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Synthesis, utility and medicinal importance of 1,2-& 1,4-dihydropyridines

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Dihydropyridine (DHP) is among the most beneficial scaffolds that have revolutionised pharmaceutical research with unprecedented biological properties. Over the years, metamorphosis of easily accessible 1,2- and 1,4-dihydropyridine (1,4-DHP) intermediates by synthetic chemists has generated several drug molecules and natural products such as alkaloids. The 1,4-dihydropyridine (1,4-DHP) moiety itself is the main fulcrum of several approved drugs. The present review aims to collate the literature of 1,2- and the 1,4-DHPs relevant to synthetic and medicinal chemists. We will describe various methodologies that have been used for the synthesis of this class of compounds, including the strategies which can furnish enantiopure DHPs, either by asymmetric synthesis or by chiral resolution. We will also elaborate the significance of DHPs towards the synthesis of natural products of medicinal merit.

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1. Introduction

Arthur Hantzsch added one of the most valuable scaffolds to the toolbox of medicinal chemists, reporting the synthesis of dihydropyridine (DHP) in 1882. Among five possible regioisomers only 1,2- and the 1,4-DHP (Fig. 1) have gained significant attention. The 1,4-DHP scaffold has served as a nucleus for several blockbuster drugs such as nifedipine and amlodipine.¹ Close resemblance to nicotinamine adenine dinucleotide (NADH) coenzyme, which has an important role in biological

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^bDepartment of Chemistry, Kirori Mal College, University of Delhi, Delhi-110007, India. E-mail: chem.sunil@gmail.com oxidation–reduction reactions, has made the 1,4-DHP core even more lucrative. Perhaps less studied in the past, the potential of 1,2-dihydropyridines has recently been explored as a critical scaffold for the synthesis of alkaloids and other drugs. 1,2-DHPs are now popular as a precursor for the synthesis of the 2-azabicyclo[2.2.2]octanes (isoquinuclidines) ring system present in alkaloids, ibogaine and dioscorine. The anti-influenza drug, oseltamivir phosphate (Tamiflu), is also synthesised from 1,2-DHP *via* an isoquinuclidine intermediate (Fig. 1).²

Recently, we reviewed reactions of 1,2- and the 1,4-dihydropyridines.^{3a} The present manuscript aims to highlight the importance of 1,2- and the 1,4-dihydropyridines relevant to both synthetic and medicinal chemists. We will describe various methodologies that have been used for the synthesis of this class of compounds. We then focus on strategies which can



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Fig. 1 Structures of 1,2-DHP, Hantzsch 1,4-DHP, NADH/NADPH and some medicinally important compounds/cores accessible from DHPs.

furnish enantiopure DHPs, either by asymmetric synthesis or by chiral resolution. We will also spotlight the utility of DHPs towards the synthesis of natural products of medicinal merit. In



Scheme 1 Synthesis of 1,2- and 1,4-dihydropyridines 1 and 2 by reduction of pyridine using NaBH $_4$.



Scheme 2 Dihydropyridine 4 generated from precursor chromium complex 3.

2002, Rodolfo Lavilla compiled the synthesis, reactivity, and applications of DHPs in medicinal chemistry.^{3b}

2. Synthesis of dihydropyridines

Substituted dihydropyridine are usually prepared either by the cyclization reactions (Hantzsch ring closure) or by reduction of pyridinium ions. The reviews by Eisner and Kuthan,^{3e} and Stout and Meyers^{3d} covers the chemistry of DHPs from early development till 1982. Beside these, R. Lavilla^{3b} in 2002 and Silva, *et al.*^{3e} in 2013 also compiled the literature for the synthesis of DHPs.

2.1. Synthesis of 1,2-dihydropyridine

In 1972, Fowler *et al.*⁴ reported the synthesis of both *N*-carbomethoxy-1,2- and 1,4-dihydropyridine by treating a mixture of pyridine and sodium borohydride with methyl chloroformate in various organic solvents like, ether, glyme, THF, methanol and water. They observed that reaction in THF at 0 °C gave a mixture of dihydropyridines containing about 35–40% of 1,4-dihydropyridine along with the 1,2-dihydropyridine. However, the amount of 1,4-isomer can be reduced to 2–4% by performing the reaction in methanol at -70 °C giving 1,2-DHP in 86–88% yields (Scheme 1).

Kutney, *et al.*⁵ have described the synthesis of novel and stable chromium complex of *N*-methyl-3-ethyl-1,2-



Scheme 3 Synthesis of N-substituted 1,2-dihydropyridines 10a-q

dihydropyridine. This metal carbonyl complex **3** has been used for the synthesis of essentially pure *N*-methyl-3-ethyl-1,2dihydropyridine **4**, which can be used as a precursor to synthesize a number of useful heterocyclic compounds such as **5** and **6** (Scheme 2).

Beeken, *et al.*⁶ have developed a synthetic methodology for the synthesis of 1,2-dihydropyridines **10a–g** *via* 2-azabicyclo [2.2.0]hex-5-ene **8** as a synthetic equivalent. The amine **8** was conveniently synthesized by methyl lithium mediated hydrolysis of carbamate derivative of 1,2-dihydropyridine 7 which in turn was photochemically synthesized from compound 1. Alkylation and acylation of amine 8 has lead to the formation of **9a-g** which were easily isolated. The alkylated/acylated analogues **9a-g** were converted into the corresponding 1,2dihydropyridines **10a-g** under thermal heating condition (Scheme 3).



Scheme 4 Synthesis of 1,2-dihydropyridines 14 and 15 from 3-ethyl pyridine 11.







Scheme 6 Asymmetric synthesis of 1-acyl- α -alkyl-1,2-dihydropyridines 25 and 26.

Further, Fowler *et al.* have successfully prepared dihydropyridines **14** and **15** from 3-ethyl pyridine **11** (Scheme 4). 3-Ethyl pyridine **11** was first converted into *N*-carboxymethyl amine **12** using ClCOOCH₃ and sodium borohydride, which on hydrolysis yield amine **13**. This method is significantly important as it can be applied to relatively more complex **1**,2-DHP structures which may serve as an intermediate for the synthesis of alkaloids, *e.g.* compound **15** is an intermediate in a biomimetic synthesis of *Strychnos* alkaloids.

Fowler, *et al.*⁷ has synthesized the 1,2-dihydropytidines 1, **21a–d** by the thermal cyclisation of hydroxamic acid esters **20**. Reaction of the hydroxamic acid ester **17** with 5-bromopenta-1,3-diene **16** gave the compound **18**. The removal of *t*-Boc protecting group from compound **18** followed by acylation with various acid chlorides gave the hydroxamic acid derivatives **20**. Evaporation of these hydroxamic acid derivatives through a hot tube gave the 1,2-dihydropyridines **1**, **21a–d** as the only isolable products in 32 to 58% yields (Scheme 5).

2-Substituted-1,2-dihydropyridine analogues are useful intermediate for the synthesis of natural products such as piperidine, indolizidine, quinolizidine and *cis*-decahydroquinoline alkaloids. Comins, *et al.*⁸ have reported the asymmetric synthesis of 2-substituted-1,2-dihydropyridines **25** & **26** from *N*-acyl pyridinium salt **24**, which was synthesized *via* the addition of 3-(triisopropylstannyl)pyridine **22** to an enantiopure chloroformate **23a–b** derived from (–)-8-(4-phenoxyphenyl)menthol or (–)-8-phenyl-menthol. The reaction of *N*-

Table T	synthesis of		25 25 810 20		
Entry	R*OCOCl	RMgX	Product	Yield%	de
1	23a	<i>n</i> -PrMgCl	25a	72	82
2	23b	n-PrMgCl	25b	81	78

25c

25d

25e

25f

25g

25h

81

58

71

85

87

86

n-HexMgCl

PhCH₂MgCl

p-MePhMgBr

VinylMgBr

PhMgCl

PhMgCl

23a

23a

23a

23a

23b

23a

3

4

5

6

7

8

acyl pyridinium salt **24** with different Grignard reagents followed by treatment of the reaction mixture with silica gel containing oxalic acid provided chiral 1,2-dihydropyridines **25** and **26** (Scheme 6, Table 1).



Scheme 8 Reduction of electron deficient pyridine 33: preparation of 1,2-dihydropyridines 34.

Table 2 Reduction of pyridine **33** by using method A or B and their alkylation^a

Entry	R-X	R	Method	Yield (%)
1	MeI	Ме	А	99
2	MeI	Ме	В	86
3	EtI	Et	Α	98
4	EtI	Et	В	78
5	iBuI	iBu	Α	93
6	Epibromohydrin	No.	В	84
7	Allyl-Br	Allyl ^c	Α	90
8	I(CH ₂) ₃ Cl	(CH ₂) ₃ Cl	Α	96
9	I(CH ₂) ₃ Cl	(CH ₂) ₃ Cl	В	96
10	$I(CH_2)_4Cl$	$(CH_2)_4Cl$	Α	99
11	$I(CH_2)_4Cl$	$(CH_2)_4Cl$	В	91
12	I(CH ₂) ₅ Cl	$(CH_2)_5Cl$	Α	97
13	$I(CH_2)_5Cl$	$(CH_2)_5Cl$	В	94

^{*a*} Method A: Na (3.5 equiv.), NH₃/THF, -78 °C, then R-X (3.5 equiv.), then NH₄Cl after 5-30 s (time delay depends upon the electrophile). Method B: Na (3.5 equiv.), naphthalene (5 equiv.), THF, -78 °C, then R-X (3.5 equiv.), then NH₄Cl after 5-30 s (time delay depends upon the electrophile). b = formed as a mixture of diastereomers. c = this compound will aromatize in approximately 24 h at room temperature and should be stored in the freezer.



91

76

90

89

84

92

Scheme 7 A highly enantioselective synthesis of 1,2-dihydropyridines 32a-b.

The presence of the chiral auxiliary in **25** may find application in the several transformations. Another asymmetric synthesis was developed for the synthesis of 1,2-dihydropyridines as shown in Scheme 7. The chiral salt **27** prepared *in situ* from 4-methoxy-3-



Scheme 9 Regioselective synthesis of 1,2-dihydropyridine.



Scheme 10 1,2-Dihydropyridine via [3 + 3] cycloaddition reaction.



Scheme 11 Indium catalysed synthesis of 1,2-dihydropyridine.



Scheme 12 Vinylogous imino-aldol reaction with vinyloxiranes: synthesis if 1,2-dihydropyridines.

(triisopropylsilyl)pyridine and (–)-8-phenylmethyl chloroformate, was treated with Grignard reagent (RMgX) to give tetrahydropyridone **28a–b** in high yield and high diastereomeric excess (de). The chiral auxiliary and the triisopropyl silyl groups were removed from purified diastereomers **28** with sodium methoxide/methanol and oxalic acid to give enantiopure dihydropyridones **29a** (88% yield) and **29b** (81% yield) *via* one pot reaction. Deprotonation of **29** with *n*-BuLi and addition of benzyl chloroformate provided **30** in almost quantitative yield. Reduction of **30** to alcohols and subsequent dehydration gave the desired enantiomerically pure 1-(benzyloxycarbonyl)-1,2-dihydropyridine **32a** and **32b** in 58 and 74% yields, respectively (Scheme 7).

Donohoe, *et al.*⁹ has used Birch conditions or sodium naphthalene in THF for the partial reduction of electron deficient pyridines for the synthesis of 1,2-dihydropyridines **34**. Reductive alkylation of electron deficient pyridine diester **33** under Birch type conditions (Scheme 8, method A, quenching the reaction with an electrophile followed by a proton source) gave excellent yield of the corresponding monoalkylated dihydropyridine **34**. The partial reduction using sodium and naphthalene in THF (Scheme 8, method B) was also accomplished, thus avoiding the use of liquid ammonia. Moreover, both sets of reducing conditions were compatible with a range of electrophiles (Table 2).

Palacios, *et al.*¹⁰ has reported the synthesis of 1,2-dihydropyridine 37 using enamines 35 and 2-azadienes 36 (readily prepared by aza-Wittig reactions). The compounds and 36 under reflux in toluene form a broad variety of substituted dihydropyridines 37 in a regiospecific manner (Scheme 9).

Vinylogous amides **38** undergo [3 + 3] cycloaddition reaction with α , β -unsaturated iminium ions **39** to yield 1,2-dihydropyridines **40**. Intramolecular and stereoselective versions of this process have been successfully developed (Scheme 10).¹¹

Loh, *et al.*¹² has reported the indium-promoted allylations of *N*-acetylpyridinium salt **41** with allyl bromide **42** in DMF, to furnish 1,2-dihydropyridines **43** regioselectively in good yields (Scheme 11).

Brunner, *et al.*¹³ has synthesized the functionalized 1,2dihydropyridine in moderate to good yield by using vinyloxiranes as dienolates in imino-aldol reactions. Under the optimized reaction condition the reaction of vinylepoxide 44 (1.5 equiv.) with benzhydril protected aldimine 45 (1.0 equiv.) in the presence of catalytic amount of Sc(OTf)₃ (15.0 mmol) lead to the formation of stable 1,2-dihydropyridine 46 in upto 63% yield (Scheme 12). Further it has been illustrated by the author



Scheme 13 Pt(II) catalyzed synthesis of 1,2-dihydropyridines.

that the reaction proceeds *via* the vinylogous imino-aldol type reaction.

Motamed, *et al.*¹⁴ has reported the first Pt(π) catalyzed cycloisomerisation of aziridinyl propargylic esters **49a-i** to afford 1,2-dihydropyridines **50a-i** (Scheme 13). The aziridinyl propargylic ester substrates (Table 3) were prepared by acylation of the corresponding aziridine propargylic alcohols **48**, which were synthesized from aziridinyl aldehyde **47** *via* a highly diastereoselective (dr > 95%) 1,2-addition of the corresponding alkyllithium or Grignard reagent. The aziridinyl propargylic esters **49a-i** on cycloisomerisation using Pt(π) catalysis (10 mol% of PtCl₂, 0.2 M in toluene, 100 °C, 3 h) afforded the corresponding 1,2-DHP products **50a-i** in moderate to good yields (Table 3).

To explore the scope of the substrates that participate in the reaction, other substituents at the aziridine nitrogen were explored. The *N*-acyl substrates **49j-m** (Scheme 14) were

subjected to the $Pt(\pi)$ catalyzed reaction to afford the 1,2-dihydropyridines **50j-m** in 65–74% yield along with the another heterocycle **51a-d** as by product, which were not isolated.

Hodgson, *et al.*¹⁵ have developed a new methodology of radical deoxygenation process on 3-azatricyclo[$2.2.1.0^{2,6}$] heptan-5-ols **53** using tributyltin hydride to afford the 1,2-dihydropyridines. 3-Azatricyclo[$2.2.1.0^{2,6}$]heptan-5-ols **54a-b** were synthesized from the corresponding epoxide **52** (readily available from cycloaddition of the *N*-Boc pyrrole and tosyl ethyne, followed by the epoxidation of the resulting bicyclic diene), which on radical deoxygenation (*via* the xanthate) using Bu₃SnH (2.0 equiv.) gave the 1,2-dihydropyridines **54a-b** in 37 and 10% yields, respectively (Scheme 15).

Wan, *et al.*¹⁶ have reported the three component sequential reaction enaminones 55, α , β -unsaturated aldehydes 56a–b and amines 57a–k to afford 1,2-dihydropyridines 58 in highly regioselective manner. This novel regioselectivity has been



^a Standard conditions: 10 mol% of PtCl₂, 0.2 M in toluene at 100 °C over 3 h.^b Isolated yields after column chromatography.













 Table 4
 Regioselective synthesis of 1,2-DHPs and 1,4-DHPs^a

Entry	\mathbb{R}^1	R ³	R^{2} (57a-k)	% yield ^{b} of 58	% yield ^{b} of 59
1	Н	Н	(57a) <i>p</i> -NO ₂	(58a) 63	nd
2	p-OCH ₃	Н	$(57a) p-NO_2$	(58b) 14	(59c) 53
3	H	Н	(57b) <i>o</i> -F	(58c) nd ^c	(59c) 70
4	p-OCH ₃	Н	(57b) <i>o</i> -F	(58d) nd	(59d) 52
5	H	Н	(57c) o-Cl	(58e) 59	(59e) nd
6	o-Cl	o-Cl	(57d) H	(58f) 52	(59f) nd
7	o-Cl	Н	(57c) o-Cl	(58g) 60	(59g) nd
8	Н	Н	(57e) <i>o</i> -Br	(58h) <10	(59h) 46
9	Н	Н	(57d) <i>o</i> -I	(58i) 27	(59i) 51
10	Н	Н	(57g) o-CH ₃	(58j) nd	(59 j) 65
11	Н	Н	(57 h) 2,4,6-trimethyl	(58k) < 10	(59k) 51

 a General conditions: 0.3 mmol of enaminones, 0.35 mmol of aldehyde, 0.3 mmol of amine, 0.3 mmol of TMSCl mixed in 1 mL of solvents (0.5 mL H₂O + 0.5 mL of DMF), stirred at 85 °C for 10 h. b Isolated yield based on the corresponding enaminone. c nd = not determined.







Scheme 18 Four component one-pot synthesis of functionalized 1,2-dihydropyridines 63m-p

assigned to both steric and electronic effects originating from the amine partner (Scheme 16).

To examine the factors contributing to the selectivity, a series of reactions by taking *p*-nitroaniline and *ortho*-substituted anilines, have been carried out with enaminones and α , β unsaturated aldehydes. The results are highlighted in Table 4. As shown in Table 4 both 1,2-DHPs **58** and/or 1,4-DHPs **59** could be furnished depending on the properties of the substituent on phenyl ring of the anilines. *p*-Nitroaniline mainly offered 1,2-DHPs **58** as a major product, while with different *ortho*-anilines indicate that the regioselectivity was affected by both the size and the electronic profiles of the *ortho* groups. The reaction of *o*haloanilines, fluoro- and bromoaniline gave 1,4-DHP **59c**, **59d** and **59h** as the major product (entries 3, 4, and 8), while *o*chloroaniline gave 1,2-DHP **58e**, **58f** and **58g** as the only isolated



Scheme 19 Synthesis of 1,2-dihydropyridines 66a–d from propargyl ethers.

product (entries 5–7). Integrating the 1,2- and/or 1,4-DHP furnished in the 2-iodoaniline, 2-methylaniline, and 2,4,6-trimethylaniline entries (entries 9–11), it is evident that the bulky *ortho* group is important, but not the only inducing factor for 1,2-DHP formation. Further it was observed that the sequence of adding the reactants did not make a visible difference in the regioselectivity of the reactions.

Yavari, *et al.*¹⁷ has reported one pot synthesis of highly functionalized 1,2-dihydropyridines from alkyl isocyanide **60a-b**,



Scheme 20 Two step *versus* domino reaction: synthesis of 1,2-dihydropyridine 69a.

Table 5 Domino synthesis of 1,2-dihydropyridines 69a-q from propargyl enol ethers 67 and primary amines^a



14	Н	Ph	Н	a	PMB^{g} (62c)	n	78			
15	Η	Ph	Н	a	Ph (57f)	0	93			
16	Н	Ph	Н	a	4-Cl-C ₆ H ₄ (70d)	р	88			
17	Η	Ph	Н	a	<i>p</i> MeOC ₆ H ₄ (62h)	q	100^{h}			
^a Pro	^{<i>a</i>} Propargyl vinyl ether 67 (1.0 equiv.), primary amine 62h (1.1 equiv.) in									
tolue	ne(5 m)	J. $L = 0$	$J_2 CH_3$.	800	$W, 150^{\circ}C, 2 \text{ n.} 300^{\circ}$	W, 1	50°C, 3 N,	, L		
= CC	$V_2 CH_2 CH_2 CH_2 CH_2 CH_2 CH_2 CH_2 CH$	$1_3. \ L = h$	50210	. AC	$1 = adamantyi.^{\circ} 50\%$	o de.	PMB =	р-		
meth	oxybenz	yl. "(R)	-1-Pher	iylpro	p-2-yn-1-ol was us	sed	to prepa	re		
enan	tiopure	(R)-69q; 1	product	69q	obtained as a racem	ic mi	xture.			

Bn (62a)

Allyl (70a)

Ad^e (70b)

(S)PhCHMe (70c)

83

72

87

83^f

k

1

m



Entry	Catalyst (mol%)	Solution	$TsNH_2$ (mol%)	Yield (%)
1	AuCl	DCM	200	ND ^b
1		DOM	200	INK
2	PPh ₃ AuCl/AgOI ⁴	DCM	200	NR ⁵
3	PPh ₃ AuCl/AgBF ₄	DCM	200	84
4	PPh ₃ AuCl/AgSbF ₆	DCM	200	92
5	PPh ₃ AuCl	DCM	200	NR^{b}
6	AgSbF ₆	DCM	200	NR^{b}
7	$PdCl_2(CN)_2$	DCM	200	NR^{b}
8	PtCl ₂	DCM	200	NR^{b}
9	PPh3AuCl/AgSbF6	Toluene	200	Trace ^c
10	PPh3AuCl/AgSbF6	CH ₃ CN	200	NR^{b}
11	PPh3AuCl/AgSbF6	DCE	200	77
12	PPh ₃ AuCl/AgSbF ₆	DCM	120	80

^a Reactions were conducted with 0.4 mmol of **1a** in 3 mL of solvent at room temperature. ^b No reaction. ^c Most of the material decomposed.

acetylenic esters 61a-b and primary alkylamine (62a-i). The reaction of alkyl isocyanides 60a-b, dimethyl acetylenedicarboxylate (61a), and primary amines 57a, 62a-h, proceeded smoothly in CH₂Cl₂ at room temperature and produced tetramethyl 4-(alkylamino)-1-alkyl(aryl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylates 63a-k in good yields after purification (Scheme 17). Similarly, taking two equivalent of diethyl acetylenedicarboxylate 61b in above reaction gives 63l in 69% yield. A wide range of structurally varied primary amines were employed in this cyclocondensation reaction. Addition of a solution of equimolar amounts of primary amine 62a, 62c & 62d and 61a to a 1:1 mixture of cyclohexyl isocyanide (60a), and diethyl acetylenedicarboxylate (61b) in CH₂Cl₂ at rt, produced 5,6-diethyl 2,3-

Table 7 Tandem synthesis of 1,2-dihydropyridines from propargyl vinyl ethers and $TsNH_2^a$



^a Reactions were conducted with 0.4 mmol of 67 in 3 mL of solvent. ^b Isolated yield after column chromatography.



Scheme 21 Tandem synthesis of 1,2-dihydropyridines 73a-h from allenic vinyl ethers and TsNH₂.

10

11

12

13

н

н

Н

н

Ph

Ph

Ph

Ph

н

н

н

н

a

а

a

a

dimethyl 4-(cyclohexylamino)-1-(arylmethyl)-1,2-dihydropyridine-2,3,5,6-tetracarboxylates **63m–o** which contain two different ester groups (Scheme 18). Similarly reaction of **62a** and **61b** in a 1 : 1



Scheme 22 The conversion of 74a-o in 1,2-dihydropyridines 76a-o.

mixture of **60a** & **61a** yields **63p**. The formation of a single product when two different acetylenic esters are used is presumably controlled by the sequence in which the reaction is carried out.

Binder and Kirsch *et al.*¹⁸ has synthesized 1,2-dihydropyridines **66a–d** from propargyl vinyl ethers **64a–d** through a sequence of propargyl-Claisen rearrangement, condensation, and heterocyclization (Scheme 19). The scope of this protocol was quite limited, only four examples of 1,2-dihydropyridines with low to moderate yields are known.

Tejedor, *et al.*¹⁹ has developed a convenient domino access to substituted alkyl 1,2-dihydropyridine-3-carboxylates from propargyl enol ethers and primary amine. After some experimental work, it has been found that microwave irradiation of a solution of **67a** in toluene (150 W, 120 °C, 30 min) afforded the corresponding dienal **68a**, which could be isolated as a mixture of E/Z (1 : 1) isomers in 59% yield after flashchromatographic purification (Scheme 20). Subsequent treatment of dienal **68a** with *p*-anisidine (**62h**; 1.0 equiv.) at room temperature in toluene for 1 h afforded 1,2-dihydropyridine **69a** in quantitative yield. The direct microwave irradiation of **67a** with **62h** in toluene (150 W, 120 °C, 30 min) afforded the



Scheme 23 One pot synthesis of 1,2-dihydropyridines 79a-d starting from propargylic alcohols 77a-c.



Scheme 24 Electrochemical synthesis of 1,2-dihydropyridines 84a-d.



Scheme 25 Electrochemical synthesis of enantiomerically pure 1,2-dihydropyridine 87.

corresponding 1,2-dihydropyridine **69a** in almost quantitative yield.

After the development of one step domino process the scope of this reaction has been extended with regard to the propargylic component and amine (Table 5). In general, the reaction presented a broad spectrum for the amine although aromatic amines gave better yields than aliphatic amines (compare entries 1, 15 and 16 with entries 10–14). The effect of diastereo induction by the amine component was studied with the chiral amine **70c**, which in turn yields chiral 1,2-dihydropyridine **69m** with a significant 50% de (entry 13).

Wei, et al.²⁰ has reported the synthesis of 1,2-dihydropyridines from propargyl vinyl ethers and allenic vinyl ethers by gold-catalyzed Claisen rearrangement and 6π -azaelectrocyclization. No reaction occurred with AuCl₃ or AuPPh₃Cl/AgOTf (5 mol% each) in CH₂Cl₂ at room temperature (entries 1 and 2, Table 6). 1,2-Dihydropyridine was obtained in 84% yield when AuPPh₃Cl/AgBF₄ (5 mol%) was used (entry 3). It was interesting result that 92% yield was realized by using AuPPh₃Cl/AgSbF₆ (5 mol%) at room temperature (entry 4). Ag(I) could serve to abstract the chloride from AuPPh₃Cl to form a more electrophilic catalyst. On the contrary, when Au(PPh₃)Cl or AgSbF₆ was used alone (entries 5 and 6), the tandem reaction did not take place at all. On the other hand, other transition metal catalysts such as PtCl₂ or $PdCl_2(CN)_2$ did not promote any transformation (entries 7 and 8). The investigation on the solvent effect showed that the best choice of the solvent was CH₂Cl₂ (entries 9-11). However, the yield decreased when the amount of TsNH2 was reduced from 2.0 to 1.2 equivalents (entry 12). Thus the use of 5 mol% of AuPPh₃Cl/AgSbF₆, with 2.0 equivalents of TsNH₂ in CH₂Cl₂ at room temperature constituted the optimal reaction conditions.

The scope of the reaction has been explored in gold catalysed tandem reaction by studying a wide variety of substrates (Table



Scheme 26 Microwave-assisted domino synthesis of 1,2-dihydropyridines 89 from propargyl vinyl ether 88.



Scheme 27 Cascade synthesis of 1,2-dihydropyridine 91 by variation of aldehydes and amines.

7). Substrates containing electron-rich or electron-deficient aryl groups at the propargylic position gave good to excellent yields of desired 1,2-dihydropyridines (entries 2–9).

The scope of this reaction has been extended by Wei, *et al.* on allenic vinyl ethers **72a-h** and it has been found that 5 mol% AuPPh₃Cl/AgBF₄ in presence of 2.0 equiv. TsNH₂ gave the moderate to good yield of diversified 1,2-dihydropyridines **73a-h** (Scheme 21).

1,2-Dihydropyridines 76a-o were synthesized in good to excellent yields by using a standardized protocol of Kirsch



Scheme 28 Annulation reaction between unsaturated imines and alkynes for the formation of 1,2-dihydropyridines 93.



Scheme 29 Hantzsch dihydropyridine synthesis.



Scheme 30 An example of Kröhnke procedure.



Scheme 31 Grignard and organocopper reagents catalyzed exclusive synthesis of 1,4-dihydropyridine **97**.

*et al.*²¹ with internal alkynes **74a–o** and used a sequential addition of reagents and catalysts to obtain reproducibly high yields [(i) AuCl (5 mol%), 23 °C; (ii) R_3NH_2 (**57d, 62a, 62c, 62h** and **75a–c**); (iii) *p*-TsOH (20 mol%), 40 °C, CH₂Cl₂] (Scheme 22). The formation of 1,2-dihydropyridines **76a–o** tolerated substitution of R_1 and R_2 with both aryl and alkyl groups (Scheme 22). Compound **76l** bearing no substituent in the 2-position ($R_1 = H$) was obtained in only moderate yield.



Scheme 32 Comins copper hydride catalyzed regioselective synthesis of 1,4-dihydropyridines 99a–i.

Further this one-pot procedure is extended by an additional step that is the formation of the propargyl vinyl ethers. When propargylic alcohols **77a–c** were reacted with 1.0 equiv. of ethyl propiolate **78a**/methyl propiolate **78b** and 5 mol% of P(*n*-Bu)₃, the Michael-addition remained an efficient process. Subsequent addition of both AuCl and AgSbF₆ (5 mol% each) furnished the allenylcarbonyl compounds. Notably, only the use of both catalysts together provided good and reproducible results; neither one was able to catalyze the reaction on its own. The sequence was terminated by condensation with 1.5 equiv. of an amine and 0.2 equiv. of *p*-TsOH at 40 °C for 15 h to give the desired products in good yields (Scheme 23). It is of particular note that this one-pot procedure presents the possibility to access 1,2-dihydropyridines **79a–d** even in cases when the required propargyl vinyl ether is not accessible due to poor stability.

Shono, *et al.*²² have developed a convenient and regioselective method for the synthesis of 1,2-dihydropyridines, especially those possessing substituents at certain positions of the pyridine nucleus. 2-Substituted 1-(methoxycarbonyl)-1,2-dihydropyridines have been synthesized from piperidines electrochemically (Scheme 24).

Optically active 1,2-dihydropyridine **87** has been synthesized starting from L-lysine derivative **85** by electrochemically in two steps *via* the synthesis of tetrahydropyridine **86** in 75% yield, ee \sim 100% (Scheme 25).







Scheme 34 Synthesis of 4-functionalized 3,5-diacyl-4-aryl-1,4-dihydropyridines 108a-e.

Tejedor, *et al.*²³ has developed a general and practical metalfree protocol for the synthesis of 1,2-dihydropyridines (Scheme 26) with variety of structural/functional diversity at the ring and featuring mono, double, or spiro substitution at the sp³

hybridized carbon position. The protocol contains a microwave-

assisted domino reaction of propargyl vinyl ether 88 (secondary

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or tertiary) and a primary amine (aliphatic or aromatic) in toluene or methanol.

Challa, *et al.*²⁴ has developed a convenient synthesis of 1,2dihydropyridine (**91**) from dienaminodioate **90** and an imine (generated *in situ*) mediated by CF_3COOH in a one-pot cascade synthesis. The advantages associated with this transformation include conditions that are metal-free, room temperature,



^{*a*} Benzaldehyde : 1,3-cyclohexanedione : ethyl acetoacetate : ammonium acetate (1 : 1 : 1 : 1). ^{*b*} Crude isolated yield.

 Table 9
 Iodine catalyzed synthesis of 1,4-dihydropyridine derivatives through Hantzsch reaction

ArCHO +			I NH₄OAc —	l₂ (15 or 30 mol %) RT	
	109	110a			Н 111а-ј

Entry	105	Ar	Iodine (mol%)	Time (h)	Yield ^a (%)
1	111a	C_6H_5	30	2.5 h	99
2	111a		15	30 min	93
3	111b	p-Me-C ₆ H ₄	30	1.5 h	90
4	111b		15	35 min	99
5	111c	p-Me-C ₆ H ₄	30	4 h	97
6	111c		15	40 min	87
7	111d	p-F-C ₆ H ₄	30	3.5 h	91
8	111d		15	35 min	87
9	111e	p-CI-C ₆ H ₄	30	6 h	99
10	111e		15	40 min	90
11	111f	p-OH-C ₆ H ₄	30	2.5 h	99
12	111f		15	45 min	92
13	111g	$o-NO_2-C_6H_4$	30	1.5 h	94
14	111g		15	25 min	91
15	111h	m-NO ₂ -C ₆ H ₄	30	1.5 h	99
16	111h		15	25 min	92
17	111i	p-NO ₂ -C ₆ H ₄	30	3 h	99
18	111i		15	25 min	85
19	111j	Isopropyl	30	5 h	99
20	111j		15	40 min	99

^a Crude isolated yield.

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undistilled solvent, and expeditious in excellent yields. Out of the several acid catalyst used for the optimisation of the reaction condition trifluoroacetic acid was found to me excellent, which yield 1,2-dihydropyridine in excellent yield (Scheme 27). The substrate scope has been demonstrated with various aromatic, heteroaromatic, unsaturated aldehydes, and anilines, benzylic amines in impressive yields.

Fallon, *et al.*²⁵ has developed a convenient one-pot synthesis of highly substituted 1,2-dihydropyridines **93** from unsaturated imines **92** and alkynes *via* C–H activation/ 6π -electrocyclisation

pathway (Scheme 28). The reaction proceeds with high regioselectivity, and the author has disclosed the first example of isolated 1,2-dihydropyridines lacking substitution at 2 position. A low valent cobalt complex without reducing agents or additives provides C–H activation.

2.2. Synthesis of 1,4-dihydropyridines

Over the years many outstanding discoveries have been made in the field of drug development and research with multifaceted



Scheme 35 Ionic liquid supported synthesis of 1,4-DHPs. Reagents and conditions (i) DCC (1.0 equiv.), DMAP (5%), dry MeCN, rt, 24 h; (ii) method A: 110 (1.0 equiv.), 114 (1.0 equiv.), mw: 120 °C (power level: 50%, 150 W), 10 min or method B: 110 (2.0 equiv.), NH₄OAc (2.0 equiv.), mw: 120 °C (power level: 50%, 150 W); (iii) MeONa 30%, MeOH, reflux, 18 h; (iv) LiOH 60%, THF, rt, 20 h then 3 M HCl; (v) 110 (1.0 equiv.), 117 (1.0 equiv.), NH₄OAc (2.0 equiv.), mw: 120 °C (power level: 50%, 150 W).



Scheme 36 Baker's yeast catalyzed synthesis of 1,4-DHPs 121 and 122.





Scheme 37 Proposed mechanism for the baker's yeast catalysed synthesis of 1-4-DHPs.



Scheme 38 Heterogeneous catalyst (HClO₄-SiO₂) catalyzed synthesis 1,4-DHPs 123

drugs having great potential. 1,4-Dihydropyridine is one such privileged structure which has revolutionized the pharmaceutical industry. It is a well explored scaffold which binds to multiple receptors, possesses a wide variety of biological features and also has its basis in biologically active natural products. The first synthesis of 1,4-dihydropyridines was reported by Arthur Hantzsch in 1882.²⁶ He observed that in the process of synthesizing pyridine by a one pot three-component condensation reaction of acetoacetic ester, aldehyde and ammonia, an intermediate 1,4-dihydropyridine (1,4-DHP) **94** is formed, which could be isolated easily. Since then this reaction has been successfully employed in the synthesis of 1,4-DHPs and bears his name as "Hantzsch dihydropyridine synthesis" (Scheme 29).

The addition of nucleophiles to α - and γ - positions of *N*substituted pyridinium salts gives both 1,2- and 1,4-dihydropyridines. The regioselectivity of the addition reaction depends on the hardness of the nucleophile: hard nucleophiles preferentially attack at C-2 whereas soft ones attack at C-4 position of the pyridinium salts. The addition is also believed to proceed at both the α - and γ -carbon centres under kinetic control and only at the γ -carbon under thermodynamic control.²⁷ The Kröhnke procedure²⁸⁻³⁰ and sodium dithionite reduction³¹⁻³³ are examples of reactions involving addition of nucleophiles at γ -position. The Kröhnke procedure,²⁸⁻³⁰ consisting of base-catalysed reaction of ketones with alkyl or *N*-acyl pyridinium salts, was investigated years ago (Scheme 30). It is of particular synthetic interest since it constitutes a useful method of forming new carbon–carbon bonds to give γ -substituted 1,4-dihydropyridines **95**.²²

Table 10	One-pot synthesis of 1,4-DHP under solvent free conditions
using HC	$O_4 - SiO_2^a$

Entry	(Ar) 123	110	Reaction time (min.)	% vield
	()		()	<i>j</i> ====
1	C_6H_5 (123a)	110b	20	95
2	<i>p</i> -CH ₃ -C ₆ H ₄ (123b)	110b	25	90
3	p-CH ₃ O-C ₆ H ₄ (123c)	110b	28	92
4	p-Cl-C ₆ H ₄ (123d)	110b	20	89
5	p-OH-C ₆ H ₄ (123e)	110b	26	90
6	$o-NO_2-C_6H_4$ (123f)	110b	35	92
7	o-Cl-C ₆ H ₄ (123g)	110b	26	87
8	$p-NO_2-C_6H_4$ (123h)	110a	33	92
9	o-CH ₃ O-C ₆ H ₄ (123i)	110a	42	90
10	p-Br-C ₆ H ₄ (123j)	110a	40	92
11	o-Br-C ₆ H ₄ (123k)	110a	40	89
12	2-Furyl (123l)	110a	52	86
13	2-Thienyl (123m)	110a	56	90
14	3-Pyridyl (123n)	110a	55	82
15	C_6H_5 (1230)	110b	20	94
16	$p-CH_3-C_6H_4$ (123p)	110b	25	92
17	<i>o</i> -CH ₃ O-C ₆ H ₄ (123q)	110b	25	90
18	$o-NO_2-C_6H_4$ (123r)	110b	22	91

^{*a*} The structures of the products were determined from their spectroscopic (IR, NMR and MS) data.



Scheme 39 Synthesis of 1,4-DHPs 126a-n via addition reaction of Grignard reagent to N-triisopropylsilylpyridinium ions 125a-b

Comins, *et al.*³⁴ and Yamaguchi, *et al.*³⁵ have reported the reaction of 1-acetylpyridinium chloride with alkyl Grignard reagent, which lead to the formation of 1,4-dihydropyridines **97** and 1,2-dihydropyridines **98**.^{34a} However, when a catalytic amount of CuI is present, the addition is regiospecific and resulted in the exclusive formation of 1,4-dihydropyridines **97**. Stoichiometric organocopper reagent (*e.g.* R₂CuLi, RCu, RCu·BF₃) also give 1,4-addition product and resulted into the formation of 1,4-dihydropyridines **97** (Scheme 31).³⁶

Several hydride reagents *e.g.* NaBH₄,³ NaBH₃CN, (PPh₃)₂-CuBH₄,³⁷ (Ph₂MeP)₃CuBH₄,³⁸ Semmelhack's "NaCuH₂"³⁹ and Semmelhack's "LiCuH₂"³⁹ has been used for the regioselective synthesis of 1,4-dihydropyridines from 1-(phenoxycarbony1) pyridinium chloride **99a** (generate *in situ* by the reaction between pyridine and phenyl chloriformate), but none of these procedure resulted into the regioselective formation of 1,4-DHP. Comins, *et al.*⁴⁰ has used a copper hydrido reagent prepared from lithium tri-*tert*-butoxyaluminum hydride (3.0 equiv.) and copper bromide (4.5 equiv.) as a reducing agent for the regioselective reduction of 1-(phenoxycarbony1)pyridinium chloride **96a** in almost quantitative yield (Scheme 32). Further this procedure has been extended to the variety of the 1-(alkoxy/

 Table 11
 Addition of various dialkylmagnesium reagents to N-triisopropylsilylpyridinium ions 125a-b

Entry	125	$R_2Mg (128)^a$	Product	% yield ^b	Product ratio 126/127/125 (%)
1	125a	Et ₂ Mg	126a, 127a	78	90/4/6
2	125a	nBu ₂ Mg	126b. 127b	82	100/0/0
3	125a	Bn ₂ Mg	126c, 127c	92	95/2/3
4	125a	Ph ₂ Mg	126d, 127d	0	$5/95^{d}/0$
5	125a	Me ₂ Mg	126e, 127e	0	0/59/41
6	125a	iPr ₂ Mg	126f, 127f	91	99/0/1
7	125a	tBu ₂ Mg	126g, 127g	56	80/3/17 ^e
8	125a	Allyl ₂ Mg	126h, 127h	20	$20/78^{d}/2$
9	125b	Et ₂ Mg	126i, 127i	73	86/2/12
10	125b	nBu ₂ Mg	126j, 127j	54	54/6/40
11	125b	Bn ₂ Mg	126k, 127k	85	95/0/5
12	125b	iPr ₂ Mg	126l, 127l	78	100/0/0
13	125b	tBu ₂ Mg	126m, 127m	5	$6/0/94^{f}$
14	125b	Allyl ₂ Mg	126n, 127n	12	21/70/9

^{*a*} After addition of the organomagnesium compound R₂Mg to the *N*-silylpyridinium ion **125** at -78 °C the mixture was slowly warmed to -50 °C. ^{*b*} Isolated yield. ^{*c*} According to ¹H NMR of the crude reaction product. ^{*d*} Sum of **127** and non oxidized 1,2-addition product, which were both present. ^{*e*} Yield 63%, ratio 86/2/12 when addition performed by warming the mixture from -78 °C to room temperature. ^{*f*} Yield 29%, ratio 32/0/68 when addition performed by warming the mixture from -78 °C to room temperature.

aryloxy/acyloxycarbony1)pyridinium chlorides **99b-i** (generated *in situ* by the reaction between substituted pyridine and corresponding alkyl/phenyl chloroformate or acid chloride). This convenient one-pot preparation of 1-(alkoxycarbonyl)-1,4-dihydropyridines by using the Comins' copper hydride complements the two-step procedure developed by Fowler.⁴

De Lucas, *et al.*⁴¹ have developed a novel methodology for the synthesis of *N*-substituted 1,4-dihydropyridines **103a–d** by the reaction of 2-amino-5-formyl-4*H*-pyran **101** with primary amines **57d**, **62a**, **70d** and **102** in moderate yield (Scheme 33). The formation of 1,4-dihydropyridines involves cleavage of the 4*H*-pyran ring by nucleophilic attack of the respective amine and subsequent 6-*exo*-dig cyclisation.

Bennasar, *et al.*⁴² have developed a regioselective synthesis of 4-functionalized 3,5-diacyl-4-aryl-1,4-dihydropyridines **108a–e** by the copper-mediated addition of functionalized arylmagnesium reagent **105a–e** to the *N*-benzhydrilpyridinium salt **104**,



Scheme 40 Screening of the catalysts for the three-component domino reaction between 56a, 129a and 110a.



Scheme 41 Three-component domino reaction between 56, 110 and 129a–h, 57d \div 70d.

Table 12 Scope and yields of the CAN-catalyzed synthesis of 1,4-dihydropyridines 130a-s

Entry	Compound	110	56	R_2	R_3	R_4	R_5	Amine	Time (h)	Yield (%)
1	130a	110a	56a	CH ₃	Н	Н	Н	129a	1	74
2	130b	110a	56a	Н	Н	Н	Н	57 d	1	71
3	130c	110a	56a	Н	CH_3	Н	Н	129b	1	70
4	130d	110a	56a	Н	F	Н	Н	129c	1	76
5	130e	110a	56a	Н	Cl	Н	Н	70d	1	74
6	130f	110a	56a	CH_3	CH_3	Н	Н	129d	1	70
7	130g	110a	56a	Cl	Н	Н	Н	129e	1	72
8	130h	110a	56a	Н	Br	Н	Н	75 b	1	74
9	130i	110a	56a	CH_3	Н	CH_3	Н	129f	1	72
10	130j	110a	56a	OCH_3	Н	Н	Н	129g	1	65
11	130k	110a	56c	Н	Н	Н	Н	57 d	1	50
12	130 <i>l</i> ^{<i>a</i>}	110a	56a	Н	CH_3	Н	CH_3	129h	1	72
13	130m	110c	56a	Н	Н	Н	Н	57 d	2	52
14	130n	110c	56a	Н	CH_3	Н	Н	129b	2	61
15	1300	110c	56a	Н	Cl	Н	Н	70d	2	65
16	130p	110d	56a	Н	Н	Н	Н	57 d	1	61
17	130q	110d	56a	Н	F	Н	Н	129c	1	62
18	130r	110d	56a	Н	Cl	Н	Н	70d	1	63
19	130s	110d	56a	Н	CH_3	Н	Н	129b	1	61

^{*a*} Isolated as an 1.1 : 1 rotamer mixture.







Scheme 43 Enantioselective synthesis of 1,4-dihydropyridine 133c catalyzed by chiral Brønsted acids 134a-c.

R ₁	PPh ₃	One	Pot synthes (i) HCl (ii) 56a/ 56i	$ \xrightarrow{\mathbf{N}_1} \\ \mathbf{HN} \\ \mathbf{HN} \\ \mathbf{R}_1 $	COOR ₂ COOR ₂ R ₃		
135a; R ₁ 135b, R- 135c; R ₁	$H_1 = H, R_2 = I$ $H_1 = R_2 = Me$ $H_2 = Ph, R_2 = HCI$	Et		15	88a-e ▲ 136a-c		
H N F R ₁ 0 136a-c 136a; R ₁ = 136b; R ₁ =	$p_{Ph_3} =$	0 6 a ; R ₃ = 6 f ; R ₃ = 6 i ; R ₃ =	- R ₃ = Ph = <i>p</i> -NO ₂ -C ₆ H, = 2-furyl		n ₃ O OOR ₂ (INT ₄₂)		
Starting	Product	R ₁	R ₂	R ₃	React	ion conditi	ons
Material					T (°C)	Time (h)	Yield (%) ^a
136a/56a 136a/56f 136b/56a 136c/56a 136c/56i	138a 138b 138c 138d 138e	H H Me Ph Ph	Et Et Me Et Et	$C_{6}H_{5}$ p-NO ₂ -C ₆ H ₄ $C_{6}H_{5}$ $C_{6}H_{5}$ 2-furyl	40 40 40 40	19 30 20 25 48	66 62 65 51 ^b 57 ^b
^a Purified by	chromatog	raphy. ^b	Obtained in	"one pot" proc	cess from ph	osphazene	135c.

Scheme 44 Reaction of enamino-phosphonium salts 136 with α,β -unsaturated aldehydes 55a, 56f and 56i: preparation of symmetrical dihydropyridines 138a-e.

followed by acylation with trichloroacetic anhydride. The subsequent haloform reaction on **106a–e** yields **107a–e**, which on *N*-deprotection gives **108a–e** (Scheme 34).

Table 13 The reaction of imines 139a-m with 78a ^a							
N ^R R ₂ 139a-m	1 +	COOEt 78a	Sc(OTf) ₃ (Toluene, refl	10 mol%) uxed, 24h	EtOOC F 140	COOEt	
Entry	Imine	R ₁	R ₂	Proc	luct 140	Yield ^b (%)	

		1	2		(/
			_		
1	139a	<i>c</i> -Hex	Ph	140a	22^{c}
2	139b	<i>t</i> -Bu	Ph	140b	18
3^d	139c	Bn	Ph	140c	28
4	139d	$CHPh_2$	Ph	140d	35
5	139e	Ph	Ph	140e	45^{c}
6	139f	<i>p</i> -MeOC ₆ H ₄	Ph	140f	75 ^c
7^d	139g	p-MeC ₆ H ₄	Ph	140g	62^c
8^d	139h	$2,6-MeC_6H_3$	Ph	140h	77
9	139i	<i>p</i> -MeOC ₆ H ₄	p-MeC ₆ H ₄	140i	78
10	139j	<i>p</i> -MeOC ₆ H ₄	p-CI-C ₆ H ₄	140j	54
11	139k	p-MeOC ₆ H ₄	p-FC ₆ H ₄	140k	47
12	139l	<i>p</i> -MeOC ₆ H ₄	$p-NO_2C_6H_4$	140l	34
13	139m	p-MeOC ₆ H ₄	PhCH ₂ CH ₂	140m	0
		- 01			

 a 133 (0.5 mmol), 78a (1.25 mmol), Sc(OTf) (0.05 mmol) in toluene (5 mL) at reflux for 24 h. b Isolated yield. c GC yield. d BTF was used as a solvent instead of toluene.

Yao, et al.43 have developed a simple, inexpensive and efficient one-pot synthesis of 1,4-dihydropyridine derivatives with excellent product yields at room temperature using catalytic amount of molecular iodine. Initially, benzaldehyde, 1,3-cyclohexanedione 109, ethyl acetoacetate 110a and ammonium acetate were stirred at room temperature in a few mL of ethanol. After 4 hours, only 56% of product 111a was realized after recrystallization of the crude product from ethanol (entry 1, Table 8). To improve the product yields and to optimize the reaction condition, molecular iodine was used in catalytic amount (15 mol%) and a reaction was carried out under similar reaction conditions to give the product 111a in 99% yield (entry 2). The increase in the quantity of molecular iodine from 15 to 30 mol% not only reduced the reaction time from 4 to 2.5 h, but also enhanced the product yield from 56% to 99% (entry 3). Similarly, using 50 mol% of iodine as catalyst the reaction time further reduced to 1.5 h along with a decrease in the yield of the product 111a (70%) (entry 4).



Scheme 45 $\mbox{Sc}(\mbox{OTf})_3$ catalyzed reaction of aniline 57d and 78a: preparation of 1,4-DHP 141.

A range of aryl and alkyl aldehydes were subjected to react with **109**, **110a** and NH₄OAc in the presence of either 15 or 30 mol% of iodine to generate corresponding 1,4-DHP **111b**. The results are summarized in Table 9, *e.g.* with 30 mol% of iodine as catalyst, *p*-chlorobenzaldehyde is converted into the product in 6 h with 99% yield, whereas the same reaction takes place within 40 min with 15 mol% of iodine without significant loss of yield (Table 9, entries 9 & 10). In general, the yields are little less with 15 mol% of catalyst and the reaction times are also short. Both aliphatic and aromatic aldehydes react equally good to give the products with excellent yields. The aryl group substituted with different groups and same groups located at different positions of the aromatic ring has not shown much effect on the formation of the final product.

Bazureaua, *et al.*⁴⁴ have developed a three component one pot microwave dielectric heating assisted liquid phase synthesis of 1,4-dihydropyridines using task specific ionic liquid as a soluble solid support. They synthesized the ILP bound aldehydes **113a–d** in high yields by the esterification of PEG-ILPs



^a Isolated yield based on the corresponding aldehydes

Scheme 46 Synthesis of 1,4-dihydropyridines under ultrasound at room temperature.



Scheme 47 Synthesis of 1,4-dihydropyridines catalyzed by montmorillonite K10 clay.

112a–d with 4-formylbenzoic acid in dry MeCN with dicyclohexylcarbodiimide (DCC) and 5% of dimethylamino pyridine (DMAP) as catalyst. The ILP bound 1,4-dihydropyridines **115** has been synthesized in an excellent yields *via* two methods. Method A involves the condensation of aldehydes **113a–d** and 1.0 equiv. of β -ketoester ethyl acetoacetate **110a** or methyl acetoacetate **110b** and 1.0 equiv. of aminocrotonate **114** under microwave irradiation (120 °C, 150 W, 50% power level, time exposure: 10 min), in the method B the IL-phase bound 1,4-DHP **115** was prepared by the condensation from β -ketoester **110a** or **110b** (2.0 equiv.) and NH₄OAc (2.0 equiv.) using the same



Entry	Product (R)	104	Time (min)	Isolated yield (%)
1	3-pyridyl (123n)	110a	25[a]	93
2	4-Cl-C ₆ H ₄ (144a)	110b	20	91
3	4-pyridyl (144b)	110a	10 [b]	90
4	4-Br-C ₆ H ₄ (144c)	110b	10	89
5	Me ₂ N-C ₆ H ₄ (144d)	110b	25	93
6	Me ₂ N-C ₆ H ₄ (144e)	110a	15	91
7	2-pyridyl (144f)	110a	20 [c]	93
8	3-NO ₂ -C ₆ H ₄ (142a)	110a	5	95
9	$3-NO_2-C_6H_4$ (144g)	110b	20	92
10	$2-NO_2-C_6H_4$ (123f)	110a	25	92
11	2-Furyl (123I)	110a	10	95
12	2-Furyl (144h)	110b	15	98
13	β-Naphthyl (144i)	110a	22	88
14	β-Naphthyl (144j)	110b	25	89
15	CH ₃ CH=CH (144k)	110b	15	93
16	CH ₃ CH=CH (144I)	110a	15	94
17	$C_6H_4CH=CH(144m)$	110b	20	86
18	$2,3-(OH)_2-C_6H_3$ (144n)	110b	25	89
19	C ₆ F ₅ (144 0)	110a	45	90
20	$C_{6}F_{5}$ (144p)	110b	45	90
21	$4 - CF_3 - C_6H_4$ (144 q)	110a	30	95

^{a,b,c} Reaction time 5, 6, 3, and 3 hrs respectively at 80 °C without any catalyst.

Scheme 48 Synthesis of 1,4-dihydropyridines in presence of 5 mol% of the barium nitrate.



^a Reaction condition: aldehyde (1.0 mmol), acetoacetate ester (2.0 mmol), NH₄OAc (1 mmol), TFE (2 mL), 3 h. ^b Isolated yield.

Scheme 49 Synthesis of 1,4-dihydropyridines through Hantzsch reaction in TFE.

microwave reaction conditions (120 °C, 10 min) (Scheme 35). ILphase, the bound products **115a–b** were subjected to cleavage by: (i) transesterification with 30% of MeONa in refluxed MeOH during 18 h, (ii) saponification with 60% of LiOH in THF at room temperature, followed by controlled acidification with a solution of 3.0 M HCl to obtain the desired 1,4-DHP **116a–b** in an good yield. Similarly **118a–b** was synthesized by the condensation of **113a–d** with **110a** or **110b** (1.0 equiv.) and **117** (1.0 equiv.) and NH₄OAc (2.0 equiv.) under the same microwave radiation condition. **118a–b** on transesterification followed by saponification yielded **119a–b**.

J. H. Lee⁴⁵ has described an efficient method for the synthesis of 1,4-DHP under mild reaction condition using Baker's yeast. In a typical procedure a solution of 100 mL of pH 7.0 phosphate buffer, 5.0 g of p-glucose, and 2.0 g of yeast extract was warmed at 35 °C. Further 5.0 g of dry active Baker's yeast was added to this solution and the mixture was stirred at

30 °C for 30 min, after which, acetoacetic ester **110a** or **110b** (1.0 mmol) and ammonium acetate or 3-amino crotonitrile **120** were added. The mixture was stirred at room temperature for 24 h and then extracted with diethyl ether. The organic layer was dried and concentrated *in vacuo* and the resulting crude products were recrystallized using ether–*n*-hexane to afford pure products **121a–b** and **122a–b** in 46–70% yields (Scheme 36).

The glycolytic pathway from D-glucose to pyruvate is one of the most universal metabolic pathway known. In yeast, glycolysis is supposed to be the main pathway for the catabolism of glucose. According to the classical concept of glycolysis, metabolic acetaldehyde, resulting in the formation of acetoin, should be released from pyruvate in aerobic conditions. It is assumed that this acetaldehyde is involved in this Hantzschtype reaction (Scheme 37).



^a Compound **146** was dissolved in CH₂Cl₂ and treated with 1.0 equiv. of silyl triflate at room temperature. After 15 min the solution was cooled to -75 °C and 2.0 equiv. of the corresponding organomagnesium reagent was added. Work up was performed by addition of phosphate buffer (pH 7.0, c= 1.0 M) and extraction of the aqueous layer with CH₂Cl₂. ^b According to ¹H NMR of the crude product. ^c Isolated yield. ^d Not determinable.^e Not isolated. ^f Contaminated with 9% **148d**. ^g Addition of 20 mol %. ^h 1.0 equiv.

98/2/0

63/37

148g

Scheme 50 Addition of various organomagnesium reagents to N-triisopropylsilylpyridinium ions 147: preparation of 1,4-dihydropyridines.

Ph₂Mg

25

46

Sridhar, et al.46 have reported an efficient and convenient procedure for the one-pot synthesis 1,4-dihydropyridine derivatives 123a-r in excellent yields (Scheme 38) by the condensation of β -dicarbonyl compounds **110a** or **110b**, aldehydes and ammonium acetate, by using heterogeneous catalyst (HClO₄- SiO_2) under solvent-free conditions. The experimental procedure has been found very simple, convenient, and has the ability to tolerate a variety of other functional groups on phenyl ring of the aromatic aldehydes such as methoxy, nitro, hydroxyl and halides under the reaction conditions. Further the optimized reaction condition has been examined to prove the universality of this catalyst application. Various aromatic, aliphatic and heterocyclic aldehydes were selected to undergo the Hantzsch condensation in the presence of heterogeneous catalyst (HClO₄-SiO₂). The results of this study are summarized in (Table 10).

Wanner, et al.47 have synthesized N-silvl protected 1,4-DHP 126a-n by the addition reaction of dialkylmagnesium reagents (R₂Mg) to N-triisopropylsilylpyridinium ions 125a-b (Scheme 39). The N-triisopropylsilylpyridinium ions 125a-b were generated in situ by the reaction of 4-substituted pyridines 124a**b** and triisopropylpyridinium-triflate (TIPS-OTf). The regioselectivity of 4-addition product of this reaction was quite satisfactory (Table 11, entries 1, 2, 3, 6, 7, 9, 10, 11 and 12).

Perumal, et al.48-50 has carried out an initial study in search for the suitable catalyst and solvent for the synthesis of 1,4-DHP using cinnamaldehyde 56a, m-toluidine 129a and ethyl acetoacetate 110a. Author first assayed indium trichloride,44 triphenylphosphonium perchlorate,45 and potassium hydrogen sulfate as catalysts,46 which have been successfully employed in related condensation reactions, but the yields obtained were only moderate, even with high catalyst loadings. The best results were obtained with cerium ammonium nitrate (CAN) in ethanol, which gave the desired dihydropyridine derivative in 71% isolated yield (Scheme 40). Further Perumal, et al.⁵¹ have developed cerium ammonium nitrate (CAN) catalyzed threecomponent domino reaction between aromatic amines 57d, 70d & 129a-h, α,β-unsaturated aldehydes 56a & 56c and alkyl acetoacetate 110a, 110c & 110d to afford the 1,4-dihydropyridines 130a-s in moderate to good yields (Scheme 41, Table 12).

Renaud, et al.52 has developed Brønsted acid 132 catalyzed addition of β -enaminoacrylates 131a-d to α , β -unsaturated aldehydes 56a, 56c and 56d-h to afford the corresponding Nsubstituted 1,4-dihydropyridines 133a-m in 31-89% yields (Scheme 42).

Further author have also reported the enantioselective synthesis of 1,4-dihydropyridine 133c starting from 131a and 56a using three different chiral Brønsted acids 134a-c in ee 33-50% (Scheme 43).

Palacios, et al.53 explored the reactivity of enaminophosphonium salts 136a-c derived from phosphazenes 135a-c with α , β unsaturated aldehydes 56a, 56f and 56i (Scheme 44). The reaction of enaminophosphonium salt 135a, prepared by hydrochloric acid treatment of N-vinylic phosphazene 135a, with cinnamaldehyde 56a or p-nitrocinnamaldehyde 56f in refluxing CH₂Cl₂ led to the formation of 4-(2-phenylethenyl)-3,5-diethoxycarbonyl-

1,4-dihydropyridine 138a and 4-[2-(4-nitrophenyl)ethenyl]-3,5diethoxycarbonyl-1,4-dihydropyridine 138b in 66 and 62% yields, respectively. The formation of these dihydropyridines 138 could be explained by means of a formal [4 + 2]-cyclization process involving an initial 1,4-addition of the γ -carbon atom of the enaminophosphonium salt 136a to the carbonyl group of the aldehydes 56a to give the cycloadduct intermediate 1,2,5oxaazaphosphoranes 137 (INT_{42}) followed by regioselective attack of a second molecule of the phosphonium salt 130a (Scheme 44). 1,4-DHPs 138d and 138e were also obtained in "one pot" process from phosphazene 135c in 51 and 57% yields, respectively.

Fukuzawa, et al.54 have developed a procedure for the synthesis of N-substituted-1,4-dihydropyridines 140a-m in moderate to good yields by scandium(m) triflate catalyzed reaction of imines **139a-m** with ethyl propiolate **78a** (2.5 equiv.) in toluene or benzotrifluoride (BTF) under refluxed conditions (Table 13).

Further, it has also been reported by the author's that the Sc(OTf)₃ catalyzed reaction of aniline 57d and ethyl propiolate 78a (3.2 equiv.) yielded another 1,4-dihydropyridine 141 bearing three ester groups in 42% yield under the same reaction conditions (Scheme 45).

Wang, et al.55 has developed a three-component one pot condensation of aldehydes, ethyl acetoacetate 110a and ammonium acetate to afford the 1,4-dihydropyridines 123a, 123c, 123d, 123e, 123f, 123g and 142a-f in 82-99% yields under ultrasound irradiation without solvent and catalyst at room temperature (Scheme 46). The main advantages of this procedure are mild reaction condition, shorter reaction time and high product yield.

Zonouz, et al.56 have developed a three-component one pot condensation of aldehydes ethylacetoacetate 110a/

CHO +	0 0 Me → 0Et + NH₄OAc - 110a	Catalyst, rt Solvent free	Eto Me H 123a
Entry	Catalyst	Time (min)	yield (%) ^a
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	40 wt% PW/K10 (0.2g) 40 wt% PMo/K10 (0.2g) 40 wt% SiW/K10 (0.2g) 40 wt% SW/KSF (0.2g) 40 wt% PM/KSF (0.2g) 40 wt% SiW/KSF(0.2g) 40 wt% SiW/SF(0.2g) 40 wt% SiW/g-Al ₂ O ₃ (0.2g) 40 wt% PW/YC (0.2g) 40 wt% PW/C (0.2g) 40 wt% SiW/C (0.2g) 40 wt% SiW/C (0.2g) 40 wt% SiW/SiO ₂ (0.2g) 40 wt% PMo/SiO ₂ (0.2g) 40 wt% PW/SiO ₂ (0.2g) 20 wt% PW/SiO ₂ (0.2g)	11 10 15 16 20 20 20 25 20 25 20 25 30 18 5 5 9	80 80 91 95 94 96 90 91 70 58 59 52 85 85 90 35
17 18 19	40 wt% PW/SiO ₂ (0.2g) 40 wt% PW/SiO ₂ (0.14g) 40 wt% PW/SiO ₂ (0.4g)	9 5 5	40 30

H₃PW₁₂O₄₀ (PW), H₄SiW₁₂O₄₀ (SiW), and H₃PMo₁₂O₄₀ (PMo)

Scheme 51 Effect of different catalyst on the yield of 1,4dihydropyridine.

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Table 14 Synthesis of Hantzsch 1,4-dihydropyridines by the condensation of aldehydes, β -dicarbonyl compounds and ammonium acetate/ amines using PW/SiO₂ as catalyst

	R-CHO	+ Ме	0 0 +	NH ₄ OAc/amine — Solvent free PW/SiO ₂	Product		
Entry	Aldehyde	х	Amine	Product		Product no.	Time (min)/ % yield ^a (%)
1	<i>С</i> -сно	OEt	NH4OAc	O O Me O Me OEt		123a	5/190
2	СНО	OEt	NH4OAc	O O Me NH NH O Me OEt		123m	13/94
3	Сно	OEt	NH4OAc	OEt Me NH O OEt Me OEt		123l	4/98
4	— Сно	OEt	NH4OAc	O O Me NH O Me OEt		123b	35/96
5	СІ—	OEt	NH4OAc	CI O Me O Me O Et		123d	8/92
6	СНО	ОМе	NH ₄ OAc	OEt PhHC H O OEt Me OEt		142b	20/91
7	МеО-СНО	Ph	NH4OAc	MeO MeO MeO MeO Me Ph		151a	32/55
8	О ₂ N-СНО	ОМе	OH(CH ₂) ₂ NH ₂		1	151b	15/86



^{*a*} Isolated yield, based on aldehyde. ^{*b*} Aldehyde : β-dicarbonyl compound : ethanolamine (1 : 3 : 1.5).

phenylacetylacetone **110e** and NH₄OAc in the presence of a solid catalyst (montmorillonite K10 clay) to afford 1,4-dihydropyridines **123a**, **123b**, **123g**, **123i**, **142a** and **143a–c** in good yields (Scheme 47). This procedure has advantages such as short reaction time, high yield and simple reaction workup conditions. Rawat, *et al.*⁵⁷ have developed an efficient methodology for the three-component one pot condensation of aldehydes, alky-lacetoacetate **110a/110b** and NH₄OAc using barium nitrate as a efficient catalyst to afford 1,4-dihydropyridines **123n**, **123f**, **123l**, **142a** and **144a–q** (Scheme 48).



^a Isolated yield.

Scheme 52 Triphenylphosphine-catalyzed Hantzsch synthesis of 1,4-dihydropyridines.

Heydari, *et al.*⁵⁸ has synthesized 1,4-dihydropyridines **123a**, **123b**, **123d**, **123e**, **123h**, **123j**, **123l**, **144m** and **145a–b** in excellent yields by the reaction of aldehydes, alkyl acetoacetate **110a–b**, and ammonium acetate (Scheme 49) at 70 °C in trifluoroethanol (TFE). The advantage of this reaction was the solvent (TFE), which can be readily separated from reaction products and recovered in excellent purity for reuse.

Wanner, *et al.*⁵⁹ have developed a methodology for the synthesis of 4,4-disubstituted 1,4-dihydronicotinates 148a-g by the regioselective addition of Grignard reagents RMgX or R₂Mg to nicotinic acid ester 146, activated with triisopropylsilyl triflate 147 (Scheme 50). The regioselectivity of this reaction, where 4-unsubstituted and 4-substituted pyridine derivatives were employed as starting materials, was examined. Depending on the structure of the organomagnesium reagent varying ratios of 1,2- (149a-g), 1,4- (148a-g), and 1,6-regioisomers (150a-g)

were obtained but in all the cases 1,4-addition products were predominating one.

Rafiee, *et al.*⁶⁰ have prepared 12-tungstophosphoric acid (PW) supported on different metal oxides and their catalytic performances have been evaluated in the three component condensation of benzaldehyde, ethyl acetoacetate **110a** and ammonium acetate to afford the corresponding 1,4-dihydropyridine **123a** (Scheme 51). A high catalytic activity was found over silica supported PW. Effect of PW loading, catalyst loading and solvent has been studied by the author to find out the best reaction condition. 40% PW onto SiO₂ (0.2 g) under solvent-free condition has been found to be the best catalyst for the synthesis of 1,4-dihydropyridines.

A series of 4-aryl, *N*-alkyl, and *N*-aryl substituted 1,4-dihydropyridines **123a**, **123b**, **123m**, **123l**, **123d**, **142b** and **151a–f** have been synthesized using different aldehydes in good to excellent yield in short reaction times (Table 14).



123a, 123b, 123c, 123d, 123f, 123h, 123i, 123l, 123m,142a, 144i,153a-d

Entry	Product (R)	Time (h)	Yield ^a (%)
1	C ₆ H ₅ (123a)	3	80
2	4-OMe-C ₆ H ₄ (123c)	4	82
3	4-F-C ₆ H ₄ (153d)	3.5	86
4	4-Cl-C ₆ H ₄ (123d)	4	91
5	4-CH(CH ₃) ₂ -C ₆ H ₄ (153a)	5	81
6	4-C(CH ₃) ₃ -C ₆ H ₄ (153b)	5	86
7	4-NO ₂ -C ₆ H ₄ (123h)	3.5	82
8	$2-NO_2-C_6H_4$ (123f)	5.6	65
9	3-NO ₂ -C ₆ H ₄ (142a)	5	71
10	β-Naphthyl (144i)	5	72
11	4-Me-C ₆ H ₄ (123b)	3	82
12	2-OMe-C ₆ H ₄ (123i)	6	61
13	2-Furyl (123I)	5.5	92
14	2-Thienyl (123m)	5	94
15	Isopropyl (153c)	5	89

^a Isolated yield.

Scheme 53 CeCl₃·7H₂O-catalyzed synthesis of Hantzsch 1,4-dihydropyridines.



Scheme 54 Optimization of Lewis acid catalysts for the synthesis of 1,4-dihydropyridine 155

Debache, *et al.*⁶¹ have developed triphenylphosphinecatalyzed Hantzsch three-component reaction of an aromatic aldehydes, ethyl acetoacetate **110a** and ammonium acetate to afford Hantzsch 1,4-dihydropyridines **123a**, **123b**, **123c**, **123d**, **123h**, **123j**, **123l**, **123m**, **142a**, **142b**, **142d** and **152** in good to excellent yields (Scheme 52).

Yadav, *et al.*⁶² have developed an efficient one-pot synthesis of 1,4-dihydropyridines **123a**, **123b**, **123c**, **123d**, **123f**, **123h**, **123i**, **123m**, **142a**, **144i**, **153a–d** in good to excellent yields *via* the CeCl₃·7H₂O-catalyzed Hantzsch three-component reaction of an aromatic aldehydes, ethyl acetoacetate **110a** and ammonium acetate (Scheme 53).

Ajavakom, *et al.*⁶³ have screened several Lewis acid catalysts such as $BF_3 \cdot OEt_2$, $AlCl_3$, and $TiCl_4$ on β -amino acrylates **154**, for the synthesis of 1,4-dihydropyridine **155** (Scheme 54). The yield of product **155** obtained from these initial screening of the Lewis acid catalyst were not satisfactory, which may be likely due to the decomposition of the acetal group in β -amino acrylate **154** under acidic conditions. Out of the several screened Lewis acid catalyst TiCl₄ in dichloromethane was found to be best catalyst for the synthesis of 1,4-dihydropyridine **155**.

Several 1,4-dihydropyridines derivatives **141** and **157a–h** has been synthesized from β -amino acrylates **156a–i** using TiCl₄ as a Lewis acid catalyst (0.2/0.5 equiv.) at 0 °C – rt (Scheme 55).

Li, *et al.*⁶⁴ have screened several experimental conditions to synthesize 1,4-dihydropyridines by the condensation of (*Z*)-3-(4-methoxyphenylamino)-1-phenylprop-2-ene-1-one (**158a**) with *p*-nitrobenzaldehyde in the presence of catalytic amount of Lewis acids. The reaction of **158a** with *p*-nitrobenzaldehyde in the presence of a catalytic amount of TsOH·H₂O, TFA or NaAuCl₄- $2H_2O$ yielded the desired 1,4-DHP **159a** in 71–79% yield (Table 15, entries 2–4). Increase in the aldehyde equivalent from 0.75 to 1.0 not only lessened the reaction time, but also enhanced the yield of the desired product (Table 15, entry 2 *vs.* 6). The high yield of the 1,4-DHP **159** was achieved in the presence of TsOH·H₂O as a catalyst (85–87%; Table 15, entries 6 and 7).

		EtOOC				
H		TiCl₄ (0.2/0.5	EtOO equiv.)	c↓↓c	OOEt	
R ^{^ N} \	COOEt	0 °C-rt		^ℓ N [′]		
		0.011		Ŕ		
156a-156i			1	141 and 157a	a-h	
Entry	Acrylate	R TiCl	₄ (equiv)	Product	Yield (%)	
1	156a	<i>п</i> -Ви	0.2	157a	81	
2	156b	<i>п</i> -С ₁₈ Н ₃₇	0.2	157b	83	
3	156c	Bn	0.2	157c	79	
4	156d	HOCH ₂ CH ₂	0.2	157d	81	
5	156e	Ph	0.5	141	82	
6	156f	<i>p</i> -MeO-C ₆ H₄	0.2	157e	52	
7	156f	<i>p</i> -MeO-C ₆ H₄	0.5	157e	76	
8	156g	<i>p</i> -I-C ₆ H ₄	0.2	157f	58	
9	156g	<i>p</i> -I-C ₆ H ₄	0.5	157f	79	
10	156h	<i>p</i> -F-C ₆ H ₄	0.5	157g	70	
11	156i	m-CI-C ₆ H ₄	0.5	157ĥ	76	

Scheme 55 TiCl₄ catalysed synthesis of 1,4-dihydropyridines 141 and 157a-h.

Tamaddon, *et al.*⁶⁵ have developed a green, efficient one-pot synthesis of various 4-alkyl/aryl-1,4-dihydropyridines in an excellent yields *via* the Hantzsch three-component reaction of an aromatic/aliphatic aldehydes, alkyl acetoacetate **110a/110b** and ammonium carbonate in water (Scheme 56).

Shimizu, *et al.*⁶⁶ have developed an efficient one-pot synthesis of 1,4-dihydropyridines **161a–z** in moderate to good yields *via* the Yb(OTf)₃-catalyzed Hantzsch three-component reaction of an aromatic aldehydes, 3,3-dimethoxy propionate **160** and aromatic amines in 1,4-dioxane at 90 °C (Scheme 57).

Wang, *et al.*⁶⁷ have developed an efficient one-pot synthesis of 1,4-dihydropyridines in an excellent yields *via* the Hantzsch three-component reaction of an aromatic/aliphatic aldehydes, alkyl acetoacetate **110a/110b** and ammonium acetate in PEG-400 as solvent at 90 °C (Scheme 58). PEG-400 facilitates the reactants converting into corresponding products smoothly in excellent yields because of its good immiscibility with a number of organic reagents. Moreover, PEG-400 is inexpensive, thermally stable, nonvolatile, and nontoxic.

2.3. Synthesis of enantiopure 1,4-dihydropyridines

2.3.1. Resolution of racemic 1,4-dihydropyridine carboxylic acids *via* diastereomeric salt formation. Chiral crystallization





Entry	<i>p</i> -NO ₂ -C ₆ H ₄ -CHO (eq.)	Catalyst (mol%)	Time (h)	% yield of 159a ^a
1	0.75	$Sc(OTf)_3(5)$	12	34
2	0.75	$TsOH \cdot H_2O(10)$	3	75
3	0.75	TFA (10)	5	71
4	1.0	NaAuCl ₄ \cdot 2H ₂ O (5)	1	79
5	1.0	TFA (5)	20	91
6	1.0	$TsOH \cdot H_2O(10)$	1	85
7	1.0	$T_{sOH} \cdot H_{2O}(5)$	1	87
8	1.0	$FeCl_3 \cdot 6H_2O(10)$	3	48
9	1.0	_	10	NR^{b}

^{*a*} Isolated yields. ^{*b*} NR = no reaction.



Scheme 56 Synthesis of 1,4-dihydropyridines using ammonium carbonate in water.

with the use of resolving agents to form diastereomeric salts is a widely used technique for resolving chiral compounds. Cinchonidine, cinchonine and quinidine are the most commonly

used natural chiral amine bases applied which are used to resolve racemic 1,4-dihydropyridinecarboxylic acid *via* forming their diastereomeric salts. It has been observed that these alkaloids



[a] Isolated yields based on arylamine. [b] PMP = p-Methoxyphenyl.

Scheme 57 Yb(OTf)₃ catalyzed one-pot synthesis of 1,4-DHPs 161a-z.



Scheme 58 Synthesis of 1,4-dihydropyridines in PEG-400.

behave as quasi-mirror images and are used in a complementary way to obtain both enantiomers of 1,4-dihydropyridines in a pure form. The method involves treatment of racemic acid with a chiral base which leads to the formation of diastereomeric salts (Scheme 59). The enantiomer is then obtained in pure acid form by repeated crystallization followed by acidification. The other enantiomer is recovered from the mother liquor and resolved using other suitable chiral base reagent by going through the same procedure. The first resolution of racemic dihydropyridinecarboxylic acids through this method was carried out by Shibanuma, et al.68 to synthesize nicardipine from 1-ethoxymethyl-5-methoxycarbonyl-2,6-dimethyl-4-(m-nitrophenyl)-1,4dihydropyridine-3-carboxylic acid (\pm) -162 using cinchonine and cinchonidine (Scheme 59). Various other 1,4-dihydropyridine derivatives have been synthesized similarly through optical resolution of racemic mixture of 1-ethoxymethylated dihydropyridines and by subsequently removing the ethoxymethyl group.69

Synthesis of optically-active 1,4-dihydropyridine derivatives from 1-ethoxymethylated carboxylic acid **162** involves protection and deprotection approach for NH group in 1,4-DHP ring. Use of unprotected racemic acid for direct resolution has also been investigated in detail. Zhang, *et al.*⁷⁰ treated racemic acid (\pm)-**165** with cinchonidine to form diastereomeric salt (*S*)-(+)-**167** (Scheme 60). (*S*)-(+)-**167** enantiomer was formed by repeated crystallization and further treatment with hydrochloric acid. When quinidine was used (*R*)-(-)-**166** was formed.

The separation of (*R*)- and (*S*)-amlodipine **170** has been achieved by treatment of racemic acid **168** with cinchonidine in methanol. Dilution with water formed a crystalline precipitate which was recrystallized to yield diastereomerically pure cinchonidine salt **169**, which was further converted to enantiomerically pure (*R*)- and (*S*)-amlodipine in several synthetic steps (Scheme 61).⁷¹

Various chiral acids have been used for the separation of racemic basic dihydropyridines. Racemic amlodipine **170** has been resolved using (1S)-(-)-camphanic acid chloride (Scheme 62) by Goldmann, *et al.*⁷² The diastereomeric amides **171** obtained were easily separated chromatographically on Chiralcel OD column followed by crystallization from DMF/water.

Another remarkable method to get *R*-(+) and *S*-(-) amlodipine **170** is through L or D-tartaric acid respectively in DMSO.⁷³ It has been reported that (*R*)-amlodipine tartrate crystallizes out preferentially when naturally occurring L-tartaric acid is used with racemic amlodipine in DMSO. Recently it has been described that (*S*)-isomer of amlodipine could also be obtained with L-tartaric acid just by changing the solvent system (Scheme 63). By using DMF/H₂O (85 : 15 ratio) desired (*S*)-(-)-**172** crystallized out with 99% purity.⁷⁴ By reacting **172** with benzenesulfonic acid, active pharmaceutical ingredient (*S*)-(-)-amlodipine besylate hemipentahydrate salt **173** was obtained.

2.3.2. Separation of racemic 1,4-dihydropyridines by using chiral auxiliary. This synthetic strategy utilizes chiral auxiliary for the synthesis of optically active 1,4-dihydropyridines by forming diastereomeric esters which can be separated and eventually the chiral auxiliary can be regioselectively removed. Synthesis of 5-cyano-1,4-dihydropyridines from isoxazolo[5,4-*b*]



Scheme 59 Synthesis of enantiopure 1,4-dihydropyridines 165 via diastereomeric salt formation method.



(R)-(-)-165, , Quantitative yield (S)-(+)-165, , Quantitative yield

Scheme 60 Synthesis of chiral 1,4-dihydropyridine 165 via diastereomeric salt formation method.

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pyridines have been achieved by Taylor, *et al.*⁷⁵ The monoester derivative **174** was reacted with nitrile oxide to produce isoxazolo[5,4-*b*]pyridine **175** in 74% yield (Scheme 64). Its saponification formed an acid which was then re-esterified with (–)-menthol. The resulting diastereomeric esters **176** were separated through flash chromatography, which on hydrolysis and decarboxylation yielded the desired 5-cyano-1,4dihydropyridine-3-carboxylic acid **177**.

Arrowsmith, *et al.*⁷⁶ esterified (\pm)-**178** using optically pure (*S*)-(+)-2-phenylethanol to give diastereomeric mixture **179**. It was chromatographically separated on silica gel to form pure diastereomers and further treatment with sodium ethoxide and finally reduction of azide group by palladium on calcium carbonate yielded pure enantiomers (*R*)-(-)-amlodipine and (*S*)-(+)-amlodipine **170** (Scheme 65).

Lamm, *et al.*⁷⁷ disclosed the formation of pure enantiomers of felodipine **185**, a calcium channel antagonist by chromatographic separation of diastereomeric esters **183** prepared from (*R*)-1-(*p*-toluenesulfonyl)-3-tritylpropan-2-ol **181** (Scheme 66). This chiral auxiliary was removed easily by β -elimination reaction using potassium hydroxide in methanol at room temperature. Esterification of **184** with iodomethane successfully yielded (*R*)- and (*S*)-enantiomers of felodipine **185**.

Racemic isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4pyridinylpyridine-5-carboxylate isomers with *in vitro* calcium channel modulating activities have been described by Vo, *et al.*⁷⁸ Out of them the most promising 4-(2-pyridinyl) compound was resolved into pure enantiomers with the help of L-threonine **186** (Scheme 67). Through a multistep synthesis L-threonine was converted to β -aminocrotonate derivative **187**, which through



Scheme 61 Separation of (R)- and (S)-amlodipine 170 by treatment of racemic acid 168 with cinchonidine in methanol.



Scheme 62 Resolution of racemic amlodipine 170 using (15)-(-)-camphanic acid chloride.

Hantzsch condensation afforded the mixture of 1,4-DHP diastereomers 188 separable by silica gel column chromatography. This was followed by removal of chiral auxiliary using DBU to yield 189 and desired enantiopure (-)-190 and (+)-190 were synthesized using isopropyl bromide and potassium carbonate in DMF.

Similarly synthesis of (S)-(-)- and (R)-(+)-enantiomers of 2nitrooxyethyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate79 192 exhibiting dual cardioselective agonist/smooth muscle selective antagonist activity⁸⁰ were synthesized utilizing D-threonine 191 as chiral auxiliary (Fig. 2). In both the cases the chiral esterifying group was easily removed by non-nucleophilic base 1,8-diazabicyclo [5.4.0]-undec-7-ene (DBU).

To synthesize chiral β -ketoester 195, (4R,5R)-(-)-2,3-O-isopropylidine-p-threitol was used as chiral auxiliary (Scheme 68).⁸¹ Using **195** as chiral β-ketoester, phenylpropargyl aldehyde 194 and benzyl 3-amino-3-phenyl-2-propenoate 193, 1,4-DHP diastereomers 196 were obtained which were resolved through HPLC. 2,2-Dimethyl-1,3-dioxolane-4-methanol and 2,3-O-isopropylidine-D-threitol moieties on the chiral ester were replaced by ethyl group through deprotection of diol by acidic treatment followed by transesterification in ethanol to afford 197.

2.3.3. Synthesis of enantiomerically pure 1,4-DHPs using chiral aldehydes. Synthetic methodology to synthesize 4-alkyl-3,5-dialkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines 200a-c has been developed by utilizing chiral aldehydes 198a-c (Scheme 69).82 Enantiomerically pure 1,4-DHPs 200a-c were synthesized by Michael addition of ethyl aminocrotonate 114a to chiral α -acetylacrylates **199a–c**. The synthesis of α -acetylacrylates 199a-c was carried out by knoevenagel condensation of methylacetyl acetate and the corresponding chiral aldehyde.

2.3.4. Organocatalytic asymmetric synthesis to form enantiomerically enriched dihydropyridines. Chiral



Scheme 64 Separation of 174 using nitrile oxide as a chiral auxiliary.

phosphonic acids 134b, 201a-c and 202 have been recognized as promising catalysts for asymmetric synthesis of 1,4-dihydropyridines (Scheme 70). A three-component cyclization of an α , β -unsaturated aldehyde 56f, a primary amine 62h and ethyl acetoacetate 110a in presence of chiral phosphonic acids 134b, 201a-c and 202 have been explored to generate chiral 1,4dihydropyridines 203 with excellent ee upto 98% (Scheme 70).83 The screening of phosphonic acids 134b, 201a-c and 202 showed that increasing size of substituents at 3,3'-positions of the chiral catalyst and increase in the reaction temperature leads to enhanced enantioselectivities (Table 16). It was concluded that in PhCN at 50 °C phosphonic acids 201c and 202 afforded 203 with 89% and 90% ee, respectively. Decreasing the amount of 202 from 20 mol% to 10 mol% led to an improved ee of 203 up to 92%.



Scheme 63 Resolution of R_{+} and S_{-} among moduli and R_{+} and $R_$









Yamamoto, *et al.*⁸⁴ described an efficient asymmetric synthesis of 1,4-dihydropyridine derivatives. The key step of this reaction was the stereoselective Michael addition using *t*-butyl ester of L-valine **207** as a chiral auxiliary to achieve good ee of **209** (>95%) and moderate yield (Scheme 71). With this method, (+)-4-(3-chlorophenyl)-6-dimethoxymethyl-2-methyl-1,4-dihydropyridine-3,5-dicarboxylic acid cinnamyl ester (+)-**209** was obtained and was characterized as a promising N-type calcium channel blocker with improved selectivity over L-type compared to its (–)- and racemic isomers.

3. Utility of dihydropyridines in the synthesis of natural products

3.1. Utility of 1,2-dihydropyridines in the synthesis of natural products

Kutney, *et al.* have synthesized two pyridocarbazole alkaloids, olivacine **212** and guatambuine **213** by utilizing the tricarbonylchromium complex **211** of the suitable 1,2-dihydropyridine, which was synthesized from indole **210** (Scheme 72).⁸⁵

COOCH

COOCH₃

Ν̈́ΗR

CH₃

N

(+)-188

021





R'CHO

CH₃COCH₂NO₂

EtOH





The synthesis of (\pm) -elaeokanine A 216 has been achieved in a regioselective manner from 1-methoxycarbonyl salt of 3-(iPr)₃ silyl pyridine 214 by Comins and Myoung.86 The 1-methoxycarbonyl salt of 3-(iPr)₃ silyl pyridine was first converted into the 1,2-dihydropyridine derivative 215, which was then converted into the (\pm) -elaeokanine A into several number of synthetic steps (Scheme 73).

2-Substituted-1,2-dihydropyridine and piperidines has been synthesized in regio- and stereoselective manner from unsubstituted pyridinium salt. The approach relies on stereoselective formation of (E)-isomer of N-pyridinium imidate 218 from amide 217 in which the nitrogen lone pair is oriented at the proper position to direct the addition of Grignard reagent 219 at the 2-position. This approach has been used for the synthesis of 2-substituted-1,2-dihydropyridine 220 and R-(-)-coniine 221 (Scheme 74).87

2,3-Disubstituted-1,2-dihydropyridines 224 and 225 have been synthesized from the 3-substituted pyridinium salts 222 and 223, respectively (Scheme 75). This methodology has been applied for the synthesis of (-)-L-733 061 (226) and (-)-CP-

99 994 (227), two members of a new class of highly potent, nonpeptide, substance P antagonists.88

A simple synthesis of the fused tetrahydro-imidazopyridine 229 was accomplished via selective addition of protected guanidine 228 to N-carbomethoxy-1,2-dihydropyridine 1 in the presence of bromine at room temperature. Base-mediated semicleavage of the aminal gave 4-substituted 2-aminoimidazole 230 (Scheme 76). With this new method, natural marine metabolite 3-amino-1-(2-aminoimidazol-4-yl)-prop-1ene (marine C6N4 2-aminoimidazole alkaloids) 231 and its derivatives may be prepared starting from pyridine.⁸⁹

The asymmetric synthesis of 2,6-disubstituted 3-piperidinols having a 2,3-cis and 2,6-trans relative stereochemistry has been accomplished from 2-substituted 1,2-dihydropyridine 233 (synthesized from unsubstituted pyridinium salt 232) via a onepot, highly diastereoselective epoxidation-nucleophilic addition with a heteroatom nucleophile or an organometallic reagent. This methodology was applied to the expedient asymmetric synthesis of (+)-julifloridine 234 in four steps (Scheme 77).90



Scheme 68 Use of (4R,5R)-(-)-2,3-O-isopropylidine-D-threitol was used as chiral auxiliary in the separation of 1,4-DHP.

Table 16	Effect	of	phosphonic	acids	134b,	201a-c	and	202	and
increase i	n the re	acti	ion temperat	ure on	the er	nantiosele	ectivi	ty of	203

Catalyst	Solvent	Temperature (°C)	Yield (%)	ee (%)	Product
201-	QUO	25	70	10	(0) 202
201a	CHCI ₃	25	12	19	(3)-203
134b	$CHCl_3$	25	85	19	(S)-203
201b	$CHCl_3$	25	62	31	(S)-203
201c	$CHCl_3$	25	67	73	(S)-203
201c	$CHCl_3$	40	80	80	(S)-203
201c	$CHCl_3$	50	85	82	(S)-203
201c	PhCN	50	82	89	(S)-203
202	$CHCl_3$	25	69	64	(R)-203
202	$CHCl_3$	50	86	72	(R)-203
202	PhCN	50	83	90	(R)-203
202 (10 mol%)	PhCN	50	82	92	(R)-203

Marine metabolites pyrrole-2-aminoimidazole oroidine, hymenidin and clathrodine have been synthesized *via* one pot oxidative bromine mediated addition of 2-aminopyrimidine **237** to the *N*-acyl-1,2-dihydropyridine **236** to form compound **238**. The *N*-acyl-1,2-dihydropyridine was synthesized by the reaction of pyrrole-2-carbonyl chloride **235** with pyridine followed by the reduction using sodium borohydride. The compound **238** was treated with hydroxylamine hydrochloride and resulted into the formation of amide **239** and **240**. The treatment of amide **239** and **240** with trifluoroacetic acid in dichloromethane resulted



Scheme 69 Synthesis of chiral 1,4-DHPs 200a-c using chiral aldehydes.



Scheme 70 Chiral phosphonic acids catalyzed synthesis of 1,4-DHP 203.



Scheme 71 Stereoselective synthesis of 1,4-dihydropyridine 209.

into the formation of oroidine **241** and hymenidine **242** or clathrodine **243** in good yields (Scheme 78).⁹¹

Stereoselective synthesis of L-picolic acid and (2S,3S)-3hydroxypipecolic acid were achieved from a chiral 1,2-dihydropyridine intermediate 244. L-Picolic acid 248 has been obtained via reduction of 244 to 245, removal of chiral auxiliary yields 246, oxidation yields 247 and basic hydrolysis of 247 yields 1-picolic acid 248. (2S,3S)-3-Hydroxypipecolic acid 253 was obtained in five steps (i) tandem hetero Diels-Alder reaction of 244 with oxygen to yield 249, (ii) alane reduction to yield 250, (iii) N and O-protection to afford 251, (iv) reduction of double bond to yield 252, and (v) sharpless oxidation to yield 253 (Scheme 79). L-Picolic acid is a naturally occurring nonproteinogenic a-amino acid and many biological alkaloids contain this moiety as a key structural unit or are derived from it. (2S,3S)-3-Hydroxypipecolic acid is found in febrifugine a potent antimalarial agent. Both L-picolic acid and (2S,3S)-3hydroxypipecolic acid are conformationally constrained amino acids relevant to the study of peptide structure and drug design.92



Scheme 72 Synthesis of pyridocarbazole alkaloids.



Scheme 73 Synthesis of (\pm) -elaeokanine A using 1,2-dihydropyridine derivative.



Scheme 74 Synthesis of R-(–)-coniine.



Scheme 75 Synthesis of 2,3-disubstituted-1,2-DHP: synthesis of (-)-L-733, 061 and (-)-CP-99, 994.



Scheme 76 Synthesis of marine C₆N₄ 2-aminoimidazole alkaloids.

3.2. Utility of 1,4-dihydropyridine in the synthesis of natural products

Yohimbines are pentacyclic indole alkaloids containing five chiral centres. A convergent six steps synthesis of (\pm) -pseudoyohimbines has been accomplished from methyl- β -(β -pyridyl) acrylate **254** (Scheme 80). Methyl- β -(β -pyridyl)acrylate **254** was converted into pyridinium salt **256** using tryptophyl bromide **255**, which was then converted into 1,4-dihydropyridine derivative **257**. The 1,4-dihydropyridine **257** was converted into (\pm)-pseudo-yohimbines **258** in several steps.⁹³

Indoloquinolizine alkaloid, deplancheine has been synthesized starting from pyridinium salt **256**. The pyridinium salt **256** was reduced to 1,4-dihydropyridine derivative **259** using sodium dithionate. The treatment of 1,4-dihydropyridine with HCl·MeOH resulted into the formation of cyclised product **260**. The chloride salt **261** was synthesized using HCl·H₂O from **260**, which was reduced selectively to yield (\pm)-deplancheine **262** in good yield (Scheme 81).⁹⁴

Vinoxine is amino indole alkaloid and its first total synthesis is based on the intramolecular cyclisation of suitably substituted 1,4-dihydropyridine–indole conjugate **265**. The dihydripyridine–indole conjugate was synthesized by the reaction between methyl 2-(1*H*-indol-1-yl)acetate **263** and pyridinium salt **264** in the presence of LDA in THF. The intramolecular cyclization reaction on compound **265** was



Scheme 77 Synthesis of (+)-julifloridine from 1,2-dihydropyridine.







Scheme 79 Synthesis of L-picolic acid and (2S,3S)-3-hydroxypipecolic acid.

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carried out using C_6H_6 ·HCl to afford **266**. The chloride salt **267** of **266** was synthesized using 4 N HCl followed by the esterification and selective reduction afford the vinoxine **268b** in good yield (Scheme 82).⁹⁵

Bosch, *et al.*⁹⁶ has reported the synthesis of vinoxine analogue bearing C-16 methoxycarbonyl substituent, 19,20dihydro-16-epivinoxine **275**. The synthesis of 19,20-dihydro-16epivinoxine **275** has been achieved from 3-ethyl-4-pyridine

260

261

CI

 HCI/H_2O \triangle , 5h

NaBH₄, MeOH

COOMe



259

1,4-Dihydropyridine

(±)-Deplancheine ¹ 262, yield 25 %

Scheme 81 Synthesis of (\pm) -deplancheine.



Scheme 82 Synthesis of vinoxine 268b.

carboxylate **269** *via* the synthesis of 1,4-dihydropyridine analogue **274** (Scheme 83).

An efficient route for the synthesis of tetracyclic ABCD ring substructures of *Strychnos* alkaloids has been carried out by synthesizing the 1,4-dihydropyridine 277 derivative from indole-2-carboxylate 276 and 264. The compound 1,4-dihydropyridine 277 was converted into disulfane analogue 278 in six steps, which was converted into pentacyclic compound 279 by generating the carbanion of compound 278 using DMTSF (dimethyl(methylthio)sulfonium fluoroborate). The resulting pentacyclic compound has been converted into tubifolidine 280 by treating 279 with RANEY® Ni. Tubifoline 281 and 19,20dihydroakummicine 282 were synthesized by first *N*-protection with methyl carboxylate and desulferisation to yield 281 followed by treatment with sodium methoxide and photolysis, respectively (Scheme 84).⁹⁷

Ervitsine 289 is a minor 2-acylindole alkaloid isolated in 1977 from Pandaka boiteau. The first total synthesis of ervitsine 289 through a straightforward, biomimetic sequence involving only three separate synthetic steps (Scheme 85) has been reported by Bennasar, et al.98 The key intermediate was the iminium cation 286. The iminium cation 286 was synthesized from 1,4-dihydropyridine derivative 285 using Me_2N^+ = CH_2I^- . The 1,4-dihydropyridine derivative 285 was synthesized using 2acetyl indole 283 and pyridinium salt 284. The iminium cation 286 would undergo regioselective cyclization to the bridged tetracyclic system 287, which was converted into N-methyl ervitsine 289a and ervitsine 289b into two synthetic steps first by treatment with mCPBA to yield 288 followed by borohydride reduction. A short four-step synthesis of N-methyl ervitsine involving the nucleophilic addition of acetyl indole to pyridinium salt, with subsequent C6H5SeBr-promoted cyclization



Scheme 83 Synthesis of 19,20-dihydro-16-epivinoxine 275.



Scheme 84 Synthesis of tubifolidine 280, tubifoline 281 and 19,20-dihydroakummicine 282.

of 1,4-dihydropyridine instead of $Me_2N^+ = CH_2I^-$ promoted cyclization has been further reported by Bennasar, *et al.*⁹⁹

The first total synthesis of (\pm) -2,7-dihydropleiocarpamine **295** has been reported by Bennasar, *et al.*¹⁰⁰ *via* the synthesis of 1,4-dihydropyridine **291** as an intermediate (Scheme 86). The 1,4-dihydropyridine **291** was synthesized from nucleophilic addition of **263** on pyridinium salt **290** in the presence of LDA in THF. The key step is the photocyclization of the tetracyclic chloroacetamide **294** to give the required six membered ring *via* closure of C-6/C-7 bond formed by diradical coupling, which was not achieved by electrophilic cyclization.

The ervatamine alkaloids (19,20-dehydroervatamine **307**, 20-epiervatamine **308** and ervatamine **309**) constitute a group of 2-acylindole alkaloids. Bennasar, *et al.*¹⁰¹ has reported the total synthesis of 19,20-dehydroervatamine and 20-epiervatamine, whereas ervatamine was synthesized from 19,20-dehydroervatamine *via* catalytic hydrogenation. The intermediate 1,4-dihydropyridine **299** formed *via* the nucleophilic

attack of *N*-benzyl-2-acetyl indole **296** to the γ -position of the pyridinium salt **297**. The 1,4-dihydropyridine **298** was functionalized to give 3,5-diacyl-1,4-dihydropyridine **299**, which was reduced to tetrahydropyridine **300**, and was further converted to *cis*-fused pentasubstituted piperidines (19,20-dehydroervatamine **307**, 20-epiervatamine **308** and ervatamine **309**) in number of steps by using suitable reagents (Scheme 87).

Bennasar, *et al.*¹⁰² has reported a general route for the synthesis of tetracyclic ring system of silicine–methuenine alkaloids **311** and **312**. The key step in the synthesis was the selective reduction of the intermediate **299** by using PtO₂ followed by debenzylation to afford **301**, which on cyclisation using trimethylsilyl polyphosphate PPSE yielded **310** (Scheme 88). The compound **310** was further converted into tetracyclic ring system of silicine–methuenine alkaloids **311** and **312** in number of steps. The 1,4-dihydropyridine intermediate **299** was synthesized according to the literature procedure reported by Bennasar, *et al.*¹⁰¹



Scheme 85 Synthesis of N-methyl ervitsine 289a and ervitsine 289b.



Scheme 86 Synthesis of (\pm) -2,7-dihydropleiocarpamine 295

Bennasar, *et al.*¹⁰³ has reported a general route for the synthesis of 6-oxo-16-episilicine **320** (a silicine-methuenine alkaloid), involving the nucleophilic addition of an acetylindole enolate **296** to the pyridinium salt **284** to yield 1,4dihydropyridine **313** as an intermediate. The 1,4-dihydropyridine **313** was functionalized to give 3,5-diacyl-1,4dihydropyridine **314**, which was reduced to tetrahydropyridine **315**, and was subjected to PPSE-induced cyclisation to yield **316**. Hydrolysis of compound **316** using MeOH \cdot H₂O, HCl followed by decarboxylation using 2,2'-dithiobis-(pyridine-*N*oxide) yielded **317**, which on *N*-debenzylation yielded **318**. The debenzylated compound **318** on reduction using NaBH₃CN







Scheme 88 Synthesis of silicine-methuenine alkaloids 311 and 312.

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yields **319**, which on oxidation with MnO_2 yield 6-oxo-16episilicine **320** (Scheme 89).

Pyridoacridines are a family of alkaloids based on 1H-pyrido[4,3,2,*mn*]acridine skeleton. The synthesis of pyridoacridine ring **329** of alkaloid amphimedine **330** was achieved by condensing ^{*t*}butyl-protected 2-lithio-1,4-DHP **324** with 3,4-disubstituted cyclobutanediones **325** to yield **326** followed by thermolysis to yield **327**. The conversion of **327** in aniline derivative **328** was achieved using hydroxylamine hydrochloride and oxidation with ^{*t*}-BuOOH in presence of KOH yielded dihydroquinoline hydroquinine ring system **329**. The Boc-protected 2-lithio-1,4-DHP was synthesized by the reaction between the Grignard reagent of *N*-(2-bromophenyl)-2,5-dimethylpyrrole **321** with *N*-carboxyphenylpyridinium chloride (Scheme 90).¹⁰⁴ Akagerine **338** is a tetracyclic indole alkaloid. A formal stereoselective synthesis of akagerine **338** had been reported *via* pentacyclic dilactam **337**.¹⁰⁵ The intermediate dilactam **337** was synthesized starting from **1**,4-dihydropyridine **333**, which was synthesized from the nucleophilic attack of the *N*-acetyl indole **331** on pyridinium salt **332**. Compound **333** was converted into **334** using sulfonic acid. The hydroxyl group of the compound **334** was removed *via* first triflation followed by reduction to afford compound **335**. The key step is the formation of piperidine ring of compound **336**, which was accomplished by cyclization of thionium ion generated by Pummerer rearrangement using TFAA in presence of 2,6-di(*t*-butyl)pyridine. Dilactam **337** was obtained by the treatment of compound **336** with tributyltin hydride in benzene (Scheme **91**).¹⁰⁶



Scheme 89 Synthesis of 6-oxo-16-episilicine 320.



Scheme 90 Synthesis of 5,6-diisopropyl-oxypyrido[2,3,4,kl]acridin-4-one 330.





Scheme 92 Synthesis of geissoschizine 345.

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Formal synthesis of (\pm) -geissoschizine had been carried out using 1,4-dihydropyridine derivative $340.^{107}$ The 1,4dihydropyridine derivative 340 was synthesized from nucleophilic attack of the *N*-acetyl indole 331 on pyridinium salt 339. Compound 340 was converted into 341 using sulfonic acid in benzene, which on treatment with HCl followed by borohydride reduction yielded 342a. Compound 342a was first converted into sulfone 342b, followed by treatment with sodium methoxide resulted into the formation of compound 343, which on desulferisation using tributyltin hydride and AlBn give compound 344 (Scheme 92). Compound 344has been converted into geissoschizine 345 by Yamada, *et al.*¹⁰⁸ A concise total synthesis of (±)-camptothecin and natural (+)-camptothecin has been reported starting from 2-fluoro-1,4dihydropyridine adduct 351.¹⁰⁹ The 1,4-DHP adduct 351 was achieved from compound 346 in three steps. 2-Fluoro-1,4dihydropyridine adduct 351 on oxidation with DDQ resulted into the formation of compound 352, which on treatment with hydrogen atom donor tris(trimethylsilyl)silane-AIBN give compound 353 (Scheme 93). Formation of the pyran ring in compounds 354 and 20-dioxycamptothecin 355 takes place by the treatment of compound 353 with DIBAL and borohydride reduction. 20-Dioxycamptothecin 355 was further used for the synthesis of (±)-camptothecin and natural (+)-camptothecin *via* the literature procedure.¹¹⁰



Scheme 93 Synthesis of (\pm) -camptothecin and natural (+)-camptothecin.



Scheme 94 Synthesis of (+)-camptothecin 356.

The synthesis of natural (+)-camptothecin **356** has been reported by the nucleophilic addition of a chiral auxiliary **357** to the pyridinium salt **349** (Scheme 94). The remaining synthetic steps are similar as used in Scheme 93.¹⁰⁹

Putkonen, *et al.*¹¹¹ has reported the total synthesis of (\pm) -tangutorine **368** and modified the first synthetic procedure reported by Berner, *et al.*¹¹² For the synthesis of (\pm) -tangutorine **368**, desired quinoline derivative **362** was reacted with





Scheme 96 Synthesis of lyadine 375 and lyaline 376.

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tryptophyl bromide 255 to afford pyridinium salt 363. Since the total yield of the tangutorine skeleton was relatively low due to the different stereoisomers formed in the Fry reaction.¹¹² The total synthesis of indole alkaloid (\pm)-tangutorine 368 has been carried out using dithionite reduction of pyridinium salt 363 to afford the 1,4-dihydropyridine intermediate 365. Cyclization of compound 364 in HCl/MeOH to compound 365 and reduction with sodium borohydride in glacial acetic acid for overnight yielded a mixture of isomers of compound 366. (\pm)-Tangutorine 368 was afforded after dehydration of compound 366 and finally reduction of the ester group in compound 367 (Scheme 95).

The harman-1,4-dihydropyridines **373a-b**, which constitutes the original proposed structures for the indole alkaloid lyadine **375** and lyaline **376** have been synthesized by Bennasar, *et al.*¹¹³ (Scheme 96). The harman-1,4-dihydropyridines **373a-b** were synthesized starting from harman **369** and pyridine **371**. The nucleophilic addition reaction of Grignard reagent of harman **370** with pyridinium salt **372** prepared from pyridine **371**. The harman-1,4-dihydropyridine **373a** was converted into lyadine **375** in two synthetic steps first by *N*deacetylation followed by borohydride reduction, whereas lyaline **376** was obtained from the *N*-deacetylation of compound **373b**.

Amat, *et al.*¹¹⁴ has proposed a model for the synthesis of *Strychnos* alkaloid *e.g.* dihydroakuammicine **380** could be obtained starting from a suitable functionalized enantiopure 2-(1,4-dihydro-4-pyridylmethyl)indole **377** (Scheme 97).

The nucleophilic addition of indole acetic ester **381** and *N*-alkyl pyridinium salt **382a–b** followed by acid cyclization gave a mixture of expected tetracyclic compound **383a–b** along with regioisomer **384a–b** (Scheme 98). It is probably the bulkiness of chiral auxiliary hinders the approach of the nucleophile to the adjacent 4-position of pyridine ring.

The strategy for the synthesis of tetracyclic precursors ABCD of dihydroakuammicine using chiral auxiliary suffers two major drawbacks (i) low facial stereoselectivity due to inefficient coordination of nucleophile with the chiral auxiliary and (ii) low regioselectivity due to bulkiness of chiral auxiliary.¹¹⁴

4. Medicinal importance of dihydropyridines

The first synthesis of 1,4-dihydropyridine (1,4-DHP) nucleus was reported in 1881 by A. Hantzsch.26a It took 80 years to test these compounds for their biological activity, and finally Bossert and Vater at Bayer AG got the Hantzsch type 1,4-DHP possessing outstanding coronary vasodilator activity.115 Nifedipine, the 2-nitrophenyl derivative (Table 17) was then introduced for the treatment of coronary diseases.¹¹⁶ Due to the resemblance with NADH and also interesting biological activities, subsequently several other 1,4-DHPs (Table 17) have been introduced for clinical use as hypertensive agents that have a worldwide market of several billion dollars.117 Amlodipine (Norvasc), with sales of more than \$ 5 billion in recent years is among the top-five best selling drugs. DHP's have also been explored as anti-inflammatory,118 anti-tumor,119 antitubercular,120 anti-convulsant activity121 etc. 1,4-DHP drugs can be divided into three generations depending on their pharmacologic and pharmacokinetic profiles.¹²² Because of the short duration and rapid onset of vasodilator action, nifedipine activated sympathetic tone.123 Therefore, in the quest of better therapeutic standard, the first-generation drug, nifedipine has been extensively modified. The second generation drugs exert less sympathetic reflex by designing slow-release formulations of preparations of the short-acting drugs.124



Scheme 97 Proposed procedure for the synthesis of dihydroakuammicine 380.



Scheme 98 Synthesis of tetracyclic precursors 383 and 384 of dihydroakuammicine.

Table 17 Commercially important 1,4-DHP's









The third generation drugs exhibit more stable pharmacokinetics than the second-generation. These are less cardioselective and, hence well tolerated in patients with heart failure.¹²⁵ Now second and third generation 1,4-DHPs are being explored for the treatment of hypertension, angina, hypertrophic cardiomyopathy,¹²⁶ post-hemorrhagic cerebral vasospasm¹²⁷ and pulmonary hypertension, Raynaud's phenomenon.¹²⁸

5. Conclusion

Dihydropyridine (DHP) scaffold has certainly revolutionalised the pharmaceutical research with its unprecedented biological properties. We have reviewed various methods for the synthesis of 1,2- and 1,4-dihydropyridine including the strategies which can furnish enantiopure DHPs, either by asymmetric synthesis or by chiral resolution. DHPs accept wide range of reactions that has triggered the synthesis of different class of compounds of great medicinal value, including natural products. Alkaloids deplancheine, tangutorine, dihydroakummicine, olivacine, (\pm)-guatambuine, L-pipecolic acid, (\pm)-geissoschizine, (\pm)-akagerine, lyaline, lyadine, harman-dihydropyrimidine, camptothecin, 20-deoxycamptothecin, akuammiline alkaloids precursor, silicine-methuenine alkaloids, vinoxine, (\pm) -2,7dihydropleiocarpamine, tubifoline & tubifolidine, ervitsine and several other alkaloids have been synthesized following two simple reaction methodologies of DHPs. First, both 1,2 and 1,4dihydropyridines give 1,3-dipolar addition reaction and readily undergo [2 + 2] cycloaddition reactions with dienophiles. Second, reaction of enamine functional group in dihydropyridines with electrophile (x^{\dagger}) to form iminium salt, which undergoes *a*-attack of nucleophiles in a regio- and stereoselective manner (non-biomimetic oxidation) to give substituted tetrahydropyridine derivatives.

We have collated vast amount of literature regarding the strategies for the synthesis of DHPs. However, the continuously growing field of DHPs demands more diversity, tethering/ merging of new moieties with DHP scaffold. Therefore this is still a vibrant and challenging area for medicinal chemists to explore new synthetic methodologies or sync different methodologies together to develop new DHP-drugs. Many DHPbased drugs have been blockbuster of their time; therefore, we have also highlighted commercial value of previously approved DHP-based drugs in brief.

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