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Facile ultrasound promoted one-pot synthesis of polyhydroquinoline derivatives using $RuCl_3$

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Abstract: A facile and convenient protocol was developed for the four component coupling of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate to form polyhydroquinoline derivatives in the presence of $RuCl_3$ under ultrasound irradiation in good to high yields (70-94%) and short reaction times (5-20 min).

Keywords: Polyhydroquinoline; Ultrasound; $RuCl_3$; Multicomponent; Dimedone.

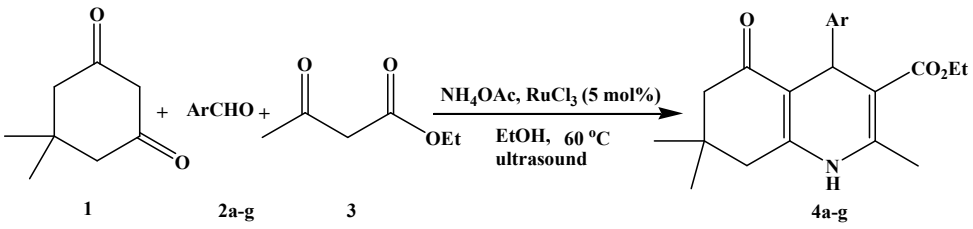
Introduction

In recent years, much attention has been devoted to the synthesis of polyhydroqunoline compounds owing to their diverse therapeutic and pharmacological properties, such as vasodilator, anti-tumor, bronchodilator, antiatherosclerotic, geroprotective and hepatoprotective activity [1-2]. Several methods have been employed for the preparation of polyhydroquinolines, including the use of molecular iodine [3], ionic liquids [4], $HClO_4$-SiO_2 [5], rare earth metal triflates [6], heteropolyacids [7] and HY zeolites [8]. Some of these methods however, involve long reaction time and harsh reaction conditions. Therefore, further improvement toward milder reaction conditions and higher yields is required. In view of this fact, and our continued interests in the synthesis of heterocyclic compounds [9], we have developed an efficient method for the four-component synthesis of polyhydroquinolines in the presence of catalytic amount of $RuCl_3$ under ultrasound irradiation.

Results and discussion

This reaction was carried out simply by mixing aldehydes (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol) and RuCl3 (5 mol %) in ethanol (5 mL) under ultrasound irradiation at 60 ˚C for the required reaction times (Scheme 1). The corresponding polyhydroquinoline derivatives were obtained in good to high yields. The results are summarized in Table 1.

Scheme 1



Ar = C_6H_5, 4-MeC_6H_4, 4-MeOC_6H_4, 2-MeOC_6H_4, 4-Cl C_6H_4, 3-ClC_6H_4, 4-BrC_6H_4

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Table 1. Synthesis of polyhydroquinolines **4a-g**

Entry	Ar	Time (min.)	Yield (%)[a]	mp (˚C)	mp (˚C) (lit)	mp (˚C)
a	C_6H_5	20	75 (70)[b]	223-224	225-227 [7]	218-220
b	4-MeC_6H_4	5	77	266-267	261-262 [14]	266-267
c	4-$MeOC_6H_4$	10	81	257-259	258-259 [14]	257-259
d	2-$MeOC_6H_4$	5	94	255-258	-	255-258
e	4-ClC_6H_4	15	75	245-248	245-246 [15]	245-248
f	3-ClC_6H_4	20	70	210-211	-	210-211
g	4-BrC_6H_4	20	77	258-260	254-255 [14]	258-260

[a]Isolated yield. [b]The reaction in the absence of ultrasound irradiation produced **4a** in lower yield (70%) and much longer reaction time (15 h).
The structures of products were established by melting point and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) analysis.

In this study the catalyst was recovered and reused in another run. The main catalytic activity was remained even after third reuse of the catalyst.
In conclusion, a facile and convenient method was developed for the synthesis of polyhydroquinolines using $RuCl_3$ as efficient catalyst under ultrasound irradiation in short reaction times (5-20 min) and good to high yields (70-94%).

Experimental

All chemicals were purchased from Merck and Fluka. For the ultrasound reactions, ultrasound apparatus Astra 3D (9.5 L, 45 kHz frequency, input power with heating, 305 W, number of transducers, 2) from TECNO-GAZ was used. IR spectra were determined on a Shimadzo IR-8900 spectrometer. NMR spectra were recorded on a 500 MHz Bruker DRX-500 using $CDCl_3$ and DMSO as the solvent. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS as internal standard. All solvents used were dried and distilled according to standard procedures.

*General procedure for the synthesis of **4a-g** under ultrasound irradiation:*
A mixture of aldehyde (1 mmol), dimedone (140 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), ammonium acetate (77 mg, 1 mmol) and $RuCl_3$ (5 mol%) in ethanol (5 mL) was irradiated in a water bath at 60˚C under ultrasound (45 kHz) for the required reaction times (Table 1) then the resulting solid product was filtered, washed with water, and dried in vacuum to afford the crude products **4a-g**. The filtrate containing the catalyst can be evaporated under vacuum in order to recover the catalyst for reusing it in another run. The pure products of **4a-g** were obtained by recrystalization of crude product from ethanol.

Physical and spectroscopic data for selected products:
2, 7, 7-trimethyl-5-oxo-4-(2-methoxyphenyl)-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylic acid ethyl ester (4d):
White solid; mp = 255-258˚C; IR (KBr, cm^{-1}) ν_{max} 3286, 3220, 3060, 2953, 1688, 1616, 1489, 1379, 1280, 1215, 1163, 1066, 760; ^{1}H NMR (500 MHz, $CDCl_3$ / DMSO 5%) δ_H: 0.81 (3H, s), 0.95 (3H, s), 1.08 (1H, t, *J* = 7.31 Hz), 1.95 (1H, d, *J* = 16.20 Hz), 2.06 (1H, d, *J* = 16.20 Hz), 2.12 (1H, d, *J* = 16.80 Hz), 2.19 (3H, s), 2.22 (1H, d, *J* =16.80 Hz), 3.69 (3H, s), 3.89 (2H, m), 5.12 (1H, s), 6.66-6.70 (2H, m), 6.95 (1H, dt, *J* = 1.40, 7.50 Hz), 7.17 (1H, dd, *J* = 1.40, 7.46 Hz), 7.63 (1H, s) ppm; ^{13}C NMR (125.75 MHz, $CDCl_3$ / DMSO 5%) δ_C: 195.5, 168.4, 157.8, 149.9, 144.6, 135.5, 131.5, 127.3, 120.2, 111.1, 110.7, 104.6, 59.6, 55.7, 51.2, 41.1, 33.6, 32.7, 29.9, 27.2, 19.2, 14.5 ppm.

2, 7, 7-trimethyl-5-oxo-4-(3-chlorophenyl)-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carboxylic acid ethyl ester (4f):
Light-green solid; mp = 210-211˚C; IR (KBr, cm^{-1}) ν_{max} 3267, 3200, 3067, 2943, 1707, 1640, 1603, 1489, 1375, 1205, 1153, 1067, 870, 770, 690; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.99 (3H, s), 1.11 (3H, s), 1.24 (3H, t, *J* = 7.10 Hz), 2.20 (1H, d, *J* = 16.30 Hz), 2.26 (1H, d, *J* = 16.80 Hz), 2.27 (1H, d, *J* = 16.30 Hz), 2.35 (1H, d, *J* = 16.80 Hz), 2.39 (3H, s), 4.10 (2H, m), 5.07 (1H, s), 6.56 (1H, s), 7.11 (1H, d, *J* = 7.61 Hz), 7.16 (1H, t, *J* = 7.70 Hz), 7.25 (1H, d, *J* = 7.51 Hz), 7.29 (1H, s) ppm; ^{13}C NMR (125.75 MHz, $CDCl_3$ / DMSO 5%) δ_C: 196, 167.6, 149.5, 149.2, 144.4, 134.1, 129.5, 128.6, 126.9, 126.6, 111.9, 105.9, 60.3, 51.1, 41.4, 37.1, 33.1, 29.8, 27.6, 19.8, 14.6 ppm.

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