Regular Article

ORGANIC CHEMISTRY RESEARCH
Published by the
Iranian Chemical Society
www.orgchemres.org

Org. Chem. Res., Vol. 5, No. 1, 95-104, March 2019.

A Facile Three-component Green Synthesis of Polyhydroacridines Using Fe^{3+}@mont-modified Montmorillonite

M. Mamaghani*, S. Yazdanfar and R. Hossein Nia

Department of Chemistry, Faculty of Sciences, University of Guilan, P. O. Box: 41335-1914, Rasht, Iran

(Received 23 May 2018, Accepted 23 September 2018)

In this report a green strategy for the synthesis of polyhydroacridine derivatives *via* one-pot three-component coupling reaction of arylaldehydes, 1,3-cyclohexanedione and aniline derivatives in the presence of modified montmorillonite with ferric ion (Fe^{3+}@mont.) as heterogeneous and reusable catalyst was developed. The reaction in the presence of this catalyst furnished the desired products in short reaction times (10-15 min) and high to excellent yields (78-98%) under solvent-free conditions.

Keywords: Polyhydroacridine, 1,4-Dihydropyridine, Fe^{3+}@mont., Solvent-free

INTRODUCTION

Multi-component reactions (MCRs) are one-pot processes that combine three or more substrates simultaneously. In this process, two or more steps in the synthetic sequence can be carried out without the isolation of intermediates. This leads to reduction of time and energy providing an economical way for developing new pharmaceutically important compounds [1-4]. In addition, the design of multi-component strategies based on green chemistry such as solvent-free, green solvents, and catalytic systems gives a possibility to achieve "ideal synthesis."

The Hantzsch reaction and their products, 1,4-dihydropyridines (DHPs), have attracted enormous attention of synthetic chemists due to their pharmacological properties such as anti-cancer [5,6], anti-microbial [7], anti-viral [8] and anti-HIV [9] activities. Acridine and its hydro derivatives, such as polyfunctionalized 1,4-dihydro-pyridines, have a wide spectrum of biological activities such as anti-tumor [10], anti-cancer [11], anti-malarial [12,13], anti-Alzheimer's disease drugs [14], anti-leishmanial activities [15] and potassium channel blockers [16]. In addition, many industrial applications for acridine derivatives have been reported in the literatures since they were first used as dyes and pigments [17-19]. These findings have attracted the organic chemists' attention and thus led to the synthesis of several acridine based drugs. For example, 2-methoxy-6-chloro-9 aminoacridine (A) and 3-(6,6,6-trifluorohexyloxy)-6-chloro-9-aminoacridine (B) are synthesized acridinens showing antimalarial activity [20], and ethacridine lactate (C) is a drug that is used as an antiseptic [21] (Fig. 1).

Many procedures have been reported for the synthesis of acridine derivatives using multi-component reactions of dimedone or 1,3-cyclohexadione, aldehydes and different nitrogen sources such as amines and ammonium acetate [22-28]. Although most of these procedures offer distinct advantages, some of them still have disadvantages such as prolonged reaction times, low yields, use of toxic organic solvent, and difficulty in work-up.

In continuation of our research on the multi-component synthesis of biologically important heterocyclic compounds [29-32], and also, considering our previous works on using modified montmorrilonite (Fe^{3+}@mont.) as efficient and recyclable catalyst to prepare pyrazolopyrimidynes [33], pyrazolopyridines [34] and spiro-oxindoles [35], here, we investigate the use of this catalyst to prepare polyhydroacrine derivatives. We describe an eco-friendly protocol for the synthesis of polyhydroacridines, in the presence of Fe^{3+}@mont., under solvent-free conditions,

*Corresponding author. E-mail: m-chem41@guilan.ac.ir

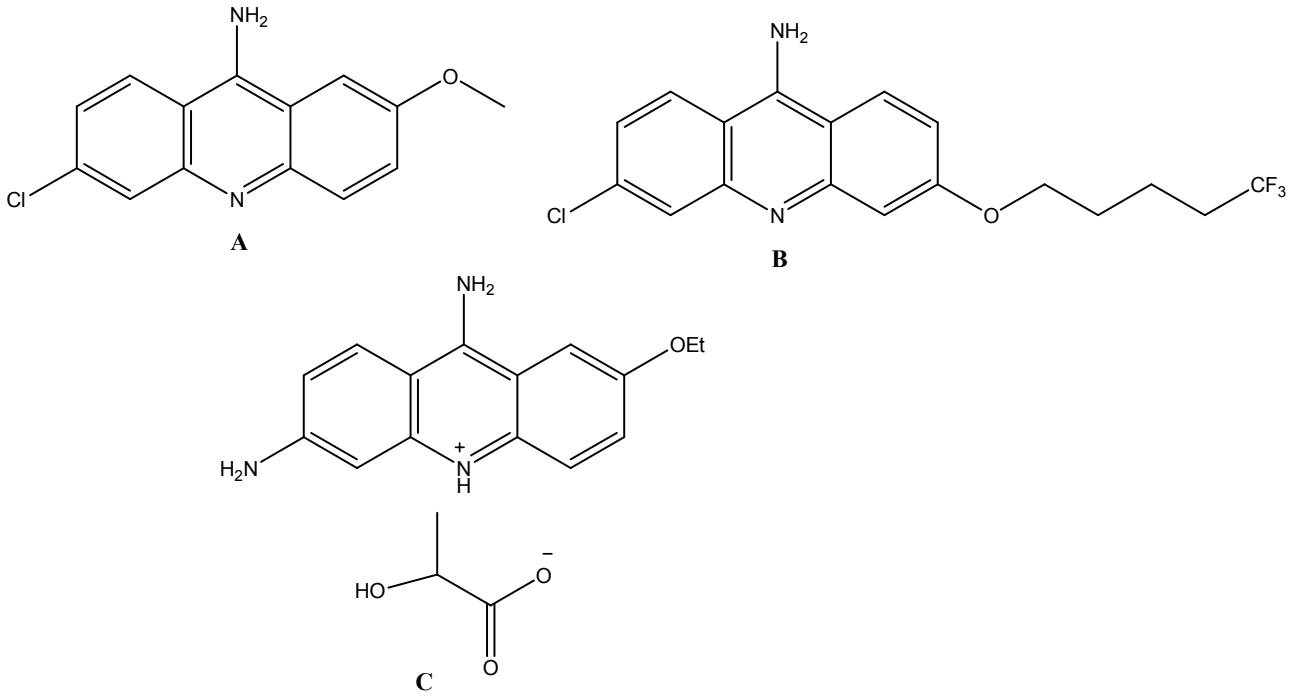


Fig. 1.

(Scheme 1).

EXPRIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo IR-470 spectrometer (Japan). ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500MHz Bruker DRX-500 and 400MHz Bruker DRX-400 in $CDCl_3$ as a solvent and TMS as an internal standard. Chemical shifts on ^{1}H and ^{13}C NMR were expressed in ppm downfield from tetramethylsilane. Elemental analyses were carried out on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values. All the chemicals were purchased from Merck and used without further purification. All solvents used were dried and distilled according to standard procedures [36].

General Method for the Synthesis of Polyhydroacridines 4a-j

A mixture of aryl aldehyde (1 mmol), aniline derivatives (1 mmol) and 1,3-dicyclohexadione (2 mmol) was heated at 80 °C in the presence of Fe^{3+}@mont. (0.05 g) under solvent-free conditions. The progress of the reaction was monitored by TLC (EtOAc/petroleum ether: 8/5). After completion of the reaction, 30 ml of $CHCl_3$ was added to the reaction mixture and solid catalyst was removed by filtration. The filtrate was evaporated under the reduced pressure to remove the solvent. The resulting solid was purified by recrystallization from H_2O/DMF.

Preparation of Fe^{+3}-montmorillonite (Fe^{+3}@mont.) [37]

A 1% suspension of montmorillonite (K10) in a 1.5 M solution of $FeCl_3.6H_2O$ was stirred overnight. On settling, the supernatant solution was discarded and exchange process repeated three times. The ion-exchanged material was filtered and washed free of chloride ion (checked by 0.1 M $AgNO_3$) with demonized water and dried in air.

3,4,6,7-Tetrahydro-9-(4-methoxyphenyl)-10-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4a). Yellow powder; m. p.: 240-241 °C (m. p. reported [35]: 235-238 °C); IR (KBr): ν (cm^{-1}) 3020, 2920, 2860, 1635, 1570, 1600, 1505, 1464, 1370, 1280, 1230, 1020, 820. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.92-1.72 (4H, m, $2CH_2$-$\underline{CH_2}$-CH_2-CO), 2.29-2.15 (4H, m, $2\underline{CH_2}$-CH_2-CH_2-CO), 2.36, 2.07 (4H, dt, J = 17.2, 4.6 Hz, $2CH_2$-$\underline{CH_2}$-CO), 2.46 (3H, s,

CH_3), 3.76 (3H, s, OCH_3), 5.33 (1H, s, CH), 6.8 (2H, d, *J* = 8.6 Hz, Ar-H), 7.15 (2H, br s, Ar-H), 7.33 (2H, m, Ar-H), 7.35 (2H, d, *J* = 8.6 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 21.1, 21.2, 28.3, 31.2, 36.8, 55.2, 113.6, 115.7, 128.7, 129.6, 130.8, 136.4, 139.2, 139.5, 151.6, 157.8, 196.2. Anal. Calcd. for $C_{27}H_{27}NO_3$ (413.51): C, 78.42; H, 6.58; N, 3.39. Found: C, 78.33; H, 6.69; N, 3.28.

4-(1,2,3,4,5,6,7,8,9,10-Decahydro-1,8-dioxo-10-*p*-tolylacridin-9-yl)benzonitrile (4b). Yellow powder; m.p.: 268-270 °C (m. p. reported [38]: 230-233 °C); IR (KBr): ν (cm^{-1}) 3050, 2930, 2875, 2210, 1630, 1565, 1600, 1510, 1455, 1358, 1225, 835. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.95-1.72 (4H, m, $2CH_2$-$\underline{CH_2}$-CH_2-CO), 2.31-2.17 (4H, m, $2\underline{CH_2}$-CH_2-CH_2-CO), 2.36, 2.08 (4H, dt, *J* = 17.2, 4.6 Hz, $2CH_2$-CO), 2.47 (3H, s, CH_3), 5.4 (1H, s, CH), 7.14 (2H, br s, Ar-H), 7.35 (2H, d, *J* = 7.6 Hz, Ar-H), 7.53 (2H, d, *J* = 8.8 Hz, Ar-H), 7.56 (2H, d, *J* = 8.8 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 21.2, 28.3, 33.1, 36.6, 109.6, 114.5, 119.4, 128.7, 129.4, 130.4, 132.1, 136.0, 139.9, 152.0, 152.4, 196.0. Anal. Calcd. for $C_{27}H_{24}N_2O_2$ (408.49): C, 79.39; H, 5.92; N, 6.86. Found: C, 79.28; H, 5.85; N, 6.71.

3,4,6,7-Tetrahydro-9-(3,4-dimethoxyphenyl)-10-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4c). Yellow powder; m. p.: 243-245 °C; IR (KBr): ν (cm^{-1}) 3015, 2910, 2860, 2805, 1630, 1568, 1600, 1512, 1460, 1375, 1355, 1280, 1220, 1020, 840, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.94-1.73 (4H, m, $2CH_2$-$\underline{CH_2}$-CH_2-CO), 2.30-2.16 (4H, m, $2\underline{CH_2}$-CH_2-CH_2-CO), 2.38, 2.06 (4H, dt, *J* = 17.0, 4.6 Hz, $2CH_2$-CO), 2.46 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 5.35 (1H, s, CH), 6.77 (1H, d, *J* = 8.2 Hz, Ar-H), 6.83 (1H, dd, *J* = 8.2, 1.8 Hz, Ar-H), 7.12 (2H, br s, Ar-H), 7.15 (1H, d, *J* = 2.0 Hz, Ar-H), 7.32 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 28.3, 21.2, 31.3, 36.8, 55.82, 55.84, 111.0, 112.1, 115.6, 118.7, 128.8, 129.6, 136.4, 139.5, 139.6, 147.2, 148.5, 151.6, 196.2. Anal. Calcd. for $C_{28}H_{29}NO_4$ (443.53): C, 75.82; H, 6.59; N, 3.16. Found: C, 75.70; H, 6.47; N, 3.25

9-(4-Trifluoromethylphenyl)-3,4,6,7-tetrahydro-10-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4d). Yellow powder; m. p.: 246-248 °C; IR (KBr): ν (cm^{-1}) 3010, 2950, 2900, 2870, 1625, 1570, 1505, 1450, 1360, 1230, 1100, 825. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.31-2.17 (4H , m, $2\underline{CH_2}$-CH_2-CH_2-CO), 2.37, 2.08 (4H, dt, *J* = 17.2, 4.6 Hz, $2CH_2$-CO), 2.47 (3H, s, CH_3), 1.94-1.71 (4H, m, $2CH_2$-$\underline{CH_2}$-CH_2-CO), 5.43 (1H, s, CH), 7.15 (br s, 2H, 2Ar-H), 7.34 (2H, d, *J* = 8.0 Hz, Ar-H), 7.51 (2H, d, *J* = 8.6 Hz, Ar-H), 7.54 (2H, d, *J* = 8.6 Hz, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 21.2, 28.3, 32.5, 36.7, 114.8, 125.1 (q, $^3J_{CF}$ = 3.7 Hz), 127.1 (d, $^1J_{CF}$ = 270.5 Hz), 128.0 (d, $^2J_{CF}$ = 31.6 Hz), 128.8, 129.5, 130.4, 130.9, 136.2, 139.8, 150.5, 152.2, 196.1 ppm. Anal. Calcd. for $C_{27}H_{24}F_3NO_2$ (451.48): C, 71.83; H, 5.36; N, 3.10. Found: C, 71.75; H, 5.49; N, 3.25.

9-(2,4-Dichlorophenyl)-3,4,6,7-tetrahydro-10-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4e). Yellow powder; m. p.: 284-286 °C; IR (KBr): ν (cm^{-1}) 3020, 2910, 2850, 1630, 1560, 1505, 1460, 1360, 1225, 1180, 1135, 850, 820, 760. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.89-1.69 (4H, m, $2CH_2$-$\underline{CH_2}$-CH_2-CO), 2.33-2.02 (8H, m, $2\underline{CH_2}$-CH_2-CH_2-CO and $2CH_2$-CO), 2.47 (3H, s, CH_3), 5.46 (1H, s, CH), 7.13 (2H, m, Ar-H), 7.18 (1H, dd, *J* = 8.4, 2.0 Hz, Ar-H), 7.26 (1H, d, *J* = 2.0 Hz, Ar-H), 7.34 (2H, m, Ar-H), 7.65 (1H, d, *J* = 8.4 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2, 21.3, 28.5, 34.9, 36.6, 112.9, 126.4, 129.3, 129.4, 129.7, 130.4, 130.7, 135.0, 136.4, 139.6, 140.9, 153.0, 196.2 ppm. Anal. Calcd. for $C_{26}H_{23}Cl_2NO_2$ (452.37): C, 69.03; H, 5.12; N, 3.10. Found: C, 69.11; H, 5.02; N, 3.17.

9-(4-Fluorophenyl)-3,4,6,7-tetrahydro-10-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4f). Yellow powder; m. p.: 297-298 °C; IR (KBr): ν (cm^{-1}) 3050, 2930, 2870, 1630, 1565, 1600, 1500, 1450, 1358, 1225, 1180, 835, 750. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.91-1.77 (4H, m, $2CH_2$-$\underline{CH_2}$-CH_2-CO), 2.30-2.17 (4H, m, $2\underline{CH_2}$-CH_2-CH_2-CO), 2.37, 2.09 (4H, dt, *J* = 17.15, 4.6 Hz, $2CH_2$-CO), 2.48 (3H, s, CH_3), 5.37 (1H, s, CH), 6.94 (2H, t, *J* = 8.74 Hz, 2Ar-H), 7.15 (br s, 2H, 2Ar-H), 7.35 (2H, d, *J* = 8.02 Hz, Ar-H), 7.39 (2H, dd, *J* = 8.51, 5.6 Hz, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 21.5, 21.6, 28.7, 32, 37.2, 115.2 (d, $^2J_{CF}$ = 21.0 Hz), 115.8, 129.2, 129.6 (d, $^3J_{CF}$ = 7.75 Hz), 130.7, 136.7, 140.1, 142.9 (d, $^4J_{CF}$ = 2.75 Hz), 152.3, 161.7 (d, $^1J_{CF}$ = 242.0 Hz), 196.5 ppm. Anal. Calcd. for $C_{26}H_{24}FNO_2$ (401.47): C, 77.78; H, 6.03; N, 3.49. Found: C, 77.69; H, 5.92; N, 3.38

10-(4-Ethylphenyl)-3,4,6,7-tetrahydro-9-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4g). Yellow powder;

m. p.: 185-186 °C; IR (KBr): ν (cm^{-1}) 3015, 2920, 2870, 1630, 1565, 1600, 1510, 1448, 1358, 1225, 855. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.33 (3H, t, *J* = 7.6 Hz, CH_2-$\underline{CH_3}$), 1.92-1.72 (4H, m, 2CH_2-$\underline{CH_2}$-CH_2-CO), 2.27-2.16 (4H, m, 2$\underline{CH_2}$-CH_2-CH_2-CO), 2.29 (3H, s, CH_3), 2.37, 2.06 (4H, dt, *J* = 17.0, 4.4 Hz, 2CH_2-CO), 2.76 (2H, q, *J* = 7.6 Hz, $\underline{CH_2}$-CH_3), 5.36 (1H, s, CH), 7.07 (2H, d, *J* = 8.0 Hz, Ar-H), 7.17 (2H, br s, Ar-H), 7.32 (2H, d, *J* = 8.0 Hz, Ar-H), 7.35 (2H, d, *J* = 8.4 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.3, 21.1, 28.3, 28.5, 31.6, 36.8, 115.6, 127.7, 128.9, 129.5, 129.7, 135.4, 136.6, 143.8, 145.7, 151.8, 196.2 ppm. Anal. Calcd. For $C_{28}H_{29}NO_2$ (411.54): C, 81.72; H, 7.10; N, 3.40. Found: C, 81.58; H, 7.18; N, 3.25.

9-(4-Chlorophenyl)-3,4,6,7-tetrahydro-10-(4-methoxyphenyl)acridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4h). Yellow powder; m.p.: 238-240 °C; IR (KBr): ν (cm^{-1}) 3080, 2920, 2875, 2840, 1620, 1570, 1510, 1480, 1360, 1250, 1225, 1030, 860, 840, 815. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.94-1.71 (4H, m, 2CH_2-$\underline{CH_2}$-CH_2-CO), 2.30-2.16 (4H, m, 2$\underline{CH_2}$-CH_2-CH_2-CO), 2.36, 2.08 (4H, dt, *J* = 17.4, 4.4 Hz, 2CH_2-CO), 3.9 (3H, s, OCH_3), 5.34 (1H, s, CH), 7.03 (2H, d, *J* = 9.2 Hz, Ar-H), 7.16 (2H, br. m, Ar-H), 7.22 (2H, d, *J* = 8.4 Hz, Ar-H), 7.35 (2H, d, *J* = 8.4 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 28.3, 31.8, 36.7, 55.7, 114.8, 115.2, 128.2, 129.2, 130.1, 130.7, 131.4, 145.2, 152.3, 160.0, 196.1. Anal. Calcd. for $C_{26}H_{24}ClNO_3$ (433.93): C, 71.97; H, 5.57; N, 3.23. Found: C, 71.86; H, 5.51; N, 3.11.

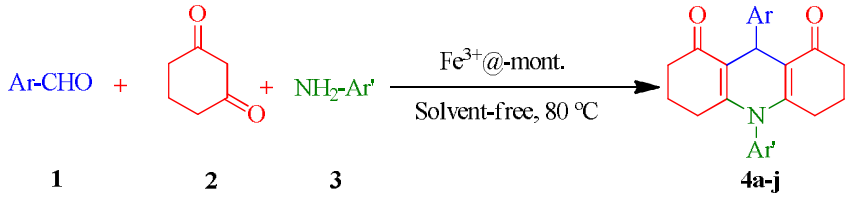
3,4,6,7-Tetrahydro-9-(4-isopropylphenyl)-10-(4-methoxyphenyl)acridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4i). Yellow powder; m. p.: 222-224 °C; IR (KBr): ν (cm^{-1}) 3020, 2950, 2900, 2860, 1630, 1565, 1510, 1458, 1380, 1280, 1225, 1020, 840, 825. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.21 (6H, d, *J* = 7.0 Hz, -CH($\underline{CH_3}$)$_2$), 1.91-1.74 (4H, m, 2CH_2-$\underline{CH_2}$-CH_2-CO), 2.29-2.15 (4H, m, 2$\underline{CH_2}$-CH_2-CH_2-CO), 2.37-2.08 (4H, dt, *J* = 17.2, 4.6 Hz, 2CH_2-CO), 2.86 (1H, sept., *J* = 7.0 Hz, -$\underline{CH}$(CH_3)$_2$), 3.9 (3H, s, OCH_3), 5.36 (1H, s, CH), 7.02 (2H, d, *J* = 9.2 Hz, Ar-H), 7.1 (2H, d, *J* = 8.0 Hz, Ar-H), 7.18 (2H, m, Ar-H), 7.32 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 24.0, 28.3, 31.5, 33.6, 36.8, 55.6, 114.7, 115.1, 115.7, 126.2, 127.5, 131.7, 144.0, 146.1, 151.9, 159.8, 196.2 ppm. Anal. Calcd. for $C_{29}H_{31}NO_3$ (441.56): C, 78.88; H, 7.08; N, 3.17. Found: C, 78.97; H, 7.15; N, 3.03.

10-(4-Chlorophenyl)-3,4,6,7-tetrahydro-9-(4-methoxyphenyl)acridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4j). Yellow powder; m. p.: 258-260 °C; IR (KBr): ν (cm^{-1}) 3100, 3050, 2920, 2870, 2810, 1640, 1565, 1510, 1485, 1360, 1275, 1225, 1178, 1025, 840, 825. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (2H, d, *J* = 8.8 Hz, 2Ar-H), 7.3 (2H, d, *J* = 8.8 Hz, 2Ar-H), 1.94- 1.74 (4H, m, 2CH_2-$\underline{CH_2}$-CH_2-CO), 2.29-2.14 (4H, m, 2$\underline{CH_2}$-CH_2-CH_2-CO), 2.37, 2.04 (4H, dt, *J* = 17.2, 4.6 Hz, 2CH_2-CO), 3.76 (s, 3H, OCH_3), 5.32 (s, 1H, CH), 6.8 (2H, d, *J* = 8.8 Hz, Ar-H), 7.24 (2H, br. d, *J* = 7.6 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.1, 28.3, 31.2, 36.7, 55.2, 113.6, 116.0, 128.7, 129.3, 130.4, 135.5, 137.6, 138.8, 150.9, 157.8, 196.1 ppm. Anal. Calcd. for $C_{26}H_{24}ClNO_3$ (433.93): C, 71.97; H, 5.57; N, 3.23. Found: C, 71.82; H, 5.48; N, 3.08.

RESULTS AND DISCUSSION

The multi-component reaction between arylaldehydes (1), 1,3-cyclohexadion (2) and aniline derivatives (3) in the presence of a catalytic amount of Fe^{3+}@mont. under solvent-free conditions afforded the corresponding polyhydroacrines (4a-j) in short reaction times (10-15 min) and high to excellent yields (78-98%) (Scheme 1).

In initial experiments, in order to optimize the reaction conditions, synthesis of 3,4,6,7-tetrahydro-9-(4-methoxyphenyl)-10-*p*-tolylacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4a) was performed by the reaction of 4-methoxybenzaldehyde (1a), 1,3-cyclohexadione (2) and *p*-toluidine (3a) with molar ratio of 1:2:1, respectively, as a model reaction. Various solvents and solvent-free conditions were screened to provide the desired product (Table 1). The results showed that the reaction under solvent-free condition at 80 °C without catalyst is the best condition. This reaction was also carried out in the presence of Fe^{3+}@mont. at different temperatures under solvent-free conditions (Table 2). The results demonstrated that the reaction in the presence of Fe^{3+}@mont. afforded the desired product with higher efficiency compared to without catalyst conditions and the best result was obtained at 80 °C (Table 2, Entry 2), and in deceased reaction time (15 min). We also verified the amount of Fe^{3+}@mont. (0.03, 0.05, 0.08 and 1 g) required for the synthesis of 4a, and the shortest reaction times (15 min) and highest yield (80%), were obtained using 0.05 g



Scheme 1. Synthesis of polyhydroacridine derivatives using Fe^{3+}@mont

Table 1. Synthesis of 4a in Various Conditions without Catalyst

Entry	Solvent[a]	Time (min)	Yield (%)[b]
1	EtOH	200	50
2	H_2O	250	40
3	CH_3CN	180	45
4	1,4-Dioxane	230	35
5	$CHCl_3$	250	42
6	DMF	180	52
7	Solvent-free	180	20[c]
8	Solvent-free	180	59[d]
9	Sovent-free	180	60[e]

[a]Reflux condition. [b]Isolated yields. [c-e]Reactions under solvent-free at 50, 80 and 100 °C, respectively.

Table 2. The Effect of Temperature on the Model Reaction in the Presence of Fe^{3+}@mont. (0.05 g $mmol^{-1}$ Substrate) under Solvent-free Conditions

Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	70	30	65
2	80	15	80(10)[b](20)[c]
3	90	13	78
4	100	13	77

[a]Isolated yields. [b]Reaction in the presence of montmorillonite K10. [c]Reaction in the presence of $FeCl_3$.

Table 3. Optimization of the amount of Fe^{3+}-mont. in the Synthesis of 4a at 80 °C under Solvent-free Conditions

Entry	Amount of Fe^{3+}-mont. g $mmol^{-1}$ substrate (mol%)	Time (min)	Yield (%)[a]
1	Without catalyst	180	59
2	0.03	45	72
3	0.05	15	80
4	0.08	12	80
5	0.1	10	80

[a]Isolated yields.

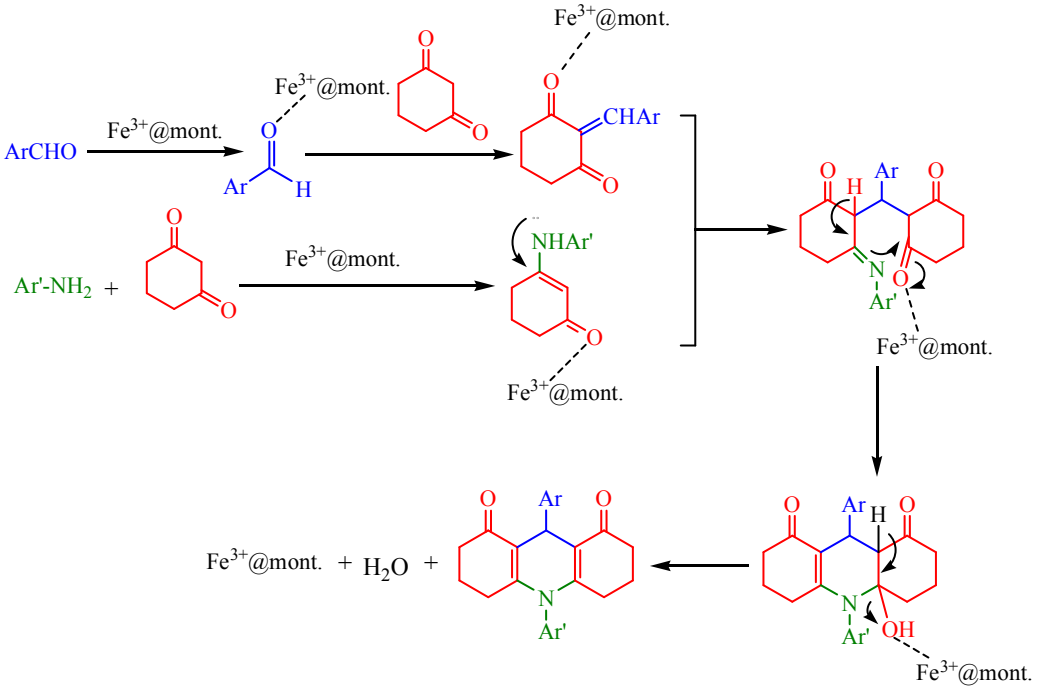
Table 4. Synthesis of Polyhydroacridine Derivatives (4a-j) under Optimized Conditions

Entry	Product	Ar	Ar'	Time (min)	Yield (%)[a]
1	4a	4-$MeOC_6H_4$	4-MeC_6H_4	15 (6 h)[b]	80 (84%)[b]
2	4b	4-CNC_6H_4	4-MeC_6H_4	12 (6 h)[b]	98 (79%)[b]
3	4c	3,4-$(OMe)_2C_6H_3$	4-MeC_6H_4	15	78
4	4d	4-$CF_3C_6H_4$	4-MeC_6H_4	12	98
5	4e	2,4-$Cl_2C_6H_3$	4-MeC_6H_4	12	92
6	4f	4-FC_6H_4	4-MeC_6H_4	15	91
7	4g	4-MeC_6H_4	4-EtC_6H_4	15	93
8	4h	4-ClC_6H_4	4-$MeOC_6H_4$	15	98
9	4i	4-$CH(CH_3)_2C_6H_4$	4-$MeOC_6H_4$	10	83
10	4j	4-$OMeC_6H_4$	4-ClC_6H_4	15	78

[a]Isolated yields. [b]Reported [38].

Fe^{3+}@mont. per mmol substrate, while increasing the amount of catalyst (0.08 and 1 g) did not have a significant impact on the efficiency of the reaction (Table 3).

Using optimized conditions in our hand, various derivatives of polyhydroacridine (4a-j) were prepared under optimized conditions to show the generality and limitation of the protocol, and the results are summarized in Table 4. The results reveal that arylaldehyde and aniline derivatives with both electron-deficient and electron-rich substituents afford desired products in high yields (78-98%) and short



Scheme 3. Plausible mechanism for the formation of polyhydroacridine derivatives 4a-j

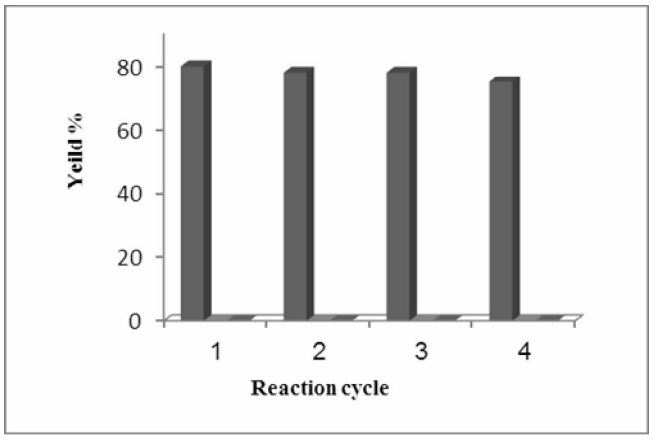
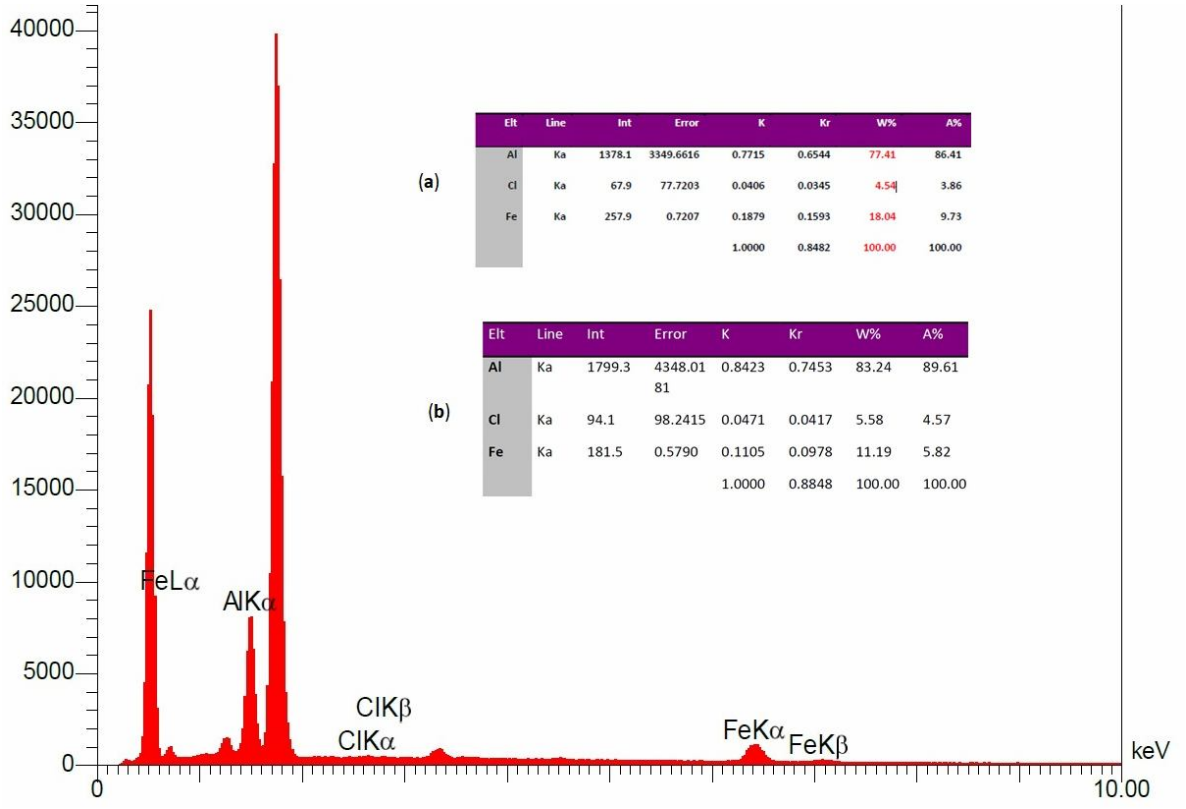


Fig. 1. The reusability of the catalyst in four runs for the synthesis of compound 4a.

reaction times (10-15 min). The structures of all the products were established on the basis of their analytical and spectroscopic data (^{1}H NMR and ^{13}C NMR). The diastereotopic protons related to cyclohexanone were exhibited *dt* or *m* in approximately 1.5-2.5 ppm, on all isomers.

A plausible mechanism for the formation of polyhydroacridines 4a-j is outlined in Scheme 2. At all stages, Fe^{3+}@mont., as Lewis acid, contributes in accelerating various stages such as Knoevenagel condensation, Micheal addition and cyclization [40,41].

The catalyst was prepared according to the literature [37,39], and its reusability was also examined in preparation of 4a. The catalyst was recycled and reused in the model



(a)

Elt	Line	Int	Error	K	Kr	W%	A%
Al	Ka	1378.1	3349.6616	0.7715	0.6544	77.41	86.41
Cl	Ka	67.9	77.7203	0.0406	0.0345	4.54	3.86
Fe	Ka	257.9	0.7207	0.1879	0.1593	18.04	9.73
				1.0000	0.8482	100.00	100.00

(b)

Elt	Line	Int	Error	K	Kr	W%	A%
Al	Ka	1799.3	4348.0181	0.8423	0.7453	83.24	89.61
Cl	Ka	94.1	98.2415	0.0471	0.0417	5.58	4.57
Fe	Ka	181.5	0.5790	0.1105	0.0978	11.19	5.82
				1.0000	0.8848	100.00	100.00

Fig. 2. EDS analysis of the catalyst (Fe^{3+}@mont.) before (a) and after (b) four runs.

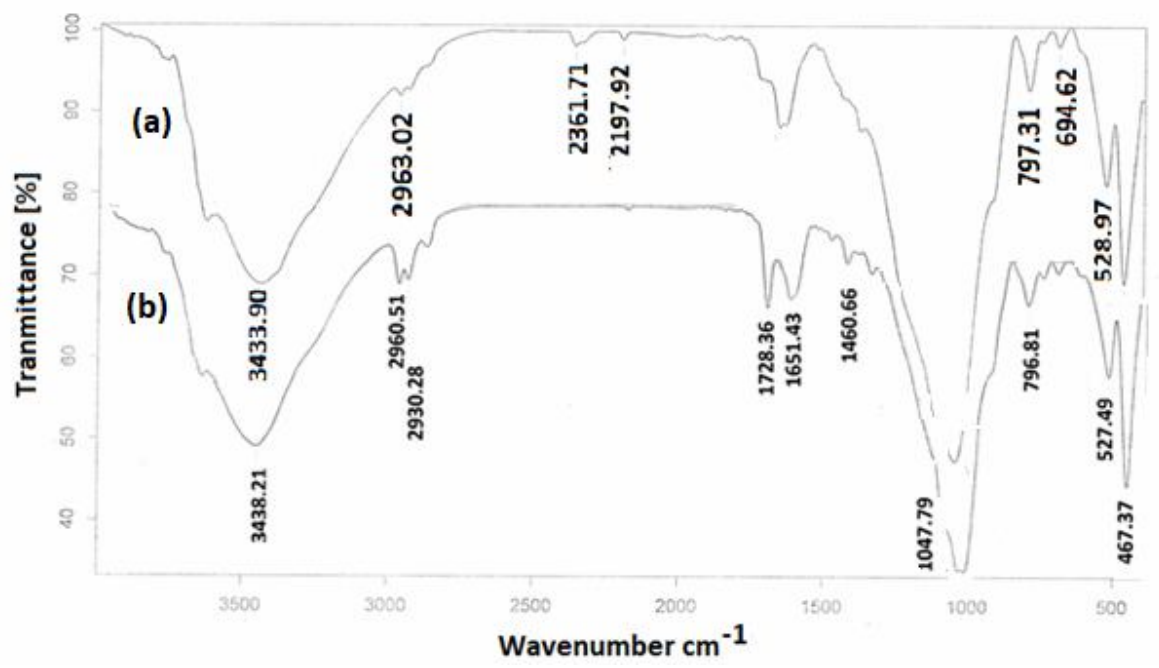


Fig. 3. (a) FT-IR of fresh Fe^{3+}@mont. (b) FT-IR of the catalyst after 4 runs.

reaction, under the optimized conditions. In each run, after completion of the reaction, indicated by TLC, the catalyst was filtered, washed, dried and activated at 120 °C. The results revealed (Fig. 1) that after four successive runs, the activity of the catalyst was almost retained without a significant loss.

EDS mapping for Fe^{3+}@mont. is shown in Figure 2. As clearly seen in this figure, Fe, Al and Cl are present in the structure. The Fe content of the synthesized material is 18% in accordance with EDS analysis (Fig. 2a). The EDS analysis after 4 consecutive runs showed Fe content 11.2%. Comparing FT-IR results for the fresh catalyst (Fig. 3a) and the catalyst after 4 runs (Fig. 3b) showed no appreciable changes in vibration bands.

CONCLUSIONS

In summary, an efficient and green approach for the synthesis of polydydroacridines by reaction of arylaldehydes, 1,3-cyclohexadione and aniline derivatives by employing Fe^{3+}@mont. as a heterogeneous recyclable Lewis acid catalyst under solvent-free condition was successfully established. The application of an inexpensive, easily available, reusable, and easy work-up catalyst that produces high yields under short reaction times, and solvent-free conditions makes this protocole, practical and economically attractive. This strategy provides an easy access to functionalized polydydroacridines.

ACKNOWLEDGMENTS

The authors are grateful to the Research Council of University of Guilan for the partial financial support of this research work.

REFERENCES

[1] H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, Chem. Eur. J. 6 (2000) 3321.
[2] C. Hulme, V. Gore, Curr. Med. Chem. 10 (2003) 51.
[3] L.F. Tietze, A. Modi, Med. Res. Rev. 20 (2000) 304.
[4] D.J. Ramón, M. Yus, Chem. Int. Ed. 44 (2005) 1602.
[5] R. Surendra Kumar, A. Idhayadhulla, A. Jamal Abdul Nasser, K. Murali, Indian J. Chem. Sect. B 50 (2011) 1140.
[6] M.S. Al-Said, M.S. Bashandy, S.I. Al-Qasoumi, M.M. Ghorab, Eur. J. Med. Chem. 46 (2011) 137.
[7] A.M. Vijesh, A.M. Isloor, S.K. Peethambar, K.N. Shivananda, T. Arulmoli, N.A. Isloor, Eur. J. Med. Chem. 46 (2011) 5591.
[8] B.A. Saeed, K.Y. Saour, R.S. Elias, N.A. Al-Masoudi, Am. J. Immunol. 6 (2010) 25.
[9] A.M. Li, X.Y. Liu, X.W. Wang, J.Y. Liu, J. Chin. Pharm. Sci. 20 (2011) 447.
[10] V.A. Bacherikov, T.C. Chou, H.J. Dong, C.H. Chen, Y.W. Lin, T.J. Tsai, T.L. Su, Bioorg. Med. Chem. Lett. 14 (2004) 4719.
[11] P. Belmont, J. Bosson, T. Godet, M. Tiano, Anti-Cancer Agents Med. Chem. 7 (2007)139.
[12] S. Girault, P. Grellier, A. Berecibar, L. Maes, E. Mouray, P. Lemiere, M. Debreu, E. Davioud-Charvet, C. Sergheraet, J. Med. Chem. 43 (2000) 2646.
[13] F. Gay, B. Traore´, J. Zanoni, M. Danis, A. Fribourg-Blanc, Trans. Roy. Soc. Trop. Med. Hyg. 90 (1996) 516.
[14] J. Zhou, X. Hu, H. Zhang, H. Qian, W. Huang, F. Qi, Y. Zhang, Lett. Drug Des. Discovery, 6 (2009) 623.
[15] D. Carole, D. Michel, C. Julien, D. Florence, N.J. Anna, D. Se´verine, T. Ge´rard, G.P. Pierre, Bioorg. Med. Chem. 13 (2005) 5560.
[16] M.G. Gunduz, A.E. Dogan, R. Simsek, K. Erol, C. Safak, Med. Chem. Res. 18 (2009) 317.
[17] A. Albert, The Acridines, 2th ed., Edward Arnold Ltd, London, 1996.
[18] S.P.N. Ramamurthy, P. Shanmugasundaram, V.T. Ramakrishana, J. Org. Chem. 61 (1996) 5083.
[19] S.P.N. Ramamurthy, P. Shanmugasundaram, V.T. Ramakrishana, Acta Specttrochemica 54 (1998) 245.
[20] R. Winter, J. Kelly, M. Smilkstein, R. Dodean, G. Bagby, R. Rathbun, J. Levin, D. Hinrichs, M. Riscoe, Exp. Parasitol. 114 (2006) 47.
[21] Merck Index, 11th Ed., 3668.
[22] Sh. Jin, J.-Sh. Zhang, T.-T. Guo, A.-Q. Wang, T.-Sh. Li, Synthesis 12 (2004) 2001.
[23] B. Das, P. Thirupathi, I. Mahender, V.S. Reddy, Y.K. Rao, J. Mol. Catal. A: Chem. 247 (2006) 233
[24] S. Chandrasekhar, Y.S. Rao, L. Sreelakshmi, B. Mahipal, Ch. R. Reddy, Synthesis 11 (2008) 1737.

[25] K. Venkatesan, S.S. Pujari, K.V. Srinivasan, Synth. Commun. 39 (2009) 228.
[26] K. Venkatesan, S.S. Pujari, K.V. Srinivasan, Synth. Commun. 39 (2009) 228.
[27] M. Kidwai, D. Bhatnagar, Tetrahedron Lett. 51 (2010) 2700.
[28] S.M. Vahdat, S. Khaksar, M. Akbari, S. Baghery. Arab. J. Chem. (2014) https://doi.org/10.1016/j.arabjc.2014.10.026.
[29] R. Hossein Nia, M. Mamaghani, F. Shirini, Kh. Tabatabaeian, M. Heidary, Org. Prep. Proc. Int. 46 (2014) 152.
[30] M. Mamaghani, F. Shirini, M. Sheykhan, M. Mohsenimehr, RSC Adv. 5 (2015) 44524.
[31] M. Mamaghani, F. Shirini, E. Bassereh, R. Hossein Nia, J. Saudi. Chem. Soc. 20 (2016) 570.
[32] P. Farokhian, M. Mamaghani, N.O. Mahmoodi, Kh. Tabatabaeian, J. Iran Chem. Soc. 15 (2018) 11.
[33] R. Hossein Nia, M. Mamaghani, F. Shirini, Kh. Tabatabaeian, J. Heterocyclic Chem. 51 (2014) 363.
[34] M. Mamaghani, Kh. Tabatabaeian, M. Bayat, R. Hossein Nia, M. Rassa, J. Chem. Res. 37 (2013) 494.
[35] M. Mamaghani, Kh. Tabatabaeian, M. Pourshiva, R. Hossein Nia, J. Chem. Res. 39 (2015) 314.
[36] Vogel's Textbook of Practical Organic Chemistry, 5th ed., Logman Scientific and Technical, 1989.
[37] M.P. Hart, D.R. Brown, J. Mol. Catal. A: Chem. 212 (2004) 315.
[38] K. Venkatesan, S.S. Pujari, K.V. Srinivasan, Synth. Commun. 39 (2009) 228.
[39] P. Laszlo, A. Mathy, Helv. Chim. Acta 70 (1987) 577.
[40] Y. Ogiwara, K. Takahashi, T. Kitazawa, N. Sakai, J. Org. Chem. 80 (2015) 3101.
[41] R.D. Little, M.R. Masjedizadeh, O. Wallquist, J.I. McLoughlin, J. Org. React. 47 (1995) 315.