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Ferric Perchlorate-Catalyzed Multicomponent Synthesis of 3-aryl-2-cyclohexylamino-6,7-dihydro -1H-indole-4(5H)-ones

Bita BAGHERNEJAD[1], Hossein A. OSKOOIE[1♠], Majid M. HERAVI[1]

[1] *Azzahra University, Department of Chemistry, Vanak, Tehran, Iran*

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ABSTRACT

An efficient synthesis of 3-aryl-2-cyclohexylamino-6,7-dihydro-1H-indole-4(5H)-ones using ferric perchlorate as the catalyst via four-component reaction between cyclohexylisocyanide, an aldehyde, a cyclic 1,3-dicarbonyl compound and ammonium acetate in acetonitrile is described.

Key Words: *cyclohexylisocyanide, cyclic 1,3-dicarbonyl compound, multi-component reaction; 1H-Indole-4(5H)-ones.*

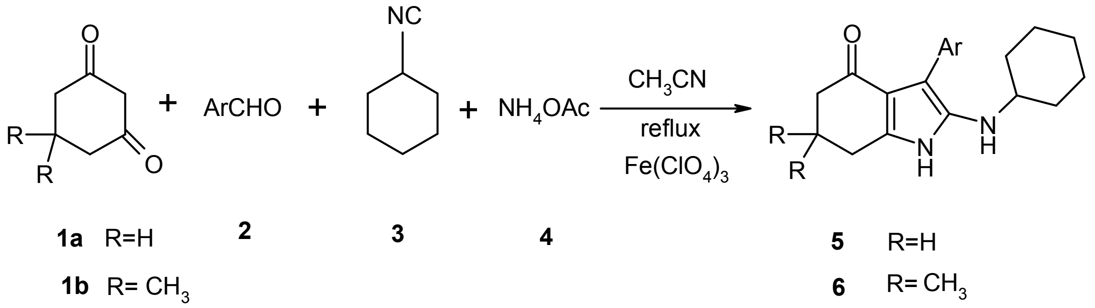
1. INTRODUCTION

Multicomponent reactions (MCRs) offer a unique way to generate efficiently libraries of complex molecules with high degree of diversity [1,2]. Among them, the Ugi four component reaction (Ugi-4CR) is without doubt one of the most powerful transformations that has been extensively investigated for the past twenty years [3].

Isocyanide-based multicomponent reactions (IMCR) now occupy a position of importance in synthetic organic chemistry, mainly due to the contributions of Ugi and co-workers [4, 5].

The indole pharmacophore is a fundamental constituent of a number of natural and synthetic products with multiple biological activities[6].Indoles have been designated as privileged structures in medicinal chemistry [7]. Oxoindoles are useful intermediates in the synthesis of a variety of molecules[8]. Although a number of synthetic methods for the preparation of indoles have been reported, simple and efficient approaches still remain scarce. Recently, isocyanide was used for the synthesis of Indoles[9] and we used it for the synthesis of 2-(cyclohexylamino)-6,7 - dihydro-3-aryl-1*H*-indole-4(5*H*)-ones by $KHSO_4$.[10]. Herein, we report a mild, practical and highly efficient procedure for the preparation of these compounds using $Fe(ClO_4)_3$ as a catalyst under refluxing conditions (Scheme 1).

Corresponding author: mmheravi@azzahra.ac.ir



Scheme 1

To show the merits and advantages of using $Fe(ClO_4)_3$ as a catalyst, our method is compared with reported reactions[10]. The reaction in the presence of $Fe(ClO_4)_3$ requires shorter reaction times than that used in the case of $KHSO_4$, but gives higher yields.

2. EXPERIMENTAL

All products were characterized by their melting points, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX Avance spectrometer at 500 and 125 MHZ, respectively, with $CDCl_3$ as solvent. IR spectra were recorded for KBr discs 2 on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. Elemental analyses were carried out on a Perkin–Elmer C, H, N analyzer.

2.1. Preparation of 2-(cyclohexylamino)-6,7-dihydro–3-aryl-1H-indole-4(5H)-ones: Typical Procedure

To a magnetically stirred solution of 1,3-dicarbonyl compound (1 mmol), aldehyde (1 mmol), ammonium acetate (1.5 mmol) and ferric perchlorate (3 mol%) in acetonitrile (5 mL) was added cyclohexyl isocyanide (1 mmol) and the reaction was refluxed for 3 h. The progress of the reaction was monitored by TLC (ethyl acetate-hexane 1:3). After completion of the reaction, acetonitrile was removed in vacuo and then diethyl ether was added to the solid residue in order to separate the catalyst from the mixture. The filtrate was washed twice with 5% $NaHCO_3$ (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the product was recrystallized from CH_2Cl_2: EtOH (1:2) to give the pure product.

2-(cyclohexylamino)-6,7-dihydro-3-phenyl-1H-indole-4(5H)-one (5a):

IR (KBr) (ν_{max}, cm^{-1}): 1630 (C=N), 1670 (C=O), 3320 (N-H). 1H NMR (CDC13, 300 MHz) δH (ppm): 1.11-1.99 (10H, m), 2.44 (2H, m), 2.71 (2H, t, J = 5.9), 2.90 (2H, t, J = 6.0), 3.02 (1H, m), 7.45-7.53 (5H, m, arom), 8.22 (1H, s, NH), 9.48 (1H, s, NH). GC/MS: 308 (M+).

2-(cyclohexylamino)-6,7-dihydro-3-(2-nitrophenyl)-1H-indole-4(5H)-one (5c):

IR (KBr) (ν_{max}, cm^{-1}): 1325 and 1515 (NO_2), 1630 (C=N), 1670 (C=O), 3320 (N-H). ^{1}H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.11-1.96 (10H, m), 2.38 (2H, m), 2.68 (2H, t, J = 6.1), 2.89 (2H, t, J = 5.9), 3.20 (1H, m), 7.45-7.84 (4H, m, arom), 8.08 (1H, s, NH), 9.32 (1H, s, NH). GC/MS: 353 (M^+).

2.2. Recycling of the Catalyst

At the end of the reaction, the solvent was removed and then diethyl ether was added to the solidified mixture in order to separation of catalyst from the mixture since the catalyst is not soluble in organic solvents. Then the catalyst was filtered, washed with diethyl ether, dried at 80°C for 2 h, and reused in another reaction. The recycled catalyst was used for three reactions without observation of appreciable loss in its catalytic activities.

3. RESULTS AND DISCUSSION

Ferric perchlorate is a hygroscopic compound which is readily prepared by the reaction of ferric hydroxide and perchloric acid and can be stored for a long time in a desiccator. It's a nontoxic, inexpensive and soluble in most of the organic solvents and not explosive even when heated in solution. In recent years, ferric perchlorate[11] has gained importance as a versatile medium for affecting various organic transformations such as regio- and stereoselective alcoholysis and hydrolysis of epoxides[12], transformation of allylic and benzylic ethers[13] and synthesis of amides from benzylic alcohols[14]. We have recently reported the protection of alcohols with DHP and deprotection of THP ethers[15] and aromatization of Hantzsch 1,4-dihydropyridines using ferric perchlorate [16]. Armed with these experiences, herein, we wish to report an efficient and convenient route for the synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones in the presence of catalytic amount of ferric perchlorate.

These compounds were obtained by the MCR of cyclohexylisocyanide, an aldehyde, dimedone or 1,3-cyclohexandione and ammonium acetate in the presence of a catalytic amount of ferric perchlorate in acetonitrile (Scheme 1) in good yields (Table 1). The products were obtained with cyclic 1,3-dicarbonyl compounds and we could not get good results using linear 1,3-dicarbonyl compounds. We optimized the amount of ferric perchlorate for the procedure and found that 3 mol% of ferric perchlorate even catalyzed the reaction to some extent, but a longer reaction time (>3 h) required.

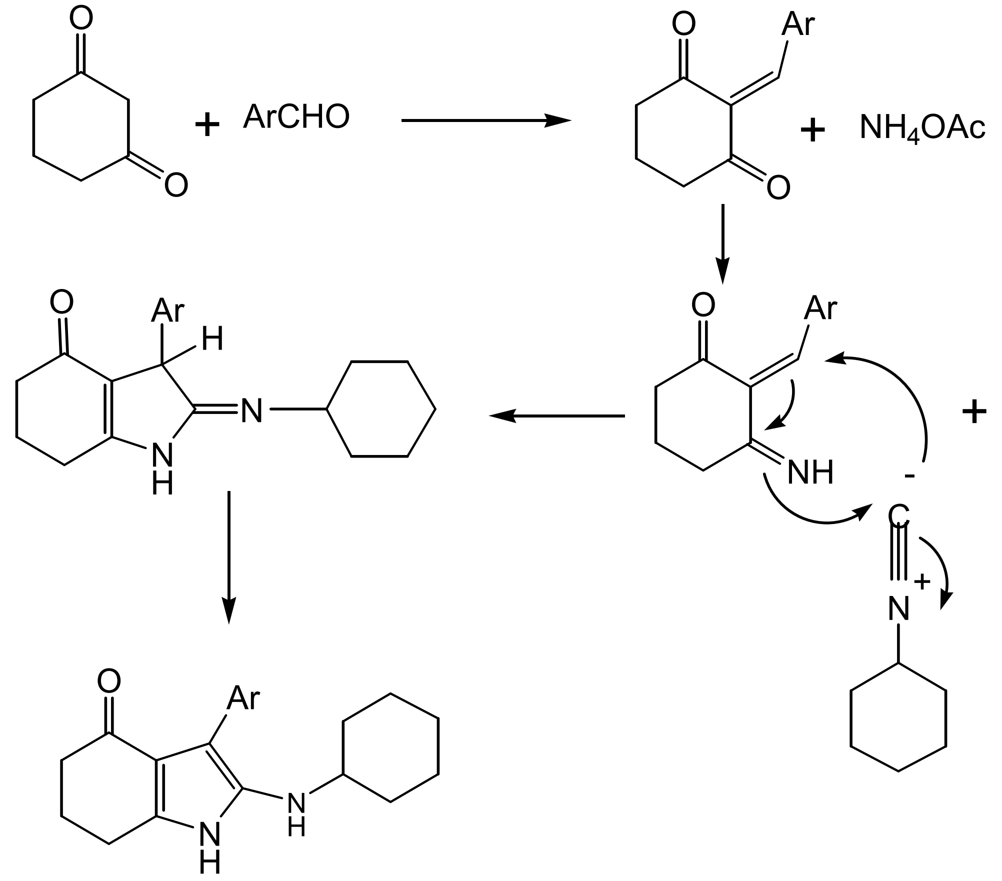
Table 1. Synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1*H*-indole-4(5*H*)-ones using various aldehydes.

Entry	Substrate	Product	Ar	Yield (%)[a]
1	**1a**	**5a**	C_6H_5	93
2	**1a**	**5b**	4-Cl-C_6H_4	87
3	**1a**	**5c**	2-NO_2-C_6H_4	87
4	**1a**	**5d**	4-NO_2-C_6H_4	86
5	**1a**	**5e**	4-CH_3-C_6H_4	92
6	**1a**	**5f**	4-CH_3O-C_6H_4	93
7	**1b**	**6a**	C_6H_5	89
8	**1b**	**6b**	4-Cl-C_6H_4	94
9	**1b**	**6c**	2-NO_2-C_6H_4	87
10	**1b**	**6d**	4-NO_2-C_6H_4	90
11	**1b**	**6e**	4-CH_3-C_6H_4	93
12	**1b**	**6f**	4-CH_3O-C_6H_4	93

[a]Yield of isolated products.

The use of an increased amount of catalyst did not improve the yield significantly. The scope of the reaction with respect to the aldehyde component was examined. As shown in Table 1, aromatic aldehydes containing both electron donating or withdrawing groups gave excellent yields of the product. In each reaction, the yield seemed to depend on the reaction time, which was later optimized to be 3 h at reflux temperature.

A plausible mechanism for this reaction is suggested in Scheme 2. The first step may involve adduct formation by condensation of 1,3-cyclohexanedione with the aromatic aldehyde, followed by attack of ammonium acetate to give the intermediate 2-benzylidiene-3-imino-cyclohexanone. Reaction of cyclohexyl isocyanide with this intermediate then gives the desired product.



Scheme 2

In summary, we reported a mild and efficient four-component synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl-1H-indole-4(5H)-ones using one pot condensation of cyclohexyl isocyanide, an aldehyde, a 1,3-dicarbonyl compound and ammonium acetate in the presence of ferric perchlorate as an available and inexpensive catalyst. The notable features of this procedure are mild reaction conditions, experimental simplicity, easy work-up, use of an easy to handle and safe catalyst, and high yields of products which makes it a useful process for the synthesis of these compounds.

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