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Cp_2ZrCl_2-catalyzed synthesis of 2-substituted quinozolin-4(3*H*)-ones

Jagannath Jadhav, Sharanabasappa Khanapure, Rajashri Salunkhe and Gajanan Rashinkar*

Zirconocene dichloride (Cp_2ZrCl_2) in the presence of DMF was found to be a highly efficient catalyst for the synthesis of structurally diverse 2-substituted quinozolin-4(3*H*)-ones by reaction of anthranilimide with a wide range of aryl aldehydes.

Keywords: zirconocene dichloride; Lewis acid; quinozolin-4(3*H*)-ones

Introduction

Organozirconocenes have become useful scaffolds in synthetic organic chemistry since the pioneering work of Schwartz[1] and Negeshi.[2] Among them, the cationic zirconocene compounds have been used as valuable reagents for mediating synthetically important transformations.[3] Zirconocene dichloride (Cp_2ZrCl_2) and its derivatives constitute an important class of cationic zirconocene complexes that are regarded as stable, non-hazardous and ideal catalysts.[4] The catalytic activity of Cp_2ZrCl_2 is attributed to its weak acidity. Cp_2ZrCl_2 has been an extensively used catalyst in polymerization reactions.[5] However, despite the impressive catalytic potential of Cp_2ZrCl_2, its utility in organic synthesis is only sporadically demonstrated. Some of the catalytic processes initiated by Cp_2ZrCl_2 include synthesis of multi-substitutedvinyl silanes,[6] bis (indolyl) methanes[7] and cyclobutenyl phosphaonates.[8] Cp_2ZrCl_2 has also been reported to catalyze acetylation of phenols/alcohols/amines,[9] coupling of terminal alkynes as well as intramolecular coupling of imines and alkynes[10] and Refortmastky and Barbier reactions.[11] To tap the barely exploited potential of Cp_2ZrCl_2 in organic synthesis, we sought to explore the catalytic potential of Cp_2ZrCl_2 in the synthesis of heterocyclic compounds with a high therapeutic value.

Quinozolin-4(3*H*)-ones have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals.[12] The inclusion of this skeleton in more complex structures has led to a diverse range of bioactive molecules which exhibits a wide range of pharmacological properties such as antiviral,[13] antibacterial,[14,15] antitumor,[16] antimalerial,[17] antihypertensive[18] and anti-inflammatory activities.[19] Moreover, many of their derivatives are selective COX II inhibitors as well as inhibitors of derived growth factor receptor phosphorylation.[20] Owing to their therapeutic efficacy, development of facile protocols for the synthesis of quinozolin-4(3*H*)-ones with a diverse structural pattern has been a subject of immense interest to organic chemists. The synthetic strategies employed for the construction of 4(3*H*)-quinazolinone skeletons include cyclization of *o*-acylaminobenzamides,[21] amidation of 2-aminobenzonitrile followed by oxidative ring closure[16,22] and Pd-catalyzed heterocyclization of nitroarenes.[23] However, the reaction of aryl aldehydes with anthranilamide is one of the most classical and established methods for the synthesis of quinozolin-4(3*H*)-ones. Although several catalysts have been used to promote this transformation,[24] there is still scope of improvement, especially towards developing a facile approach using highly an active and efficient catalyst.

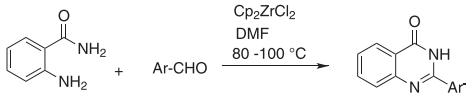
In continuation of our work directed towards the use of organometallic catalysts in organic synthesis,[25] we wish to report herein the synthesis of 2-substituted quinozolin-4(3*H*)-ones by reaction of anthranilimide with aryl aldehydes using Cp_2ZrCl_2 as a catalyst (Scheme 1).

Results and Discussion

Benzaldehyde and anthranilimide were chosen as model substrates for optimization of the reaction conditions. The initial effort was directed towards optimization of catalyst loading. The various quantities of Cp_2ZrCl_2 were assessed for the model reaction using DMF as solvent at 100 °C. The model reaction was restrained by the use of 5 mol% of catalyst. The 10 mol% concentration of catalyst promoted the reaction, furnishing an excellent yield of corresponding product (Table 1, entry 6). The use of excess amounts of the catalyst (15 and 20 mol%) did not have a marked influence on the yield of the product (Table 1, entries 7 and 8). It is noteworthy that in a blank experiment no reaction was observed under similar reaction conditions in the absence of Cp_2ZrCl_2. The influence of the solvent on model reaction was also investigated. While polar protic solvents such as methanol and ethanol afforded the desired product in lesser yield (Table 1, entries 1 and 5), polar aprotic solvents such as THF, acetonitrile and 1,4-dioxane afforded the anticipated product in moderate yield (Table 1, entries 2–4). In DMF, the conversion of anthranilimide into

* *Correspondence to: G. Rashinkar, Department of Chemistry, Shivaji University, Kolhapur, 416004 MS, India. E-mail: gsr_chem@unishivaji.ac.in*

Department of Chemistry, Shivaji University, Kolhapur, 416004, MS, India



Scheme 1. Synthesis of 2-substituted quinozolin-4(3*H*)-ones.

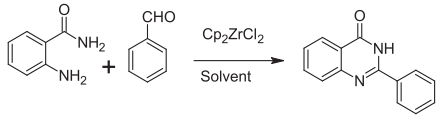
quinozolin-4(3*H*)-one was found to be exclusive. In the course of our study, we found that temperature plays a very crucial role in bringing out the desired transformation (Table 1, entries 6–8). The maximum yield of desired product was obtained by employing the reaction at 100 °C in DMF. From the above observations we inferred that reaction of benzaldehyde (1.0 mmol) and anthranilimide (1.0 mmol) with 10 mol% of Cp_2ZrCl_2 in DMF as the solvent at 100 °C would be the ideal condition for the reaction.

Having established the optimized condition, a series of quinozolin-4(3*H*)-ones were prepared by reacting anthranilimide with a wide range of aryl aldehydes with diverse substituent patterns. The results of reactions are summarized in Table 2. The reactions proceeded smoothly in all cases, affording the desired products in good yields. Several sensitive functionalities such as OMe, Cl, F, Br and NO_2 (Table 2, entries 3–8) on the aryl aldehyde nucleus were unaffected under the present reaction conditions. The reactions of heteroaromatic aldehydes (Table 2, entries 9–11) gave comparatively poor yields, which may be rationalized on the basis of participation of heteroatom in the formation of stable complex with Zr, which greatly reduces the catalytic activity. 9-Anthracenealdehyde was found to be inactive under optimized reaction conditions, presumably due to steric hindrance (Table 2, entry 13). All the synthesized quinozolin-4(3*H*)-ones are known compounds and were characterized by comparing their melting point, IR, ^{1}H NMR, ^{13}C NMR and mass spectra with those found in the literature.[24,26]

The catalytic role of Cp_2ZrCl_2 in the formation of quinozolin-4(3*H*)-ones from anthranilimide was evident from the observation that its presence is necessary for the occurrence of reaction. A plausible mechanism showing the catalytic role of Cp_2ZrCl_2 is depicted in Scheme 2. Initially, Zr of Cp_2ZrCl_2 activates carbonyl group by coordinating with carbonyl oxygen.[11] This facilitates nucleophilic attack of the amino group on the carbonyl carbon leading to the formation of intermediate **A**. The catalyst further activates an imine[27] intermediate (**B**), thereby leading to cyclization, which furnishes the desired product.

In conclusion, we have developed a simple and efficient methodology to synthesize quinozolin-4(3*H*)-one derivatives using Cp_2ZrCl_2 as a catalyst. The methodology has much scope for extension to a variety of substrates with various functional groups. The

Table 1. Optimization studies on cyclocondensation of anthranilimide and benzaldehyde[a]

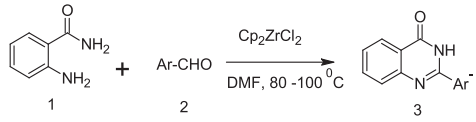


Entry	Solvent	Catalyst (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)
1.	Methanol	10	65	28	26
2.	THF	10	70	20	32
3.	Acetonitrile	10	70	22	40
4.	1,4 Dioxane	10	80	28	54
5.	Ethanol	10	80	17	67
6.	DMF	10	100	8	85
7.	DMF	15	100	8	86
8.	DMF	20	100	7	88

[a]Anthranilimide (1 mmol), benzaldehyde (1 mmol) and zirconocene dichloride in 5 ml of solvent were stirred at the appropriate temperature.

[b]Isolated yields after chromatography.

Table 2. Cp_2ZrCl_2-catalyzed synthesis of 2-substituted quinozolin-4(3*H*)-ones[a]

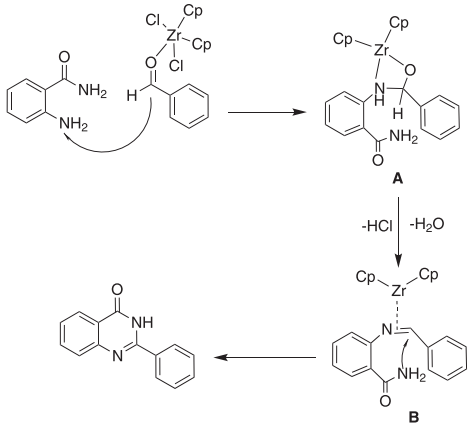


Entry	Ar	Product[b] [ref.]	Time (h)	Yield[c] (%)
1	Ph	**3a**[26a]	8	85
2	*p*-MePh	**3b**[26a]	7	80
3	*p*-OMePh	**3c**[26a]	7	78
4	*p*-ClPh	**3d**[26a]	4	82
5	*p*-FPh	**3e**[26b]	4	76
6	*p*-BrPh	**3f**[26b]	6	75
7	*m*-NO_2Ph	**3g**[22a]	3	82
8	*p*-NO_2Ph	**3h**[24a]	2	80
9	3-Pyridine	**3i**[26a]	2	60
10	2-Furan	**3i**[26a]	4	46
11	2-Thiophene	**3k**[26a]	4	39
12	2-Naphthalene	**3l**[26a]	6	68
13	9-Anthracene	—	10	—

[a]Anthranilimide (1 mmol), aromatic aldehyde (1 mmol) and zirconocene dichloride(10 mol%) in DMF (5 ml) were stirred at a temperature of 100 °C.

[b]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

[c]Isolated yields after chromatography.



Scheme 2. A proposed mechanism for the synthesis of quinozolin-4(3*H*)-ones using Cp_2ZrCl_2.

easy formation of substituted quinozolin-4(3*H*)-ones from inexpensive starting materials makes this process a viable alternative to more traditional syntheses of quinozolin-4(3*H*)-ones.

Experimental

General Procedure for Synthesis of Quinozolin-4(3*H*)-ones

A mixture of anthranilimide (1 mmol), aromatic aldehyde (1 mmol) and zirconocene dichloride in DMF (5 ml) were stirred at an appropriate temperature. After completion of reaction, as indicated by thin-layer chromatography, the reaction mixture was quenched in cold water. The obtained crude solid was filtered and purified by column chromatography on silica gel (Merck; 60-120 mesh, ethyl acetate:hexane) to afford the pure product.

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