

Programming of Fe-catalyzed cascade Knoevenagel-Michael-cyclocondensation reaction: create out pseudo acridine derivatives under solvent free conditions

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Abstract

Nano-ferrous ferric oxide (nano-Fe₃O₄) was successfully applied as an efficient and heterogeneous catalyst for the synthesis of 1,8-dioxo-decahydroacridines by the condensation reaction of dimedone with aromatic aldehydes and ammonium acetate or aniline derivatives under mild and solvent-free conditions. Also, optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)} compared to empirical research.

Keywords: Nano-Fe₃O₄; cascade reaction; 1,8-dioxo-decahydroacridine; heterogeneous catalyst.

Introduction

Multi-component reactions (MCRs) have significant role in combinatorial chemistry due to the ability to afford expected products with high efficiency and atomic economy by the reaction of three or more compounds together in a one step. Also, MCRs increase simplicity and synthetic efficiency on the conventional organic transformations [1-5].

Organic transformations catalyzed by transition-metal are often followed the principles of “Green Chemistry” due to minimization of waste and energy, cleaner auxiliaries, catalysts and reagents [6]. Magnetite nanoparticles (MNPs) are

very attractive catalysts due to their magnetic properties and high specific surface area [7,8]. They can be easily collected with a magnet to reuse it to proceed another reactions. Recently, the chemists focused their attention on catalytic aspects of nano-Fe₃O₄ to modify methods of catalytic activity [9-14].

1, 8-Dioxo-decahydroacridines are poly-functionalized 1, 4-dihydropyridine derivatives which have received less attention than other 1, 4-DHP derivatives [15]. Several methods have been reported for the synthesis of 1, 8-dioxo-decahydroacridine derivatives [16-31]. However, some of them suffer from the

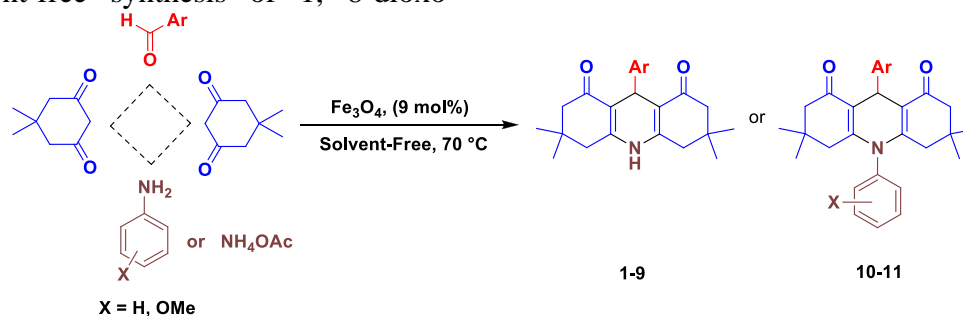
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drawbacks such as the use of toxic metals, the use of volatile organic solvents, high cost and low yields. Solvent-free reactions have been illustrated to be as an efficient technique for different organic transformations instead of using harmful organic solvents [32-37].

Herein, we have introduced the solvent-free synthesis of 1, 8-dioxo-



Scheme 1. The synthesis of 1,8-dioxo-decahydroacridines

Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. The ^1H NMR (400 MHz) and ^{13}C NMR (100) were run on a Bruker Avance DPX, FT-NMR spectrometers, δ in ppm.

General procedure for the synthesis of 1, 8-dioxo-decahydroacridines using nano- Fe_3O_4 :

A mixture of dimedone (0.28 g, 2 mmol), aldehyde (1 mmol), ammonium acetate (or aniline derivatives) (1 mmol, 0.077 g), and nano- Fe_3O_4 (9 mol%) in a 25 mL round-bottomed flask connected to a reflux condenser was stirred magnetically. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature and warm EtOH (30 mL) was added,

decahydroacridine derivatives in the presence of Nano- Fe_3O_4 as an efficient, heterogeneous and reusable catalyst with high yields and short reaction times (Scheme 1). Optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)}.

stirred and refluxed for 4 minutes. The catalyst was collected by a magnet and separated from the solution of the product and remaining starting materials and reused for the next run. The crude product was purified by recrystallization from ethanol (95%).

9-(2, 3-Dichlorophenyl)-3, 3, 6, 6-tetramethyl-3, 4, 6, 7, 9, 10-hexahydroacridine-1, 8(2H, 5H)-dione (4)

^1H NMR (400 MHz, CDCl_3) δ = 1.10 (s, 6H, 2 CH_3), 1.23 (s, 6H, 2 CH_3), 2.19 (s, 2H, CH_2), 2.28 (s, 2H), 2.34 (d, $J=6.80$ Hz, 1H), 2.39 (s, 1H), 2.43 (s, 1H), 2.48 (s, 1H), 5.49 (s, 1H), 7.03 (s, 2H, ArH), 7.28 (s, 1H, ArH), 11.16 (s, 1H, NH). ^{13}C NMR (100 MHz, CDCl_3) δ = 27.5, 29.6, 31.4, 32.4, 46.4, 47.0, 115.5, 126.7, 135.5, 189.3, 190.5.

3, 3, 6, 6-Tetramethyl-9-(2-nitrophenyl)-3, 4, 6, 7, 9, 10-hexahydroacridine-1, 8(2H, 5H)-dione (6)

^1H NMR: (400MHz, CDCl_3) δ = 1.03 (s, 6H, 2 CH_3), 1.16 (s, 6H, 2 CH_3), 2.21 (s, 2H, CH_2), 2.25 (s, 1H, CH), 2.33 (d,

$J=16.00$ Hz, 2H, CH₂), 2.43 (s, 1H, CH), 2.48 (d, $J=10.00$ Hz, 1H, CH), 2.53 (s, 1H, CH), 6.05 (s, 1H, CH), 7.27 (t, $J=4.40$ Hz, 1H, ArH), 7.34 (t, $J=7.60$ Hz, 1H, ArH), 7.490 (t, $J=8.00$ Hz, 1H, ArH), 7.61 (d, $J=8.40$ Hz, 1H, ArH), 11.60 (s, 1H, NH); ¹³C NMR (100MHz, CDCl₃) δ 28.1, 28.5, 30.0, 31.9, 46.2, 46.8, 114.6, 124.3, 127.1, 129.5, 131.3, 132.1, 149.7, 189.1, 190.1.

3, 3, 6, 6-Tetramethyl-9-(naphthalen-2-yl)-3, 4, 6, 7, 9, 10-hexahydroacridine-1, 8(2H,5H)-dione (8)

¹H NMR (400 MHz, CDCl₃) δ = 1.15 (s, 6H, 2CH₃), 1.32 (s, 6H, 2CH₃), 2.34 (s, 1H), 2.40 (d, $J=12.00$ Hz, 1H), 2.45 (s, 1H), 2.51 (s, 1H), 2.55 (s, 1H), 5.70 (s, 1H, CH), 7.26 (t, $J=8.80$ Hz, 1H), 7.41-7.46 (m, 1H), 7.53 (s, 1H), 7.71-7.80 (m, 4H), 11.96 (s, 1H, NH); ¹³C NMR (100MHz, CDCl₃) δ = 27.4, 29.6, 31.5, 33.0, 46.4, 47.1, 115.6, 125.3, 125.9,

127.4, 127.8, 127.8, 131.8, 133.2, 135.5, 189.5, 190.5.

9, 9'-(1, 4-Phenylene)bis(3, 3, 6, 6-tetramethyl-3, 4, 6, 7, 9, 10-hexahydroacridine-1, 8(2H, 5H)-dione) (9)

¹H NMR (400 MHz, DMSO-*d*₆) δ = 0.85 (s, 6H, 2CH₃), 0.94 (s, 6H, 2CH₃), 0.93 (s, 6H, 2CH₃), 1.03 (s, 6H, 2CH₃), 2.03 (m, 2H), 2.14 (s, 2H), 2.24 (d, $J=9.60$ Hz, 2H), 2.30 (s, 2H), 2.37 (d, $J=15.60$ Hz, 2H), 2.51 (d, $J=11.60$ Hz, 2H), 2.67 (d, $J=12.80$ Hz, 2H), 3.16 (s, 2H), 4.59 (s, 2H, 2CH), 5.86 (s, 1H, NH), 6.98 (s, 1H, ArH), 7.06-7.19 (m, 2H, ArH), 7.38 (d, $J=7.60$ Hz, 1H, ArH), 10.95 (s, 1H, ArH).

Results and discussion

Nano-Fe₃O₄ was prepared according to the previous literature [13]. Transmission electron microscopy (TEM) of nano-Fe₃O₄ was studied to confirm that the obtained particles were prepared in nano size (Figure 1).

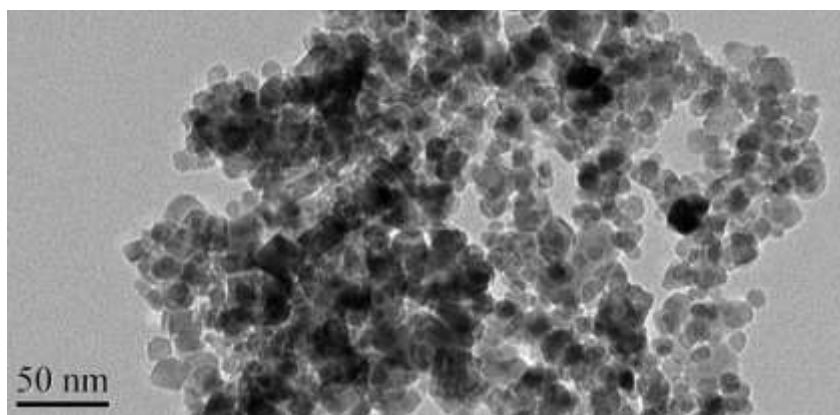


Figure 1. Transmission electron microscopy (TEM) of the nano-Fe₃O₄.

Initial studies with programming of the reaction, to find the optimal condition for the synthesis of 1,8-dioxo-decahydroacridine derivatives by the reaction of dimedone (2 mmol) with 2-nitrobenzaldehyde (1 mmol) and ammonium acetate (1.2 mmol), as a model reaction, were started. The response surface method {Central Composite Design (CCD)} with three

replicates at central point was selected and a second order model was developed. We found that temperature and amount of catalyst are two key factors in terms of selectivity, time and yield. Levels of the variables (investigation area) for temperature (A) and amount of catalyst (B) were 25 to 100 °C and 1 to 10 mol% respectively. Also, dependent variables including

yield and time of the reaction were suitable for fitting to a quadratic polynomial model (Table 1).

Table 1. Levels of the experimental variables and the corresponding response values of the CCD

Run	Independent variables		Dependent variables	
	A (°C)	B (mol%)	Time (min)	Yield (%)
1	25	5.5	15	85
2	25	1	30	50
3	62.5	5.5	4	95
4	62.5	5.5	4	95
5	100	10	3	95
6	62.5	1	20	50
7	100	5.5	3	95
8	62.5	5.5	4	95
9	25	10	15	85
10	62.5	10	4	95
11	100	1	15	50

Based on significant levels and actual values, two polynomial response surface models were obtained as follows;
 Time: $3.087 A^2 + 0.362 B^2 - 0.559 A - 5.580 B + 46.884$ (Equation 1)

Yield: $-2.619 A^2 - 1.0461 B^2 + 0.148 AB + 0.334 A + 15.211 B + 26.668$ (Equation 2)

After optimization studies and programming, optimal point was found at A (70 °C) and B (9.1) (Figure 2).

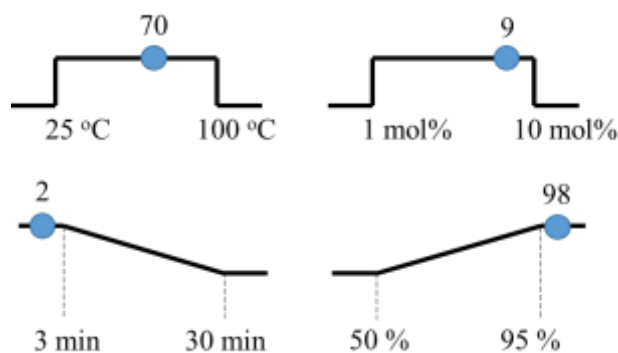


Figure 2. Introduced optimal point of variables

In Figure 3, two and three-dimensional profiles of yield from the model are illustrated. It can be seen from time and yield equations that the amount

of catalyst has the main linear effect on the temperature of the reaction and there is a significant interaction between the amount of catalyst and temperature.

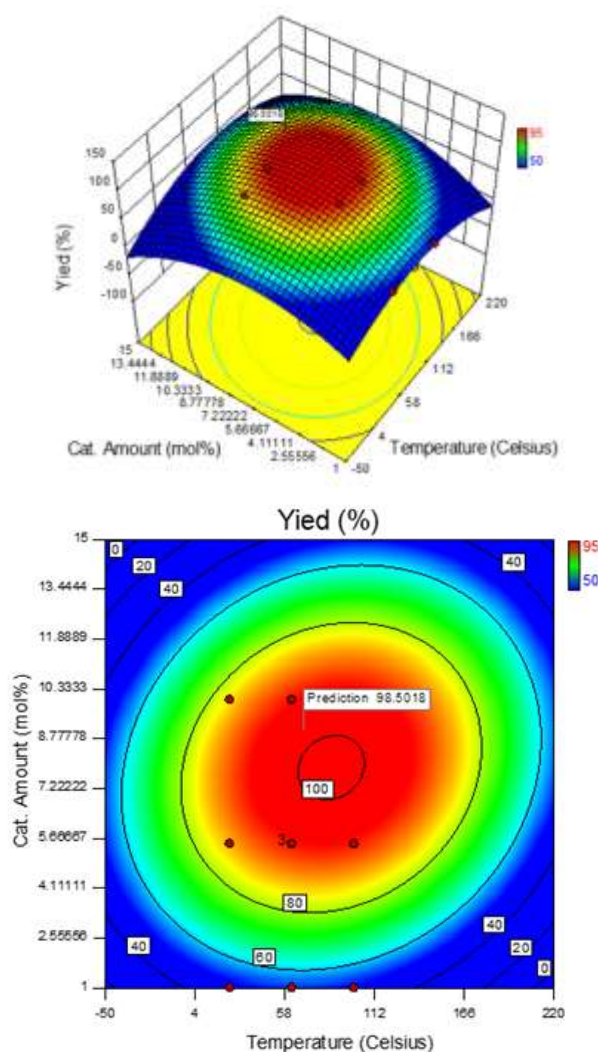


Figure 3. Three and two dimensional response surfaces for the effect of factors on yield of reaction

Further experiments, to compare the efficiency of the solvent-free versus solvent conditions, were conducted at the optimal point (Table 2) and results

showed that reaction was more favoured than the other conditions (such as CHCl_3 , EtOAc, EtOH, H_2O , Acetone and THF).

Table 2. Effect of various solvents on the reaction of dimedone (2 mmol), 2-nitrobenzaldehyde (1 mmol), and ammonium acetate (1.2 mmol), in the presence of Fe_3O_4 (9 mol %):

Entry	Solvent	Temp. ($^{\circ}\text{C}$)	Time (min)	Yield ^a (%)
1	CHCl_3	Reflux	20	85
2	EtOAc	70	25	85
3	EtOH	70	25	83
4	CH_2Cl_2	Reflux	30	79
5	H_2O	70	45	50
6	Acetone	Reflux	15	85
7	THF	Reflux	30	80
8 ^b	-	70	4	95

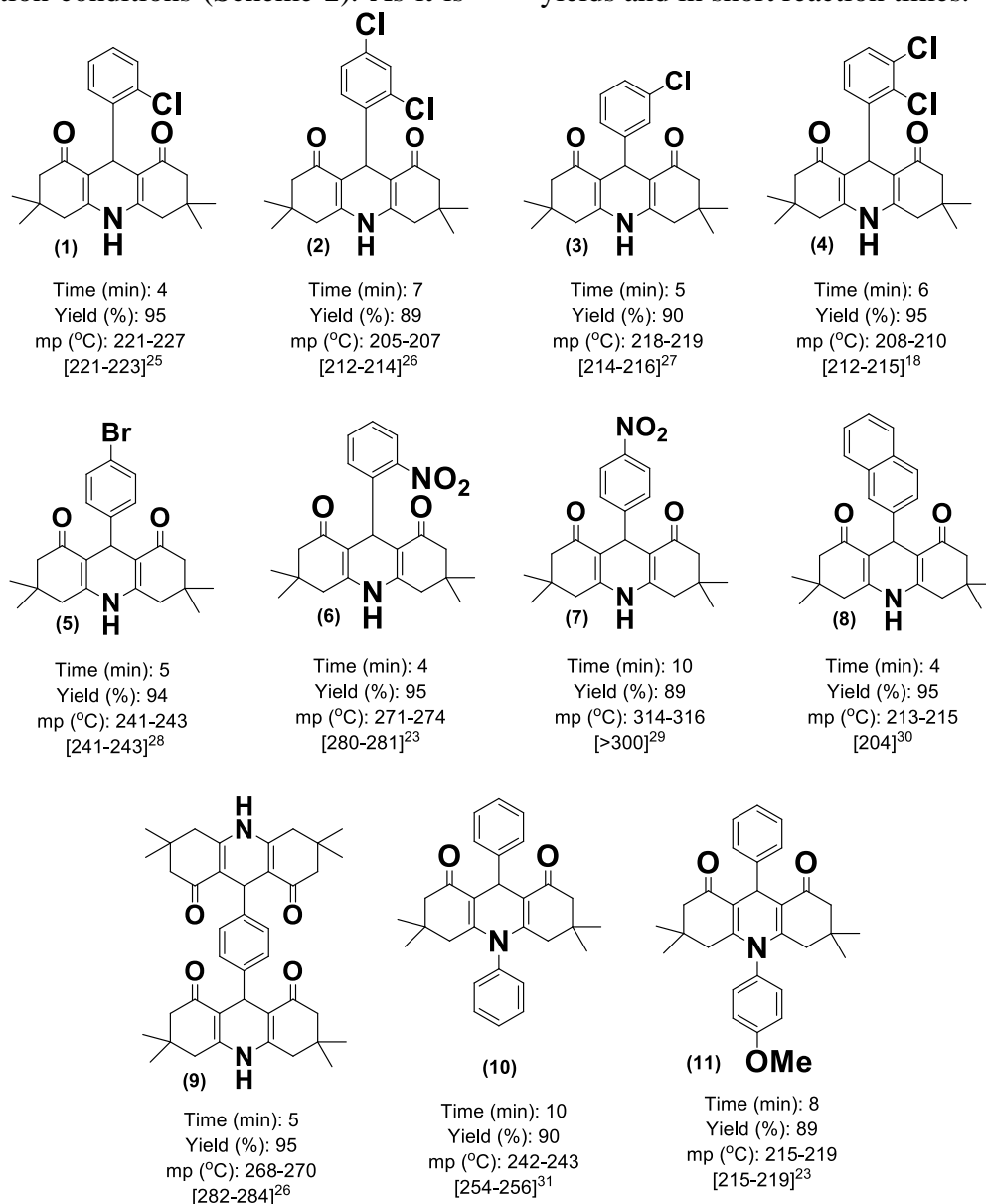
^aIsolated yield. ^bThe reaction was proceeded in the absence of solvent.

To study the efficacy and the generality of the catalyst, dimedone was

reacted with various aromatic aldehydes (aromatic as well as aliphatic containing

electron-withdrawing groups, electron-donating groups and halogens) and ammonium acetate under the optimized reaction conditions (Scheme 2). As it is

shown in Scheme 2, all reactions proceeded efficiently to give the desired 1, 8-dioxo-decahydroacridines in high yields and in short reaction times.



Scheme 2. Scope of 1, 8-dioxo-decahydroacridines

To investigate the reusability of nano-Fe₃O₄, after completion the reaction, the catalyst was collected by an external magnet and separated from product and remaining starting materials were tested again on the reaction of dimedone (2 mmol) with 2-nitrobenzaldehyde (1

mmol) and ammonium acetate (1.2 mmol) as a model reaction. As it is found in Figure 4, it is clarified that the catalyst could be reused for eleven times without significant changes in the yield of the product and reaction time.

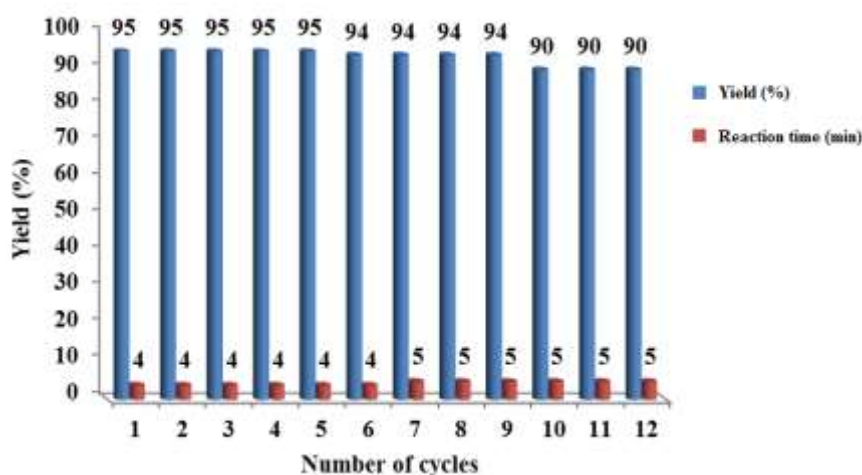


Figure 4. The reusability of the catalyst

Conclusion

In summary, we have reported nano-Fe₃O₄ as a reusable, stable, general and heterogeneous catalyst for the preparation of 1, 8-dioxo-decahydroacridines under solvent-free conditions. Also, the optimization of the reaction condition was investigated using the response surface method {Central Composite Design (CCD)} which was in a good accordance with empirical research.

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