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Iron (III) Phosphate Catalyzed the Synthesis of 4-quinolones

Samaneh Samadi, Farahnaz K. Behbahani*

Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran.

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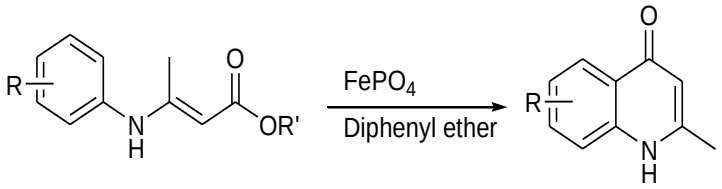
ABSTRACT

New and efficient methods have been developed for the synthesis of 4-quinolones throughout Conrad–Limpach synthesis in diphenyl ether under reflux condition. This method possesses various advantages such as using a green and versatile catalyst, easy procedure, work up and separation, being free from column chromatography, and atom economic. Also, this kind of solvent and the reaction temperature has an important role in the yield of reaction. When toluene, ethanol, acetonitrile and chloroform were subjected as solvent in ambient temperature and reflux condition, the desired product did not result. Moreover, when diphenyl ether was employed in room temperature – at 100, 150 and 200 °C – it was observed that the product was obtained. Interestingly, the desired product was obtained in good yield under reflux condition in diphenyl ether.

*Corresponding author, email: farahnazkargar@yahoo.com
Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran

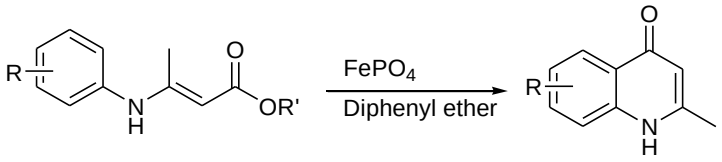
Graphical Abstract



Introduction

4-Quinolones are important compounds and valuable synthetic intermediates for derivatives that have various types of biological activities, e.g. tuberculostatic activity [1]. 4-Quinolone derivatives have attracted attention due to their use as antibacterials, e.g. ciprofloxacin and other 6-fluoroquinolones [2]. It is worth mentioning that they are active against a great variety of infections including anthrax, and have also shown to be antitumor [3–5] and antimitotic [6] agents.

The Conrad–Limpach reaction between anilines and a bketoester is a general method for synthesizing 4-quinolones [7, 8]. Moreover, various procedures for performing the mentioned reaction are reported in the literature. However, depending on the reaction temperature, solvent and molar ratio of the reactants [9, 10], aromatic amines react with methyl acetoacetate yielding alkyl β-arylaminocrotonates, acetoacetanilides, diphenylureas or 4-quinolones. In this communication, we wish to report synthesis of 4-quinolones using β-arylaminocrotonates under reflux condition in diphehyl ether (Scheme 1).



Scheme 1.

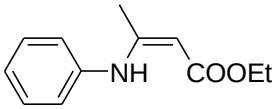
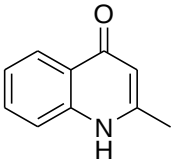
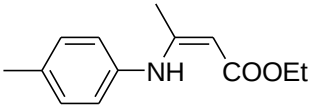
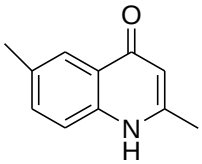
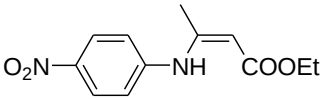
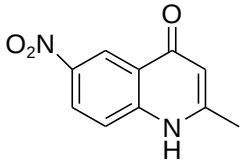
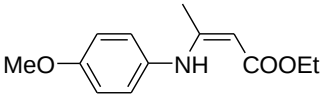
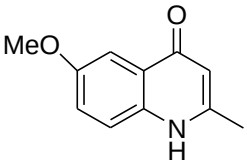
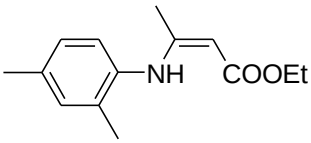
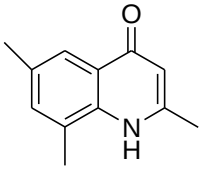
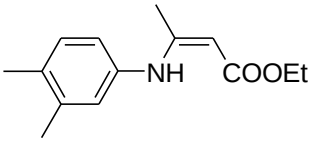
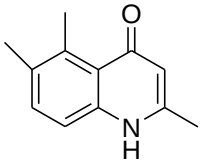
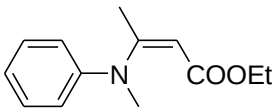
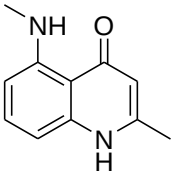
Results and discussion

In this paper, several β-arylaminocrotonates with catalytic amounts of iron(III)phosphate were mixed in diphenyl ether. The reaction proceeded well with β-arylaminocrotonates of carrying either electron-donating or electron withdrawing substituents to produce their corresponding 4-quinolones in high yields (Table 1).

In this project, the author found that the solvent and the temperature play an important role in the yield of reaction. When toluene, ethanol, acetonitrile and chloroform were subjected as solvent in

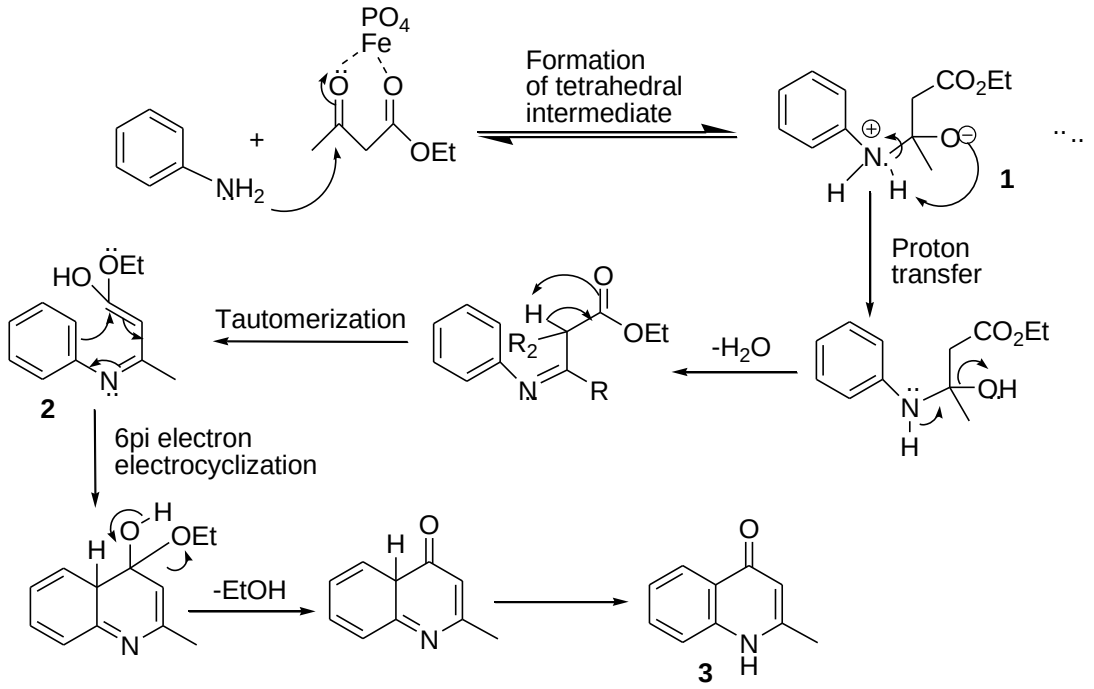
ambient temperature and reflux condition, the desired product did not result. Also, when diphenyl ether was employed in room temperature and at 100, 150 and 200 °C. It was observed that the product was obtained. Interestingly, the desired product resulted in good yield under reflux condition in diphenyl ether

Table 1. Synthesis of 4-quinolones using $FePO_4$ under reflux condition in diphehyl ether

Entry	β-arylaminocrotonates	Product	Yield %	Time (h)	M.P. °C[ref]
1			78	1:30	130-141[7]
2			77	1:25	104-110[7]
3			46	1:20	98-104[7]
4			82	1:05	52-59[8]
5			90	1:30	40-48[8]
6			88	1:30	Oil[8]
7			80	1:15	Oil[8]

The suggested mechanism has also been shown in scheme 2. $FePO_4$ as a catalyst activates carbonyl group of ethyl acetoacetate to give intermediate **1**. After proton transfer of **1** and dehydration of the

following tautomerization, intermediate **2** is obtained. Afterwards, 6pi electron electrocyclization, elimination of ethanol and 1,3-hydrogen shift result desired product **3**



Scheme 2. Suggested mechanism for the catalytic synthesis of 4-quinolones

Experimental

Synthesis of 4-quinolones under reflux condition in diphehyl ether. General procedure.

β-Phenylaminocrotonate (1.0 mmol) and $FePO_4$ (20 mol%) were added to diphenyl ether under reflux condition and maintained for appreciate time. Then, cooled at RT, the reaction mixture was subjected to column chromatography on silica in order to give pure 2-methyl-4-quinolones. Moreover, it was identified by Perkin Elmer FT-IR spectrometer and ^{1}HNMR spectra on Bruker DRX-300 MHZ NMR instrument.

Conclusion:

This work was carried out in the presence of a new, green, reusable and eco-friendly catalyst, thus, this methodology is a new procedure which is applicable for the synthesis of 4-quinolones. Having in mind the previously reported procedures and also the important contribution of the current method to perform acid reactions by applying new clean technologies, our work can be regarded as a useful and innovative one.

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