RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2016, **6**, 66074

Received 5th June 2016
Accepted 27th June 2016

DOI: 10.1039/c6ra14583c

www.rsc.org/advances

Ethanol promoted titanocene Lewis acid catalyzed synthesis of quinazoline derivatives†

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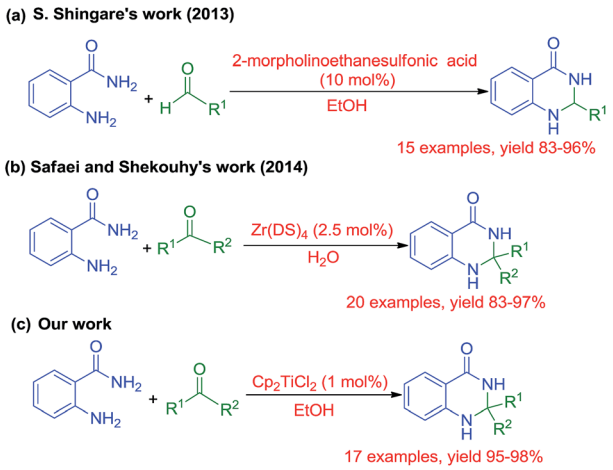
An efficient catalytic system involving *in situ* activation of kinetically inert titanocene dichloride with alcoholic solvent for the synthesis of quinazoline derivatives was developed. 1 mol% Cp_2TiCl_2 at 30 °C afforded 17 examples of quinazoline derivatives with yields of 95–98% in 7–12 minutes. Mechanistic experiments using *in situ* NMR and HRMS established that the coordination of ethanol to the titanocene moiety released the catalytic species $[Cp_2Ti(OCH_2CH_3)_2]$.

Quinazoline derivatives are an important class of heterocycles with a wide range of pharmacological and biological activities.[1] The catalytic condensation of anthranilamide with aldehydes/ketones provides a direct synthetic method for quinazolinone derivatives. 10 mol% of 2-morpholinoethanesulfonic acid (Scheme 1a) can promote the condensation reaction with yields of 83–96%.[2–4] Lewis acids of simple metal salts are more active,[5–8] for example, $Zn(PFO)_2$ gave yields of 80–91% with a 2.5 mol% catalyst loading. Notably, group IVB transition metal Lewis acids are efficient for this transformation. 2 mol% $ZrCl_4$ catalyzed the reaction of anthranilamide with aldehydes/ketones, giving yields of 80–97%.[9] Dodecylsulfate radical was employed to stabilize Zr^{4+} in aqueous solution, and 2.5 mol% $Zr(DS)_4$ successfully catalyzed the condensation reaction in water with yields of 83–97% (Scheme 1b).[10] Therefore, developing an efficient and robust Lewis acid catalyst is highly desirable for the synthesis of quinazoline derivatives.



Scheme 1 Approaches for the synthesis of quinazoline derivatives.

Group IVB metallocenes are promising Lewis acid catalyst precursors[11] due to their kinetic stability, electronically tunable metal centres and intrinsic metallic Lewis acidity.[12–15] Our previous research found that O-donor ligands such as salicylic acid, methanol and phenol derivatives enhanced the Lewis acidity of the titanocene centre, which showed cooperative catalytic activity in various organic condensation reactions, such as the Mannich[16–18] and Friedel–Crafts reactions.[19] Herein, we report the direct activation of Cp_2TiCl_2 by alcoholic solvent for the rapid synthesis of quinazoline derivatives.

In ethanol, as little as 1 mol% Cp_2TiCl_2 catalyzed the condensation reaction of anthranilamide and aldehydes with yields of up to 98% in 7 min. The catalytic system of Cp_2TiCl_2 in ethanol showed a wide functional group tolerance with 17 examples with yields of 95–98%. Mechanistic experiments unveiled $Cp_2Ti(OCH_2CH_3)_2$ as the catalytic species, and illuminated the superior activity of Cp_2TiCl_2 in ethanol for the condensation reaction.

Initially, we chose anthranilamide and benzaldehyde as the model substrates to optimize the reaction conditions. As shown in Table 1, $ZrCl_4$ and $TiCl_4$ catalyzed the reaction with yields of 56% and 63%, respectively (entries 1 and 2). Organometallic Lewis acid precursors significantly accelerated the condensation reaction, Cp_2ZrCl_2 afforded the desired quinazoline product in 89% yield, and Cp_2TiCl_2 gave a 98% yield of quinazoline (entries 3 and 5). Half sandwich Cp^*TiCl_3 gave a 71%

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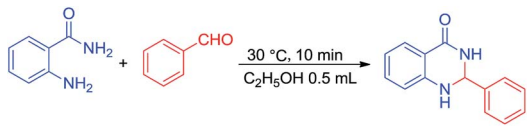
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra14583c

Table 1 Catalyst and concentration screening in the reaction of anthranilamide with benzaldehyde[a]



Entry	Catalyst	Catalyst (mol%)	Yield[b] (%)
1	$ZrCl_4$	5	56
2	$TiCl_4$	5	63
3	Cp_2ZrCl_2	5	89
4	Cp^*TiCl_3	5	71
5	Cp_2TiCl_2	5	98
6	Cp_2TiCl_2	4	98
7	Cp_2TiCl_2	3	98
8	Cp_2TiCl_2	2	97
9	**Cp_2TiCl_2**	**1**	**97**
10	Cp_2TiCl_2	0.5	83
11	$CuCl_2$	5	30
12	$MgCl_2$	5	20
13	$ZnCl_2$	5	42
14	$SrCl_2$	5	55
15	HCl	5	30

[a] Reaction conditions: anthranilamide (1 mmol), benzaldehyde (1 mmol). [b] Yield of the isolated product.

yield of the desired product (entry 4). Further experiments showed that 1 mol% of Cp_2TiCl_2 still afforded a 97% yield, and 0.5 mol% of Cp_2TiCl_2 gave a yield of 83% (entries 5–10). This solvent activation method was applied for other Lewis acids such as $CuCl_2$, $MgCl_2$, $ZnCl_2$ and $SrCl_2$, giving yields of 30%, 20%, 42% and 55%, respectively (entries 11–14). The control experiment using 5 mol% HCl afforded a 30% yield, which eliminated the possibility that the alcoholysis of titanocene chlorides released HCl as a catalytic species (entry 15). The effects of solvent and temperature were also screened (see ESI†).

The activation effects of various alcohols were investigated to demonstrate the pronounced accelerating effect on the titanocene dichloride catalyzed condensation reaction of anthranilamide with benzaldehyde (Fig. 1). It was found that ethanol was the best solvent, in which the yield was 97%. Methanol, *n*-propanol and *n*-butanol showed less of an accelerating effect and gave yields from 77–87%. Based on the facile substitution reactions of alkoxy groups with titanocene dichloride in alcohols,[20] a probable explanation for this effect is that the coordination between alcohols and titanocene species results in enhanced Lewis acidity of the Ti centre and thus improves the catalytic efficiency. This hypothesis was further supported by the condensation reaction catalyzed by titanocene dichloride in sterically hindered *t*-butanol, as the yield of the condensation reaction dramatically decreased to 50%. Furthermore, it was also found that polyol suppressed the activity of titanocene dichloride: the reaction in ethylene glycol afforded only a 30% yield. This is because titanocene dichloride in polyol, which readily formed a stable complex, was not an effective catalyst, indicating that chelation might be an unfavourable

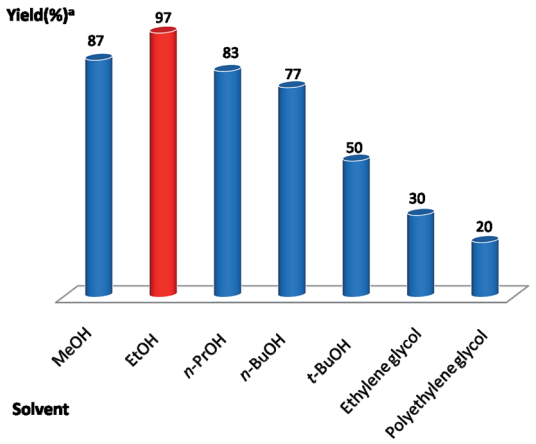


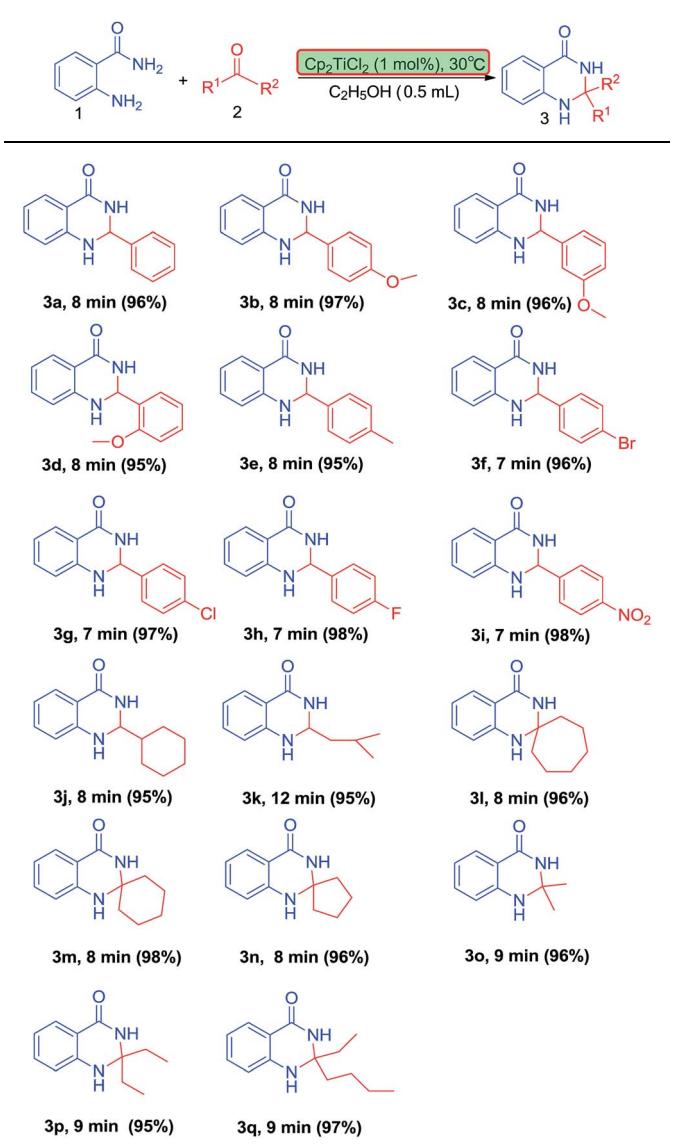
Fig. 1 Alcohol-accelerated Cp_2TiCl_2 catalysis of the condensation reaction of anthranilamide with benzaldehyde. [a] Yields are of the isolated product.

coordination mode for unleashing the Lewis acidity of titanocene dichloride. Owing to the fact that steric hindrance is disadvantageous for the coordination of alcohols to organometallic centres, the yield of the condensation reaction dramatically decreased with the use of polyethylene glycol, affording only a 20% yield. These findings led us to establish a new protocol for the activation of inert Cp_2TiCl_2 using a solvent strategy, thus accelerating the condensation reaction.

The scope and limitations of the new catalyst system were evaluated with anthranilamide and a range of aldehydes/ketones under the optimized conditions, as shown in Table 2. Initially, we investigated the reaction using several benzaldehyes substituted with electron-donating and electron-withdrawing groups (**3a–3i**) and anthranilamide under the optimized conditions. The electronic effects had no significant impact on the reaction rate, with yields of 96–98%. Nevertheless, when *o*-methoxy substituted benzaldehyde was used as a substrate for this reaction, the yield of the desired product was 95%, lower than *p*- and *m*- substituted benzaldehyde, which directly reflects the disadvantages of steric hindrance for this reaction. Aliphatic aldehydes such as cyclohexanecarbaldehyde (**3j**) was also readily introduced into this reaction, the desired product being formed with a yield of 95%. The reaction of anthranilamide and isovaleraldehyde (**3k**) proceeded slightly slowly and afforded a 95% yield after 12 min. Subsequently, the optimized conditions were applied for the conversion of various kinds of aliphatic ketones and anthranilamide into the corresponding quinazoline derivatives. Among the three kinds of cyclic ketones, the yield for cyclohexanone (**3m**) was 98%, higher than that for cycloheptanone (**3l**) and cyclopentanone (**3n**) which both gave yields of 96%. When the ketones were chain ketones, such as acetone (**3o**), 3-pentanone (**3p**) and 3-heptanone (**3q**), the reaction also proceeded smoothly and resulted in yields of 96%, 95% and 97%, respectively.

To shed light on the delicate accelerating effect of alcohols, the interaction between Cp_2TiCl_2 and CH_3CH_2OH was investigated by ^1H NMR and HRMS.[21] ^1H NMR experiments were conducted using Cp_2TiCl_2 in CD_3CD_2OD at intervals with

Table 2 Substrate scope for the synthesis of quinazolinone derivatives[a,b]



[a] All the reactions were carried out in the presence of 1 mmol **1**, 1.0 mmol **2**. [b] Yields of the isolated product.

addition of aniline as a base (Fig. 2). The characteristic cyclopentadienyl (Cp) protons can be regarded as a probe to measure the formation of new titanocene complexes. No coordination occurred and only one Cp singlet of Cp_2TiCl_2 at δ 6.59 ppm (●) was detected. When adding 1 equiv. aniline, the new titanocene complex species $Cp_2TiCl(OCH_2CH_3)$ (**III**) formed with a resonance at δ 6.25 ppm (◆).[22] The resonances of $Cp_2TiCl(OCH_2CH_3)$ increased while the resonance of Cp_2TiCl_2 declined gradually. When adding another 1 equiv. aniline, as the singlet at 6.25 ppm increased, one new Cp singlet for $Cp_2Ti(OCH_2CH_3)_2$ appeared at δ 6.34 ppm (▼) (**II**). $Cp_2TiCl(OCH_2CH_3)$ was consumed gradually in CD_3CD_2OD in the presence of base and formed the new titanocene species $Cp_2Ti(OCH_2CH_3)_2$ (**II**). The putative species **II** was further supported by HRMS experiments

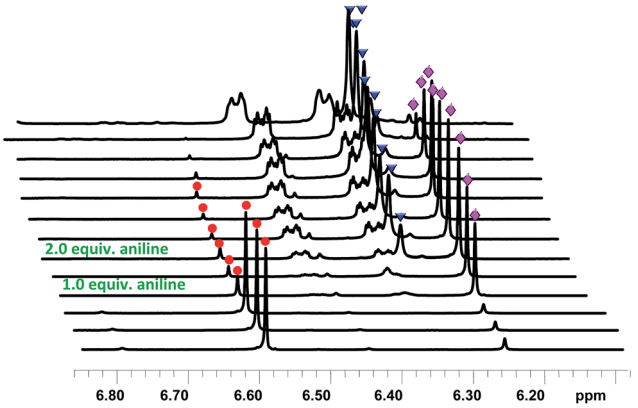
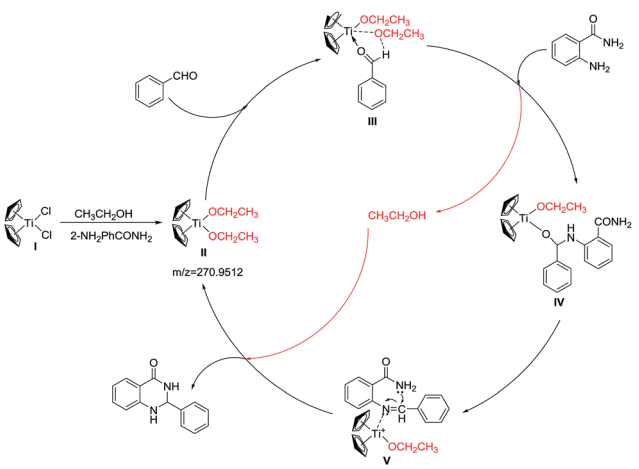


Fig. 2 Partial 400 MHz ^{1}H NMR spectra (CD_3CD_2OD) of a solution containing Cp_2TiCl_2 with addition of aniline. ● 6.59 ppm **I** [Cp_2TiCl_2]; ◆ 6.25 ppm **III** [$Cp_2TiCl(OCH_2CH_3)$]; ▼ 6.34 ppm **II** [$Cp_2Ti(OCH_2CH_3)_2$].

performed in the positive ion mode (see ESI Fig. S2 and S3†). The ion peak at m/z 270.9512 in the CH_3CH_2OH solution of Cp_2TiCl_2 corresponds to [**II** + H^+]. These observations clearly demonstrate that the CH_3CH_2OH is not just a medium to dissolve the sandwich complexes, but can also be another reactant involved in the process of activating Cp_2TiCl_2 *via* ethoxyl groups binding to the Cp_2Ti^{IV} moiety. It can be concluded that in the coordination reaction, the pre-catalyst titanocene dichloride is readily converted into the detectable titanocene species **II**, and presumably this is the organometallic Lewis acid catalyst.[23]

A plausible mechanism for the formation of quinazoline derivatives catalyzed by titanocene dichloride in ethanol solution is outlined in Scheme 2. Initially, the titanocene dichloride **I** pre-catalyst is activated by ethanol and transformed into the catalytically active titanocene diethoxy complex **II** in the presence of anthranilamide, with simultaneous release of HCl. The newly formed complex **II** coordinates with the aldehyde as shown in **III**, and the enolization is accelerated synergistically as the carbonyl coordinates to the oxophilic Ti and the ethoxy



Scheme 2 Proposed mechanism for the synthesis of quinazoline derivatives catalyzed by Cp_2TiCl_2 in ethanol.

ligand abstracts the proton. Then, the condensation of the activated aldehyde with the amino group of anthranilamide produces an imine intermediate with the H^+ in solution. In the meantime, the imine part could be activated by the cation as shown in **V**. Thus, the final product could be formed by intramolecular nucleophilic attack of the amide nitrogen on the activated imine carbon, followed by a proton transfer. Once the product is released, the catalytically active species **II** is regenerated by the coordination of CH_3CH_2OH and releases H^+ for the next cycle.

Conclusions

In summary, a robust Lewis acid catalytic system was developed through the activation of inert Cp_2TiCl_2 by ethanol for the efficient synthesis of quinazoline derivatives. As little as 1 mol% of Cp_2TiCl_2 efficiently catalyzed the condensation reaction, with 17 examples giving 95–98% yields. The mechanistic studies including ^1H NMR and HRMS analyses suggested that the coordination of CH_3CH_2OH to titanocene dichloride formed the catalytically active species $Cp_2Ti(OCH_2CH_3)_2$, which led to superior activity for the condensation reaction. These results illuminated a new catalytic system, which allows for a more concise, efficient and mild protocol for the synthesis of quinazoline derivatives. Furthermore, the moderate reaction conditions, air-stable organometallic Lewis acid catalyst, and absence of any cocatalyst or ligand make this an environmentally friendly methodology amenable to scale-up.

Acknowledgements

This work was supported by the 111 Project (B14041), grants from the National Natural Science Foundation of China (21271124, 21272186, 21371112), the Fundamental Funds Research for the Central Universities (GK201501005, GK201302015, GK201503029), the Project Supported by Natural Science Basic Research Plan in Shaanxi Province of China (Program No. 2015JQ2056), the Program for Changjiang Scholars and Innovative Research Team in University (IRT_14R33).

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