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Polymer (PVP) Supported Ferric Chloride: An Efficient And Recyclable Heterogenous Catalyst For One-Pot Synthesis Of 4(3H)-Quinazolinones Under Solvent Free Conditions

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ABSTRACT

An efficient synthesis of 4(3H)-quinazolinones by coupling of anthranilic acid, ortho esters and amines using Polymer supported ferric chloride catalyst under solvent free conditions is described. This new approach consistently has the advantage of excellent yields (80-97%) and short reaction times of 5-15 min.

KEYWORDS

Polymer supported ferric chloride;
Solvent free conditions;
4(3H)-Quinazolinones.

INTRODUCTION

4(3H)-Quinazolinones are a class of fused heterocycles and these studies were initially reported[1] more than century back. These are important class of bioactive molecules and widely used as anticonvulsant, anticancer, antimalarial, antihypertensive and antiinflammatory agents[2]. 4(3H)-Quinazolinone moiety is present in several bioactive natural products[3,4]. The synthesis of 4(3H)-Quinazolinone derivatives is achieved by cyclo addition reactions of anthranilic acid derivative together with diverse range of substrates including imidates and imino halides. Due to their wide range of applications these compounds have received a great deal of attention in connection with their synthesis. Many reagents have been reported in the literature[5] for the synthesis of 4(3H)-quinazolinones derivatives, However many of these methodologies have associated with several short coming such as multistep procedure, long reaction times, expensive reagents, harsh conditions, low product yields, occurrence of several side prod-

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ucts and difficulty in recovery and reusability of the catalysts. In continuation of our interest on polymer supported $FeCl_3$ catalyzed organic reactions[6,7] we describe here a novel efficient and high yielding protocol for the preparation of quinazolines-4-3(H)-ones through a three component one pot reaction of anthranilic acid, amines and ortho esters in solvent free conditions employing polymer supported ferric chloride as efficient and recoverable catalyst.

Recently, the use of solid supported reagents[8,9] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Among the various heterogeneous catalysts, particularly, polymer supported $FeCl_3$ has advantages of low cost, ease of preparation and catalyst recycling.

EXPERIMENTAL

General experimental procedure

To a mixture of anthranilic acid(1mmol), an orthoester(1.2 mmol) and an amine(1.2 mmol) polymer supported ferric chloride (100mg) was added. The mixture was stirred at room temperature for an appropriate time (TABLE 1). The reaction was monitored by TLC, NMR and mass were used for analysis of the products. After completion of the reaction, 10 ml of CH_2Cl_2 was added to the reaction mixture and the catalyst was recovered by filtered. The filtrate was washed with aq. HCl (5%) (3 x 5mL) and subsequently with H_2O (3 x 5mL). The organic layer was dried and the solvent was evaporated to get 4(3H)-quinazolinone. When the reaction was carried out with a nitroaniline or with 2,5-dimethoxy aniline the reaction mixture was refluxed at 60^0C. Catalyst was recovered from the residue of filtration of the reaction mixture by washing thoroughly with CH_2Cl_2, activated and recycled. The efficiently of the recovered catalyst was verified with the reaction of anthranilic acid, trimethyl orthoformate and aniline (Entry a). Using the fresh catalyst the yield of the products, 3-phenyl-4(3H)-quinazolinone**(4a)** was 97% while with the recovered catalyst in the three subsequent recyclization the yields were 93, 89 and 88%. The spectral properties of some representative 4(3H)-Quinazolinones are given below.

(4j): 3-(4-Methylphenyl)quinazolin-4(3H)-one

^{1}HNMR($CDCl_3$): δ =8.29(d, J =7.6 Hz, 1H), 8.11 (s, 1 H), 7.69-7.71(m, 2H), 7.40(t, J =7.2 Hz, 1H), 7.16 (d, J =7.6Hz, 2H), 7.28(d, J =7.6Hz, 2H), 2.26(s, 3H).

^{13} CNMR($CDCl_3$): δ =159.9, 147.32, 146.20, 134.31, 133.20, 131.58, 128.15, 127.12, 126.23, 125.14, 124.81, 124.13, 122.11, 19.30.GC/MS: m/z (%) =236.2(M+, 100), 237.2(M^++1, 14).

(4k): 3-(4-Methoxylphenyl)quinazolin-4(3H)-one

^{1}HNMR($CDCl_3$): δ =8.28(d, J =7.6Hz, 1H), 8.12(s, 1H), 7.68-7.72(m, 2H), 7.42(t, J =7.3 Hz, 1 H), 7.15(d, J =7.7Hz, 2H), 7.29(d, J =7.6Hz, 2H), 3.71(s, 3H).

^{13}CNMR($CDCl_3$): δ =161.22, 148.33, 146.20, 134.32, 133.20, 131.56, 128.11, 127.10, 126.22, 125.14, 124.81, 124.21, 122.13, 19.35.

(4l): 3-(4-Fluorophenyl)quinazolin-4(3H)-one

^{1}HNMR($CDCl_3$): δ =8.32 (d, J =7.5 Hz, 1H), 8.12(s, 1H), 7.67-7.70(m, 2H), 7.46(t, J =7.0Hz, 1H), 7.35(m, 4H).

^{13}CNMR($CDCl_3$): δ =160.12, 147.73, 146.64, 136.45, 135.26, 134.66, 132.62, 130.55, 128.33, 127.91, 126.84, 124.14, 122.43.

(4n): 3-(4-Nitrophenyl)quinazolin-4(3H)-one

^{1}HNMR($CDCl_3$): δ =8.41(d, J =7.6 Hz, 1H), 8.16(s, 1H), 7.71-7.75 (m, 2H), 7.51(t, J =7.4 Hz, 1H), 7.90(d, J =8.63 Hz, 2H), 8.0(d, J =8.7 Hz, 2H).

^{13}CNMR($CDCl_3$): δ =165.28, 152.85, 147.84, 144.84, 144.10, 133.34, 127.15, 122.16, 121.34, 123.81. GC/MS: m/z(%) =267.0(M^+, 100), 268(M^+ +1, 15).

(4o): 3-(4-Ethylphenyl)quinazolin-4(3H)-one

^{1}HNMR($CDCl_3$): δ =8.28(d, J =7.6 Hz, 1H), 8.10 (s, 1H), 7.68-7.71(m, 2H), 7.40(t, J =7.1Hz, 1H), 7.15(d, J =7.5Hz, 2H), 7.26(d, J =7.7Hz, 2H), 2.25(q, J =7.1Hz, 2H)1.01(t, J =7.0 Hz, 3H).

^{13}CNMR($CDCl_3$): δ =160.5, 148.32, 146.21, 134.35, 133.20, 131.57, 128.4, 127.15, 126.12, 125.18, 124.83, 124.14,122.43, 119.33. GC/MS:m/z(%) =250.2 (M^+, 23), 237.2 (M+1, 14), 130(100).

(4p): 3-(2-Chlorophenyl)quinazolin-4(3H)-one

^{1}HNMR($CDCl_3$): δ =8.38(d, J =7.8Hz, 1H), 8.18 (s, 1H), 7.72-7.75(m, 2 H), 7.53(t, J =7.3 Hz, 1H), 7.32-7.38(m, 4H).

^{13}CNMR ($CDCl_3$): δ =162.24, 147.83, 147.61, 136.53, 135.32, 134.60, 131.75, 130.74, 129.63, 128.12, 127.14, 126.15, 122.41. GC/MS:m/z(%) =256.0(M^+, 100), 258.0(M+2, 32), 257.0(M-1, 16).

(4q): 3-(4-Chlorophenyl)quinazolin-4(3H)-one

^{1}HNMR ($CDCl_3$): δ =8.33(d, J =7.5 Hz, 1H), 8.13(s, 1H), 7.68-7.71(m, 2H), 7.48(t, J =7.3Hz, 1H), 7.38(d, J =0.6 Hz, 2H), 7.25(d, J =8.6 Hz, 2H).

^{13}CNMR ($CDCl_3$): δ =160.2, 148.83, 146.61, 136.43, 135.21, 134.61, 132.75, 130.55, 128.33, 127.91,126.82,125.14,122.42. GC/MS: m/z(%) =256.0(M^+, 18), 130(100), 258.0(M +2, 32).

(4r): 3-(2,4-Dinitrophenyl)quinazolin-4(3H)-one

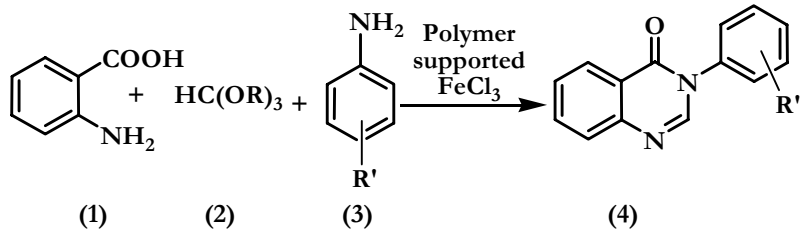
^{1}HNMR ($CDCl_3$): δ =9.10(s, 1H), 8.17-8.56(m,4H), 7.73-7.76(m, 2H), 7.51(t, J =7.4 Hz, 1H).

^{13}CNMR ($CDCl_3$): δ =167.21, 152.83, 147.86, 144.84, 144.0, 138.23, 133.3, 128.75, 127.15, 123.83,122.16,121.34,120.43.

RESULTS AND DISCUSSION

In view of recent surge in the use of heterogeneous catalysts[10-13]. We wish to report a simple, convenient and efficient method for the preparation of 4(3H)-quinazolinone derivatives using a solid supported reagent, polymer supported ferric chloride, as an inexpensive and eco-friendly catalyst and was prepared by using known procedure[14]. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. This catalyst can act as eco-friendly for a variety of organic transformations, non-volatile, recyclable, non-explosive, easy to handle, and thermally robust. Enhanced reaction rates and improved selectivity was obtained in the presence of this heterogeneous catalyst. In view of the emerging importance of the heterogeneous catalyst, we wish to explore the use of polymer supported ferric chloride as recyclable catalyst for the synthesis of 4(3H)-quinazolinone derivatives (SCHEME 1).

The treatment of anthranilic acid **(1)** with ortho esters **(2)** and anilines **(3)** in the presence of polymer supported ferric chloride[13] causes the formation of 4(3H)-quinazolinones **(4)** in 97% yield. In a similar fashion, various 4(3H)-quinazolinones **(4)** reacted were prepared (TABLE 1) using different substituted anilines. The reactions proceeded efficiently with in a few minutes in excellent yields at reflux temperature under solvent free conditions. The crude products were purified either by recrystallization from n-hexane or by silica gel column chromatography. All the products were characterized by IR, ^{1}HNMR and mass spectral analysis and also by comparison with authentic samples. The advantage of the use of heterogeneous catalyst for this transformation is that ease of catalyst/substrate separation provided by a heterogeneous catalyst.



(1) (2) (3) (4)

SCHEME 1

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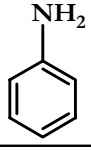
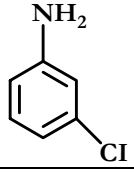
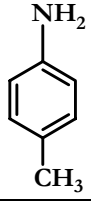
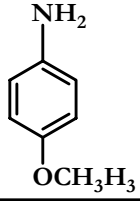
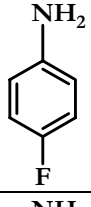
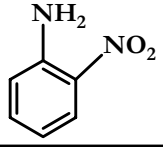
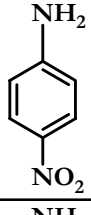
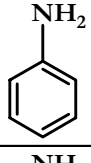
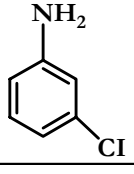
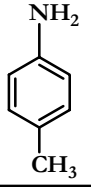
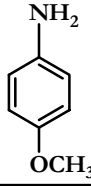
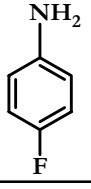
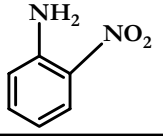
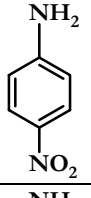
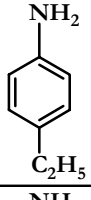
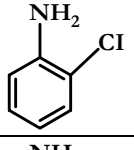
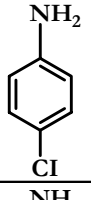
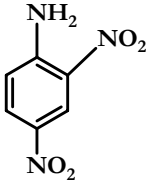
TABLE 1: Preparation of 4(3H)-quinazolinones (4a-4n)catalyzed by polymer supported $FeCl_3$

Entry	R	Anilines	Product[a]	Reaction time (min.)	Yield[b] (%)
a	Me		4a	5	97
b	Me		4b	8	95
c	Me		4c	5	97
d	Me		4d	5	97
e	Me		4e	8	90
f	Me		4f	10	85
g	Me		4g	10	87
h	Et		4h	5	97
i	Et		4i	8	94
j	Et		4j	5	95
k	Et		4k	5	95
l	Et		4l	8	90
m	Et		4m	10	84
n	Et		4n	10	87
o	Et		4o	6	95
p	Et		4p	7	97
q	Et		4q	7	95
r	Et		4r	12	80

[a]All product were chraacter is ed by ^1H NMR and IR spectors copic data and their mps compared with literature mps; [b]Isolated yields after column chromatography

CONCLUSION

In summary, we have developed a simple, convenient and effective method for facile synthesis of 4(3H)-quinazolinones by the coupling of reaction of anthranilic acid, ortho esters and amines using polymer supported ferric chloride catalyst in single step under solvent free conditions. Present methodology offers very attractive features such as reduced reaction times, reusability, higher yields and economic viability of the catalyst, operational simplicity, when compared with conventional method as well as with other catalysts, which will have wide scope in organic synthesis. The operational simplicity of the procedure is also attractive. The catalyst can be prepared easily with readily available inexpensive reagents, which is heterogeneous and non-hazardous. To our knowledge, this is first time report of an efficient general method for the synthesis of 4(3H)-quinazolinones by using polymer supported ferric chloride catalyst.

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