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ORIGINAL ARTICLE

An efficient and rapid Mn(III) complex catalyzed synthesis of polyhydropyridine derivatives via Hantzsch four component condensation

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N,N′-bis (benzoylacetone) ethylenediamine manganese(III) chloride; Dimedone; Polyhydroquinoline; Hantzsch reaction; Multicomponent reaction

Abstract A facile and an efficient one-pot synthesis of polyhydroquinoline derivatives in high yields using N,N′-bis (benzoylacetone) ethylenediamine manganese (III) chloride as an environmentally friendly mild Lewis acid catalyst with high catalytic activity and reusability via the Hantzsch reaction in short reaction time was reported. The reaction proceeded to completion within 5–25 min in 90–97% yield. All of the obtained compounds were obtained in high purity without any use of more purification and characterized by physical and spectroscopic data.

1. Introduction

Organic reactions under green solvents have attracted much interest from chemists, particularly from the viewpoints of green chemistry. Green chemistry approaches are significant due to the reduction in byproducts and waste chemicals and lowering of energy costs. The possibility of performing multi-component reactions under green solvents could enhance their ability from the economical aspect as well as from the ecological point of view (Anastas and Warner, 1998; Anastas and Williamson, 1998).

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are an important class of drugs for the treatment of cardiovascular diseases (Boecker and Guengerich, 1986), Alzheimer's disease and used as chemo sensitizer in tumor therapy (Klusa, 1995; Bretzel et al., 1993; Boer and Gekker, 1995). They can cure the disordered heart ratio as the chain-cutting agent of factor IV channel and also have the calcium channel agonist–antagonist modulation activities (Kawase et al., 2002; Suarez et al., 2003; Sabitha et al., 2003; Sawada et al., 2004; Shan et al., 2004). Current literature reveals that these compounds possess a variety of biological activities, such as vasodilator, bronchodilator, antiatherosclerotic, geroprotective, hepatoprotective, and antidiabetic agents (Godfraid et al., 1986; Sausins and Duburs,

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1988). 1,4-Dihydropyridine family are being used as antimalarial, anti-inflammatory, antiasthamatic, antibacterial, and tyrosine kinase inhibiting agents (Chen et al., 2001; Roma et al., 2000; Maguire et al., 1994). Moreover DHPs also act as NADH coenzymes for the reduction of carbonyl compounds and their derivatives (Rueping et al., 2006). Several alkaloids isolated from marine sources also exhibit interesting biological activities, whose molecular structures contain the dihydropyrimidinone moiety (Ranu et al., 2000). Therefore, their synthesis has been the focus of much interest for organic and medicinal chemists (Atwal et al., 1990).

The classical method involves the three-component coupling of an aldehyde with β-ketoester and ammonia in acetic acid or refluxing alcohol (Loev and Snader, 1965). This method, however, involves long reaction time, harsh reaction conditions, use of a large quantity of volatile organic solvents and generally gives low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-DHPs. The progress in this field has been remarkable including recently the promotion of molybdenum(VI) complex Khabazzadeh et al., 2010, ionic liquids (Ji et al., 2004), metal triflates (Wang et al., 2005), I_2 (Ko et al., 2005), polymers (Legeay et al., 2006; Dondoni et al., 2004), organo-catalyst (Kumar and Maurya, 2007), CAN (Ko and Yao, 2006), $Hf(NPf)_4$ Hong et al., 2010, silica gel/$NaHSO_4$ (Chari and Syamasundar, 2005), MCM-41 (Nagarapu et al., 2007) and Ni-nanoparticles (Sapkal et al., 2009). However, the low yields, occurrence of several side products, use of stoichiometric amount of reagents, expensive metal precursors, complicated work-up methods and longer reaction times limit the use of these methods. Therefore, exploring the new catalytic system preferably in an environmentally benign and facile synthetic methodology using less hazardous solvents to overcome these drawbacks is still the need of the day and a challenging task to the organic chemists.

In this regard, a new, simple and efficient method for the one-pot synthesis of 1,4-dihydropyrimidine derivatives is reported herein. As a part of our interest in heterogeneous catalyzed organic reactions (Mosaddegh and Islami, 2008; Mosaddegh et al., 2007; Islami and Mosaddegh, 2009) and in the application of complex catalyst in organic reactions (Khabazzadeh et al., 2010), in this paper, we wish to report a Mn(III) complex catalyzed four-component Hantzsch reaction with high catalytic activity in short reaction time (5–25 min) under reflux conditions. Moreover, the products can be easily produced in excellent yields without any use of more purification.

2. Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (^{1}H) and 125.77 (^{13}C) MHz on Bruker DRX-500 Avance spectrometer at 500 and 125.77 MHz, respectively. All compounds were known in the literature, the NMR and IR spectra of the products were in agreement with earlier data.

2.1. General procedures for preparation of N,N′-bis (benzoylacetone) ethylenediamine manganese (III) chloride

N,N′-bis (benzoylacetone) ethylenediamine H_2(bnzen) ligand was prepared according to the literature (Feng and Liu, 1996; McCarty et al., 1955). Anhydrous ethylendiamine was refluxed with benzoylacetone (2:1 mol stoichiometric ratio of amine to ketone) in ethanol for 10 h. A brown solid crude product was separated by filtration, washed several times with ethanol and finally with diethyl ether. The product was recrystallized from hot ethanol and dried. Then N,N′-bis (benzoylacetone) ethylenediamine manganese (III) chloride was synthesized according to the reported procedures (Feng and Liu, 1996; McCarty et al., 1955). The structure of Mn(III) complex was known in the literature (Feng and Liu, 1996).

2.2. General procedure for preparation of 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-chlorophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 1, entry 2)

In a typical general procedure, a mixture of 4-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1.5 mmol) in EtOH (5 mL) refluxed thoroughly in the presence of a catalytic amount of (bzacen)MnCl (10 mg, 2.5 mol%) to afford the 4-substituted- 1,4-dihydropyridine in excellent yields. After completion of the reaction (25 min) confirmed by T.L.C, the reaction mixture was cooled to room temperature. The product was crystallized from solvent when cooling. Then the mixture was filtered to separate from the soluble catalyst and washed with cold EtOH. The solid product was obtained with high purity without any use of more purification. The structures of the products were confirmed from physical and spectroscopic data (IR and ^{1}H NMR) in comparison with the literature data. The selected spectral data of four representative 4-substituted 1,4-dihydropyridine derivatives are given below.

2.2.1. 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-chlorophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 1, entry 2)

IR (KBr): 3391, 2970, 1706, 1636, 1495,1378, 1238, 1074, 1027, 863 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3), 2.13–2.33 (m, 4H, $2CH_2$), 2.37 (s, 3H, CH_3), 4.06 (q, J = 7.1 Hz, 2H, OCH_2), 5.03 (s, 1H, CH), 6.25 (s, 1H, NH), 7.15–7.25 (m, 4H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.23, 19.22, 27.17, 29.41, 32.47, 36.16, 40.87, 50.76, 59.89, 105.44, 111.52, 122.81, 129.16, 131.74, 140.25, 147.15, 149.28, 167.27, 195.52.

2.2.2. 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(2,4-dichlorophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 1, entry 3)

IR (KBr): 3297, 2970, 1706, 1659, 1612, 1495,1238, 1121, 1074, 863, 770 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.20 (t, J = 7.1 Hz, 3H, CH_3), 2.01–2.27 (m, 4H, $2CH_2$), 2.29 (s, 3H, CH_3), 4.07 (m, 2H, OCH_2), 5.36 (s, 1H, CH), 6.93 (s, 1H, NH), 7.11–7.36 (m, 3H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.25, 19.18, 27.19, 29.31, 32.47, 35.87, 40.91, 50.78, 59.88, 104.78, 110.66, 126.59, 129.26, 129.26, 132.11, 132.93, 133.90, 142.90, 144.20, 149.40, 167.28, 195.49.

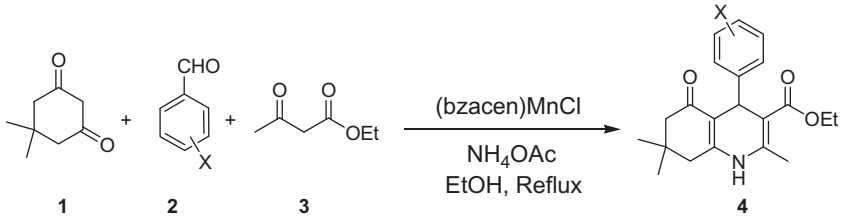
2.2.3. 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-bromophenyl)-3-quinolinecarboxyl acid ethyl ester (Table 1, entry 4)

IR (KBr): 3297, 2970, 1706, 1659, 1612, 1495,1285, 1238, 1074, 1027, 853 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.94 (s,

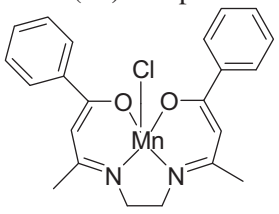
Table 1 (Bzacen)MnCl catalyzed the synthesis of polyhydroquinoline derivatives through Hantzsch reaction.

Entry	Ar	Time (min)	Yields (%)[a]	mp (°C)	mp[lit] (°C)
1	C_6H_5	20	90	203–204	203–204[20]
2	4-ClC_6H_4	25	96	243–245	245–246[20]
3	2,4-$Cl_2C_6H_3$	17	93	241–243	241–244[17]
4	4-BrC_6H_4	14	90	254–256	253–255[17]
5	4-$CH_3OC_6H_4$	7	92	258–260	257–259[17]
6	4-$CH_3C_6H_5$	5	97	257–259	260–262[20]
7	3–$CH_3OC_6H_5$	10	90	211–213	202–204[24]
8	3-OHC_6H_4	16	94	217–219	218–220[25]

[a] Yields refer to isolated pure products.



Mn(III) complex:



N,N′-bis (benzoylacetone) ethylenediamine manganese (III) chloride

Scheme 1

3H, CH_3), 1.08 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3), 2.14–2.32 (m, 4H, $2CH_2$), 2.37 (s, 3H, CH_3), 4.08 (q, J = 7.1 Hz, 2H, OCH_2), 5.03 (s, 1H, CH), 6.52 (s, 1H, NH), 7.01 (d, J = 7.9 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.22, 19.32, 27.14, 29.41, 32.68, 36.38, 41.02, 50.76, 59.90, 105.67, 111.70, 119.81, 129.86, 130.95, 143.77, 146.15, 148.53, 167.22, 195.51.

2.2.4. 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-(4-methylphenyl)-3-quinolinecarboxyl acid ethyl ester (Table 1, entry 7)

IR (KBr): 3297, 2970, 1706, 1648, 1612, 1495,1378, 1215, 1074, 1051, 863 cm^{-1}; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.96 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.23 (t, J = 7.2 Hz, 3H, CH_3), 2.15–2.32 (m, 4H, $2CH_2$), 2.27 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.08 (q, J = 7.1 Hz, 2H, OCH_2), 5.04 (s, 1H, CH), 6.73 (s, 1H, NH), 7.01 (d, J = 7.9 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 2H, ArH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 14.24, 19.24, 21.02, 27.21, 29.43, 32.67, 36.18, 40.98, 50.87, 59.76, 106.19, 112.11, 127.89, 128.61, 135.36, 143.49, 144.28, 148.67, 167.57, 195.64.

3. Results and discussion

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of DHPs, we initiated our studies by subjecting catalytic amount of [N,N′-bis(benzoylacetone)-1,2-ethylenediimine] Mn(III) chloride or (bzacen)MnCl to the mixture of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate in EtOH and water separately at room temperature. Unfortunately, the resulted yield was poor. To affect the reaction, various solvent systems were screened at different temperatures. It was interesting to observe that different products could be obtained in a different ratio of H_2O/EtOH as solvent that caused a decrease in the yield of the main product. It was seen that the synthesis of DHP was efficiently catalyzed by Mn(III) complex in EtOH at elevated temperature leading to high yield of the product (Scheme 1).

The reaction condition was then optimized by conducting the reaction in different temperatures and employing different catalyst loadings. It is evident that the best result was obtained by the application of 2.5 mol% of Mn(III) complex in EtOH as solvent at reflux condition. All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical (Sabitha et al., 2003; Ko and Yao, 2006; Hong et al., 2010; Chari and Syamasundar, 2005).

In order to examine the scope and generality of this procedure, the methodology was extended to different aromatic aldehydes. The results are presented in Table 1. Both electron-withdrawing groups such as nitro and halide groups or

electron-donating groups such as hydroxyl and alkoxy groups reacted well to afford **4** in a short experimental time with high yields (90–97%).

3.1. Reusability of Mn(III) complex

The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Thus the recovery and reusability of Mn(III) complex were investigated. Fortunately, the precipitated material in the reaction shown in Scheme 1 was successfully recycled three times. The catalyst could be recycled in two ways.

3.1.1. Method A

In the first method, the reaction mixture was filtered and washed with cold EtOH. The soluble catalyst was easily reused after distillation of solvent, washing with $CHCl_3$ and drying at room temperature. The recycled catalyst could be examined in the next run in the reaction between 4-chlorobenzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate.

3.1.2. Method B

In the second method, the reaction mixture was filtered and the solid product was washed with EtOH. Mn(III) complex is soluble in EtOH. The filtrate including soluble catalyst could be reused as such for subsequent experiments (up to 3 cycles) without any use of more catalyst loading. So, in the next run, 4-chlorobenzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate were just added to the filtrate to afford the comparable yields of the product.

It was interesting that the Mn(III) complex could be reused in three cycles via this method without any loss of its activity, more purification, distillation of solvent and dry catalyst. Thus the filtrate could be used several times to produce the 4-substituted-1,4-dihydropyridines with simple workup and not using the cumbersome apparatus for recycling of the catalyst.

4. Conclusion

In conclusion, the present method is an operationally simple and environmentally friendly and cost-effective procedure for the synthesis of compound **4** using a catalytic amount of (bzacen)MnCl. In addition, low cost, moderate Lewis acidity, excellent yields of products without any use of more purification and short reaction time make this methodology a valid contribution to the existing processes in the field of 4-substituted-1,4-dihydropyridine derivatives synthesis.

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