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A one-pot multi-component synthesis of dihydropyridine derivatives *via* Hantzsch condensations using Amberlite IRA 900 as a heterogeneous catalyst under solvent-free conditions

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ABSTRACT

The synthesis of various substituted Hantzsch 1,4-dihydropyridine derivatives has been achieved using a modified procedure in the presence of Amberlite IRA 900 as a heterogeneous catalyst under solvent-free conditions, in good to excellent yields.

Keywords: Hantzsch 1,4-dihydropyridines, Amberlite IRA 900, Solvent-free conditions, One-pot condensation, Heterogeneous Catalysis

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INTRODUCTION

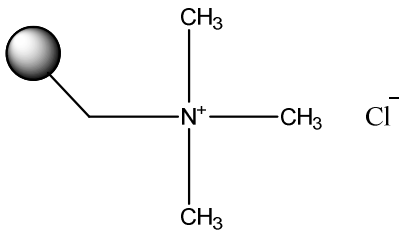
1,4-Dihydropyridine (DHP) [1] scaffold represents the heterocyclic unit of remarkable pharmacological efficiency. They are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, such as, nifedipine and nitrendipine are used for the treatment of hypertension and angina pectoris, nisoldipine is a potent vasodilator and nimodipine exhibits selectivity for cerebral vasculature [2]. A number of DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure [3].

Moreover DHPs also act as NADH mimics for the reduction of carbonyl compounds and their derivatives [4]. In human body the main metabolic route of dihydropyridine drugs involve their oxidation to pyridines catalyzed by cytochrome-450 in liver [5]. Additionally, the synthesis of heteroaromatics by oxidative dehydrogenation is of fundamental importance in organic chemistry. These ubiquitous features always encourage synthetic chemist to explore improved protocols for the synthesis as well as the oxidation of 1,4-DHPs.

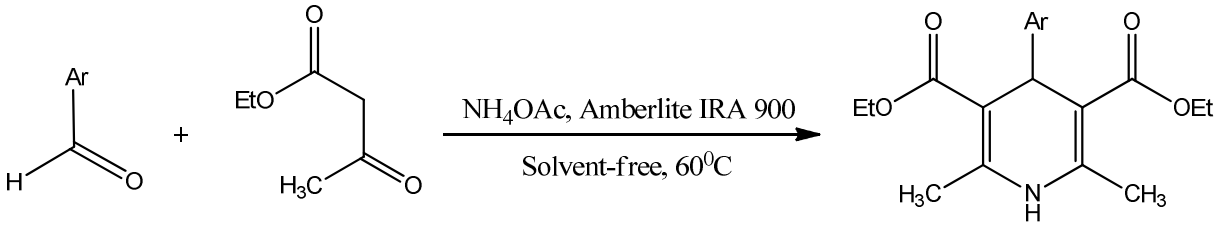
1,4-Dihydropyridines are generally synthesized by Hantzsch reaction which involves the condensation of aldehydes, β-ketoester and ammonia or ammonium acetate. A number of improved methods have been reported in the literature for this condensation which involve the use of microwave, ionic liquids, reflux at high temperature, TMSI, I_2, $Yb(OTf)_3$, CAN [6], silica gel/$NaHSO_4$ [7] and $Sc(OTf)_3$ [8]. On the other hand, a plethora of reagents have been employed for the oxidation of 1,4-DHPs [9-16]. In spite of potential utility of these reagents, most of the existing methods for the synthesis of 1,4-DHPs as well as their aromatization suffer from drawbacks such as low yields, long reaction times, occurrence of several side products, use of stoichimetric amount of reagents, use of strong oxidants,

high temperature and the use of expensive and toxic transition metallic reagents. Therefore, exploring the new catalytic system preferably in an environmentally benign method to overcome these drawbacks is a challenging task to the organic chemists.

This work represents the continuation of our studies using heterogeneous solid catalysts in organic transformations [17]. We introduce an efficient, rapid and clean procedure for the synthesis of 1,4-Dihydropyridines using Amberlite IRA 900 as a anion exchange resin, heterogeneous and reusable catalyst in a solvent free conditions (Scheme **1**).



Amberlite IRA 900C



1 **2a** **3a-f**

Scheme-1

MATERIALS AND METHODS

General

Melting points were measured using Buchi B-540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Avance DPX 300 MHz FT NMR spectrometer. Chemical shifts are expressed in δ units relative to tetramethylsilane (TMS) signal as internal reference.

General Procedure for the Synthesis of 1,4-dihydropyrines and Polyhydroquinolines 3: Aldehyde (2 mmol), β-ketoester (2 mmol), NH_4OAc (4 mmol) and Amberlite IRA 900 (50 mg) were stirred at 60^0C. After completion of the reaction as indicated by TLC, Amberlite IRA 900 was separated from reaction mixture by simple filtration due to its heterogeneous nature and washed with ethyl acetate for its further use. The crude product was purified by recrystallization from ethanol to yield the highly pure Hantzsch 1,4-dihydropyridine derivatives **3(a-f)**. The physical data (M.p., IR, NMR) of known compounds were found to be identical with those reported in the literature. Spectroscopic data for selected examples are shown below.

Ethyl-4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3a):

M.p. 158-160°C, IR (KBr): 3335, 1692, 1651, 1490, 1239, 1122, 720 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.32-7.14 (m, 5H, CHAr), 5.71 (s, 1H, NH), 5.01 (s, 1H, CH), 4.11 (q, *J*=7.1, 4H, $2CH_2$), 2.36 (s, 6H, $2CH_3$), 1.24 (t, *J*=7.1, 6H, $2CH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 167.6, 145.4, 143.8, 135.6, 128.4, 127.9, 104.2, 59.7, 39.6, 19.5, 14.2.

Ethyl-4-(2-thienyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3e):

M.p. 171-173°C, IR (KBr): 3421, 1647, 1512, 1485, 1213, 1115, 752 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.06-6.79 (m, 3H, CHAr), 6.55 (s, 1H, NH), 5.35 (s, 1H, CH), 4.16 (q, *J*=7.0 Hz, 4H, $2CH_2$), 2.32 (s, 6H, $2CH_3$), 1.28 (t, *J*=7.0

Hz, 6H, $2CH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 167.5, 152.1, 145.0, 143.7, 126.3, 123.1, 103.3, 59.9, 34.3, 19.2, 14.3.

Ethyl-4-(2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3f):
M.p. 160-162°C, IR (KBr): 3344, 1701, 1649, 1485, 1371, 1207, 1120, 727 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.22 (s, 1H, NH); 6.22-5.94 (m, 3H, CHAr), 5.20 (s, 1H, CH), 4.11 (q, *J*=7.1 Hz, 4H, $2CH_2$), 2.32 (s, 6H, $2CH_3$), 1.27 (t, 6H, *J*=7.1 Hz, $2CH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 167.5, 158.7, 145.2, 140.8; 110.0, 104.4, 100.5, 59.8, 33.3, 19.4, 14.3.

Ethyl-2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,4a,5,6,7,8,8a-octahydroquinoline-3-carboxylate (3g):
M.p. 205-207 °C, IR (KBr): 3293, 3058, 2958, 1676, 1610 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.75 (s, 1H, NH), 7.34-7.08 (m, 5H, CHAr), 5.07 (s, 1H, CH), 4.10 (q, *J*=7.1 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.22-2.10 (m, 4H, $2CH_2$), 1.23 (t, *J*=7.1 Hz, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). ^{13}C ($CDCl_3$, 63 MHz) δ: 196.1, 167.7, 153.5, 150.2, 147.3, 144.4, 128.0, 126.7, 126.0, 115.5, 111.4, 105.7, 59.8, 50.8, 40.4, 36.6, 32.6, 29.5, 27.0, 19.0, 14.2.

Ethyl-2,7,7-trimethyl-5-oxo-4-p-tolyl-1,4,4a,5,6,7,8,8a-octahydroquinoline-3-carboxylate (3h):
M.p. 260-262°C, IR (KBr): 3294, 3058, 2955, 1645, 1610, 1485, 1218 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.21 (d, *J*=8.1 Hz, 2H, CHAr), 7.01 (d, *J*=8.1 Hz, 2H, CHAr), 6.87 (s, 1H, NH), 5.02 (s, 1H, CH), 4.04 (q, *J*=7.1 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.32-2.18 (m, 4H, $2CH_2$), 1.24 (t, 3H, *J*=7.1 Hz, CH_3), 1.09 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C ($CDCl_3$, 63 MHz) δ: 195.8, 167.6, 149.0, 144.3, 143.7, 135.4, 128.6, 127.8, 127.3, 111.9, 106.1, 77.5, 76.5, 59.8, 50.7, 40.8, 36.1, 32.7, 29.4, 27.1, 19.2, 14.2.

Ethyl-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,4a,5,6,7,8,8-aoctahydroquinoline-3-carboxylate (3i):
M.p. 256-258°C, IR (KBr): 3449, 3348, 3101, 2978, 1647, 1489, 1207 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.23 (d, *J*=6.7 Hz, 2H, CHAr), 6.8 (s, 1H, NH); 6.75 (d, 2H, *J*= 6.7, CHAr); 5.00 (s, 1H, CH), 4.08 (q, 2H, *J*=7.1 Hz, CH_2), 3.74 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3), 2.28-2.17 (m, 4H, $2CH_2$), 1.23 (t, *J*=7.1 Hz, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). ^{13}C ($CDCl_3$, 63 MHz,) δ: 195.9, 167.6, 157.7, 148.8, 143.5, 139.7, 133.0, 128.9, 113.2; 106.1, 59.8; 50.7, 40.8, 35.7, 32.6, 29.5, 27.1, 19.2, 14.2.

RESULTS AND DISCUSSION

Recently, we have reported Biginelli condensation reaction is facilitated in the presence of a catalytic amount of Amberlyst 15 DRY and Triethyl ammonium acetate (TEAA) as cation exchange resin and ionic liquid respectively [18, 19]. Very recently Mustafa A. and co-workers [20] reported that alumina sulfuric acid (ASA) catalyses one-pot synthesis of DHPs *via* Hantzsch condensation from aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate.
A literature survey clearly shows that there is no report on the application of Amberlite IRA 900 as base catalyst for classic Hantzsch condensation reaction. Here, we wish to report the capacity of Amberlite IRA 900 as potential base catalyst for the one-pot synthesis of 1,4-dihydropyridines and their analogues *via* solvent-free Hantzsch condensation protocol.

In the efforts to develop an efficient and environmentally benign method for the synthesis of DHPs we initiated our study with the base-catalyzed Hantzsch condensation by subjecting catalytic amount of Amberlite IRA 900 to the mixture of 2-furaldehyde (1 equiv.), which usually gives good yields of the corresponding product, ethyl acetoacetate (2 equiv.) and ammonium acetate (2 equiv.) in ethanol at room temperature. Unfortunately, the resulted yield was very poor even after 24 h of stirring. To see the effect of reaction, various solvent systems were tested at different temperatures. We found that the synthesis of DHP **3f** was efficiently catalyzed by Amberlite IRA 900 in solvent free condition at elevated temperature leading to a good yield of product (Table **1**, entry 6). The reaction condition was then optimized by conducting the reaction in different temperatures and employing different catalyst loadings. The different experiments show that the best result was obtained by the application of 50 mg of Amberlite IRA 900 in solvent free condition at 60°C. Other amounts of the catalyst substantially reduced the yield as side products were formed.

In order to study the scope and generality of this methodology, a variety of substituted aromatic aldehydes were subjected to the previous reaction with 2-furaldehyde. Unfortunately, it was observed that even under optimized conditions, that the corresponding 1,4-DHPs were isolated in very moderate yields due to the formation of many

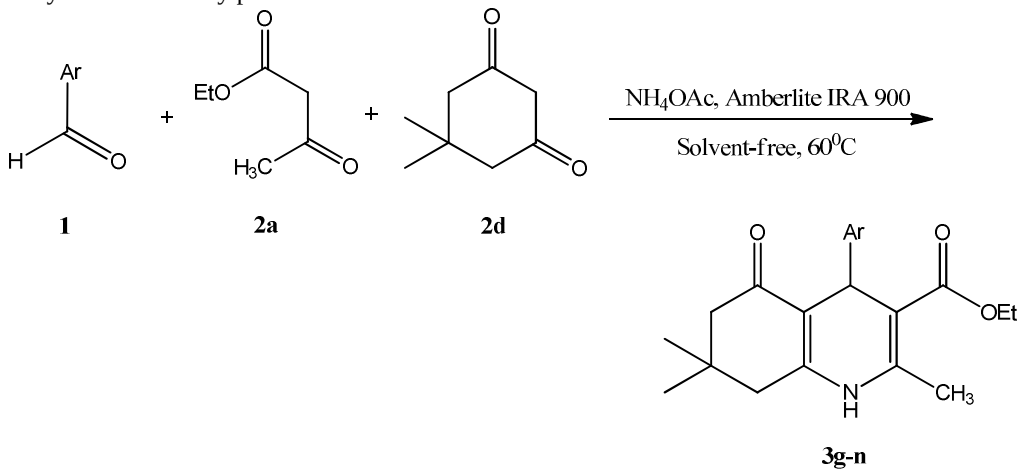
other side products, also, the starting material **2a** was still present in the crude products (according to ^{1}H NMR spectra). In comparison, good yield was obtained when 2-thiophenecarboxaldehyde was employed (Table **1**, entry 5). However, the reaction of other aromatic aldehydes led to lower yields.

Table 1: Amberlite IRA 900 Catalyzed Hantzsch Synthesis of 1,4-dihydropyridines Under Optimized Reaction Conditions[a]

Entry	DHP	Ar	Time (h)	Yield[b] (%)	M.P. (°C)	
					Found	Reported[21,22]
1	3a	C_6H_5	4	62	158-160	158-160
2	3b	2-(OCH_3)-C_6H_4	7	47	141-143	140-142
3	3c	4-(NO_2)-C_6H_4	5	56	130-132	129-131
4	3d	3-(NO_2)-C_6H_4	6	60	162-164	162-164
5	3e	2-thienyl	2	85	171-173	171-173
6	3f	2-furyl	3	90	160-162	160-161

[a]The reactions were carried out at 60°C using aldehyde (2 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (4 mmol) and Amberlite IRA 900 (50 mg) under solvent-free conditions. [b]Yields were measured by ^{1}H NMR spectra.

After many trials, we decided to employ other more reactive β-ketoesters such as dimedone **2d** (5,5-dimethylcyclohexan-1,3-dione) as a second equivalent with ethyl acetoacetate. Thus, the reaction of benzaldehyde (1 equiv.), dimedone (1 equiv.), ethyl acetoacetate (1 equiv.) and ammonium acetate (2 equiv.) in the presence of 50 mg of Amberlite IRA 900 in solvent free condition at 60°C affords after only 2h, the corresponding polyhydroquinoline in excellent yield (Scheme **2**). So, the reaction was amenable to a wide range of aromatic and heteroaromatic aldehydes and gave in all cases the desired products in very good yields and the results are summarized in Table **2**. It is noteworthy that the reactions proceeded at a faster rate with electron donating aldehydes (entries 1-4) and were slightly slow with electron withdrawing ones (entry 6) with the exception of polyhydroquinoline **3k** (entry 5) which gave the desired product in excellent yield. Good yields were also achieved for heterocyclic aldehydes such as 2-furaldehyde (entry 7). However, aliphatic aldehydes such as acetaldehyde and isobutyraldehyde afforded very poor results.



1 **2a** **2d** **3g-n**

Scheme-2

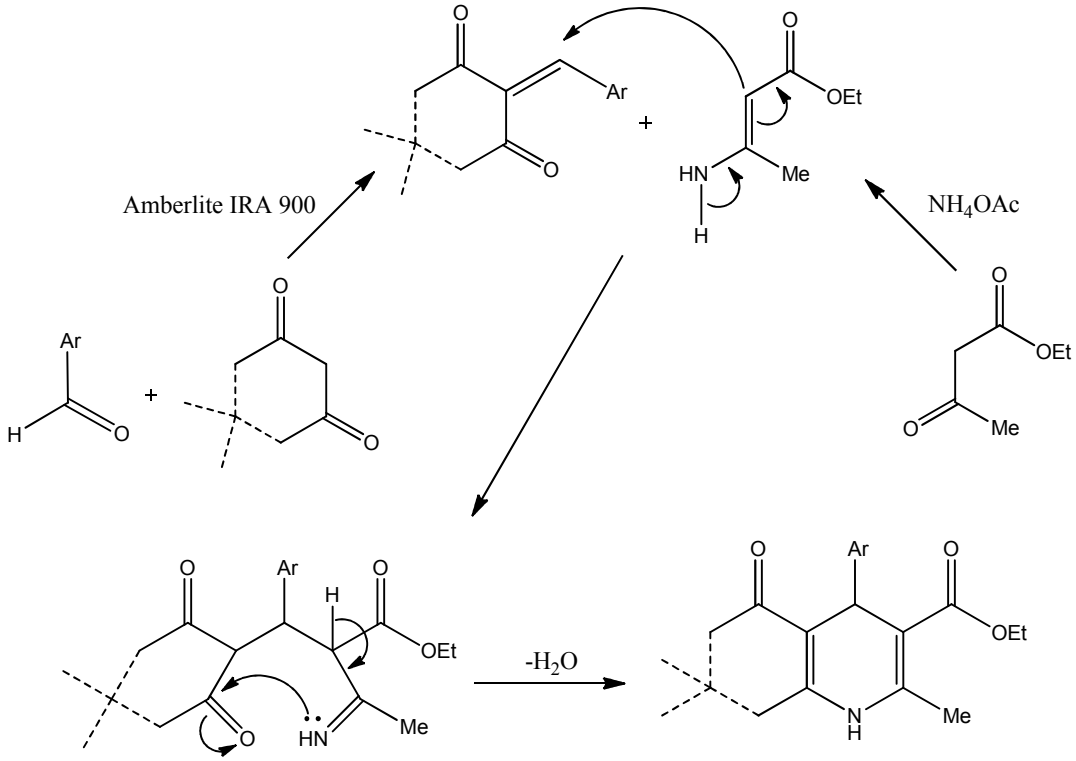
In a typical procedure, 2 mmol of aldehyde, 2 mmol of dimedone, 2 mmol of ethyl acetoacetate and 4 mmol of ammonium acetate were mixed in solvent free condition in the presence of 50 mg of Amberlite IRA 900 and the reaction mixture was stirred for 1-5 h at 60°C, after work-up, it produced the corresponding polyhydroquinolines **3(g-n)** in good yields.

Table 2: Amberlite IRA 900 Catalyzed Hantzsch Synthesis of polyhydroquinolines Under Optimized Reaction Conditions[a]

Entry	DHP	Ar	Time (h)	Yield[b] (%)	M.P. (°C)	
					Found	Reported[23-25]
1	3g	C_6H_5	2	79	205-207	202-204
2	3h	4-(CH_3)-C_6H_4	2	94	260-262	260-262
3	3i	4-(OCH_3)-C_6H_4	1	87	256-258	255-257
4	3j	4-(OH)-C_6H_4	1	95	232-234	232-234
5	3k	4-(Br)-C_6H_4	2	96	251-253	253-254
6	3l	4-(NO_2)-C_6H_4	7	90	240-242	242-244
7	3m	2-furyl	2	74	246-248	248-249
8	3n	Styryl	2	67	206-208	206-207

[a]The reactions were carried out at 60°C using aldehyde (2 mmol), ethyl acetoacetate (2 mmol), dimedone (2 mmol), ammonium acetate (4 mmol) and Amberlite IRA 900 (50 mg) under solvent-free conditions. [b]Isolated yields.

A plausible mechanism of the Amberlite IRA 900 catalyzed Hantzsch condensation is shown in Scheme (**3**) based on the previous reports, our observations and obtained results.



Scheme-3: Plausible mechanism for the formation of Polyhydroquinoline derivative

CONCLUSION

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 4-substituted-1,4-dihydropyridine derivatives from the reaction of different aromatic or heteroaromatic aldehydes, β-ketoesters and ammonium acetate in the presence of catalytic amount of Amberlite IRA 900 under solvent free conditions. The catalytic activity of Amberlite IRA 900 is notable and the use of low cost, commercially available materials for the synthesis of Hantzsch products in good to excellent yields is also significant under the aspect of environmentally benign processes. These advantages make Amberlite IRA 900 as a powerful catalyst for the synthesis of 1,4-DHPs and their analogs.

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