Journal of Fluorine Chemistry 130 (2009) 406–409

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

One-pot synthesis of quinoline-4-carboxylic acid derivatives in water: Ytterbium perfluorooctanoate catalyzed Doebner reaction

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ARTICLE INFO

Article history:
Received 24 December 2008
Received in revised form 18 January 2009
Accepted 19 January 2009
Available online 30 January 2009

Keywords:
Ytterbium perfluorooctanoate
Doebner reaction
Pyruvic acid
Quinoline-4-caboxylic acid derivatives
One-pot reaction

ABSTRACT

Ytterbium perfluorooctanoate [Yb(PFO)$_3$] has been proved to be an efficient catalyst for Doebner reaction of pyruvic acid, aldehydes and amines under mild conditions in water to afford quinoline-4-caboxylic acid derivatives with three component one-pot method in good yields. The process is operationally simple and environmentally benign and the catalyst has readily been recycled for several times with consistent activity. Furthermore, a plausible mechanism for this transformation is also presented.

1. Introduction

In the last half-century, quinoline derivatives have been extensively investigated due to their potential biological and pharmaceutical activities. It has been reported that quinoline derivatives widely served as antagonists [1], analgesic agents [2], 5HT$_3$ [3], NK-3 receptors [4], and structural subunits of natural products [5,6]. Quinoline-4-carboxylic acids are one of the most important series of quinoline derivatives because they have a variety of medicinal effects and are applied as active components in industrial antioxidants [7]. Meanwhile, quinoline-4-carboxylic acids are the key precursors for the synthesis of other useful quinoline derivatives [8]. Thus, many methods for the synthesis of these quinoline acids have been reported successively. The conventional synthesis involves the Pfitzinger reaction of acetophenone with isatin [9,10], Doebner reaction [11,12] of aniline, benzaldehyde and pyruvic acid and the condensation reaction of benzaldehyde, pyruvic acid and arsanilic acid [13]. However, these synthetic methods suffered from either long reaction time or low yields. Recently, there have been several reports about modified Doebner reaction for preparing diverse quinoline-4-carboxylic acids via solid-phase synthesis [2], the Brønsted acid catalyzed reaction of anilines with α, β-unsaturated carbonyl compounds under high temperature or microwave irradiation conditions [7], and carbonylation of 4-chloro-7-methoxyquinoline in the presence of carbon monoxide [14]. However, these procedures are still restricted with some limits which involve use of large amount of organic solvents [15], the requirement of special apparatus, low yield or harsh reaction conditions. Therefore, the development of an easy and efficient method for the preparation of 4-carboxylic quinoline derivatives is still a challenging task.

In recent years, rare earth metal catalysts have gained recognition in a variety of synthetic reactions because of their unique advantages. Meanwhile, Lewis acid-surfactants combined catalysts (LASCs) can not only be used as water-stable Lewis acids, but also solubilize organic materials or form micelles' structures in water [16]. Thus, these catalysts have been investigated in detail for different reactions in aqueous solutions, which are safe, cheap and environmentally benign compared with organic solvents [17]. With this LASCs concept in mind, we have developed a new kind of rare earth perfluorooctanoates, RE(PFO)$_3$ in our previous works [18], which are easy to handle, are fairly stable in the water and air and readily available at low cost. The catalysts have shown remarkable activities and been applied to some condensation reactions with satisfactory results. In this paper, we would like to

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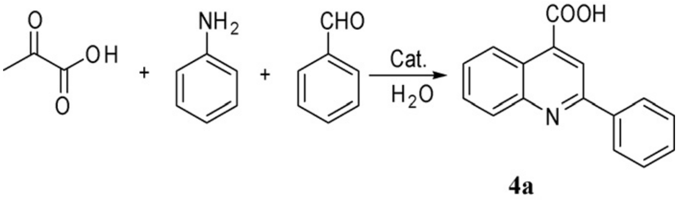
doi:10.1016/j.jfluchem.2009.01.002



Scheme 1.

disclose a facile and efficient method to prepare 2-phenylquinoline-4-carboxylic acids by Doebner reaction in the presence of Yb(PFO)$_3$ in water [19].

2. Results and discussion

In order to examine the catalytic activities of different catalysts, Doebner reaction of pyruvic acid, aniline and benzaldehyde was chosen as the model reaction (Scheme 1). The results are summarized in Table 1.

It was shown that Yb(PFO)$_3$ showed the best catalytic activity in this reaction (Table 1, entry 10) among all the catalysts. Zn(PFO)$_2$, Fe(PFO)$_3$, and La(PFO)$_3$ showed relatively better activities and gave moderate yields of the product (Table 1, entries 7–9). It is consistent with our previous reports on the Yb(PFO)$_3$ catalyzed condensation reactions. RE(PFO)$_3$ have been regarded as new types of Lewis acids. Their unique micellar dispersion and unique characteristics of the surfactant-type catalysts made these catalysts more efficient when they catalyzed the reactions in the presence of water. In contrast, owing to lack of surfactivity or high Lewis acidity, traditional Lewis acids such as $ZnCl_2$ and $AlCl_3$ failed to catalyze the reaction efficiently and the corresponding product is obtained in low yields (Table 1, entries 2–4). Perfluorooctanoic acid [$C_7F_{15}COOH$] normally acting as an excellent dispersant with favorable surfactivity [18c,20] was also found less efficient (Table 1, entry 5) due to lack of the binding with RE metal cation. In addition, it is also discovered that the catalytic activity of transition metal perfluorooctanoates is slightly less than RE(PFO)$_3$ (Table 1, entry 7 and 8 *vs.* entry 9 and 10).

Table 1
The effect of different Lewis acids catalysts in the Doebner reaction[a].

Entry	Catalyst	Amount (mol%)	Time (h)	Yield (%)[b]
1	None	–	24	Trace
2	$ZnCl_2$	3	12	11
3	$AlCl_3$	3	12	15
4	Yb(OTf)$_3$	3	12	20
5	$C_7F_{15}COOH$	4.5	12	37
6	Yb(CF_3CO_2)$_3$	3	12	13
7	Zn(PFO)$_2$	2.5	3	60
8	Fe(PFO)$_3$	2.5	3	57
9	La(PFO)$_3$	2.5	3	65
10	Yb(PFO)$_3$	2.5	3	72
11	Yb(PFO)$_3$	2.5	3	72,71,72[c]

[a] All reactions were carried out under refluxing in water.
[b] Isolated yields.
[c] Catalyst was reused three times.

Table 2
Synthesis of quinolinecarboxylic acids by Yb(PFO)$_3$ catalyzed Doebner reaction[a].

Entry	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	H	H	3	**4a**	72
2	4-CH_3	H	3	**4b**	72
3	4-NO_2	H	12	**4c**	25
4	4-Cl	H	3	**4d**	70
5	3-Cl	H	3	**4e**	54
6	2-Cl	H	12	**4f**	33
7	H	4-Cl	3	**4g**	70
8	H	4-OCH_3	3	**4h**	75
9	H	4-NO_2	3	**4i**	67
10	H	4-OH	3	**4j**	70
11	4-CH_3	4-OCH_3	3	**4k**	71
12	4-CH_3	4-CH_3	3	**4l**	76
13	4-CH_3	4-NO_2	3	**4m**	65
14	2-Cl	4-Cl	3	**4n**	48

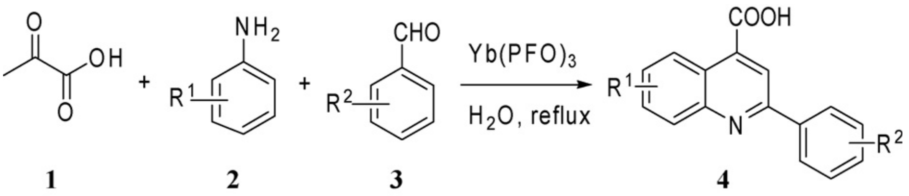
[a] All reactions were catalyzed by Yb(PFO)$_3$ in water under reflux.
[b] Isolated yields.

The optimal amount catalyst of Yb(PFO)$_3$ was also studied in Doebener reaction. It was showed that 2.5 mol% of the catalyst is preferred and increase in the amount of catalyst could not give a better result. Meanwhile, further investigation found that the better catalytic effect of Yb(PFO)$_3$ could be obtained under refluxing temperature of water. When the reaction was completed, the catalyst can be reused several times without obvious loss of activity (Table 1, entry 11).

Thus, we researched the generality of Yb(PFO)$_3$ in Doebner reaction by conducting a series of reactions with structurally diverse amines and aldehydes under the same condition (Scheme 2). The results were listed in Table 2. It is noted that the anilines with para-or meta-electron-donating groups (such as methyl-) are favorable for the transformation. However, the ortho-substituted anilines did not proceed successfully, which is probably attributed to the steric interference (entry 6). It was found that para-substituted benzaldehydes carrying either electron-donating or electron-withdrawing groups all reacted well and the yields were satisfied (Table 2, entries 7–10).

The mechanism of Doebner reaction was studied and explained by many researchers in recent years [21]. The reaction catalyzed by Yb(PFO)$_3$ is proposed to involve 1,2-addition of the aniline to aromatic aldehyde to form Schiff's base adducts, followed by Mannich reaction with pyruvic acid to form intermediate **7**, then dehydrative ring closure and oxidation afforded the final quinolines. The rare earth metal cation Yb^{3+} could activate carbonyl group of aromatic aldehyde, facilitate the subsequent cyclization and accelerate the reaction (Scheme 3).

The colloidal solution could be created by the catalyst Yb(PFO)$_3$ in water, then the organic substrates could be dispersed into the aqueous micellar solution. The reaction would take place in the emulsion droplets' interior surfaces that is hydrophobic, and water molecules produced from Doebner reaction would be expelled out of the droplets. Accordingly, the reaction would efficiently proceed in the presence of a large amount of water.



Scheme 2.