

SYNTHESIS OF 1,4-DIHYDROPYRIDINES BY CYCLOCONDENSATION REACTIONS

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Abstract - This review surveys the latest developments pertaining to the preparation of 1,4-dihydropyridines using Hantzsch synthesis and other cyclocondensation reactions.

The chemistry of dihydropyridines (DHP) up to the year 1980 had been reviewed in several surveys of literature¹⁻³. Among the different isomers, 1,4-DHP merits special attention, the interest in these compounds increasing progressively. Investigations along these lines include the synthesis of model compounds NAD(P)H-analogues of 1,4-dihyronicotinamide - and their involvement in hydrogen transfer reactions. Recently, several review papers have appeared on the subject⁴⁻⁷ including the transfer of hydrogen and other groups by chiral DHP^{8,9}. Another big issue is the application of 1,4-DHP in medicine and industry. These compounds are chiefly obtained by using various modifications of Hantzsch synthesis. Most extensively studied are the calcium antagonists, whose synthesis¹⁰ and properties¹¹⁻¹³ have been treated in a number of reviews. Several papers describe investigations of individual drugs¹⁴⁻¹⁶ such as vasodilators and antihypertensive remedies - nifedipine, nitrendipine. Calcium transport agonists have been also found among 1,4-DHP¹⁷⁻²⁰. 1,4-DHP possess antioxidant²¹⁻²⁶ (diludin is routinely used²⁷), hepatoprotective²⁸⁻³⁰, antitumour³¹⁻³³, antimutagenic³⁴, geroprotective³⁵, antiatherosclerotic^{36,37}, bronchodilating³⁸, antidiabetic^{39,40}, herbicidal⁴¹⁻⁴³, photosensitizing⁴⁴⁻⁴⁶ activities. 1,4-DHP can be applied to promote drug transfer across the blood-brain barrier⁴⁷⁻⁴⁹.

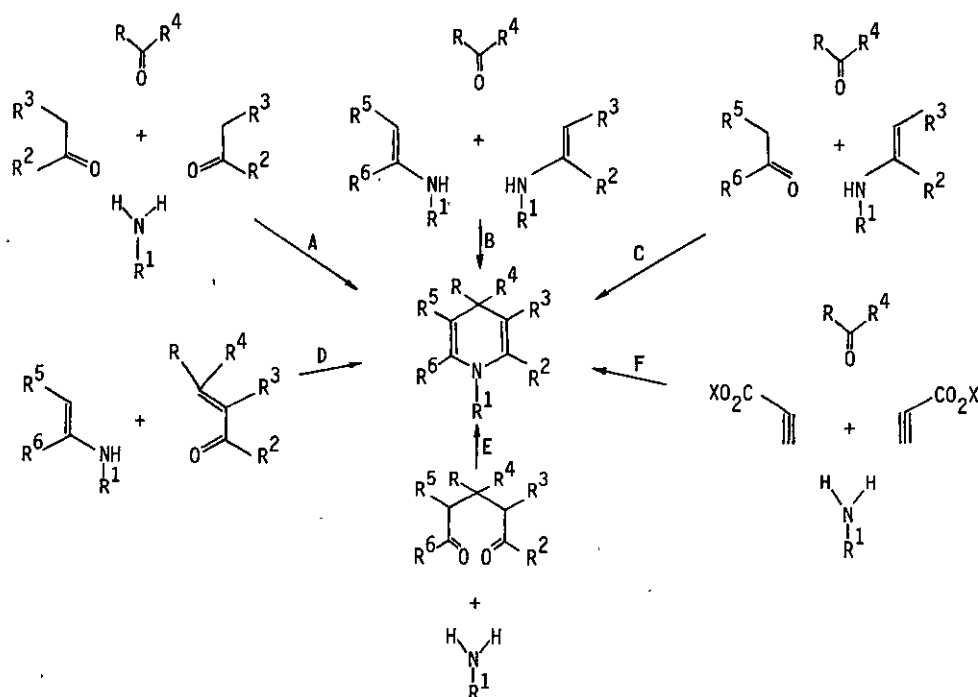
The present review paper surveys literature data on the synthesis of 1,4-dihydropyridines by way of cyclocondensation published in the years 1981-1985. Beyond the scope of this paper remain the 1,4-DHP systems with an exocyclic double bond (pyridones, pyridinethiones, pyridonimines).

1. Hantzsch Synthesis and Related Cyclocondensations

Various modifications of Hantzsch-type cyclocondensation reactions have been widely applied to prepare mono- and polycyclic 1,4-DHP, the principal pathways being outlined in scheme 1.

As the same or structurally related 1,4-DHP can be frequently obtained via different synthetic pathways, they will be discussed on the basis of their structures and not the synthetic methods used for their preparation.

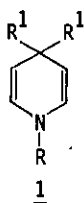
Scheme 1.



1.1. Monocyclic 1,4-Dihydropyridines

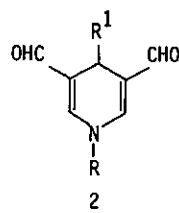
1.1.1. Substituents at Position 1

The vast majority of 1,4-DHP prepared by Hantzsch synthesis are 1-unsubstituted. Several 1-substituted α,β -unsubstituted 1,4-DHP 1 have been synthesized by method E.



a R = alkyl, R¹ = H⁵⁰

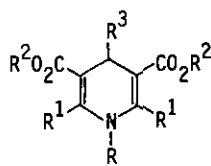
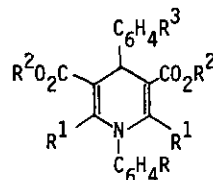
b R = Me, CO₂Et, R¹ = Me⁵¹



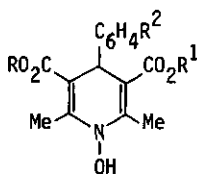
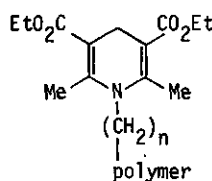
R = alkyl, aralkyl, (CH₂)_nOH, CH₂CO₂R²

Malonodialdehyde is used as a β -dicarbonyl component in method A to form 1,4-DHP 2⁵²⁻⁵⁶. A modification of method A involving the use of amine chloride in pyridine affords 1-alkyl-1,4-DHP 3.

Aromatic amines give 1-aryl-2,6-dimethyl-1,4-DHP 4a⁶⁰ (method A) and 1-aryl-2,6-unsubstituted 1,4-DHP 4b⁶¹ (method F). The cyclization of 1,5-diketones with hydroxylamine allows to obtain 1-hydr-

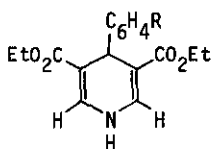
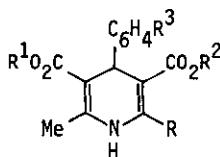
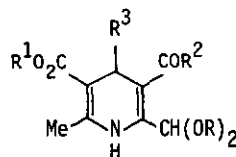
3a R = R¹ = Me⁵⁷b R = Et, R¹ = Me^{58,59}c R = Me, R¹ = C₆H₄R⁴⁵⁷4a R¹ = Meb R¹ = H

oxy-1,4-DHP 5⁶². Method E has been applied to prepare 1,4-DHP 6 on a polymer matrix⁶³. Polylysine ε-amino groups react with malonodialdehyde to afford 1,4-DHP in small amounts⁶⁴, in addition to aminopropenal derivatives.

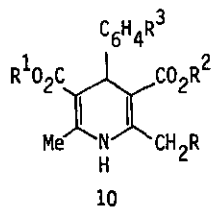
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1.1.2. Substituents at Positions 2,6

Hantzsch synthesis generally leads to 2,6-disubstituted 1,4-DHP, the most popular being the 2,6-dimethyl derivatives. In order to prepare 2,6-unsubstituted derivatives 7⁶⁵, 4b⁶¹, acetylene derivatives (method F) are used instead of the β-dicarbonyl component.

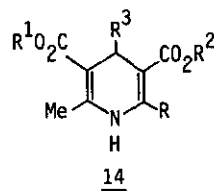
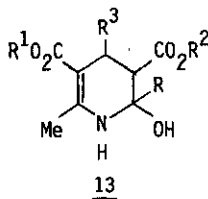
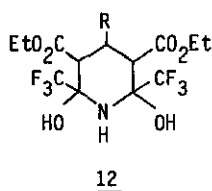
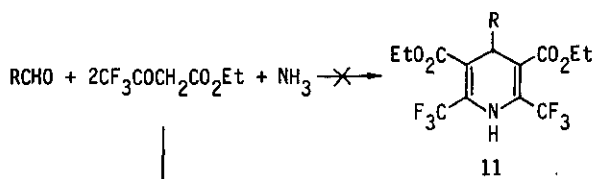
78R = Et, Pr, i-Bu, CH₂Ph,9R³ = aryl, heterylR⁴ = OR⁴⁶⁹⁻⁷⁹, NHMe⁸⁰

Only a few DHP carrying other alkyl groups (except for methyl) at positions 2, 6 have been prepared including 2,6-diethyl⁶⁶ and 2,6-dicyclopropyl-1,4-DHP⁶⁷, as well as asymmetric 8^{67,68}. A large number of 1,4-DHP 3,5-dicarboxylic acid derivatives 9 with acetal groups at position 2⁶⁹⁻⁸⁰ (sometimes 2, 6⁷⁶) have been obtained by method D (sometimes also method C). Method D or C was employed to prepare esters 10⁸⁰⁻⁹⁴ with the aid of the corresponding substituted acetoacetic acid esters. The products obtained from trifluoroacetoacetic acid ester were assigned as 1,4-DHP 11⁹⁵ (quoted in reviews^{2,3}), however analysis of their spectra revealed the structure of 2,6-dihydroxypiperidi-



R = OH⁸⁰⁻⁸², O-alkyl⁸³, O-acyl^{84,85}, S-acyl⁸⁶, CH(OH)Ph⁸⁷,
O(CH₂)_nN₃^{88,89}, O(CH₂)_nNR⁴₅⁸⁹⁻⁹², O₂CNHR^{93,94}

nes 12⁹⁶⁻⁹⁸. Depending on radical R, methods C and D yield tetrahydropyridines 13 or 1,4-DHP 14⁹⁹. Contrary to originally held views^{96,98}, dihydroxypiperidines 12^{43,100}, as well as tetrahydropyridines 13⁹⁹ undergo dehydration to give 1,4- or 3,4-dihydro isomers depending on the reagent used.



R = CF₃, CF₂CF₃, CCl₃,

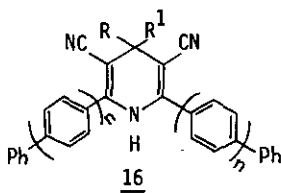
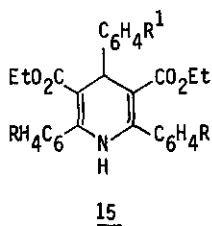
C₆H₄NO₂-4, C₆H₄Cl₂-3,4, C₆H₄Cl-4 (3), Ph

R = CH₂F, CHF₂, CHCl₂, SMe,

2-furyl, C₆H₄OMe-4,

C₆H₄Me-4, Ph

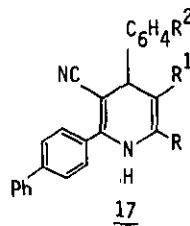
Benzoylacetic acid esters do not invariably follow method A (despite reports on the synthesis of 3c⁵⁷) and the use of method E is required for the preparation of 15¹⁰¹. A number of β-cyano-1,4-DHP 16, 17 carrying aryl groups at positions 2, 6 have been obtained.



a n = 0¹⁰²

b n = 1¹⁰³

c n = 2¹⁰⁴

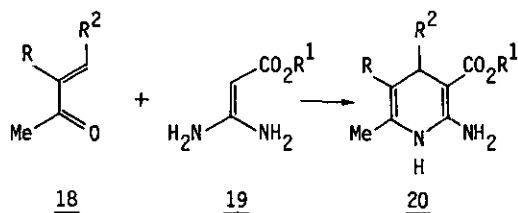


a R = Me, Ph;

R¹ = CN, CO₂Et¹⁰⁵

b R + R¹ = (CH₂)_n¹⁰⁶

Amidinoacetic acid ester 19 used as enamine according to method D (sometimes C) yields 2-amino-1,4-DHP 20, thereby enamine 19 forms 1,4-DHP even with ketones 18 lacking the electron withdrawing R.

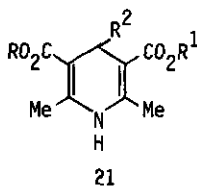


$R^2 = \text{aryl, heteryl}$

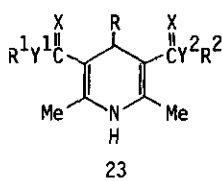
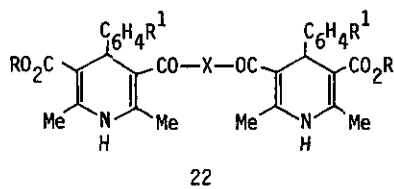
$R = \text{CO}_2R^3$ 77,107-111, SO_2R^3 ,
 COMe 107, NO_2 112, H 57,107

1.1.3. Substituents at Positions 3, 5

Symmetrically or, for the most part, asymmetrically substituted 1,4-DHP-3,5-dicarboxylic acid esters 21 remain in the highlight of attention, method D being claimed as the most suitable one for their synthesis^{113,114}.



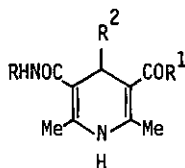
Apart from the readily available ethyl and methyl esters, alkyl esters containing long alkyl radicals^{36,67,110,113,115,116}, as well as cycloalkyl¹¹⁷⁻¹²², alkenyl^{24,25,29}, alkynyl²⁹, aralkyl¹²³, dianhydrohexitol¹²⁴ esters have been investigated. Esters 21 were prepared whose alkyl radicals R , R^1 were partially substituted with hydroxy¹²⁵, alkoxy^{29,36,67,113,115,116,126-129}, acyloxy⁸⁴, alkoxy-carbonyl¹³⁰, alkenyldihydroxy^{118,131}, alkenylthio¹²⁹, nitrate¹³²⁻¹³⁴, trimethylsilyl¹³⁵⁻¹³⁸, cyano^{29,77,84,112,139,140} groups or halogens^{57,84,141,142}. Aminoalkylesters 21, almost exclusively with amino groups in one of the ester radicals, have been extensively explored. Esters containing acyclic amino groups^{77,140,143-159}, acylated amino groups¹⁷³⁻¹⁷⁶, piperidyl or piperidylalkyl¹⁶⁰⁻¹⁶⁵, piperidinoalkyl^{107,153,166}, piperazinoalkyl^{108,109,167-170} esters, and those carrying other nitrogen-containing heterocycles^{142,171,172} have been prepared. Also known are 1,4-DHP 21, whose ester radicals R, R^1 form a macrocycle¹²², and bis-1,4-DHP 22 linked via an ester or amide bridge^{57,177}. Carbo-thiolic and carbothionic acid esters 23 have been synthesized.



- a $X = O, Y^1=Y^2 = S$;
 b $X = O, Y^1 = S, Y^2 = O$ 178-180;
 c $X = S, Y^1=Y^2 = O$ 181;
 d $X = Y^1=Y^2 = S$ 182

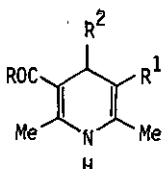
Amides of 1,4-DHP-3,5-dicarboxylic acids 24 and 3-acyl-1,4-DHP 25 (3,5-diformyl-1,4-DHP, see 2) were also prepared.

Various Hantzsch syntheses were applied to give 1,4-DHP carrying the following substituents at



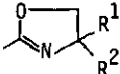
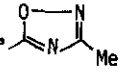
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- a $R^1 = \text{NHR}^{60}$,
 b $R^1 = \text{O-alkyl}^{41,42,183}$

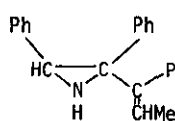


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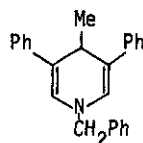
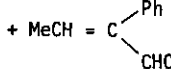
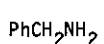
- a $R = \text{Me}$,
 $R^1 = \text{COMe}^{29,60,184,185}$;
 b $R = \text{Me}$, $R^1 = \text{CO}_2\text{R}^3$ ^{29,158};
 c $R = \text{Me}$, $R^1 = \text{CN}^{29}$;
 d $R = 2\text{-furyl}$, $R^1 = \text{CO}_2\text{R}^3$ ¹⁸⁶

positions 3 or 3, 5: $\text{CN}^{29,60,103-106,112,159,187,188}$,  ¹⁸⁹⁻¹⁹¹,  ¹⁹²,
 $\text{SO}_2\text{R}^{77,193,194}$, $\text{NO}_2^{57,112,195-197}$, Cl^{112} , $\text{PO(OR)}_2^{198-203}$, $\text{H}^{57,107,194,203}$.

3,5-Diphenyl-1,4-DHP 26 resulting from the thermolysis of vinylaziridine 27 is in fact formed via a variant of Hantzsch synthesis²⁰⁴.



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1.1.4. Substituents at Position 4

The preparation of 4-unsubstituted compounds involves either method E^{24,25,50,63,120} or methods A and C with the use of formaldehyde^{41,42,122,183,205,206} or hexamethylenetetramine^{119,130,178-182} as the source of the former. A 4-unsubstituted 1,4-DHP was formed in the reaction of phosphorylated enamine and acrolein²⁰³.

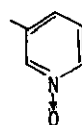
The use of diverse synthetic variants has resulted in 4-alkyl^{52-56,58,59,64,122,178-182, 188, 202-204,207,208}, 4-cycloalkyl²⁰⁸, 4-aryl^{59,208,209}, 4-CCl₃²¹⁰, 4-(2,2-dimethoxyethyl)⁵²⁻⁵⁵, 4-(1,2-dihydroxyethyl)²¹¹, 4-(substituted)aryl²¹¹, 4-benzoyl-1,4-DHP²¹¹. Most 1,4-DHP obtained by the Hantzsch synthesis contain a substituted (less frequently unsubstituted) phenyl group at position 4^{36,57,60-62,65,66,68-76,80-94,99-110,112-118,121,123-129,131-139,141-151,154-158,160-182, 184-186,189-192,194,196,198-201,212-228}. The reactions conducted in an autoclave at 110-120°C have increased yield of 4-(o-substituted)-phenyl-1,4-DHP²²⁸. A few examples of 4-naphthyl^{57,112,191,224} and biphenyl-1,4-DHP⁷⁴ are available. 1,4-DHP carrying the following 4-heterylsubstituents have been also prepared:



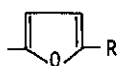
57,75,76,112,152,191



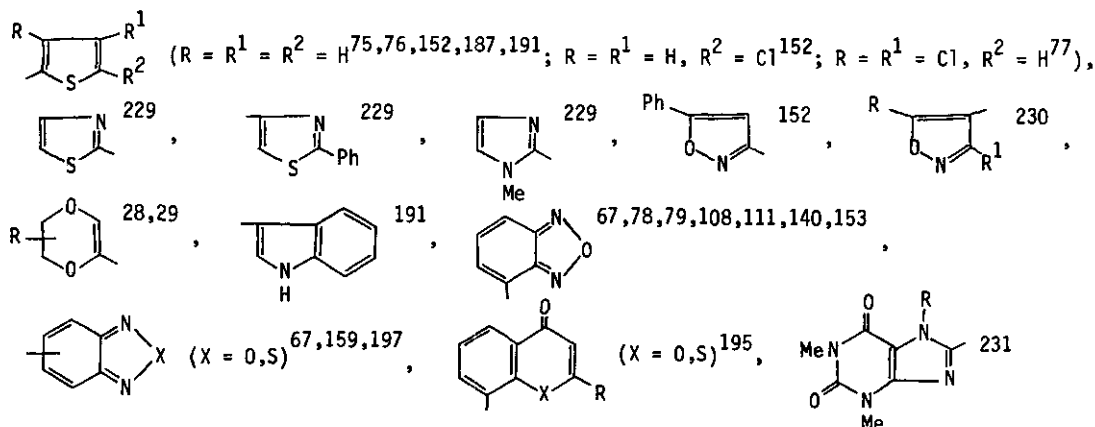
$\text{OCH}_2\text{Ph}^{226}$



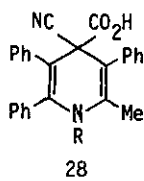
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($R = \text{H}^{75,76,103,152,187,191}$; $R = \text{Me}^{152}$),

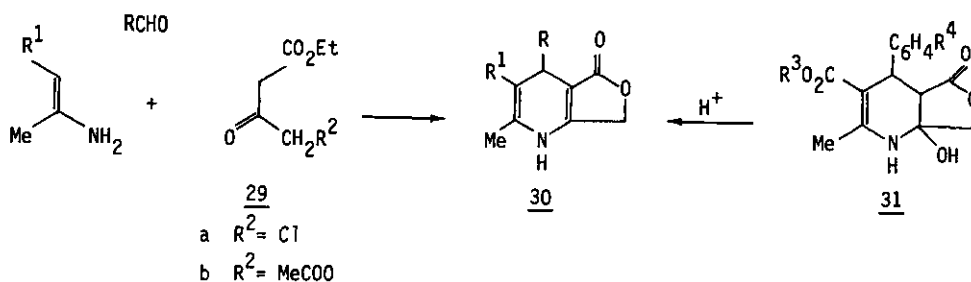


4,4-Disubstituted 1,4-DHP are formed (when ketones are applied instead of aldehydes) only in the case of 3,5-dicyano derivatives^{103,188}. 1,4-DHP 1b⁵¹ has been obtained. The preparation of 1,4-DHP 28 by method E²³² has been reported, although its structure is not adequately established.



1.2. Polycyclic 1,4-Dihydropyridines

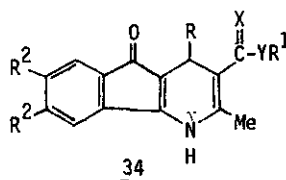
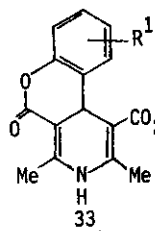
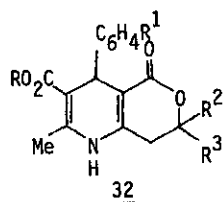
1,4,5,7-Tetrahydrofuro[3,4-b]pyridines 30 can be prepared from esters 29a^{80,193,233,234} or 29b^{57,112,233,234} with lactone ring closure in the course of synthesis or by applying tetrionic acid²³³ or its derivatives^{234,235}. Under mild conditions, hexahydrofuropyridines 31 are formed, which easily undergo dehydration to DHP 30²³⁵.



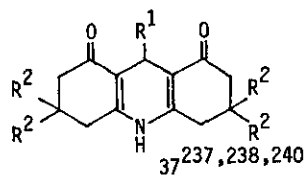
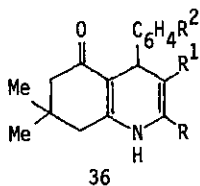
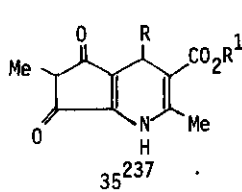
DHP 32^{57,112} and 33¹⁰ have been attained from tetrahydropyranone and 3-acetylcoumarine derivatives, respectively.

Polycyclic 1,4-DHP 34-37 were gained on the basis of cyclic β -diketones.

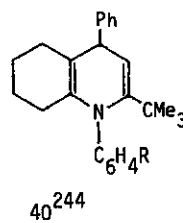
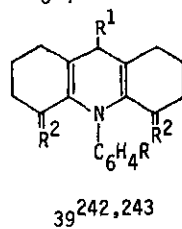
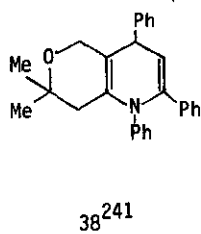
Method E may lead to a series of polycyclic 1,4-DHP 38-40 lacking electron-withdrawing groups at β -position.



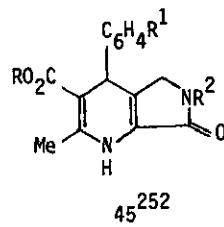
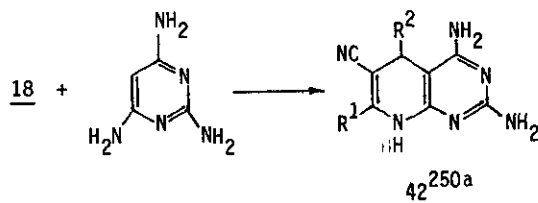
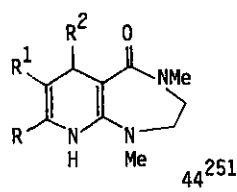
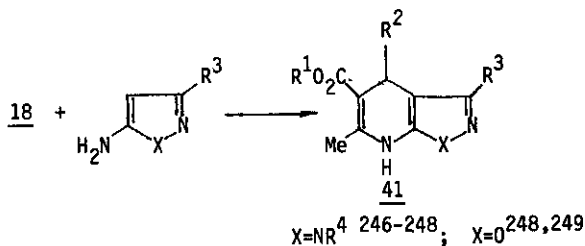
- a $X=Y=O$ ^{21,236};
 b $X=O$, $Y=S$ ^{179,180};
 c $X=S$, $Y=O$ ¹⁸¹;
 d $X=Y=S$ ¹⁸²

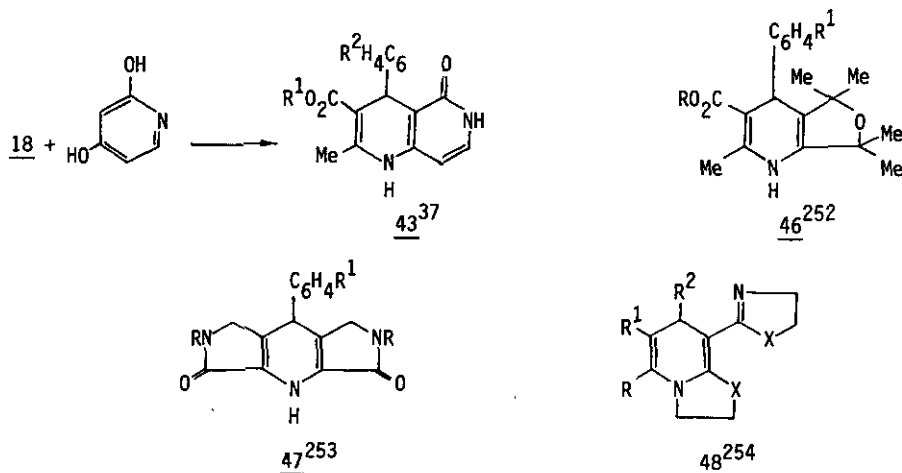


- a $R=Me$, $R^1=CO_2Et$, CN ²³⁸;
 b $R=C_6H_4R^2$, $R^1=H$ ²³⁹



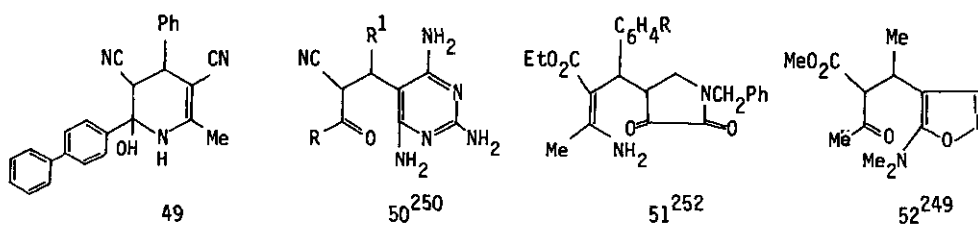
In a number of compounds (41-48) the 1,4-DHP ring is fused with another heterocycle. Their preparation occasionally relies on novel modifications of Hantzsch synthesis, e.g. on the use of heterocyclic amines instead of enamine in method D¹ or C²⁴⁵⁻²⁵⁰ and 2,4-dihydropyridine instead of the β -dicarbonyl species³⁷.





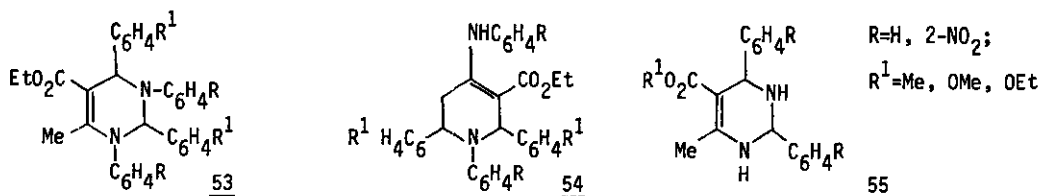
1.3. Intermediates in Hantzsch Synthesis

Several compounds have been isolated that can be regarded as intermediates in Hantzsch synthesis. 2,6-Dihydropyridine (12⁹⁶⁻⁹⁸) and 2-hydroxytetrahydropyridine (13⁹⁹, 31²³⁵ and 49¹⁰⁵) derivatives result from condensation occurring without water elimination, their formation being apparently favoured by the presence of electron-acceptors at positions 2, 6. Acyclic Michael addition products 50-52 have been also isolated.

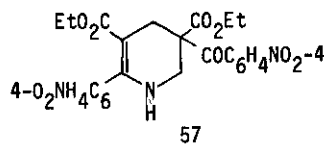
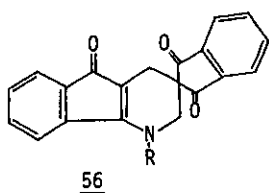


1.4. Side Products

As previously noted¹, the formation of side products in Hantzsch synthesis is a rare occurrence. The presumed N-aryl tetrahydropyrimidines 53^{1,255,256} turned out to be in fact the 4-phenylamino-1,2,5,6-tetrahydropyridines 54^{257,258}. It should be pointed out, however, that the occurrence of N-unsubstituted tetrahydropyrimidines 55 was unequivocally demonstrated in the reaction of benzaldehydes with β -dicarbonyl compounds and ammonia^{185,259,260}.

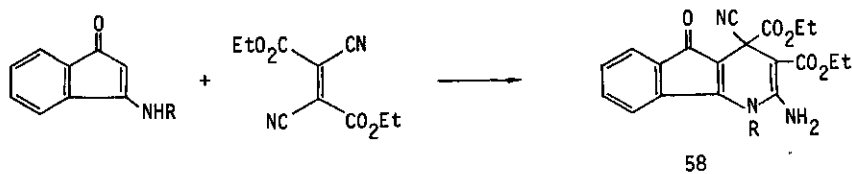


The formation of tetrahydropyridines with geminal carbonyl groups at position 3 - 56²⁶¹, 57²⁶² has been also observed.

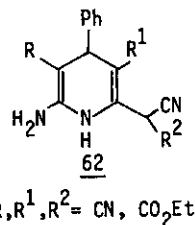
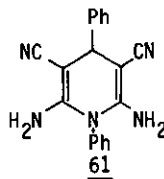
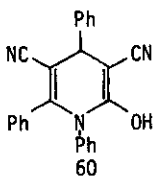
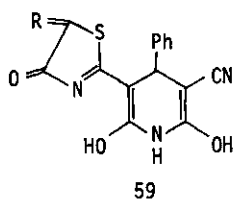


2. Other Cyclocondensations

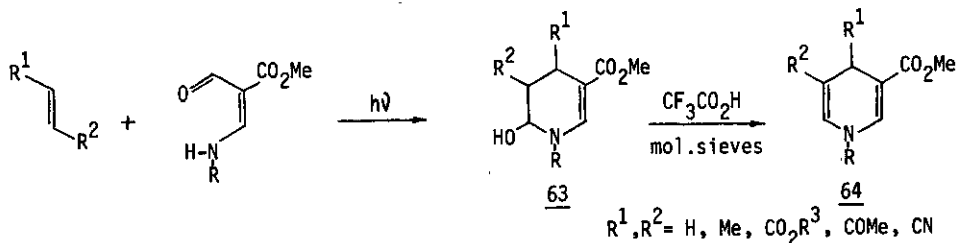
Reaction of 3-aminoindenones with dicyanofumarates affords 1,4-DHP 58²⁶³.



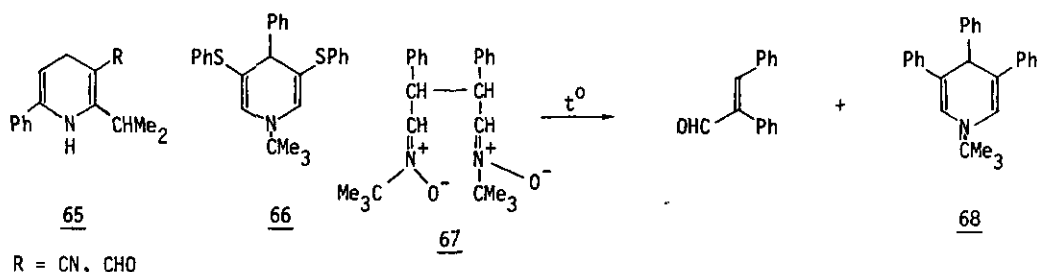
There are reports of 2-hydroxy-1,4-DHP 59²⁶⁴ and 60²⁶⁵⁻²⁶⁶ being formed, though their structure, in our opinion, requires further substantiation. The reaction of benzylidenemalononitrile with other nitriles affords 1,4-DHP 61²⁶⁷ and 62²⁶⁸⁻²⁷⁰.



A photochemically promoted addition of alkenes to enaminoaldehydes leads to tetrahydropyridines 63 that undergo dehydration to 1,4-DHP 64²⁷¹⁻¹⁷³.



Cycloaddition of alkenes to azabutadienes yields pyridines and also 1,4-DHP 65²⁷⁴, 66²⁷⁵. The thermolysis of dinitrone 67 gives a mixture of products containing an unsaturated aldehyde and 1,4-DHP 68²⁷⁶



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