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Synthesis of Hantzsch 4-aryl-1, 4-dihydropyridines catalyzed by PEG400-Na_2CO_3 under solvent-free conditions

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ABSTRACT

One-pot synthesis of the 4-aryl-1,4-dihydropyridine derivatives catalyzed by PEG400 -Na_2CO_3 combination system involving three component condensation reaction of an aromartic aldehyde, β–ketoester, ammonium acetate under solvent free conditions to afford the corresponding products in good yields.

KEYWORDS

4-aryl-1;
4-dihydropyridines;
Hantzsch reaction;
PEG400;
Solvent-free.

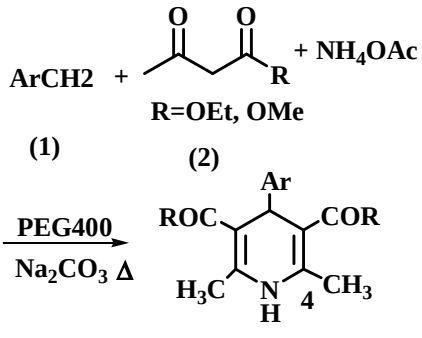
INTRODUCTION

As green chemistry has become a major concern to organic chemists in present years, reactions under solvent-free conditions have received much attention. These reactions offer several advantages in preparative procedures such as environmentally friendly, simplifying work-up, formation of cleaner products, enhanced selectivity and much improved reaction rates[1].

Hantzsch 1,4-dihydropyridines(1,4-DHPS) are biologically active compounds which including various vasodilator, antihypertensive, branchodilator, antiatherodclerotic, hepatoprotective, antitu- mor, antimutagenic, geroprotective and antidiabetic agents[2]. DHPs have found commercial utility as calcium channel blochers[3,4] such as Nifediine, Nitrendipine and Nimodipine. A number of DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure[5,6]. Among DHPs with other types of bioactivity, cerebrocrast has been introduced as a neuroprotectant and cognition enhancer. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered[7].

1,4-dihydropyridines have been synthesized by the Hantzsch reaction[8], which involves cyclocondensation of an aldehyde, β–ketoester, ammonia either in refluxing acetic acid or in refluxing ethanol. 1,4-dihdropyridines have also been synthesized on a solid phase for making combinatorial libraries[9]. Recently, Hantzsch's reaction for the synthesis of dihydropyridines has received renewed interest and several improved procedures have been reported[10-13]. However, there are several disadvantages associated with these methodologies including unsatisfactory yields, long conversion times, difficult handing of reagents, toxic organic solvents. Recently, the microwave -promoting Hantzsch's reaction has also been reported[14-17]. Thus, development of facile and environmental friendly synthetic methods to the Hantzsch's reaction is demanded.

Polyethylenes glycols(PEGs) have been are known to function as efficient phase transfer catalysts in a variety of organic reactions[18,19]. PEGs are reported to have,



SCHEME 1

TABLE 1 : 1,4-DHPS(4a) synthesis catalyzed by Na_2CO_3 in various solvents[a]

Entry	Solvent	Temperature	Na_2CO_3 (mol%)	Time (h)	Yield (%)[b]
1	CH_3CN	Reflux	5%	3	60
2	CH_2Cl_2	Reflux	5%	4	80
3	DMF	Reflux	5%	2	53
4	Toluene	Reflux	5%	1.5	78
5	Benzene	Reflux	5%	2	74
6	Solvent-free	r.t	5%	4	84
7	Solvent-free	80^0C	1%	2.5	82
8	Solvent-free	80^0C	5%	1.5	88
9	Solvent-free	80^0C	10%	1.5	87

[a]Reaction conditions: benzaldehyde 1(5mmol) ethyl atetoacetate 2(10mmol) ammonium acetate 3(5mmol); [b]Isolated yield after crystallization

at least in some cases efficiency comparable to that of crown ethers to complex and transport alkali metal cations from the aqueous medium to the organic phase. In addition to this, PEGs are nontoxic, thermally stable and inexpensive compared to the conventional phase transfer catalyst(i.e. crown ethers or quaternary ammonium salts). The reaction under solvent-free conditions has much attention in recent times in the area of green synthesis. In the continuation of our investigation on the research of using PEGs as phase transfer catalyst under solvent-free conditions[20]. In this article, we wish to report a mild and efficient version of the Hantzsch's reaction for synthesis of 1,4-dihydropyridines using a catalyst amount of anhydrous Na_2CO_3 and PEG400 as an inexpensive catalyst system under solvent-free conditions. Accordingly, treatment of benzaldehyde(**1a)**, ethyl acetate(**2)** and ammonium acetate(**3)** in the presence of 5% Na_2CO_3 and 5% of PEG400 resulted in the formation of 2,6-Dimethyl-3,5-Dicarboxylate-4-phenyl-1,4-dihydropyridine(**4a)** in 85% yield(SCHEME 1).

TABLE 2: Synthesis of substituted 4-aryl-1,4-dihydropy ridines using PEG400-Na_2CO_3 as an inexpensive catalyst system under solvent-free conditions[a]

Entry	Ar	R	Time (min)	Yield (%)[d]	M.p. Found	M.p. reported
4a	C_6H_5	OEt	90[b]	88	156-157	158-160[12]
4b	4-$CH_3C_6H_4$	OEt	80[b]	86	135-137	136-138[12]
4c	3-$NO_2C_6H_4$	OEt	85[c]	91	168-170	165-167[12]
4d	4-$OCH_3C_6H_4$	OEt	90[b]	89	155-157	153-155[12]
4e	4-ClC_6H_4	OEt	60[c]	90	144-147	143-146[12]
4f	4-$NO_2C_6H_4$	OEt	85[c]	95	128-130	128-129[12]
4g	4-OH-3-$OMeC_6H_3$	OEt	90[c]	93	159-161	158-159[14]
4h	3,4-$(CH_3O)_2C_6H_3$	OEt	90[b]	86	138-139	138-140[14]
4i	4-OHC_6H_4	OEt	70[c]	94	225-228	222-224[14]
4j	2-$NO_2C_6H_4$	OEt	90[b]	85	171-173	-
4k	C_6H_5CH=CH	OEt	85[b]	87	148-150	149-150[15]
4l	C_6H_5	OMe	80[b]	86	196-198	196-198[16]
4m	4-$OCH_3C_6H_4$	OMe	90[c]	88	185-186	186-188[16]
4n	4-OHC_6H_4	OMe	60[c]	92	231-232	230-232[16]
4o	4-ClC_6H_4	OMe	75[c]	89	195-197	196-198[16]
4p	4-$CH_3C_6H_4$	OMe	90[b]	84	172-173	174-176[16]
4q	3-$NO_2C_6H_4$	OMe	80[c]	91	211-213	210-212[16]
4r	2-ClC_6H_4	OMe	80[c]	88	196-198	194-196[16]
4s	C_6H_5CH=CH	OMe	90[b]	87	177-178	176-178[16]

[a]Reaction conditions: aldehyde 1(5mmol), β–ketoester 2 (10mmol), ammonium acetate 3(5mmol), Na_2CO_3(0.25mmol, 0.026g), PEG400(0.25mmol, 0.1g); [b]The temperature were processed at 80^0C; [c]The temperature were processed at 100^0C. [d]Isolated yields

RESULTS AND DISCUSSION

In our initial research, benzaldehyde was selected as a representative aldehyde in order to optimize the reaction conditions for synthesis of 1,4-dihydropyridines in faster and more efficient way. After some experimentation, we have found a set of conditions that generally provide 1,4-dihydropyridines in good yields. The results showed that the efficiency and the yield of the reaction in solution were much less than those obtained under solvent-free conditions(TABLE 1). The molar ratios of benzaldehyde, β–ketoester and ammonium acetate is 1:2:1, the use of 5% of Na_2CO_3 was sufficient to promote the reaction. Higher amounts of the catalyst did not improve the yields. The amounts of PEG400 has been studied from 0.5% to 10%, the best amount of PEG400 is 5%, lower amounts of PEG400 can not played the role of phase transfer catalyst very well, but higher amounts would undoubtedly lead to more of products during the washing procedure. As can be seen from the TABLE 2, aromatic aldehydes, β–ketoester and ammonium acetate in the presence of

Na_2CO_3 and PEG400 as phase transfer catalyst without any solvent gave the corresponding 4-aryl-1,4-dihydropyridines in good yields after 1-1.5h. A variety of substituted aromatic aldehyde carrying either electron-withdrawing groups(-OH, -NO_2, -Cl) or electron-donating groups(-CH_3, -OCH_3) affords good to excellent yields of products. Some of these products prepared from this method were characterized by their spectra data and known compounds by comparison with reported data.

In summary, we have described a mild and efficient protocol for the synthesis of 1,4-dihydro pyridines via Hantzsch's reaction of aromatic aldehyde with β–ketoester and ammonium acetate using PEG400–Na_2CO_3 as an inexpensive catalyst system under solvent-free conditions. The simple experimental procedure combined with the facile catalyst makes this method quite simple, convenient and environmentally. This method not only provides a good yield in short time, but also avoids the use of organic solvent(cost, handing, safety and pollution). Hence, it is a useful addition to the existing methods.

EXPERIMENTAL

^{1}H-NMR spectra were obtained on a Bruker AVANCE(400MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. IR spectra were recorded on a Bio-Rad FTS-40 spectrome ter(KBr). TLC was GF254 thin layer chromatography with petroleum ether/ethyl acetate as eluent. Aldehydes, β-ketoester and ammonium acetate were all commercial products and were used without further purification. All liquid reagents were distilled before use. Melting points were determined on a microscopy apparatus and are uncorrected.

General procedure for the synthesis of compounds (4a-4s)

A mixture of aromatic aldehyde 1(5mmol), β-ketoester 2(10mmol), ammonium acetate 3(5mmol), anhydrous Na_2CO_3(0.026g, 0.25mmol) and PEG400 (0.1g, 0.25mmol) was vigorously stirred and heating at assigned temperature for a designated time. TLC monitored the reaction. After the reaction was completed, the reaction mixture was cooled to room temperature. The crude product was isolated by precipitation upon addition of ice water to the reaction mixture followed with vigorous shaking and decanting the aqueous layer. The residue was dissolved by ethyl acetate(2×5mL) and dried over magnesium sulfate, and concentrated under vacuum(rotary evaporator) to afford the crude product. The pure product was obtained by further recrystallization using absolute alcohol or by silica gel column chromatography.

Compound(4a) ^{1}HNMR($CDCl_3$): δ: 1.24(6H, t, J=7.2Hz, 2×CH_3), 2.32(6H, s, 2×CH_3), 4.10(4H, q, J=7.2Hz, 2×CH_2O), 5.00(1H, s, CH), 5.63(1H, brs, NH), 7.12-7.31(5H, m, ArH); IR(KBr) : 3341,3060, 1688,1651,1488,1372,1229,1211,1123,1091,1020, 768,703,680cm^{-1}.

Compound(4b) ^{1}HNMR($CDCl_3$): δ: 1.24(6H, t, J=7.2Hz, 2×CH_3), 2.27(3H, s, CH_3), 2.32(6H, s, 2×CH_3), 4.10(4H, q, J=7.2Hz, 2×CH_2O), 5.02(1H, s, CH), 5.60(1H, brs, NH), 7.10(2H, d, J=7.2Hz, ArH), 7.17(2H, d, J=7.2Hz, ArH); IR(KBr) ν: 3350, 2990,1700,1649,1490,1390,1200,1100,1090,cm^{-1}.

Compound(4c) ^{1}HNMR($CDCl_3$): δ: 1.24(6H, t, J=7.2Hz, 2×CH_3), 2.36(6H, s, 2×CH_3), 4.10(4H, q, J=7.2Hz, 2×CH_2O), 5.10(1H, s, CH), 5.65(1H, brs, NH), 7.38(1H, t, J=8.0Hz, ArH), 7.65(1H, d, J=8.0Hz, ArH), 8.01(1H, d, J=8.0Hz, ArH), 8.14(1H, s, ArH). IR(KBr) ν: 3358,3093,2987,2960,1696,1651, 1603,1507,1489,1372, 1300,1245,1210,1166,1123, 1090,1018,856,786,755,695 cm^{-1}.

Compound(4d) ^{1}HNMR($CDCl_3$): δ: 1.24(6H, t, J=7.2Hz, 2×CH_3), 2.33(6H, s, 2×CH_3), 3.77(3H, s, CH_3O), 4.10(4H, q, J=7.2Hz, 2×CH_2O), 5.02(1H, s, CH), 5.66(1H, brs, NH), 6.76(2H, d, J=8.2Hz, ArH), 7.21(2H, d, J=8.2Hz, ArH); IR(KBr) ν: 3350, 2990, 1700,1650,1500,1380,1210,834,786,750cm^{-1}.

Compound(4e) ^{1}HNMR($CDCl_3$): δ:1.24(6H, t, J=7.2Hz, 2×CH_3), 2.33(6H, s, 2×CH_3), 4.10(4H, q, J=7.2Hz, 2×CH_2O), 5.02(1H, s, CH), 5.59(1H, brs, NH), 7.13(2H, d, J=8.2Hz, ArH), 7.23(2H, d, J=8.2Hz, ArH); IR(KBr) ν: 3358, 2987, 1695, 1651,1507,1489,1372,1210,1123,1090,1018,856, 786,755,695 cm^{-1}.

Compound(4g) ^{1}HNMR($CDCl_3$): δ: 1.24(6H, t, J=7.2Hz, 2×CH_3), 2.32(6H, s, 2×CH_3), 3.83(3H, s, OCH_3), 4.10(4H, q, J=7.2Hz, 2×CH_2O), 4.90(1H, s, CH), 5.48(1H, s, OH), 5.55(1H, brs, NH), 6.68(1H,

d, J=8.2Hz, ArH), 6.80(1H, dd, J=8.2Hz, 2.0Hz, ArH), 6.84(1H, d, J=2.0Hz, ArH); IR(KBr) ν: 3351, 2983,2953, 681,1653, 1598,1514,1489,1370,1303, 1272,1218,1160,1122,1095,1020,859,800, 753cm^{-1}.

Compound(4i) ^{1}HNMR($CDCl_3$): δ:1.24(6H, t, J=7.2Hz, 2×CH_3), 2.32(6H, s, 2×CH_3), 4.10(4H, q, J=7.2Hz, 2CH_2O), 5.02(1H, s, CH), 5.40(1H, s, OH), 5.49(1H, brs, NH), 6.69(2H, d, J=8.2Hz, ArH), 6.89(2H, d, J=8.2Hz, ArH); IR(KBr) ν: 3347, 2987, 2939,1660,1634,1511,1488,1369,1316,1227,1171, 1022, 856, 845, 761cm^{-1}.

Compound(4j) ^{1}HNMR($CDCl_3$): δ: 1.24(6H, t, J=7.2Hz, 2×CH_3), 2.28(6H, s, 2×CH_3), 4.10(4H, q, J=7.2Hz, 2× CH_2O), 5.02(1H, s, CH), 5.59(1H, brs, NH), 7.39(1H, dd, J=8.2Hz, ArH) 7.49-7.54(2H, m, ArH), 7.70(1H, dd, J=8.2Hz, ArH); IR(KBr) ν: 3330, 3092,2977,2931,1695,1678,1528,1489,1354,1308, 1280,1212,1100,1020,859,830,785,715cm^{-1}.

Compound(4l) ^{1}HNMR($CDCl_3$): δ: 2.32(6H, s, 2×CH_3), 3.64(6H, s, 2×CH_3OCO), 5.02(1H, s, CH), 5.60(1H, brs, NH), 7.10-7.29(5H, m, ArH); IR(KBr) ν: 3343,3081,3026, 2950,1699,1649,768,703,680 cm^{-1}.

Compound 4n) ^{1}HNMR($CDCl_3$): δ: 2.32(6H, s, 2×CH_3), 3.64(6H, s, 2×CH_3OCO), 5.02(1H, s, CH), 5.40(1H, s, OH), 5.49(1H, brs, NH), 6.69(2H, d, J=8.2Hz, ArH), 6.89(2H, d, J=8.2Hz, ArH); IR(KBr) ν: 3347,3001,2951,1680,1654,1589,1022,856,845, 761cm^{-1}.

Compound(4p) ^{1}HNMR($CDCl_3$): δ: 2.27(3H, s, CH_3), 2.32(6H, s, 2×CH_3), 3.64(6H, s, 2×CH_3OCO), 5.02(1H, s, CH), 5.60(1H, brs, NH), 7.10(2H, d, J=7.2Hz, ArH), 7.17(2H, d, J=7.2Hz, ArH); IR(KBr) ν: 3314,3105,2942,1697,1655, 1495cm^{-1}.

Compound(4q) ^{1}HNMR($CDCl_3$): δ: 2.36(6H, s, 2×CH_3), 3.64(6H, s, 2×CH_3OCO), 5.10(1H, s, CH), 5.65(1H, brs, NH), 7.38(1H, t, J=8.0Hz, ArH), 7.65(1H, d, J=8.0Hz, ArH), 8.01(1H, d, J=8.0Hz, ArH), 8.14(1H, s, ArH). IR(KBr) ν: 3358, 3003, 2960, 1705,1651,1527,1090,1018, 856, 786,755,695cm^{-1}.

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