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Hantzsch reaction: Recent advances in Hantzsch 1,4-dihydropyridines

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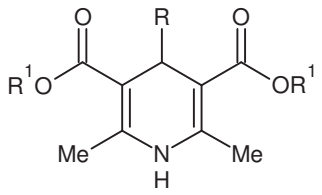
Hantzsch reaction seems to be one of the earliest procedures for the production of pyridines. Later on, Hantzsch 1,4-dihydropyridines, which mimic NADH reduction process *in vitro*, have shown promising biological activities. This review presents production procedure, major reactions of current interest, oxidation and reduction of Hantzsch 1,4-dihydropyridines, besides indication of some existing gaps and areas to be developed.

Keywords: Biological activities, Hantzsch 1,4-dihydropyridines, Hantzsch reaction

Introduction

Arthur Hantzsch described preparation of 1, 4-dihydropyridine **1** more than a century ago[1,2]. Exploration of pyridine initially were quite slow, later it picked up very fast because of their structural resemblance to reduced nicotinamide adenine dinucleotide (NADH) **2**, which is an established hydrogen transferring agent in biological processes[3]. Hantzsch pyridines are a subset of the co-enzyme **2**.



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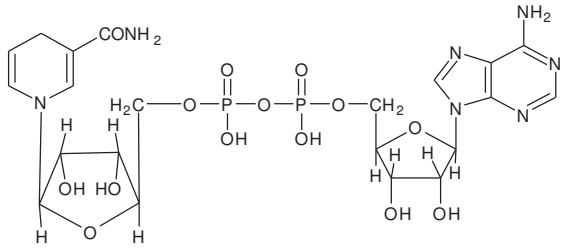
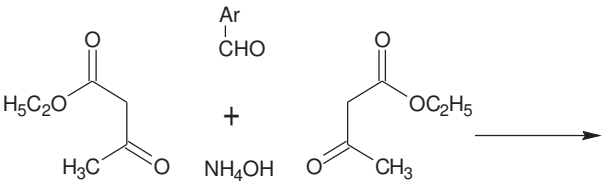
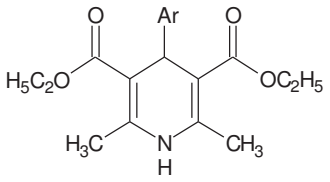


2

These pyridines are called Hantzsch pyridines and reaction as Hantzsch reaction (HR). Original synthesis reported by Hantzsch is three components (acetoacetic ester, benzaldehyde and ammonia or ammonium salts) coupling reaction in refluxing ethanol (Scheme 1).





1a

Scheme 1

Progress in the chemistry of Hantzsch pyridine can be attributed to its resemblance with NADH and interesting biological activity of these molecules as antihypertensive agents. This feature of these molecules came in sight in 1970, and in forthcoming years several new molecules having dihydropyridine (DHP) scaffold are in clinical use (Chart 1) as antihypertensive agents[4]. Apart from this activity, DHPs have been explored to possess anti-tumor[5], anti-inflammatory[6], anticonvulsant activity[7], antitubercular activity[8] etc.

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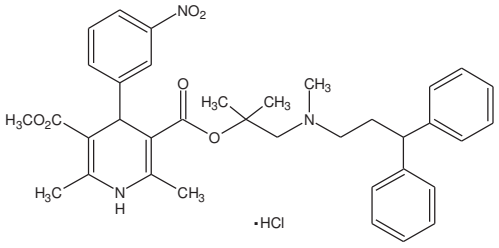
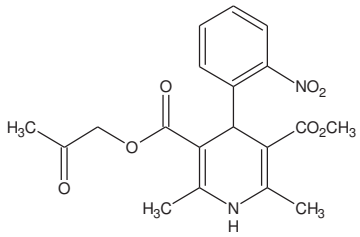
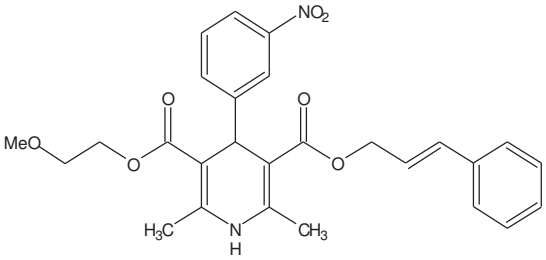


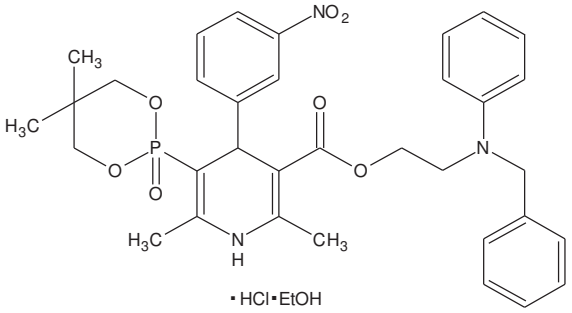
Lercanidipine
(Lerdip, Recordati, Italy, 1997)



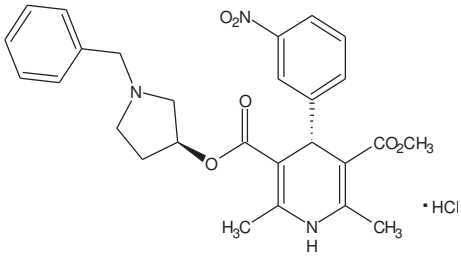
Aranidipine
Bec/Sapresta, Maruko Seiyaku, Japan, 1996)



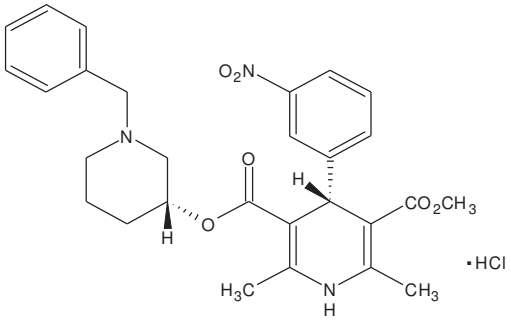
Cilnidipine
(Cinalong or Siscard, Fujirebio, Japan, 1995)



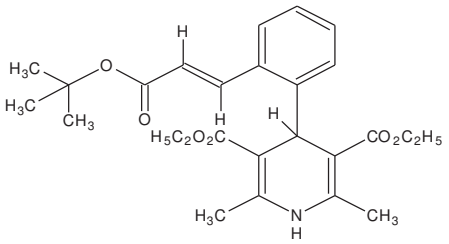
Efonidipine Hydrochloride Ethanol
(Landel, Nissan chemical, Japan, 1994)



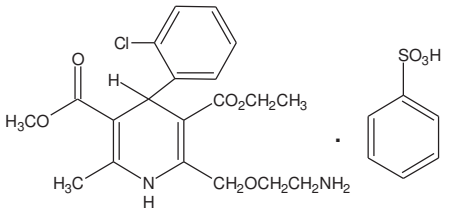
Barnidipine Hydrochloride
(Hypoca, Yamanouchi, Japan, 1992)



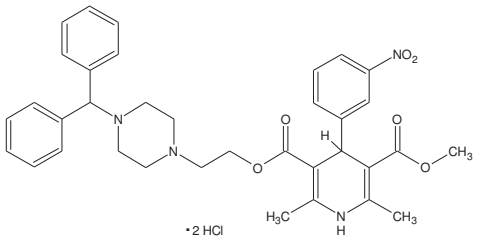
Benidipine Hydrochloride
(Coniel, Kyowa Hakko, Japan, 1991)



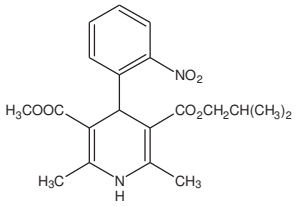
Lacidipine
(Lacipil or Lacirex, Glaxo, UK, 1991)



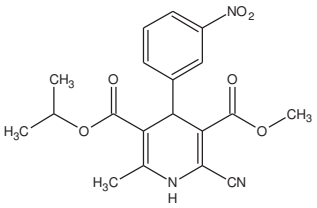
Amlodipine Besylate
(Istin, Pfizer, USA, 1990)



Manidipine Hydrochloride
(Calslot, Takeda, Japan, 1990)



Nisoldipine
(Baymycard, Bayer AG, Germany, 1990)



Nilvadipine
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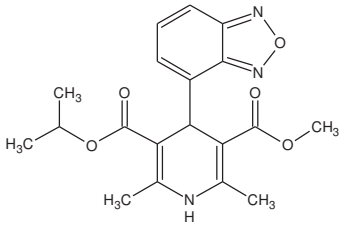
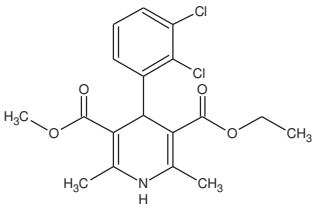
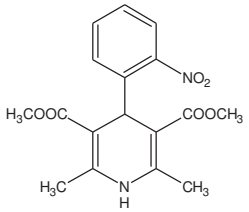


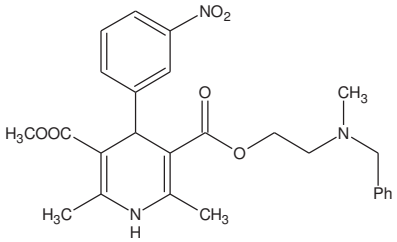
Isradipine
(Prescal, Sandoz, Switzerland, 1989)



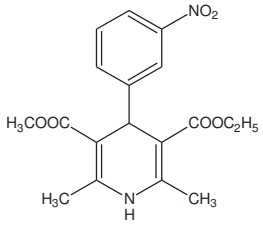
Felodipine
(Plendil, Astra, Sweden, 1988)



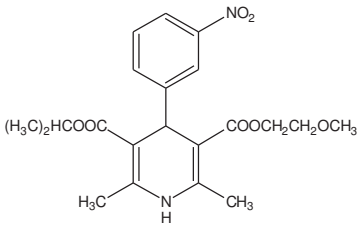
Nifedipine
(1977)



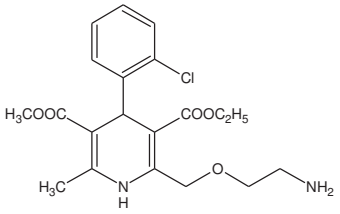
Nicardipine



Nitrendipine



Nimodipine



Amlodipine

Chart 1

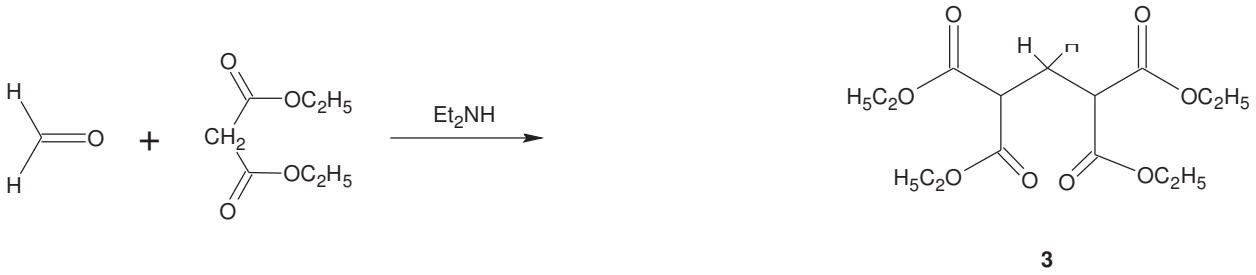
Apart from expanding the number of functional group reducible with these pyridines, large amount of work continues to be published to find out mechanisms of this reduction viz. hydride transfer from Hantzsch ester or it is H radical involved in reductions. Oxidation of Hantzsch pyridines dates back to their discovery and is of intensive researches even now[9]. All clinically used DHPs are understood to be oxidized *in vivo* by liver enzyme P-450. This account is intended to deal exclusively with Hantzsch pyridines and their chemical developments as such DHPs are very broad area, where few accounts are already available[10].

Mechanism of Hantzsch Reaction (HR)

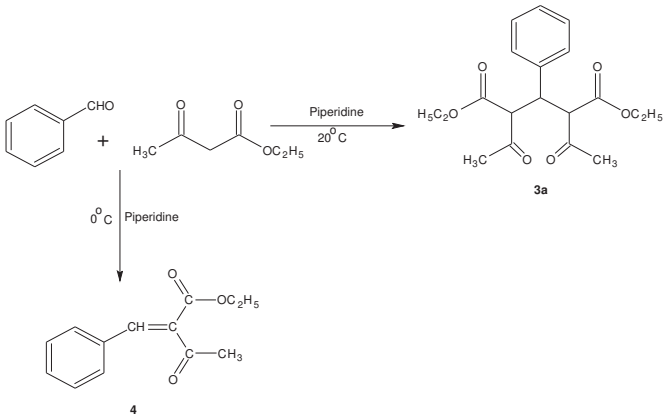
HR employed typical reactants of Knoevenagel reaction and its classical catalysts[11], ammonia, its derivatives and ammonium salts (Scheme 2).

Knoevenagel could show that with change in catalyst used, two types of products are obtainable[11,12](Scheme 3).

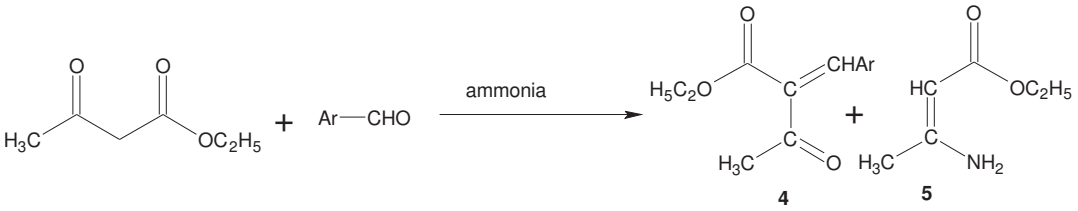
In actual practice, HR was investigated by Beyer[13] and subsequently by Knoevenagel[14], by employing arylidene/alkylidene 1,3-dicarbonyl compounds and amino carbonyl compounds to obtain Hantzsch DHPs products (Scheme 4). Evidently, conditions employed in classical HR can yield arylidene compounds, which can subsequently cyclize to yield DHPs.



Scheme 2



Scheme 3



Scheme 4

So, in HR first step seems to be Knoevenagel condensation yielding arylidene/alkylidene followed by Michael addition of aminocrotonate or enaminones arising from the reaction of active methylene compounds typically ethyl acetoacetate or corresponding diketones with ammonia. Apart from this and few more[15] two highly plausible pathways (A and B) are:

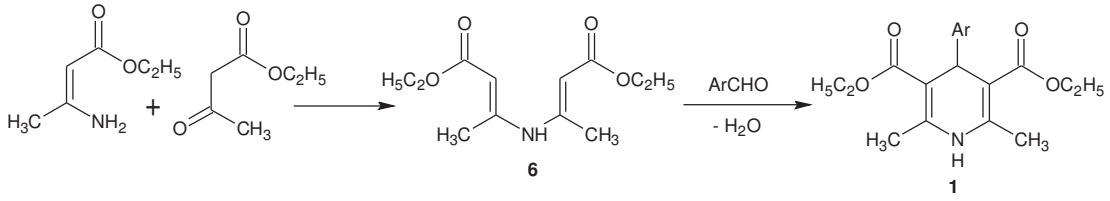
Pathway A

Enamino ketone may react with another molecule of dicarbonyl compound or acetoacetic ester to yield intermediate **6,** which may react with aldehyde, followed by water elimination to give DHP (Scheme 5).

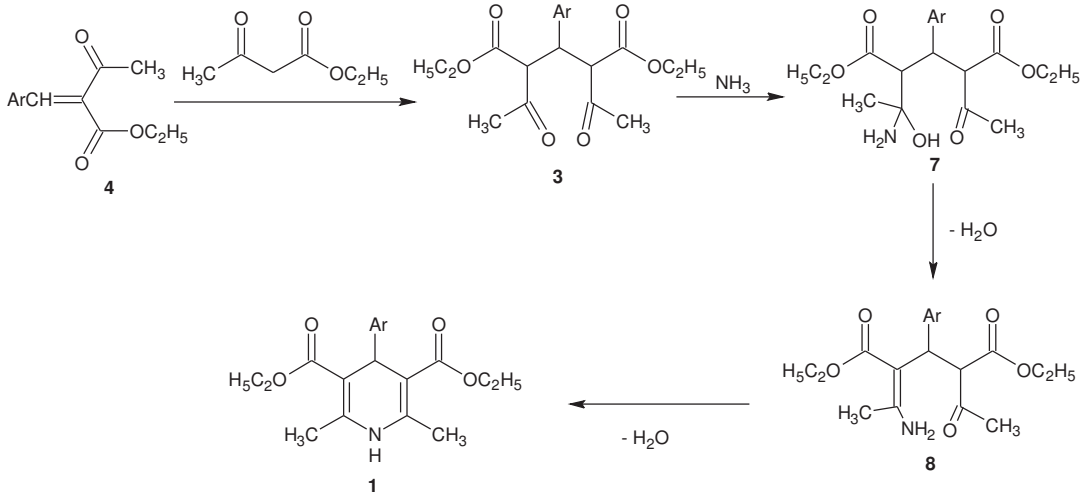
Pathway B

In this possibility, 1,5-diketone may be produced via initially produced Knoevenagel product **4,** which may add on to another molecule of active methylene compound to yield 1,5-diketone **3**. This diketone by reacting with ammonia may yield DHP, which is already precedented in a variety of heterocyclic syntheses[16] (Scheme 6).

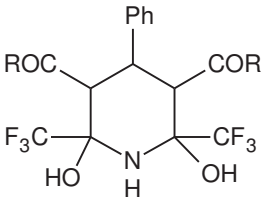
In 1986, mechanism of HR was exhaustively investigated by NMR spectroscopy and it was established that reaction proceeds via enamine intermediate[17], which combines with typical Knoevenagel product produced by the reaction of active methylene compound and aldehyde as shown in A. However, if highly electron withdrawing group (CF_3) are used in place of CH_3, reaction proceeds through 1,5-diketone formation as last dehydration could not be effected[18] and undehydrated product **9** is isolated. In conclusion, it seems that HR follows more than one route depending upon conditions used and the reactants.



Scheme 5



Scheme 6



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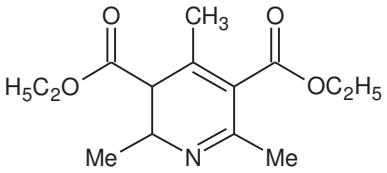
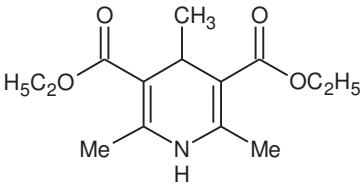
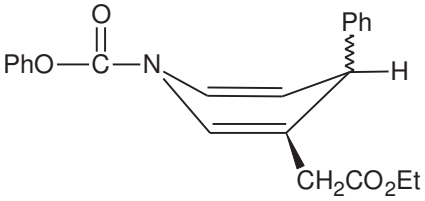


I



II



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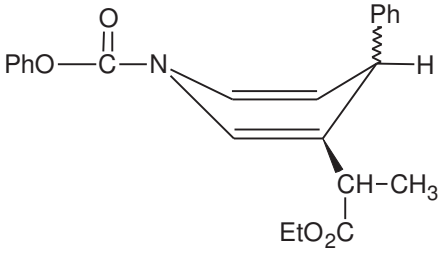


11

Scopes and Limitations

Structural Variants

Present account exclusively deals with 1,4-DHP and not 1,2-DHP or other DHP derivatives and only Hantzsch DHP synthesis is dealt here. Though original structure assigned by Hantzsch was **I** and it was subsequently discarded and established to be **II**[10,15,16,28]. Exact conformational studies have revealed[10] structure of these pyridines as **10** and **11**. Therefore particular variants/ structural constituents in the original Hantzsch synthesis are aldehyde, ethylacetoacetate and ammonia.

Aldehydes

Almost all types of conventional aldehydes (aliphatic[19-31], aromatic[29-43], spiroaldehydes[44] and a variety of heterocyclic aldehydes[29,31,36-38,45-47]) have been used in this reaction in place of acetaldehyde and formaldehyde, which were used originally. To name a few, all possible pyridine carboxyaldehydes[38] including cinchonidinal-dehyde[45] based on aldehydes. Not only this, aldehyde variations have been extended to aldosugars and some of other smaller sugar derivations to obtain sugar based Hantzsch pyridine (HP) viz C-nucleoside of Hantzsch bases[48-50] (Chart 2).

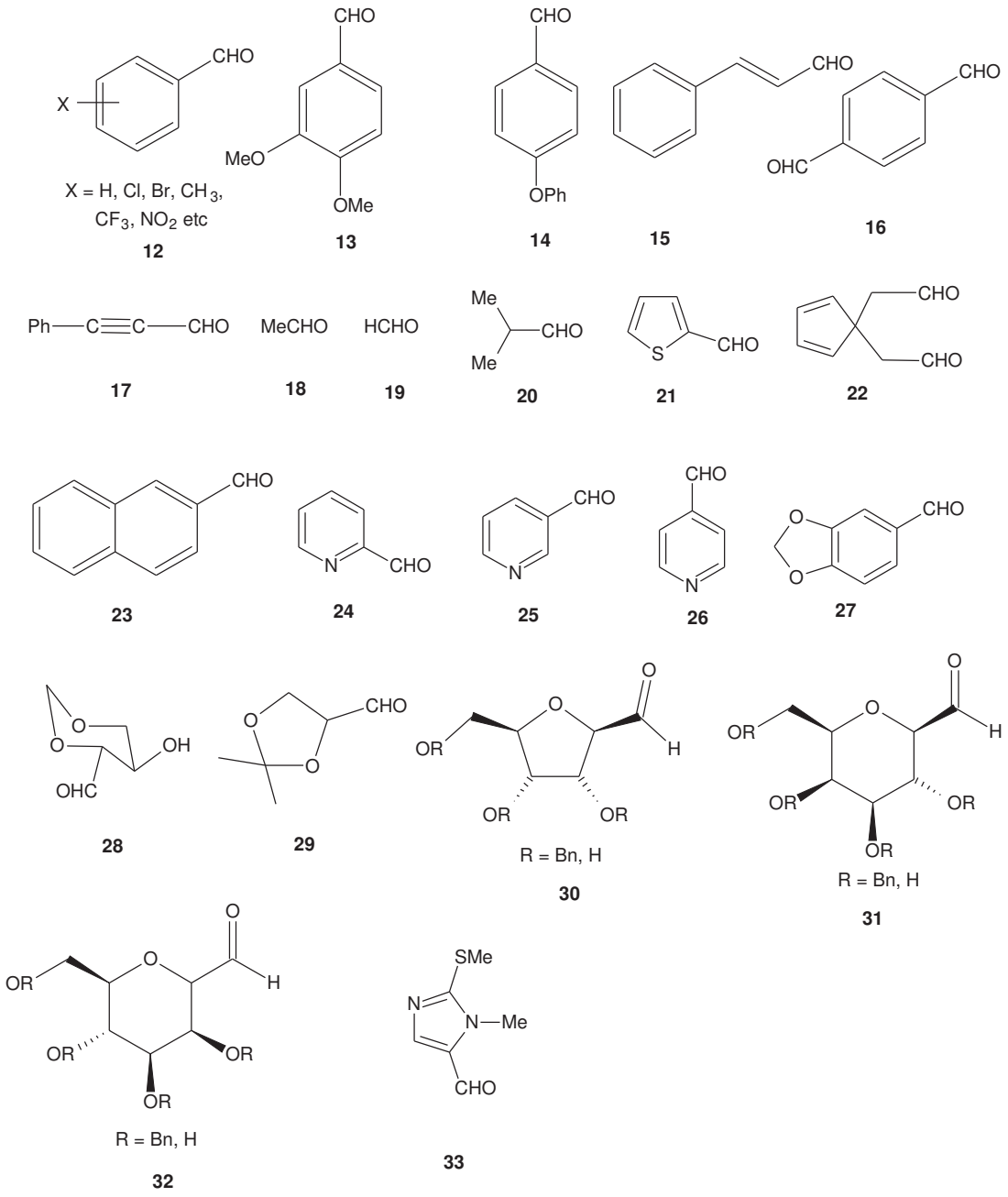


Chart 2

Active Methylene Compounds

1,3-Diketones[29-31,36,37,51-54], ω-cyanoacetophenone or ω-phenylthioacetophenone[55] are used in place of acetoacetic ester. In all these reactions, always symmetrical Hantzsch bases were obtained. Successful application of betaines[56] and activating methylene group of α-haloketones has fairly widened the scope of this reaction. Even normal ketones have been used via normal α,β-unsaturated ketones production[37,55,57]. Theoretically, once electron deficient alkenes were demonstrated to react with enamino ketones, the scope of this reaction

has widened extensively. Use of amino crotonate[17,58] or enamino ketones[59], indane-1,3-dione[60] have led to the preparation of variety of unsymmetrical HPs (Chart 3).

Use of methyl propionate[61,62] lead to production of 2,6-unsubstituted HPs (Scheme 7).

Ammonia and its Derivatives

Ammonia[36-38,46] or ammonium acetate[29,43,51,63,64] is frequently employed to supply nitrogen component in the Hantzsch DHP synthesis. But urea[65,66], ammonium nitrate[67,68], fomamide[69], hexamethylenetetramine[51], hydroxylamine[70], ammonium formate[71] have also been used. When hydroxylamine is used, corresponding oxidized pyridine is obtained instead of DHP. Primary amines[72], secondary amine[22,73] and hydrazines[74] have also been employed.

Miscellaneous

H_2SO_4[58] is shown to help this reaction and clearly there is loss of two molecules of water in this reaction. So it might have facilitated dehydration by absorbing two water moles. Some other catalysts[29] improves efficacy of this reaction and over all these are also dehydrating agents. Agudoawu & Knauss[75] accomplished enentiomeric synthesis of DHPs.

Oxidation of Hantzsch Pyridines (HPs)

Traditional Oxidants

Hantzsch reported oxidation[2] of DHP with nitric acid along with their synthesis. In 1885, Engelmann[76] observed dealkylation at 4-position of pyridine ring while oxidizing DHPs with nitrous fumes. Nitric acid is still commonly used[77-81]. MnO_2 is another oxidizing agent/reagent frequently used[82-87] for oxidation in combination with solid support of HZSM-5 zeolite[82], DDQ[83] and bentonite clay[84]. Bagley & Caterina[85] reported the use of MnO_2 coupled with microwave irradiation. Oxidized pyridines are obtained in excellent yields with no dealkylation or dearylation at 4-position. A number of DHPs have been oxidized with $KMnO_4$[88-91]. Lee & Ko[92,93] used hypervalent iodine reagent, [hydroxy(tosyloxy)iodo]benzene and polymer supported (diacetoxyiodo)benzene. With both of these reagents, dealkylation/arylation occurs in few cases. Another

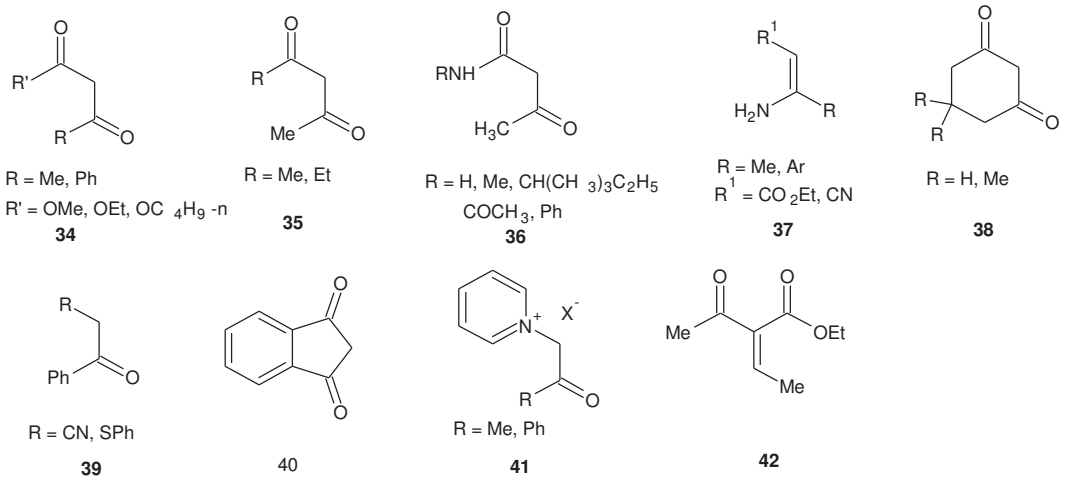
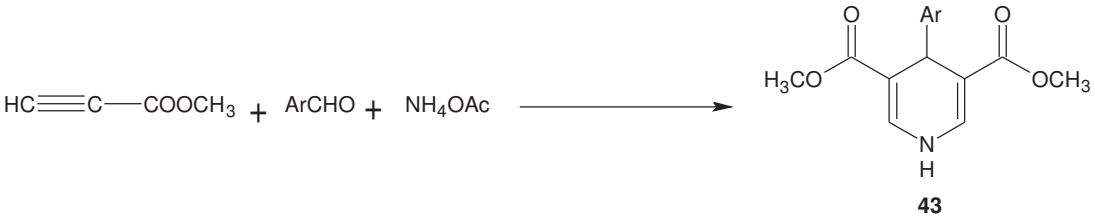
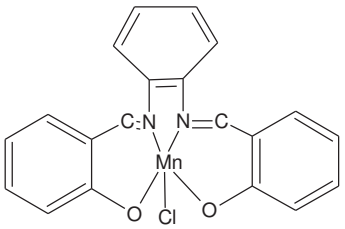


Chart 3

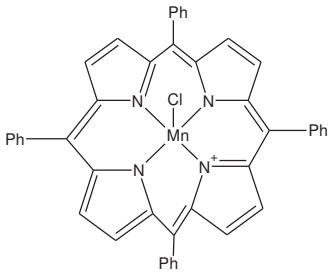


Scheme 7



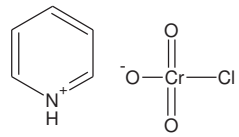
Mn (III) salophen

43



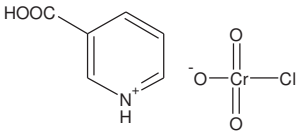
Mn(TPP)Cl

44



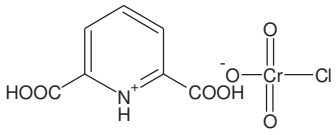
Pyridinium chlorochromate

45



3-Carboxy Pyridinium chlorochromate

46



2,6 -dicarboxypyridinium chlorochromate

47

hypervalent reagent, phenyliodine(III) bis (trifluroacetate), is also used[94] for oxidation. DHPs are aromatized by electrochemical oxidation[95,96]. Alvarez and co-workers[84,86] were the first to use microwave for oxidation of DHPs. Some applications of microwave irradiation are those using catalysts MnO_2[85], $BiCl_3$[97], Dess-Martin periodinana[98], $Bi(NO_3)_3$[99] and element S[94]. Other reagents include heteropolyacid[100], HIO_3[101], I_2O_5[101], $BiONO_3$/acidic Al_2O_3[102], $NaNO_2$[103-107], SeO_2[108], $Fe(ClO_4)_3$/AcOH[109], $Zr(NO_3)_4$[110], urea nitrate[9c], manganese triacetate[111], and H_2O_2[112]. Saini *et al*[9a] performed oxidation in most successful manner under mild and environmentally benign conditions using simple air and solvent DMSO and obtained corresponding oxidized pyridines in excellent yields. Highly electron deficient systems can work as oxidants[59].

Oxidation with Complexes

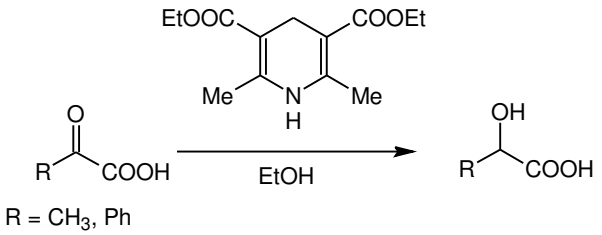
Hantzsch 1,4-DHP synthesis was developed to obtain large array of pyridines via simple oxidation. Bis(salicyaldehyde-1,2-phenylenediimine) Mn (III) chloride or Mn (III) salophen, **43**, was employed for the oxidation of DHP in combination with $NaIO_4$[9b] and urea-H_2O_2 system[113]. Tetraphenylporphyrinatom anganese (III)chloride Mn (TPP)Cl was used in presence of imidazole as axial ligand[114] and polystyrene bound Mn (TPP)Cl, **44**, in presence $NaIO_4$ for oxidation[115].

N,N'-Ethylene-bis(benzoylacetoniminato) Cu (II) has been successfully employed for this oxidation[116]. Other oxidation complexes includes pyridinium chlorochromate (PCC)[117], **45**, 3-carboxypyridinium chlorochromate (CPCC)[118], **46**, 2,6-dicarboxy pyridinium chlorochromate[119], **47**, and Co-naphthenate with O_2[120]. Saini *et al*[121] also employed conventional chromium reagents for this oxidation and obtained excellent results.

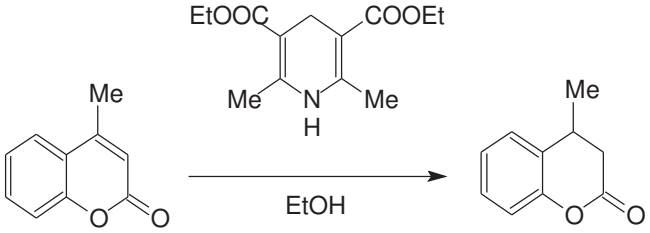
Reductions using Hantzsch Pyridines (HPs)

First ever reduction case by HPs seems to be that of keto group in pyruvic acid ($CH_3COCOOH$) into lactic acid[122] ($CH_3CHOHCOOH$), which is followed by the reduction of phenylglyoxalic acid to corresponding α-hydroxy acid[123] (Scheme 8).

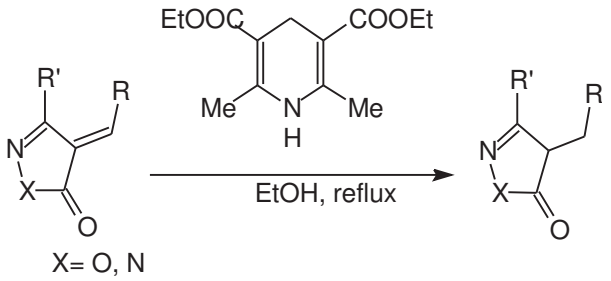
This keto group reduction is further extended to various ketone and ester functions like. reduction of α-ketoesters[124-126], α-ketomenthyl ester[127], thioketones[128] and thioesters[129]. These biomimitic molecules (HPs) found use in the selective reduction of carbon-carbon double bond (C=C) in conjugated carbonyl systems such as α,β-unsaturated aldehydes[130-132] using organocatalytic imidazolidone catalyst. This reduction further extended to α,β-unsaturated ketones[133-134], unsaturate dcarboxylic acid using catalytic amount of trfluoroacetaldehyde in acetic acid[135], maleic acid and its derivatives[133]. Also,



Scheme 8



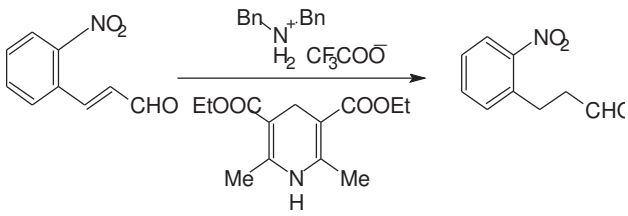
Scheme 9



Scheme 10

endocyclic double bond of coumarins scaffold[136] and exocyclic double bond of isoxazolones and pyrazolones[137] have been reduced successfully with dihydropyridines (Schemes 9,10).

In addition, reduction of other activated olefins[138-150] (cyanoolefins[142,143], nitroolefins[144-146] and indolenines[147-150]) are also documented. Selective and asymmetric reduction of C=N function is one of the prominent application of Hantzsch DHPs and used for the reduction of aldimines[151-153], ketimines[154-155], α-imino esters[156], α-imino acids[157], quinolines, isoquinolines[158,159] and reductive amination[160-165] of carbonyl function using various catalyst like thiourea[153,165], imidazolidone salts[163], metal complexes[161,163,164], diphenyl phospates[151,159] etc. These esters are also reported[166] for the reduction of pyridoxyl phosphate in presence of common metal ions like Mg^{2+}, Mn^{2+}, Ni^{2+}, Co^{2+} and Zn^{2+}. Also, reduction of



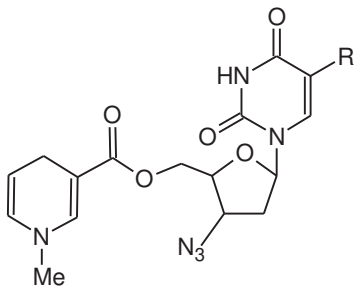
Scheme 11

nitrobenzene, o-nitrophenol, o-nitroanisole, nitrosobenzene[167] and 1,3,5-trinitrobenzene[168] have been carried using HPs as reductant. Dipyridine-*N*-oxides[169] are also reduced using HPs. Reductive cyclisation of allylic and benzylic bromides with HPs is also available[170-171]. In these processes, several promoters have been used. In one case, there is direct evidence that quaternary nitrogens are reduced faster[172]. Most of these studies have been to mimic bioprocess and selectivity of these pyridines (Scheme 11).

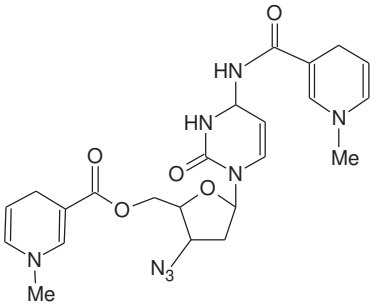
Here, only double bond is reduced leaving -CHO group and NO_2 group intact (earlier reduction of these functions is precedented[167,168]). After this selectivity observed in HP reductions, authors were tempted to use DHPs in the reduction of 4-oxo-4H[1]-benzopyran-3-carboxaldehyde imines and excellent results were obtained, and further investigation is in progress. In the forgoing reductions, whether it is hydride (H^-) transfer or hydrogen radical ($H^\cdot$) transfer, this subject is still undergoing intensive investigations and is open question.

Pharmacological Importance

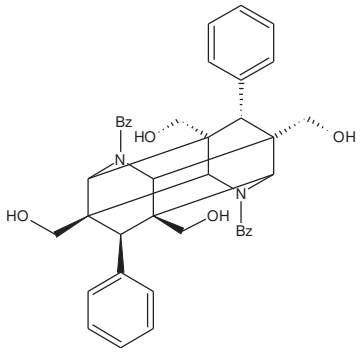
A number of bioactivities are associated with HPs. Among several bioactivities, their value as antihypertensive agents[4,173-177] is unquestioned and are reported as good calcium channel blocker,[178-180] anti-tuberculosis,[8,181] analgesic,[182] anti-inflammatory,[6,75] antithrombiotics[183-185] and anticonvulsant agents[7,186,187]. In addition to these activities, their biological activity profile is further extended as anti-HIV agents[188] by preparing/ condensing these molecules with already clinically used HIV agents *viz*. 3´-azido-2´,3´-dideoxyuridine DHP (AzddU-DHP) **48** and 3´-azido-3´-deoxythymidine DHP (AZT-DHP) **49**. Other nucleoside dihydropyridine[189], 2´,3´-dideoxycytidine (DDC) derivative (HP_2DDC) **50,** and among non peptidic dimeric, 4-aryl-1,4-dihydropyridine **51** are reported as HIV protease inhibitors[190].



48 R= H (AzddU-DHP)
49 R= Me (AZT-DHP)



50 (HP_2DDC)



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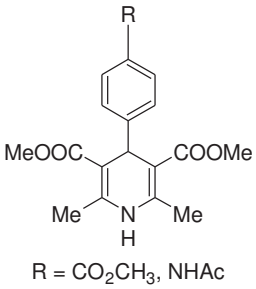

R = CO_2CH_3, NHAc

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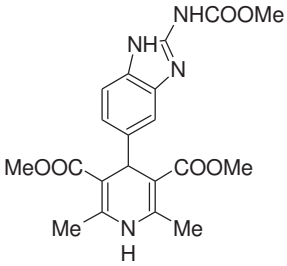

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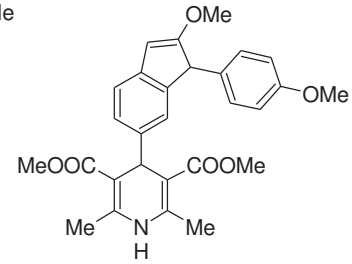

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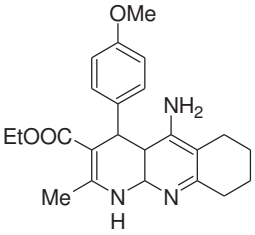

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Mukherjee *et al*[191] reported DHP derivatives **52-54** to be associated with contraceptive activities. Marco-Contelles *et al*[192] described acetylcholinesterase inhibitory and neuroprotective activities of fused DHPs (tacripyrines), e.g. **55**, for the treatment of Alzheimer's disease.

Conclusions

Present account deals exclusively with 1,4 dilydropyridines viz Hantzsch reaction or sometimes called Hantzsch Bayer reaction. In first place, large number of molecules still remain to be synthesized namely unsymmetrical Hantzsch pyridines. Also, there is wide scope to develop enamine chemistry of these molecules with election deficient systems or cyclisations. This can lead to excellent new molecules for further biological evaluations. Also, selectivities in oxidation and reduction by developing new biomimics would also receive renewed attention.

Acknowledgements

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