REACTIONS OF 1,4-DIHYDROPYRIDINES

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Abstract - Recent studies of chemical reactivity of 1,4-dihydropyridines are surveyed.

The chemistry of dihydropyridines (DHP) up to the year 1980 was treated in detail in[1]. Recently acquired data relating to the synthesis of 1,4-dihydropyridines via condensation reactions have been summarized too[2]. The present review analyses the chemical reactivity of 1,4-dihydropyridines covering literature published in the years 1981-1985.

1. OXIDATION

Aromatization is a typical reaction of the 1,4-dihydropyridine system[1]. Our review is limited to the analysis of papers describing the preparation of pyridine derivatives. As to the mechanism of hydrogen transfer and reduction with dihydropyridines, several reviews are available on the subject[3].

1.1. N-Unsubstituted 1,4-Dihydropyridines→Pyridines

The aromatization of N-unsubstituted 1,4-DHP can be attained with the aid of various oxidizing agents as well as by catalytic or thermal dehydrogenation (Table 1).

Table 1. Reagents Used for the Aromatization of N-Unsubstituted 1,4-DHP

Reagent	References
O_2	4
$NaNO_2$/AcOH	5
$NaNO_2$/HCl	6
HNO_3	5c, 7
$Fe(NO_3)_3$, $Cu(NO_3)_2$	8
Br_2 + NaOAc	4c
CrO_3	7c, 9

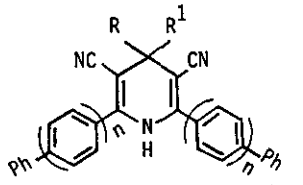
Table 1. (Continued)

Reagent	References
S	10
$KMnO_4$	11
Chloranil	7e, 9c, 12
o-Chloranil	13
BBQ*	11a, 14
Pd/C	11a, 13, 15
285-295°C (in argon)	4b
DBU**	5f

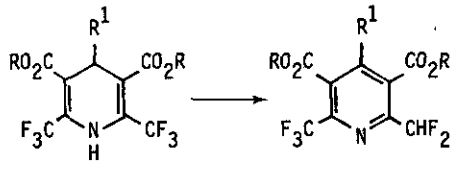
*DDQ - 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

**DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

Ferric and cupric nitrates on a solid support have been recommended for 1,4-DHP oxidation under very *mild conditions* ($CHCl_3$, 20°C)[8]. Thermal dehydrogenation has been observed with 2,6-diaryl-1,4-DHP 1, the thermal instability growing with the number of phenyl rings[4b]. The aromatization of 2,6-bis(trifluoromethyl)-1,4-DHP 2 leading to pyridines 3 results from dehydrofluorination in response to DBU or tertiary amines[5f].



1 n = 0,1,2



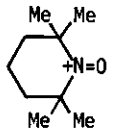
2 3

1.2. N-Substituted 1,4-Dihydropyridines→Pyridinium Salts (Table 2)

Table 2. Reagents Used for the Oxidation of N-Substituted 1,4-DHP

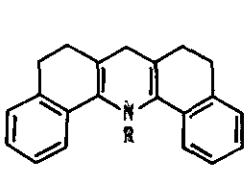
Reagent	References
$H_2O_2 + HClO_4$	16
$PhNO_2$	17

Table 2. (Continued)

Reagent	References
	18
$Fe(CN)_6^{3-}$	19
quinolinium or acridinium cations	20
Pt(colloidal)	21

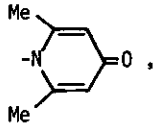
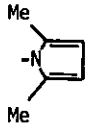
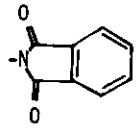
1.3. N-Substituted 1,4-Dihydropyridines→Pyridines (with Elimination of N-Substituent)

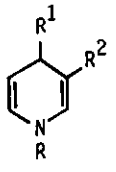
Aromatization of the DHP cycle in dibenzacridine 4 accompanied by elimination of the N-substituent occurs upon heating[22]. The cleavage of the N-N bond in 1,4-DHP 5a leading to pyridines 6 also occurs in response to heating or in the presence of compounds initiating free-radical reactions[24]. The latter are also capable of converting 1,4-DHP 5b to pyridines 6[24e].



4

5 6

5 a R =  ,  ,  ; b R = CPh_3; c R = CO_2R^2; d R = $SiMe_2Bu$-t



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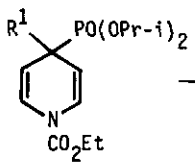


8 6

7 R = CO_2R^3, $CONEt_2$; R^2 = Cl, Br, $COCH_2Ph$, CO_2R^4, 

Some α,β-unsubstituted 1,4-DHP 5c[25] undergo oxidation to 6 in the air, the reaction proceeding more readily in the case of 5d[25b,26]. In the case of other 5c and less readily oxidizable 3-substituted

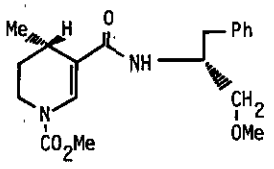
1,4-DHP 7 silver nitrate[25c], sulphur[27], o-chloranil[27c,d,28], p-chloranil[29] and DDQ[30] were used as oxidizing agents. Elimination of 1- and 4-substituents can be achieved by treating 1,4-DHP 8 with butyllithium or upon heating it with sodium iodide[31].

1.4. Electrochemical Oxidation

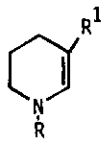
Electrochemical oxidation of 1,4-DHP[5c,32] has been reported and the mechanism of electrooxidation explored[32c-i].

2. REDUCTION

The catalytic hydrogenation of 1,4-DHP affords both tetrahydropyridines and piperidines. It has been confirmed that tetrahydropyridines 9, 10a,b, 11 are formed if one of the double bonds in the cycle is conjugated with the π-electrons of the substituent, as reported earlier[1b].



9[33]



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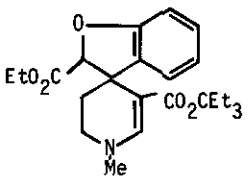


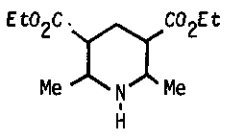
11

a R = Me, R^1 = $CONH_2$[34]

b R = CH_2Ph, R^1 = $CONH_2$[32b,34]

c R = Me, R^1 = CN[32b]

In the absence of stabilizing substituents piperidines are formed[27a,b,29b,35]. Piperidines 12[36] and 13[37] result from the catalytic hydrogenation of 3,5-disubstituted 1,4-DHP.



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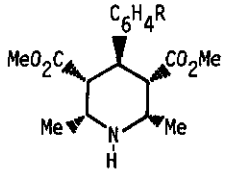
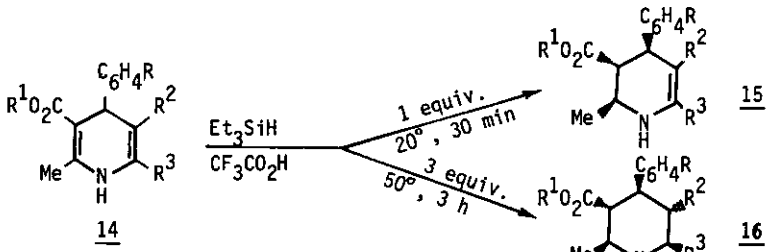


13

Another stereoisomer of piperidine (16) can be gained by the reduction of 1,4-DHP 14 with triethylsilane in trifluoroacetic acid; tetrahydropyridines 15 were isolated under mild conditions[38]. Tetrahydropyridines 10b,c[32b], 17[39] were obtained by electrochemical reduction of the corresponding 1,4-DHP.

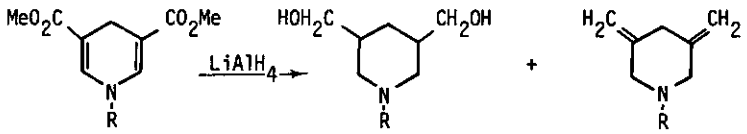
Lithium aluminium hydride reduces both the 1,4-DHP ring and the substituents[40].



14 15 16

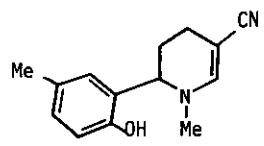
14-16 R = H, NO_2, CF_3;
R^2= CO_2R^4, COMe, CN;
R^3= Me, CO_2Et.

17 R^2 = CO_2R^3, CN



3.ADDITION REACTIONS

1-Methyl-3-cyano-1,4-DHP in alkaline medium reacts with phenols and thiophenols, their addition occurring differently, to give tetrahydropyridines 19, 20a[41]. Tetrahydropyridine 20b is one of the products resulting from the reduction of diaryl sulphides ArSSAr with 1-benzyl-1,4-dihydronicotinamide proceeding by the free-radical mechanism[42].



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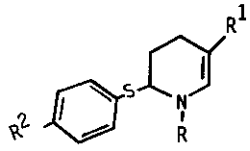
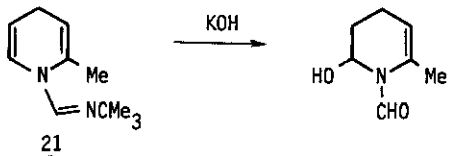


20

a R = Me, R^1= CN;
b R = CH_2Ph, R^1= $CONH_2$

The treatment of 21 with potassium hydroxide leads not only to imine hydrolysis but also to the addition of water[43]. Addition of azides to fully unsubstituted or 1-methyl-substituted 1,4-DHP affords bicyclic compounds 22[44].



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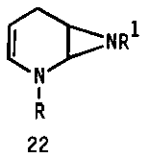
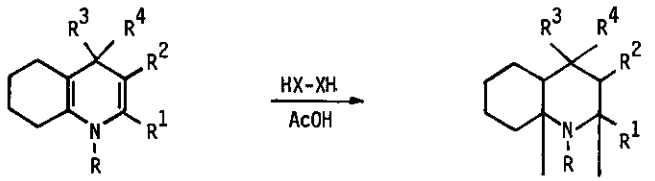


22

R = H, Me; R^1 = CN, SO_2R^2

1,4-DHP 23 lacking electron-withdrawing groups gives adducts with hydrogen peroxide[45] or disulphide[46] only upon acid protonation of DHP.

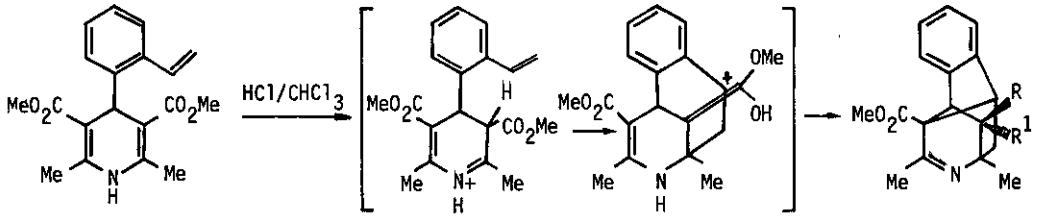


23 24

R^1= Ph, R^2= H; $R^1 + R^2 = (CH_2)_4$; X = O,S

Acids catalyze intramolecular cyclization in position 2 of 1-phenethyl-[47] and 1-[2-(3 -indolyl)ethyl] -1,4-DHP[20d,48].

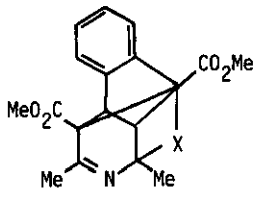
Several intramolecular addition reactions were carried out with 4-(o-substituted)phenyl-1,4-DHP. The reaction mechanism was exemplified by the formation of 27[49]. Acid catalysts promote the formation of reactive vinyliminium ion 26, the nucleophilic β-C and electrophilic α-C atoms of which react with the appropriate sites of the o-substituent. The systems 28[50], 29[49,50b], 30[51] were similarly obtained.



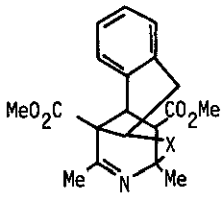
25 26 27

a R = H, R^1= CO_2Me

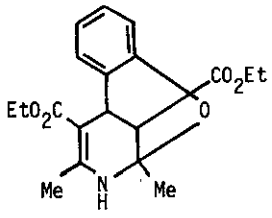
b R = CO_2Me, R^1= H



28 X = O, S

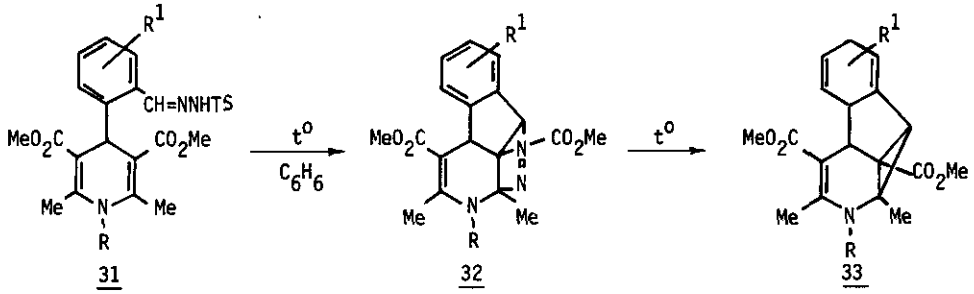


29 X = CH_2, O



30

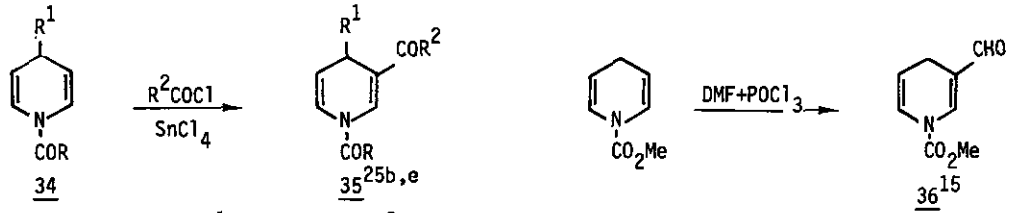
Tosylhydrazones 31 are extremely reactive yielding adducts 32 upon heating in benzene with subsequent thermal fragmentation of pyrazoline 32 to cyclopropane 33[52].



31 32 33

4. SUBSTITUTION REACTIONS OF THE DIHYDROPYRIDINE RING

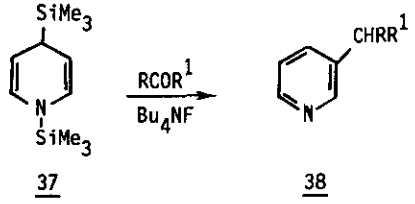
Electrophilic substitution reactions of α,β-unsubstituted 1,4-DHP including Friedel-Crafts[25b], Vilsmeier-Haack[15] reactions occur at position 3.



34 35[25b,e] 36[15]

34,35 R = NEt_2, OEt; R^1= alkyl, Ph; R^2= alkyl, OMe, Ph

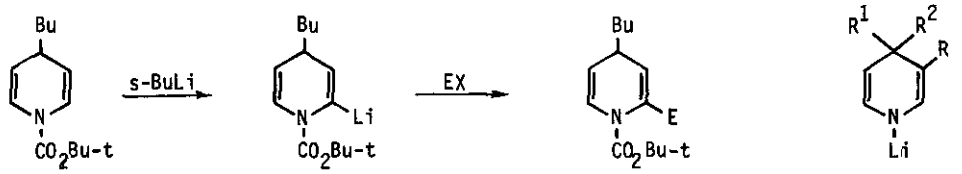
The reaction between 1,4-DHP 37 and aldehydes or ketones follows a more complex mechanism leading directly to 3-alkylpyridines 38[53].



37 38

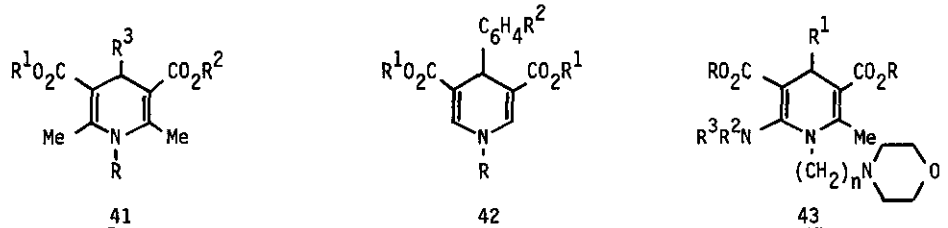
Electrophiles can be introduced at position 2 (DHP 39) by preceding metalation[27d]. Unstable 1-lithium derivatives of 1,4-DHP 40 are readily replaced with hydrogen, acyl, alkyl and cyano groups[14a,33,54].

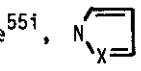
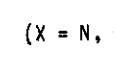
Most 1,4-DHP are very weak acids, the N-H bond cleavage requiring the use of sodium hydride. Anions obtained by this method were N-alkylated and acylated to give N-substituted 1,4-DHP-3,5-carboxylic acid esters 41[52,55], 42[56], 43[57] as well as N-derivatives of 3,5-diacetyl-1,4-DHP 44[5d], 1,4-dihydro-



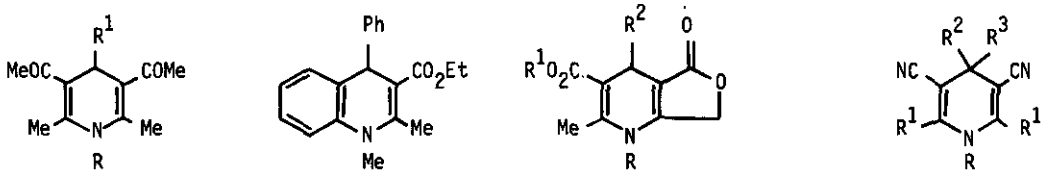
39 E = D, $SiMe_3$, Me, CO_2Me, COMe, SMe

quinoline-3-carboxylic acid esters 45[58], tetrahydrofuro[3,4-b]pyridines 46[59], 3,5-dicyano-1,4-DHP 47[55d,h]. (The naphthyridine structure[60] assigned to compounds prepared similarly [55n] by the alkylation of DHP 41 (R=H) with benzoimidoyl chlorides appears erroneous).

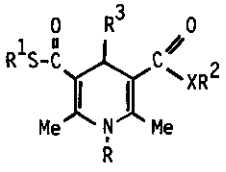


41 R = CO_2Me[52], CH_2OMe[55a], Et[55b], CH_2OEt[55c], $(CH_2)_nCO_2Et$[55d], $(CH_2)_nNR^3R^4$ [R^3,R^4= alkyl, substituted alkyl[55e-h]; NR^3R^4=  [55i], (X = N, CH)[55j],  [55k-m]], CPh = NR^3 [55n];

42 R = alkyl, $COC_6H_4R^3$, COMe, CO_2Et, CH_2CO_2Et, SO_2Me



In order to prepare DHP anion 46 lithium diisopropylamide or solid potassium hydroxide in DMSO can be also used[57]. The latter reagent has been successfully used to prepare DHP 41 (R = alkyl, R^2 = 2,1,3-benzoxadiazolyl-4)[61]. 1,4-DHP-3,5-dicarbothiolic acid esters 48a are more acidic than the O-analogues, therefore they undergo N-alkylation in the presence of potassium hydroxide in acetonitrile[32k]. The alkylation of 3,5-dicyano-1,4-DHP 47 (R^2=R^3=Me) was conducted in the presence of sodium hydroxide and a phase-transfer catalyst[62]. Dihydroindenopyridines can also form anions with alkali metal hydroxides, N-methyl derivatives 49 (R=methyl) result from the alkylation of anions with dimethyl sulphate, whereas alkyl halides afford a mixture of 49 and C-alkyl derivatives 50, the latter prevailing. The acylation of DHP anion 49 occurs at the nitrogen atom, while the nonanionic form undergoes



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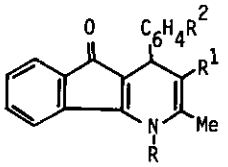
a X = S

b X = O



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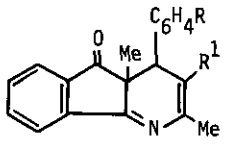
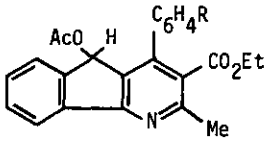


50

acylation at the oxygen atom accompanied by hydrogen migration to give pyridine 51[64].



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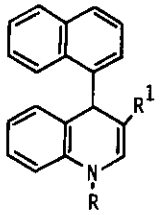
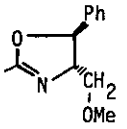


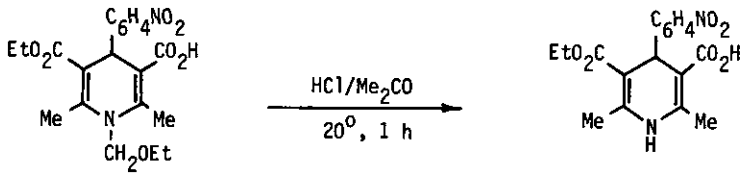
52

a R^1 = 

R = CO_2Me;

b R^1 = CHO, R = CO_2Me, H

Alkaline agents cause the cleavage of the bond N-CO in N-acyl-1,4-DHP 36[15], 42[56], 52b[14b] leading to N-unsubstituted 1,4-DHP. The N-ethoxymethyl group is easily eliminated from DHP 53 to give 54[55c].



53 54

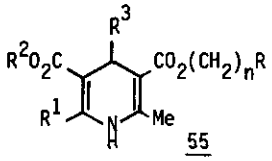
The N-silyl group in DHP 5d (R^1= Bu) is replaced by an acyl group by treatment with acyl chloride[25b].

5. REACTIONS OF SUBSTITUENTS

In recent years, evidence has been accumulated of various reactions affecting substituents in the DHP ring, the 1,4-dihydropyridine structure of the cycle remaining unaltered.

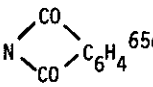
5.1. Reactions of Substituents Attached to the DHP Cycle via Side Chains

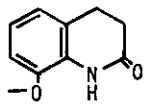
The nucleophilic substitution of halogens[9a,32k,65], tosyl[65j,66] and mesyl[67a] groups in esters 55a-c yields DHP 55d-l.

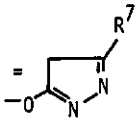
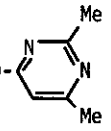


55

a R = halogen, b R = $OSO_2C_6H_4Me$-4, c R = OSO_2Me,

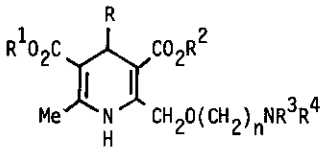
d R = NR^4R^5 65a-d,f-h,67, e R =  65e,f,67a,c

f R = SPh[32k], g R = OMe[67a], h R = OCOR[6 9a,67a], i R = ONO_2[65i], j R =  [67b],

k R =  [65j,66a,b,d], l R =  [66c], m R = OH[65j,67a]

Primary amines 55d (R^4=R^5=H) can be gained via hydrazinolysis of phthalimide derivatives 55e. Tosylates 55b and mesylates 55c were prepared from hydroxy derivatives 55m. Alkylation [65e,67c] and acylation[67a,b,68] of amines 55d, hydrolysis of acetoxy group in 55h[9a], debenzylation of the amino group over palladium catalyst in 55d (R^4= CH_2Ph, R^5= Me)[69] were performed.

Primary amines 56a have been synthesized by the reduction of azido group[70], secondary amines 56b by catalytic hydrogenolysis of the benzyl derivative 56c[70b]. Reactions with amines 56a included alkylation[70], acylation[70a,71], preparation of urea and guanidine derivatives[70a], as well as heterocycle formation[71,72]. In piperazine derivatives 56d the hydrogen R^5 was replaced by carbamoyl, thiocarbamoyl, guanyl, thiazolyl and other groups[73].

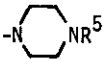


56

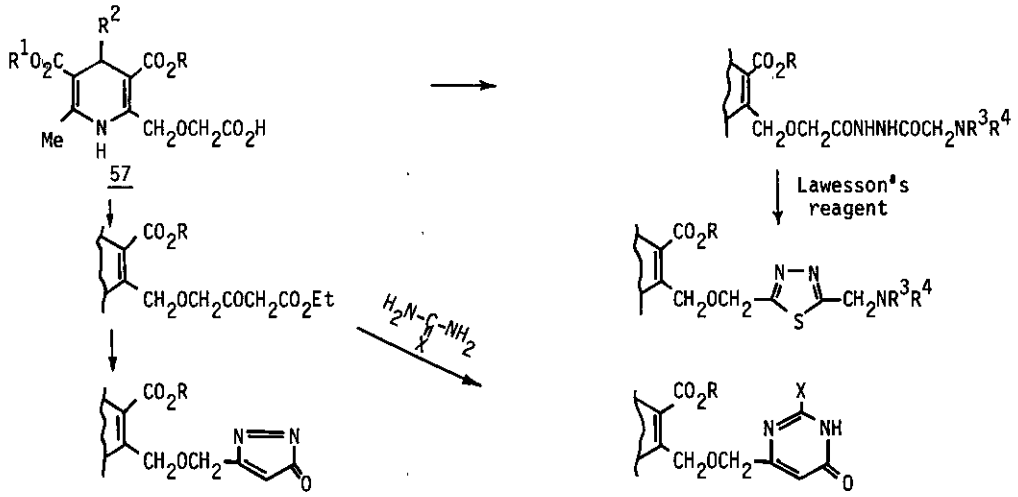
a R^3= R^4= H,

b R^3= Me, R^4= H,

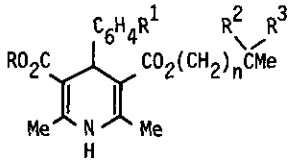
c R^3= Me, R^4= CH_2Ph,

d NR^3R^4= 

Some of the reactions involving acid 57 are shown in the scheme[71,74]:



Ketal 58a hydrolysis was performed in acid medium and new ketals 58c and thioketals 58d were obtained from 58d[75].



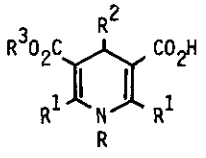
58

a $R^2+R^3 = O(CH_2)_2O$,
b $R^2+R^3 = O$,
c $R^2+R^3 = O(CH_2)_3O$,
d $R^2+R^3 = S(CH_2)_3S$

Ester groups attached to the 1,4-DHP ring via side chains readily undergo hydrolysis[29b,56,76].

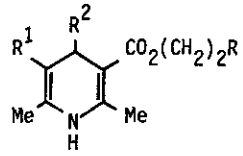
5.2. Reactions of Substituents at Positions 3, 5

The reactivity of 1,4-DHP-3,5-dicarboxylic acid esters 41, 42 depends both on steric and electronic factors. The absence of substituents at positions 2, 4, 6 facilitates hydrolysis, thus enabling the preparation of acid 59a,b from the esters 42 (R=H, alkyl, aryl)[56,77]. The hydrolysis of 2,6-dimethyl derivatives 41 requires the presence of substituent R other than H at the nitrogen atom, which sterically hinders conjugation in the aminovinylcarbonyl moiety[55c,77]. Electron acceptors in the ester radical (DHP 60) facilitate hydrolysis[9a,55a,61,78] considerably.



59

a $R^3 = H$, b R^3 = alkyl



60

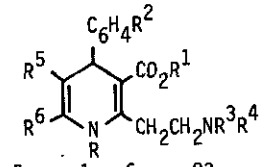
R = CN, $\overset{+}{N}R_3^3$

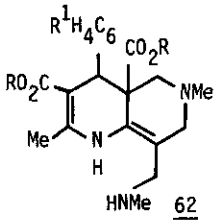
Esterification reactions have been conducted involving acids 59 or their reactive derivatives[55a,c, 61,65g,67a,b,78a,c,d,79]. Esters 41, 42 undergo transesterification in the presence of alkoxides[7d, 9d,61,65h,77,78a,80]. Transesterification of thiol esters 48b to esters 41 proceeds by treating the former with the appropriate alcohol in the presence of potassium hydroxide[32k]. Amides[81] and hydrazides[36] can be obtained from acids 59 or esters 41. Synthetic procedures for the preparation of individual stereoisomers of esters 41 ($R^1 \neq R^2$) have been developed based on the reactions of 3,5-substituents[9d,55c,61,78a,80a,b,d]. Acids 59b undergo decarboxylation upon heating[78b,d]. Lithium aluminium hydride reduces the methoxycarbonyl group in ester 41 (R^1= Me) to a methyl group[78b,d]. Lawesson's reagent was employed for thionation of the indene carbonyl in dihydroindenopyridines 49[64]. Monoximes were obtained from 3,5-diacetyl 1,4-DHP 44 by treating them with hydroxylamine or its O-alkyl derivatives[82]. The 3-oxazolinyl group in dihydroquinoline 52a was converted to an aldehyde one(52b)[14b].

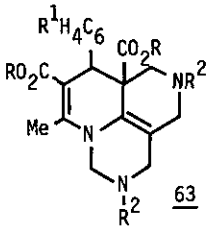
5.3. Reactions Substituents at Positions 2, 6

2-Methyl group in 1,4-DHP participates in the Mannich reaction. Secondary amines yield the ordinary products of aminomethylation 61[58,83], whereas in the case of primary amines the reaction is more com-

plicated and leads predominantly to 62, 63[84].



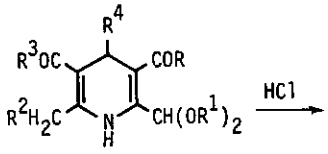




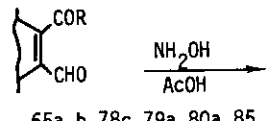
61 a $R^5=CO_2R^1$, R^6 = Me[83]

b $R^5 + R^6 = (CH)_4$[58]

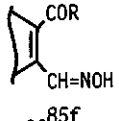
A large number of reactions are feasible based on acetals 64 as starting compounds:



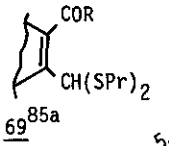
64



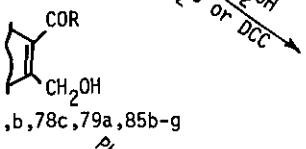
65[65a,b,78c,79a,80a,85]



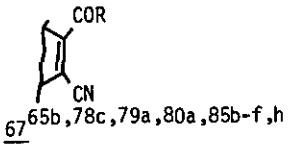
66[85f]



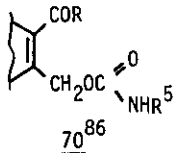
69[85a]



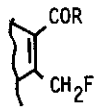
68[65a,b,78c,79a,85b-g]



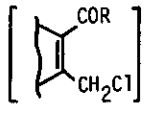
67[65b,78c,79a,80a,85b-f,h]



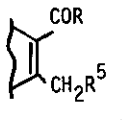
70[86]



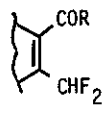
73[79a]



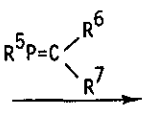
71



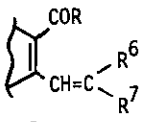
72[85f] R^5=CN,NR^6R^7



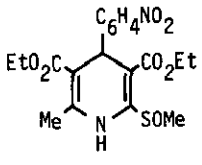
74[79a]



65

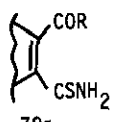


75[65b] R^6= H, Cl,Br; R^7= Cl,Br,CN,CHO



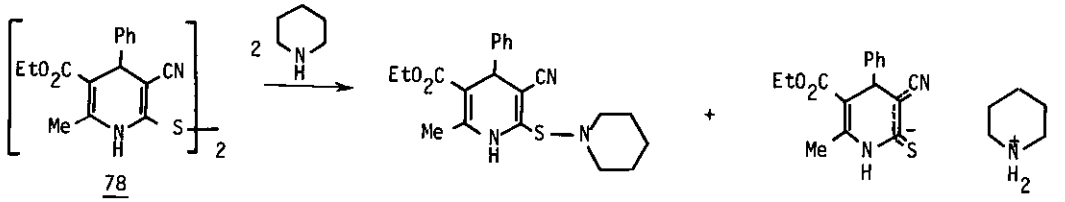
77

67



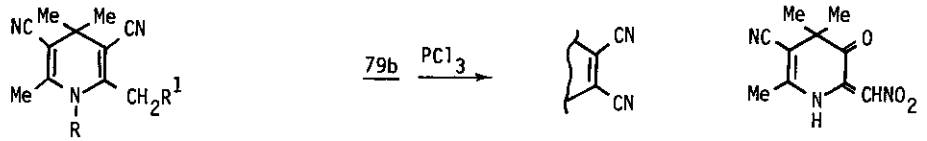
76[79a]

Peracetic acid oxidizes only the 2-methylthio group to give 1,4-DHP 77[79a]. Dimer 78 undergoes cleavage at the disulphide bond[7f].



78

2-Nitromethyl-1,4-DHP 79b resulting from the nitration of 79a[87] was converted to 2,3-dicyano-1,4-DHP 80[88]. The nitration of N-unsubstituted 79c yields pyridone 81 and rearrangement products[89].



79 80 81

a R = Me, R^1 = H

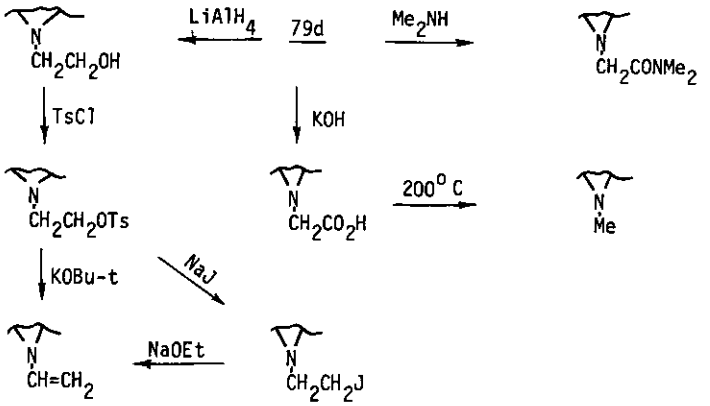
b R = Me, R^1 = NO_2

c R = R^1 = H

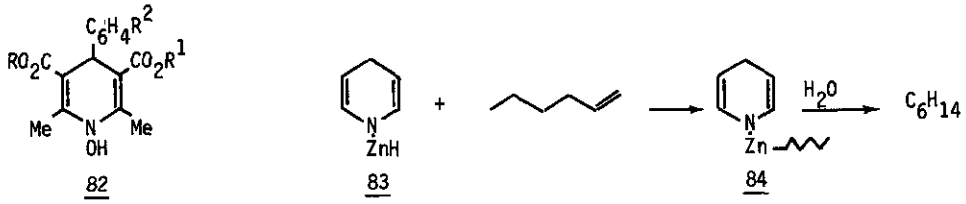
d R = CH_2CO_2Et, R^1 = H

5.4. Reactions of Substituents at Position 1

Reactions of N-substituents in DHP 79d were performed:



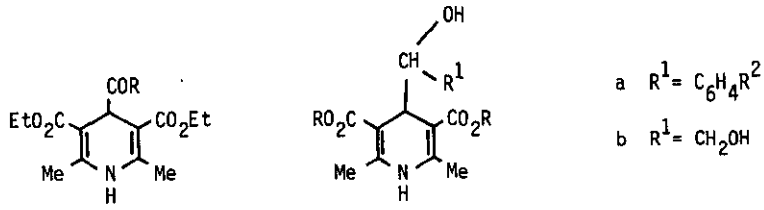
N-Hydroxy-1,4-DHP 82 undergoes alkylation and acylation at the oxygen of the hydroxy group[90]. Amide 5 (R=$CONEt_2$) was obtained by treating ester 5c (R^2= Ph) with lithium diethylamide. Hydrozincation of hexene-1 using DHP 83 followed by hydrolysis of product 84 yielded hexane[91].



82 83 84

5.5. Reactions of Substituents at Position 4

Amides[92] and hydrazides[92b] of 1,4-DHP-4-carboxylic acid 85 (R=OH) were obtained via its reactive derivatives. 4-Benzoyl-1,4-DHP was reduced with sodium borohydride to 86a (R^2=H). Acylation, silylation and mesylation of hydroxy groups in 86a,b were carried out[93].

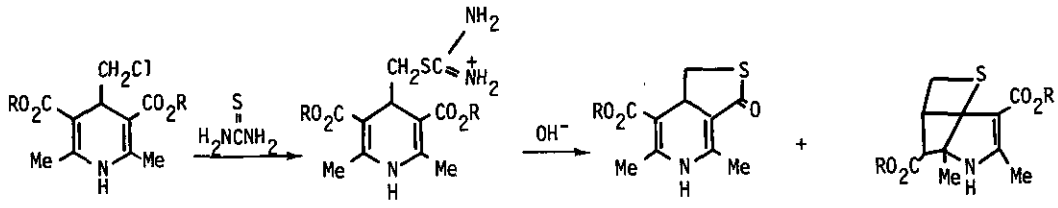


a $R^1 = C_6H_4R^2$

b $R^1 = CH_2OH$

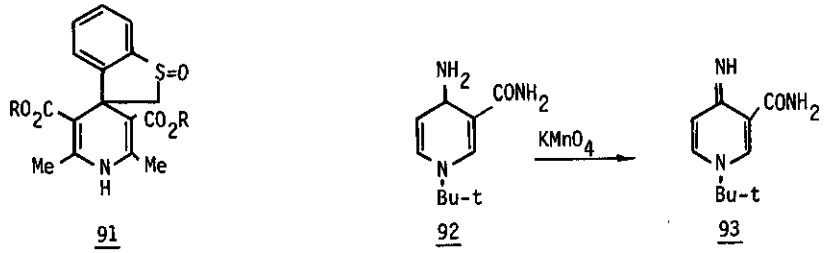
85 86

Treatment of isothiouronium salt 88 with alkali yields cyclized products 89 and 90[94].



87 88 89 90

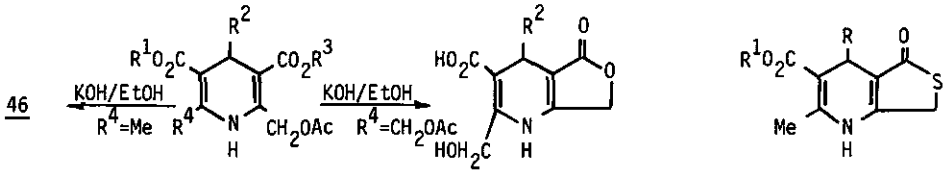
Numerous reactions of substituents in the phenyl radical of 4-phenyl-1,4-DHP are known[7g,52,69,95]. Depending on reaction conditions, the treatment of spirocyclic 1,4-DHP 91 with Raney nickel leads either to the reduction of sulphoxide group[96] or to spirocycle cleavage resulting in 4,4-disubstituted 1,4-DHP[97]. 4-Amino-1,4-DHP 92 undergoes oxidation to imine 93, whose hydrolysis affords a pyridone[98].



91 92 93

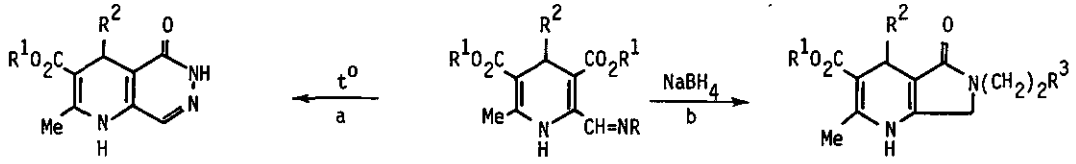
5.6. Cyclization and Reactions of Cyclized Products

Tetrahydrofuropyridines 46 were first obtained as side products in reduction of aldehyde 65 with sodium borohydride or by heating alcohols 68 in the presence of p-toluenesulphonic acid[85f]. Lactones 46[9a,b] and 95[9b] can be prepared from 2-acetoxymethyl-1,4-DHP 94. A convenient method leading to lactones 46 is the reaction of 2,6-dimethyl-1,4-DHP 41 with pyridinium bromide perbromide[99]. The heating of these lactones with aqueous alkali[85g] or amines[85g,100] induces cleavage of the lactone ring. 2-Acetylthiomethyl-1,4-DHP are converted in an acid medium to tetrahydrothienopyridines 96[101].



94 95 96

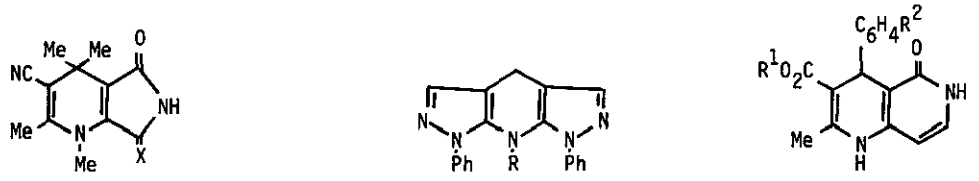
Cyclized products 98, 99 were obtained from hydrazone 97a and imines 97b[85f], respectively.



98 97 99

a R = NH_2; b R = $(CH_2)_2R^3$

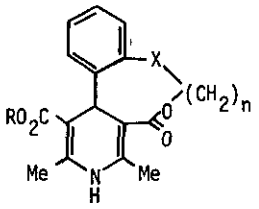
2-Nitromethyl-1,4-DHP 79b[88] yields cyclic products 100a,b. Dipyrazolo-DHP 101 was obtained by treating 2,6-dichloro-3,5-diformyl 1,4-DHP with phenylhydrazine[102]. 1,6-Naphthyridines 102 were synthesized by heating DHP 41 with sym-triazine or by treating 41 with dimethylformamide dialkylacetal with subsequent cyclization of the resulting 2-aminoethylene-1,4-DHP[103]. 1,6-Naphthyridines 102[103a], and 1,7-naphthyridines[104], undergo alkylation exclusively at N(6) and N(7), respectively.



100 101 102

a X = O; b X = NOH

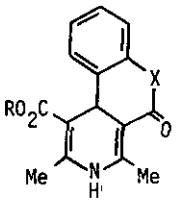
The steric proximity of substituents at position 3 of the DHP ring and at the o-position of 4-phenyl enables the formation of a new cycle between them (*DHP* 103-105).



103

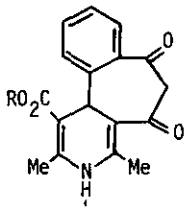
X = CH_2, O[105]

X = S[106]



104[95a]

X = O, NH



105[107]

6. MISCELLANEOUS REACTIONS

The cleavage of the 1,4-DHP ring of N-methyldihydroindenopyridines 49 (R = Me) in acid medium proceeds by way of enamine hydrolysis[64]. Rearrangements of 1,4-DHP to 4,5-dihydrodiazepines[93a, b,108] have been reported.

Photochemical conversions of 1,4-DHP have been studied[7g,9c,109].

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Received, 17th June, 1987