7.63 (t, *J* = 9.6 Hz, 1H, ArH), 7.73 (t, *J* = 12.0 Hz, 3H, ArH), 8.07 (d, *J* = 10.4 Hz, 1H, ArH), 11.64 (s, 1H, NH); HRMS calculated for $C_{16}H_{13}NO$ $[M]^+$: 235.0997, found: 235.0997.
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