



Indion 860 catalyzed green synthesis of 2,6-unsubstituted dihydropyridines in PEG-400

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ABSTRACT

Indion 860 mediated MCR of anilines, aldehydes and ethyl-3,3-diethoxypropionate in PEG-400 afforded 2,6-unsubstituted dihydropyridines depending on the nature of anilines employed. A variety of dihydropyridines were prepared by using this green methodology in good yields and Indion 860 was found to be an inexpensive and reusable catalyst. © 2015 Trade Science Inc. - INDIA

KEYWORDS

Multi component reactions;
Green synthesis;
Indion 860;
Dihydropyridine;
PEG-400.

INTRODUCTION

Multi Component Reactions (MCRs) have been gradually gaining importance in synthetic organic chemistry^[1]. These processes are great interest in diversity oriented synthesis, especially indiscovery of new chemical entities (NCEs) required by pharmaceutical and agrochemical industries. Dihydropyridines (DHP) derivatives are very attractive heterocycles in view of its vast application in medicinal chemistry and pharmacology due to their wide range of biological activities^[2, 3]. This is exemplified by a range of commonly used drugs such as Nifedipine (A), Amlodipine (B) and Nicardipine (C) and others, which have been found to be useful as calcium channel blockers^[4], and are used most frequently as cardiovascular agents for the treatment of hypertension (Figure 1)^[5].

One of the commonly used method for the synthesis of dihydropyridine is Hantzsch method, which involves cyclocondensation of aldehyde, ester and aniline in acetic acid at room temperature or refluxing in alcohol^[6] and many efficient synthetic methods for the preparation of these compounds have been reported^[7-9]. However, this method involves long reaction time, harsh reaction conditions, and gives products in low yields for along time. Recently several elegant and efficient methods have been reported for the synthesis of 1,4-DHPs^[10-13], however, many of them involves the use of expensive and environmentally harmful metal precursors and catalysts or hazardous organic solvents that are not environmentally compatible and produce a large amount of waste. In view of this, there is necessary to develop a general, efficient and green method for constructing functionalized dihydropyridine frame work from

readily available starting materials under mild conditions.

The catalyst, Indion 860 resin is a commercially available green reagent which can be recovered, activated and reused. It can be easily handled and removed by filtration from the reaction mixture^[14, 15]. Thus the process is environmentally benign. To the best of our knowledge, for the synthesis of dihydropyridines, Indion 860 catalysed reaction was not explored. Herein, we wish to describe a new efficient and eco-friendly method to synthesis of dihydropyridines by Indion 860 catalyzed reaction of aniline (1), aldehydes (2) and ethyl-3,3-diethoxypropionate (3) (Scheme-1) in presence of PEG-400 with excellent yield.

EXPERIMENTAL SECTION

Melting points are uncorrected and were obtained in open capillary tubes in sulphuric acid bath. TLC checking was done on plastic sheets coated with silica gel GF-254 (Merck). Flash column chromatography was performed over silica gel (mesh 230–400) and hexane/ethyl acetate combination was used as the eluent. ¹H NMR and ¹³C NMR spectra were determined in DMSO-*d*₆ solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS), $\delta = 0.00$) as internal standard and expressed in ppm.

Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. IR spectra were recorded using Perkin-Elmer model 1700 instrument in KBr phase. MS spectra were obtained on a mass spectrometer.

General procedure for the preparation of dihydropyridine (4)

A mixture of amine (1) (1.0 mmol), aldehyde (2) (1.1 mmol), ethyl 3,3-diethoxypropionate (3) (2.2 mmol) and Indion 860 (20 mol%) in PEG-400 (5 ml) was stirred at 95 °C for 6-8 hr. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and filtered. The filtrate was extracted with EtOAc. The organic layers were collected, combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The structure of the products was confirmed by comparison of their m.p., IR and ¹H NMR and mass data with authentic samples prepared by the literature methods.

Diethyl 4-(4-bromophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4a)^[12]

Pale yellow solid; mp 203-205 °C; ¹H NMR (CDCl₃, 400 MHz) δ 1.19 (t, *J* = 7.2 Hz, 6H), 3.86 (s, 3H), 4.02-4.18 (m, 4H), 4.90 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 3H), 7.18-7.28 (m, 3H), 7.37-7.39 (m, 2H), 7.56-7.58 (m, 2H).

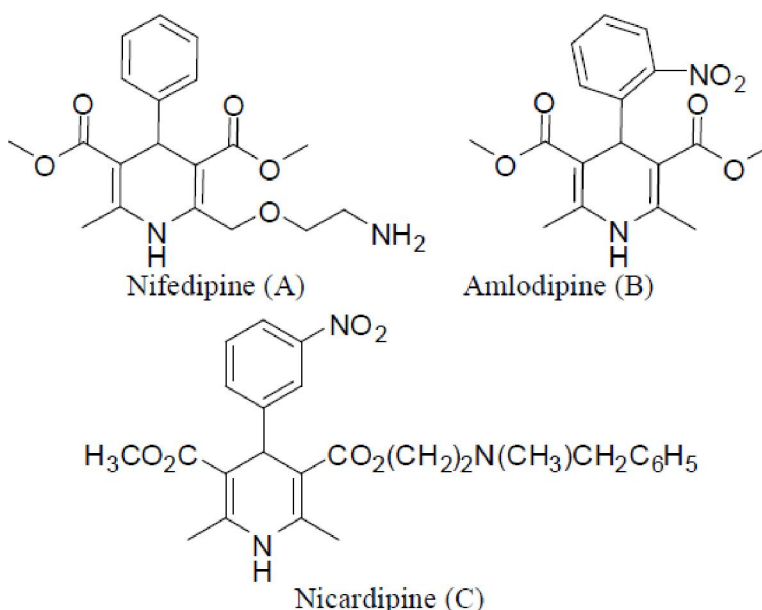
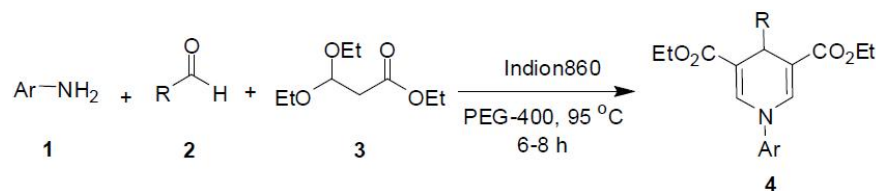


Figure 1 : 1,4-Dihydropyridine based drugs

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Scheme 1 : Indion 860 catalyzed synthesis of dihydropyridine in PEG-400

Diethyl 1-(4-methoxyphenyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4b)^[12]

Off white solid; mp 157-158 °C; ¹H NMR (CDCl₃, 400 MHz) δ 1.15 (t, *J* = 6.8 Hz, 6H), 3.80 (s, 3H), 3.98-4.10 (m, 4H), 4.98 (s, 1H), 6.95-6.98 (m, 2H), 7.16-7.38 (m, 5H), 7.35-7.38 (m, 2H), 7.59-7.63 (m, 2H).

Diethyl 4-(3-bromophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c)^[13]

Yellow solid; mp 191-194 °C; ¹H NMR (CDCl₃, 400 MHz) δ 1.22-1.25 (t, *J* = 6.8 Hz, 6H), 3.86 (s, 3H), 4.02-4.19 (m, 4H), 4.89 (s, 1H), 6.94-6.96 (m, 2H), 7.15-7.24 (m, 3H), 7.24-7.28 (m, 2H), 7.50 (s, 1H), 7.55 (s, 2H).

Diethyl 4-(4-fluorophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d)^[13]

White solid; mp 169-171 °C; ¹H NMR (CDCl₃, 400 MHz) δ 1.18-1.21 (t, *J* = 7.2 Hz, 6H), 3.88 (s, 3H), 3.99-4.15 (m, 4H), 4.99 (s, 1H), 6.92-6.97 (m, 4H), 7.18-7.28 (m, 4H), 7.56-7.58 (m, 2H).

4-(4-Cyanophenyl)-1,4-dihydro-1-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (4e)^[12]

Colour less semi solid; mp 156-158 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.18-1.21 (m, 6H), 3.72 (s, 3H), 4.02-4.10 (m, 4H), 5.01 (s, 1H), 7.03 (d, *J* = 8.6 Hz), 7.22 (d, *J* = 8.2 Hz), 7.52 (d, *J* = 7.9 Hz, 2H), 7.58-7.62 (m, 2H), 7.55 (s, 2H).

Diethyl 4-(4-chlorophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4f)^[12]

Yellow semi solid, ¹H NMR (400 MHz, CDCl₃) δ 1.17 (t, *J* = 7.8 Hz, 3H), 1.18 (t, *J* = 7.8 Hz, 3H), 3.78 (s, 3H), 4.06-4.13 (m, 4H), 4.89 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.45 (s, 2H).

Diethyl 4-(3-bromophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4g)^[13]

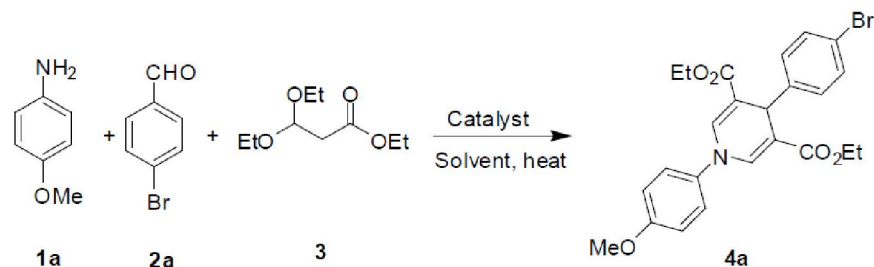
Off white solid; mp 210-212 °C; ¹H NMR (CDCl₃, 400 MHz) δ 1.18 (t, *J* = 6.8 Hz, 6H), 3.84 (s, 3H), 4.05-4.15 (m, 4H), 4.95 (s, 1H), 6.90-7.05 (m, 3H), 7.22-7.35 (m, 3H), 7.35-7.41 (m, 2H), 7.52-7.58 (m, 2H).

Diethyl 1-(2,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4i)^[13]

Brown oil; ¹H NMR (CDCl₃, 400 MHz) δ 1.21 (t, *J* = 7.8 Hz, 6H), 3.81 (s, 3H), 3.91 (s, 3H), 3.99-4.15 (m, 4H), 4.90 (s, 1H), 6.72-6.85 (m, 2H), 6.92-7.04 (m, 4H), 7.29-7.39 (m, 4H).

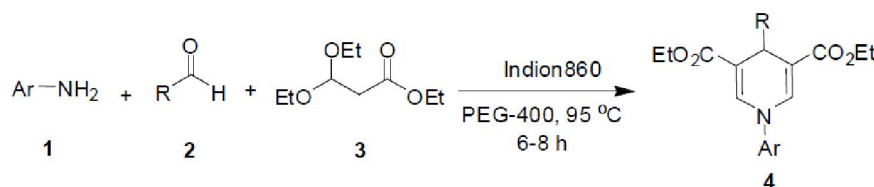
RESULTS AND DISCUSSION

At first the reactions with aniline (1a), aldehyde (2a) and 3,3-diethoxypropionate (3a) were carried out using various catalyst, solvent and temperatures and the results are summarized in TABLE 1. When the reaction was carried in the presence of Amberlite at 95 °C, the product 4a was isolated in 15% yield (entry 1, TABLE 1). When the *p*-TSA was used as catalyst at 95 °C in PEG-400 for 6 hr gave 4a was 35% yield (entry 2, TABLE 1). Surprisingly, when *p*-TSA was replaced by Indion-860, it provides 91 % yield (entry 3, TABLE 1). The use of other catalyst such as FeCl₃ and SiO₂ were used, 4a was obtained in low yields (entry 4 and 5, TABLE 1). The use of other solvents like ethanol, 1,4-Dioxane and water was found to be less effective (entry 6-8, TABLE 1), when PEG-400 (entry 3, TABLE 1) was found to be the most effective solvent. The reaction was then carried out with different temperatures (entry 9 and 10, TABLE 1), 95 °C was found to be the most effective temperature and reaction will complete with in 6 hr. To test the recyclability of the catalyst used Indion 860 was recovered by simple filtration and reused in the same reaction when 4a was isolated without significant loss of its yield.

TABLE 1 : Effect of reaction conditions on the MCR of 1a, 2a and 3^a

S. No	Catalyst	Solvent	T °C	Yield (%) ^b
1	Amberlite (20 mol%)	PEG-400	95	15
2	<i>p</i> -TSA (2.5 mol%)	PEG-400	95	35
3	Indion 860 (20 mol%)	PEG-400	95	91 (90, 88, 86, 84) ^c
4	FeCl ₃ (2.5 mol%)	PEG-400	95	32
5	SiO ₂ (20 mol%)	PEG-400	95	trace
6	Indion 860 (20 mol%)	ethanol	65	20
7	Indion 860 (20 mol%)	1,4-Dioxane	85	33
8	Indion 860 (20 mol%)	Water	95	50
9	Indion860 (20 mol%)	PEG-400	50	30
10	Indion 860 (20 mol%)	PEG-400	115	70

^a All the reactions were carried out using 1a (1.0 eq), 2a (1.1 eq) and 3 (2.2 eq) in a solvent for 6 h. ^b Isolated yield. ^c The catalyst was reused for an additional five runs and the figures within parentheses indicate the corresponding yield for each run.

TABLE 2 : Indion 860 catalysed synthesis of 1,4-dihydropyridines in PEG-400 (4)^a

Entry	Amine (1) Ar=	Aldehyde (2) R=	Dihydropyridine (4)	Time (h)	Yield (%) ^b
1	4-MeOC ₆ H ₄	4-BrC ₆ H ₄	4a	6	85
2	4-MeOC ₆ H ₄	C ₆ H ₅	4b	7	83
3	4-MeOC ₆ H ₄	3-BrC ₆ H ₄	4c	7	81
4	4-MeOC ₆ H ₄	4-FC ₆ H ₄	4d	6	85
5	4-MeOC ₆ H ₄	4-CNC ₆ H ₄	4e	7	80
6	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	4f	7	86
7	4-MeOC ₆ H ₄	3-BrC ₆ H ₄	4g	8	88
8	4-MeOC ₆ H ₄	3-ClC ₆ H ₄	4h	6	88
9	2-MeOC ₆ H ₄	4-MeOC ₆ H ₄	4i	8	72
10	2-MeOC ₆ H ₄	C ₆ H ₅	4j	6	80
11	2-MeOC ₆ H ₄	4-BrC ₆ H ₄	4k	7	88
12	2-MeOC ₆ H ₄		4l	8	60

^aAll the reactions were carried out using amine 1 (1.0 mmol), aldehyde 2 (1.1 mmol) and ethyl 3,3-diethoxypropionate 3 (2.22 mmol) and Indion 860 (20 mol%) in PEG-400 (5 ml) at 95 °C. ^bIsolated yield.

The yield of 4a was found to be 90, 88, 86 and 84 after 1st, 2nd, 3rd and 4th recovery and reuse of the catalyst. Based on these observations it was evident that a combination of Indion 860 in PEG-400 was

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optimal for the preparation of 4a.

To expand the scope of this reaction, a range of anilines (1) and aldehydes (2) were employed under the optimized reaction conditions and results are summarized in TABLE 2. Various electron-donating and withdrawing groups present on the aryl ring of aldehydes were well tolerated. The use of ethyl 2-oxoacetate (2i) was also successful and afforded the desired dihydropyridine in good yield.

CONCLUSION

In summary, a green, efficient and versatile method has been developed for the facile and one-pot synthesis of dihydropyridines (4) catalyzed by reusable and inexpensive Indion 860. In addition, the present investigation provides 1,4-DHPs in good to average yields within shorter reaction time. Hence this methodology is a green protocol to reduce the use of organic solvents and reusable and inexpensive Indion 860 catalyst.

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