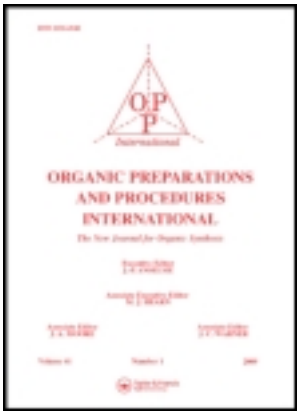

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

PEG400-Lithium Carbonate Catalyzed Synthesis of 1,4-Dihydropyridines under Solvent-free Conditions

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Version of record first published: 30 Mar 2012.

To cite this article: B. Palakshi Reddy, K. Rajesh & V. Vijayakumar (2012): PEG400-Lithium Carbonate Catalyzed Synthesis of 1,4-Dihydropyridines under Solvent-free Conditions, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 44:2, 153-158

To link to this article: http://dx.doi.org/10.1080/00304948.2012.657562

Organic Preparations and Procedures International, 44:153–158, 2012

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2012.657562

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Hantzsch 1,4-dihydropyridines (1,4-DHPs) are useful as vasodilators, bronchodilator and anti-hypertensive, hepta-protective, anti-tumor, anti-mutagenic, gero-protective and anti-diabetic agents.[1] *Nifedipine*, *nitrendipine* and *nimodipine* for example have found commercial utility as calcium channel blockers.[2–4] A number of DHP calcium antagonists have been introduced for the treatment of congestive heart failure[5,6] some DHPs have been introduced as a neuroprotectant and cognition enhancer. In addition, a number of DHPs with platelet anti-aggregatory activity have also been discovered.[7]

1,4-DHPs have been synthesized by the Hantzsch reaction[8] which involves the cyclocondensation of aldehydes with compounds containing methylene group activated by carbonyl groups (ethyl or methyl acetoacetate, acetylacetone) and ammonium acetate/ammonia/primary amine[9] under long reflux in acetic acid or ethanol. Recently, several improved procedures for the synthesis of 1,4-DHPs have been reported by using CAN,[10] silica gel/$NaHSO_4$,[11] $Sc(OTf)_3$,[12] microwave-assisted synthesis with catalysts, ionic liquids, and reflux at high temperature.[13–19] However, there are several drawbacks associated with the reported methodologies. Reactions carried out under solvent-free conditions offer several advantages such as formation of cleaner products, simpler work-up, enhanced selectivity and pronounced reaction rates. Polyethylene-glycols (PEG*s*) are known to function as efficient phase-transfer catalysts in a variety of organic reactions.[20,21] In addition, PEGs are non-toxic, thermally stable and inexpensive compared to conventional phase-transfer catalysts such as crown ethers or quaternary ammonium salts. We now report a solvent-free synthesis of 1,4-dihydropyridines using a catalytic amount of anhydrous lithium carbonate and PEG400.

The 1,4-DHPs were synthesized from various aldehydes (including acetaldehye **6a**), ethyl and methyl acetoacetate, acetylacetone and ammonium acetate (in 1:2:1 molar ratio) in solution as well as under solvent-free conditions using Li_2CO_3 and PEG400. This

Submitted June 24, 2011.
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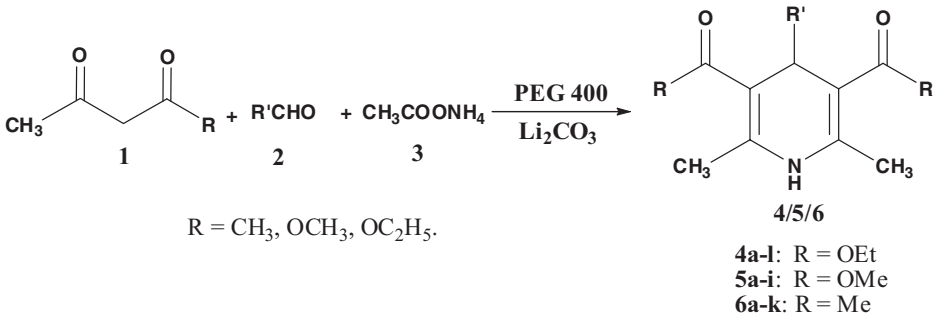

R = CH_3, OCH_3, OC_2H_5.

4a-l: R = OEt
5a-i: R = OMe
6a-k: R = Me

Scheme 1

reaction was optimized by varying the solvent, temperature, time, concentration of Li_2CO_3, concentration of PEG400 and the results clearly revealed that the efficiency and the yield of the reactions are much less compared to the solvent-free conditions (*Table 1*). The use of 5% of Li_2CO_3 afforded better yields under solvent-free conditions with 5% of PEG400 at 80°C, while less than 5% of PEG400 is inefficient and higher percentages led only to marginally increased yields. In general, the reaction proceeded in good yields (*Table 2*). Some of the compounds were characterized by IR, NMR and Mass. Spectral data for **6i** is given in *Table 3* since it is not available in literature. Compound **6g** was subjected to single crystal X-ray diffraction studies (*Figure 1*) and the data has been deposited on CCDC [R indices (all data) R1 = 0.0835, wR2 = 0.2689] since it has not been reported in literature.

Table 1
Synthesis of 1,4-DHPS with Li_2CO_3 Catalyst in Various Solvents[a]

Entry	Solvent	Temperature	Li_2CO_3 (mol%)	PEG400 (mol%)	Time (min)	Yield %
1	Acetonitrile	RT	5%	5%	180	60
2	DMF	RT	5%	5%	150	53
3	Benzene	RT	5%	5%	130	74
4	Dichloromethane	RT	5%	5%	240	80
5	Ethanol	RT	5%	5%	90	81
6	Toluene	RT	5%	5%	100	78
7	Solvent-Free	RT	5%	5%	240	84
8	Solvent-Free	80°C	1%	5%	150	82
9	Solvent-Free	80°C	5%	5%	90	88
10	Solvent-Free	80°C	5%	1%	120	78
11	Solvent-Free	80°C	5%	10%	90	89
12	Solvent-Free	80°C	10%	5%	90	90

[a]Reaction conditions: benzaldehyde (5 mmol), ethyl acetoacetate (10 mmol), ammoniumacetate (5 mmol).

Table 2
Synthesis of 1,4-Dihydropyridines using PEG400-Li_2CO_3 at 80°C[a]

Entry	R′	R	Time (min)	Yield[c] (%)	mp (°C)
4a	C_6H_5	OEt	90	88	158–160 (158–160)[23]
4b	4-ClC_6H_4	OEt	62	90	145–146 (144–146)[23]
4c	4-$CH_3OC_6H_4$	OEt	90	88	153–155 (158–160)[23]
4d	3-$NO_2C_6H_4$	OEt	85	89	165–167 (162–164)[23]
4e	4-Pyridyl	OEt	72	88	181–182 (178–180)[25]
4f	3-Pyridyl	OEt	76	85	188–190 (190–192)[25]
4g	4-BrC_6H_4	OEt	65	91	162–164 (162–164)[26]
4h	2-Thienyl	OEt	85	89	172–173 (171–173)[23]
4i	4-$CH_3C_6H_4$	OEt	82	85	136–137 (135–138)[22]
4j	4-HOC_6H_4	OEt	72	93	227–229 (227–228)[24]
4k	3-HOC_6H_4	OEt	80	89	172–175 (180–182)[25]
4l	2,5-$Me_2C_6H_3$	OEt	91	86	147–148 (146–147)[27]
5a	C_6H_5	OMe	82	84	198–200 (197–198)[28]
5b	3-$NO_2C_6H_4$	OMe	80	90	210–212 (210–212)[31]
5c	4-$CH_3C_6H_4$	OMe	90	84	174–176 (174–176)[31]
5d	2-ClC_6H_4	OMe	84	88	185–186 (185–186)[28]
5e	4-$CH_3OC_6H_4$	OMe	91	88	173–174 (173–174)[28]
5f	2-Furyl	OMe	83	89	194–197 (195–196)[30]
5g	2-Thienyl	OMe	87	91	201–203 (200–202)[29]
5h	4-HOC_6H_4	OMe	60	92	198–199 (198–199)[28]
5i	4-ClC_6H_4	OMe	75	89	196–198 (195–196)[28]
6a	CH_3	Me	86	82	155–156 (150–152)[32]
6b	3-$NO_2C_6H_4$	Me	80	91	210–211 (210–211)[32]
6c	2-$NO_2C_6H_4$	Me	86	88	195–197 (195–197)[34]
6d	2-Furyl	Me	85	87	159–160 (158–159)[34]
6e	2-Thienyl	Me	86	91	169–172 (171)[33]
6f	3-Pyridyl	Me	90	88	262–263 (262–263)[35]
6g	3-ClC_6H_4	Me	70	90	222–224 (221–222)[34]
6h	3-$CH_3OC_6H_4$	Me	90	92	200–201 (196–198)[32]
6i	4-$C_2H_5C_6H_4$	Me	95	90	179–181 (see *Table 3*)
6j	4-Pyridyl	Me	88	89	245–246 (245–246)[36]
6k	4-BrC_6H_4	Me	70	92	109–111 (109–111)[37]

[a]Reaction conditions: aldehyde (5 mmol), ethyl/methyl acetoacetate/acetylacetone (10 mmol), ammonium acetate (5 mmol), Li_2CO_3 (0.25 mmol, 0.026 g), PEG400 (0.25 mmol, 0.1 g) at 80°C.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using Thermo Nicolet AVATAR 330 equipped with DTGS detector and compared with the literature. ^{1}H NMR spectrum was obtained at 300 MHz using Bruker AMX-300 instrument at room temperature in $CDCl_3$ using TMS as an internal reference. Mass spectra

Table 3
Spectral Data for Product **6i**[a]

Cmpd	mp. (°C)	Ir (cm^{-1})	^{1}H NMR (δ, ppm)	Mass (HRMS)
6i	179–181	3343 (NH), 1689 (C=O).	0.88 (t, 3H, J = 7.05 Hz), 1.89 (s, 12H), 2.34 (m, 2H, J = 7.00 Hz), 4.81 (s, 1H), 6.63 (d, *m*, 2H, J = 7.8 Hz), 7.78 (d, *o*, 2H, J = 7.5 Hz).	297.1565

[a]*Anal.* Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.78; H, 7.86; N, 4.65.

were acquired using HRMS. All the reagents were purchased from Aldrich and SD-Fine Chemicals. Liquids were purified by distillation. The reaction was monitored using TLC silica-gel coated plates. The single crystal X-ray diffraction data was collected on a Bruker Smart Apex CCD diffractometer using graphite monochromated MoKα radiation (k = 0.71073 A°) at 293(2) K. A crystal with dimensions of 0.4 mm, 0.2 mm, 0.2 mm was used. The collected data were reduced using SAINT. The structure was solved by direct methods with the program **SHELXS-97** and refined by the full matrix least squares on F^2 with **SHELTL-97**. The graphics tool was DIAMOND Version 3.0. All crystallographic data for 3,5-diacetyl-2,6-dimethyl-1,4-dihydro-4-(3-chlorophenyl)-3,5-pyridine are deposited with Cambridge Crystallographic Data Centre (CCDC-683002). The data can be obtained free

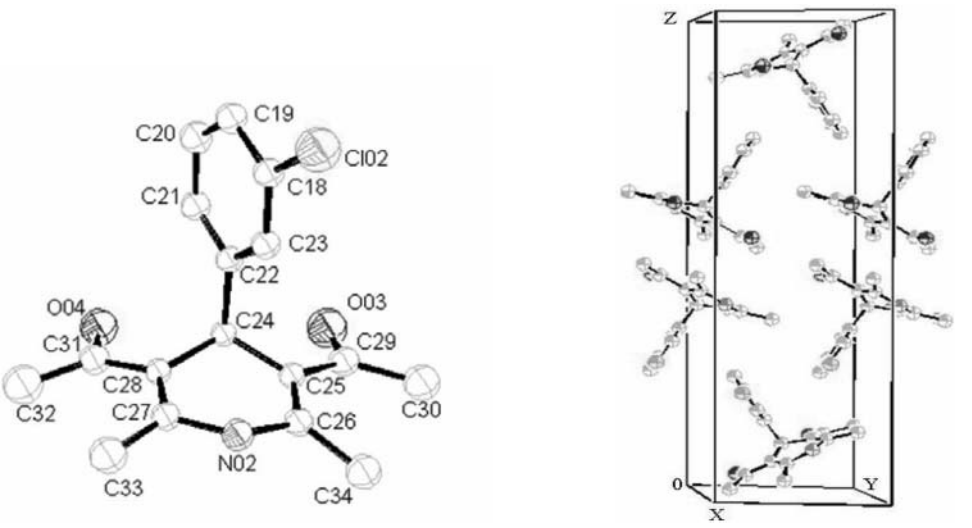

Figure 1
Ortep diagram of 3,5-Diacetyl-2,6-dimethyl-1,4-dihydro-4-(3-chlorophenyl)-3,5-pyridine (6 g) and Packing of the Molecules in the Unit cell (6 g).

of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0) 1223-336033; e-mail: deposit@ccdc.cam. ac.uk

General Procedure for the Synthesis of 1,4-DHPs

A mixture of aldehyde (0.01 mol), ethyl acetoacetate/methyl acetoacetate/acetylacetone (0.02 mol) and ammonium acetate (0.77 g, 0.01 mol), anhydrous Li_2CO_3 (0.026 g, 0.25 mmol) and PEG400 (0.1 g, 0.25 mmol) was vigorously stirred and heated at 80°C for the time as mentioned in *Table 2*. After the completion of the reaction [monitored through TLC (pet. ether/ethyl acetate 3:2)], the mixture was cooled to room temperature. Ice cold water was added to reaction mixture which was extracted with ethyl acetate (2 × 10 mL), dried over anhydrous sodium sulfate and then evaporated *in vacuo* to afford the products which were recrystallized from ethanol.

Acknowledgements

The authors thank VIT University for providing the basic facilities and the NMR Research Centre, Indian Institute of Science, Bangalore and AIIMS, New Delhi for providing NMR and single crystal diffraction facilities respectively.

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