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MANGANESE PERCHLORATE CATALYZED FACILE SYNTHESIS OF POLYHYDROQUINOLINES VIA HANTZSCH MULTI-COMPONENT CONDENSATION UNDER ULTRASONICATION

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Abstract

Hydrated Manganese perchlorate has been found as an efficient catalyst for the one pot synthesis of polyhydroquinoline derivatives via four component hantzsch condensation under ultrasonic irradiation. High yields, shorter reaction time, simple work up procedure/ operational simplicity are the key features of this protocol

Keywords

Hydrated Manganese Perchlorate, 1,4-DHP, Muticomponent Reaction, Ultrasound Irradiation,

Introduction

In recent years, the use of multi-component reactions (MCR's) for the synthesis of broad range of products have increased due to the efficiency of these processes in addition to their environmental acceptability. These processes not only increase the yield of the product but also reduce the number of laboratory operations along with the quantities of solvents and chemicals used. Therefore, research in academic and industry has increasingly emphasized the use of (MCR's) as an efficient and powerful tool in modern synthetic organic chemistry (1). The synthesis of 4-substituted 1,4-dihydropyridine (1,4-DHP) nucleus is of great significance in synthetic organic chemistry due to its biological and pharmacological properties such as vasodilator, antihypertensive, bronchodilator, antitherosclerotic, heptoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents (2,3). So, the remarkable potential of novel 1,4-DHP and polyhydroquinoline derivatives as the source of valuable drugs and useful intermediate in organic chemistry is the main reason for its synthesis by different methodologies. In view of the pharmacological significance of polyhydroquinoline derivatives, many classical methods for their synthesis were reported in the presence of organic solvents and catalysts (4). However many of these methods suffer disadvantages such as harsh reaction conditions, longer reaction times, low yields and use of excessive organic solvents. Hence it is required to develop an efficient and versatile method for the synthesis of these compounds. Recently, several methods for the synthesis of polyhydroquinolines have been demonstrated by using molecular iodine (5), $HClO_4$-SiO_2 (6), $Yb(OTF)_3$ (7), enneamolybdomanganate(IV) (8), L-proline (9), ZnO

(10), Bakers's yeast (11), organo catalysts (12) and polymers (13,14). Some of these methods are plagued by the limitations of poor yield, longer reaction times, difficult work up procedure and effluent pollution. Thus the development of new and flexible methodology is required. Hence, in continuation of our interest in developing novel synthetic methodologies and use of transition metal perchlorates (15-17) as catalysts for organic synthesis, In view of the above, we undertook a study of utility of hydrated manganese perchlorate as an efficient catalyst for the synthesis of polyhydroquinilone under ultrasonic irradiation. Herein, we report a facile one pot synthesis of polyhydroquinoline derivative from the condensation of aldehydes, ammonium acetate, dimedone and β-Keto esters.

Experimental

Material and Apparatus

All melting points recorded are uncorrected, open capillary measurements, using sulphuric acid bath. IR spectra were recorded using KBr pellets on a Perkin-Elmer spectrophotometer, NMR spectra on AL-300F (Bruker) FT NMR spectrophotometer using dimethylsulphoxide (DMSO) as internal standard. Sonication was performed in ELMA, Transsonic T 310/H Ultrasonic cleaner (with a frequency of 35 KHz), Hans Schmidbauer GmbH & Co., Germany. The reactions were performed in open vessels.

General procedure for the synthesis of polyhydroquinoline: A mixture of aldehyde (1 mmol), dimedone (1 mmol), β-keto ester (ethyl acetoacetate or methyl acetoacetate) (1 mmol) and ammonium acetate (1 mmol) and hydrated manganese perchlorate (4 mol %) in ethanol was placed under ultrasonic irradiation for the time as mentioned in **Table 2**. The reaction was monitored by TLC. After the completion of reaction the solid product was filtered. The solid product was recrystalized from ethanol.

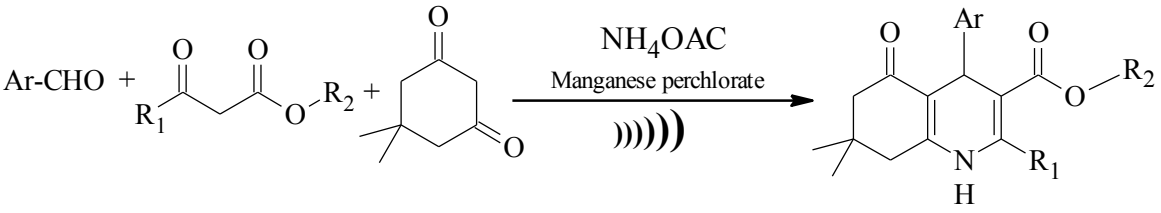
Selected spectral and physical data of products

Ethyl 1, 4, 5, 6, 7, 8 – hexahydro-4-(phenyl)-7, 7-dimethyl 5- oxoquinoline – 3- carboxylate 1a m. p. 203-204, IR (KBr, cm^{-1}) 3289, 3080, 2959, 1698, 1610; ^{1}HNMR (DMSO) δ ppm d 0.91 (s, 3H), 1.05 (s, 3H), 1.17 (t, $J^{1/47}$.1 Hz, 2H), 2.14-2.20 (m, 4H), 2.28 (s, 3H), 4.03 (q, J1/47.1 Hz, 3H), 5.02 (s, 1H) 5.96 (s, 1H), 7.04-7.09 (m, 1H), 7.14-7.19 (m, 2H), 7.23-7.26 (m, 2H).

Ethyl 1, 4, 5, 6, 7, 8 – hexahydro-4-(3, 4, 5-trimethoxyphenyl)-7, 7-dimethyl 5- oxoquinoline – 3- carboxylate 1i m. p. 195- 198, IR (KBr, cm^{-1}) 3293, 3031, 2958, 1687, 1612, 1486, 1377, 1219, 1115, 751; ^{1}HNMR (DMSO) δ ppm: 1.04,(3H, s, CH_3), 2.35-2.46 (4H, m, $2CH_2$), 3.68-3.87 (9H, m, $3OCH_3$). 4.17 (2H, q, J=7.1Hz, CH_2), 5.09 (1H, s, ArCH), 5.99 (1H, s, br, NH) 6.59 (2H, S, Ar-H).

Result and discussion:

The optimal condition for the synthesis of polyhydroquiniline was studied using benzaldehyde as a model substrate. In a typical experiment a mixture of benzaldehyde (1 mmol), dimedone (1 mmol), ethylacetoacetate (1 mmol) and ammonium acetate (1 mmol) in ethanol was placed under ultrasonic irradiation **(Scheme 1)** or without ultrasonic irradiation. To study the catalytic activity hydrated manganese perchlorate was added in varying amount. It was found that 4 mol % catalyst was optimum to carry out the reaction. Using more than 4 mol % of the catalyst did not affect the yield or time of the reaction. Further it was noted that under ultrasonic irradiation the reaction completed in 15 min.with 87% yield. While without ultrasonic irradiation only 30% product was formed in 70 min. with 30% yield. The results of the model experiment have been summarized in **Table 1**. To express the generality of reaction various aromatic aldehydes were condensed with β-keto ester (ethyl acetoacetate or methyl acetoacetate) in the presence of dimedone and ammonium acetate using manganese perchloratate as catalyst under ultrasonic irradiation. Under this procedure heterocyclic aldehyde like fufuraldehyde (**1j**, 82%) also worked well. After the completion of reaction the solid product was formed which was recrystalized from ethanol. The structure of the products **1a-t** formed was established on comparison with authentic samples prepared by other methods and from elemental analysis and spectroscopic analysis. The selected spectral and physical data is given in **Table 2**.



Scheme 1 **1a-t**

Table 1 : Effect of amount of catalyst with or without sonication for the synthesis of polyhydroquinoline derivatives at room temperature.

Entry	Mn $(ClO_4)_2$ mol%	With Sonication		Without Sonication	
		Yield (%)	Time(min.)	Yield (%)	Time(min.)
1.	1	Nil	180	Nil	180
2.	2.5	48	60	Nil	180
3.	4	87	15	30	60
4.	6	88	20	33	70

Table 2: Manganese perchlorate catalyzed synthesis of polyhydroquinoline derivatives at room temperature via hantzsch synthesis

Entry	Ar	R_1	R_2	Under ultrasonication		Without ultrasonication			
				Time (min.)	Yield (%)	Time (min.)	Yield (%)	M.pt (^{0}C)	Lit.m.pt (^{0}C)
1a	C_6H_5	CH_3	C_2H_5	15	87	60	30	203-204	202-204
1b	4-Cl C_6H_4	CH_3	C_2H_5	50	82	140	35	242-245	245-246
1c	p-OH C_6H_4	CH_3	C_2H_5	30	85	100	32	234-236	232-234
1d	o-NO_2 C_6H_4	CH_3	C_2H_5	45	76	120	27	203-205	206-208
1e	m-NO_2 C_6H_4	CH_3	C_2H_5	40	80	125	29	178-180	177-178
1f	m-Cl C_6H_4	CH_3	C_2H_5	40	83	130	32	206-209	209-210
1g	4- $CH_3C_6H_4$	CH_3	C_2H_5	20	84	90	35	258-260	261-262
1h	3,4-$(CH_3)_2C_6H_3$	CH_3	C_2H_5	25	83	105	30	290-293	288-290
1i	3,4,5-$(CH_3)_3C_6H_2$	CH_3	C_2H_5	35	80	110	26	195-198	198-199
1j	Furfural	CH_3	C_2H_5	25	82	100	26	246-248	247-248
1k	4-OCH_3 C_6H_4	CH_3	C_2H_5	15	78	55	35	251-253	252-254
1l	C_6H_5	CH_3	CH_3	20	87	80	28	211-213	213-215
1m	4-Cl C_6H_4	CH_3	CH_3	25	83	100	36	220-222	221-222
1n	4- $CH_3C_6H_4$	CH_3	CH_3	35	84	95	30	279-280	283-285
1o	o-NO_2 C_6H_4	CH_3	CH_3	15	78	60	32	250-252	253-255
1p	3-MeO C_6H_4	CH_3	CH_3	10	84	60	36	202-204	201-203
1q	3,4-$(CH_3)_2C_6H_3$	CH_3	CH_3	10	80	65	40	194-196	198-200
1r	3,4,5-$(CH_3)_3C_6H_2$	CH_3	CH_3	10	78	50	36	219-223	220-224
1s	4-N-$(CH_3)_2C_6H_4$	CH_3	CH_3	15	79	85	38	256-259	258-260
1t	4-OCH_3 C_6H_4	CH_3	CH_3	10	85	65	26	247-250	248-250

Conclusion

In conclusion, the synthesis of polyhydroquinoline was successfully carried out using hydrated manganese perchlorate as catalyst at room temperature under ultrasonic irradiation. The method offers several significant advantages, such as, high yields, shorter reaction time, easy handling, and cleaner green reaction profile which make it a useful and attractive method for the efficient synthesis of polyhydroquinoline derivatives.

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