

Review

## 4-Aryldihydropyrimidines via the Biginelli Condensation: Aza-Analogs of Nifedipine-Type Calcium Channel Modulators

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**Abstract:** Recent results from the author's laboratory in the area of dihydropyrimidine chemistry are summarized.

**Keywords:** Biginelli reaction, dihydropyridines, dihydropyrimidines, calcium channel modulators.

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### Introduction

4-Aryl-1,4-dihydropyridines of the nifedipine type (DHPs, *e.g.* **1-3**) are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975, have become almost indispensable for the treatment of cardiovascular diseases

such as hypertension, cardiac arrhythmias, or angina [1]. More than 20 years after the introduction of nifedipine (**1**), many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market (*e.g.* **2, 3**) [2]. In recent years interest has also focused on aza-analogs such as dihydropyrimidines of type **4** (DHPMs) which show a very

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### Biographical Sketch



**C. Oliver Kappe** was born in Graz, Austria in 1965. He received his diploma degree (1989) and doctoral degree (1992) from the Karl-Franzens-University in Graz where he worked with Professor Gert Kollenz on cycloaddition and rearrangement reactions of acylketenes. After periods of postdoctoral research work with Professor Curt Wentrup at the University of Queensland in Brisbane, Australia (1993-1994), and with Professor Albert Padwa at Emory University in Atlanta, USA (1994-1996) he moved back to the University of Graz in 1996 to start his independent academic career. He received the Dissertation Award of the Austrian Chemical Society in 1993, the Erwin-Schrödinger Fellowship of the Austrian Science Fund in 1994 and an APART Fellowship of the Austrian Academy of Sciences in 1996. He is currently a member of the Advisory Board of the International Society of Heterocyclic Chemistry (1998-1999) and is coauthor of more than 50 publications in the field of synthetic and mechanistic organic chemistry. His current research interests include dihydropyrimidine chemistry, N-ylide chemistry, and pseudopericyclic reactions.

similar pharmacological profile to classical dihydropyridine calcium channel modulators [3-9]. Over the past few years several lead-compounds have been developed (*e.g.* SQ 32926 (**5**) and SQ 32547) [6-8] that are superior in potency and duration of antihypertensive activity to classical DHP drugs, and compare favorably with second-generation analogues such as amlodipine and nifedipine [6,7]. These inherently asymmetric dihydropyrimidine (DHPM) derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the existing structure-activity relationships and to get further insight into molecular interactions at the receptor level [3-9].

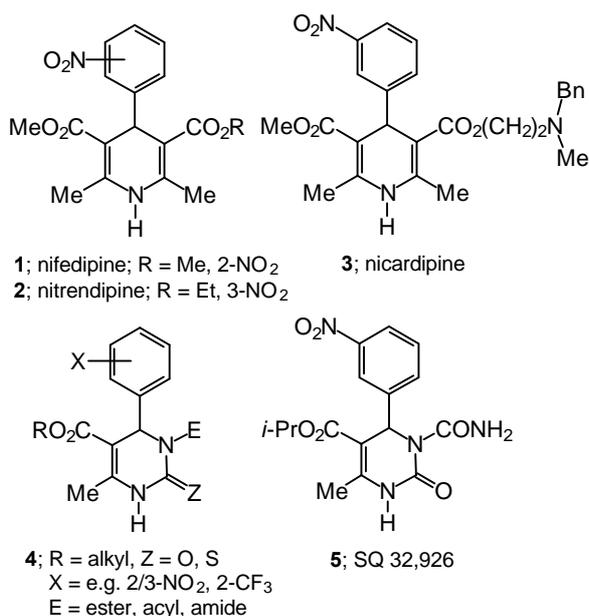
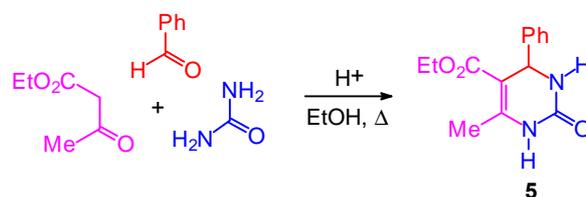


Figure 1.

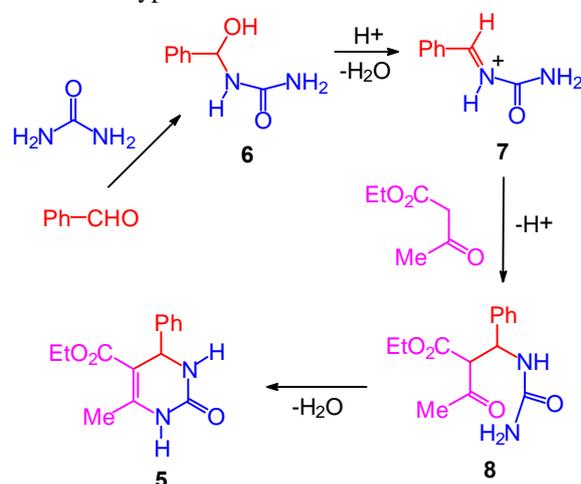
Whereas dihydropyridines of the nifedipine type (DHPs, *i.e.* **1-3**) are generally prepared by the well-known Hantzsch synthesis [10], aza-analogs of type **4** (DHPMs) are readily available through the so-called Biginelli dihydropyrimidine synthesis [11,12] (Scheme 1). This very simple one-pot, acid-catalyzed condensation reaction of ethyl acetoacetate, benzaldehyde, and urea was first reported in 1893 by Pietro Biginelli [11]. In the following decades the original cyclocondensation reaction has been extended widely to include variations in all three components, allowing access to a large number of multifunctionalized dihydropyrimidine derivatives. An extensive review of this multicomponent reaction was published by us in 1993 [12]. Since the appearance of this first review article, interest in the Biginelli reaction and DHPMs in general has increased rapidly. Several improved procedures for the preparation of DHPMs ("Biginelli compounds") have recently been reported [13], including various solid-phase modifications suitable for

combinatorial chemistry [14]. Furthermore, several marine alkaloids with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have been isolated or synthesized in the past few years [15].



Scheme 1.

In this report we summarize our results in the area of dihydropyrimidine chemistry and present a literature survey on recent developments in this field. Special attention is given to mechanistic, structural and stereochemical issues, relevant to the design of new cardiovascular drugs of the DHPM type.



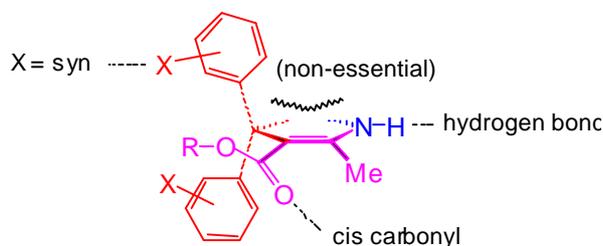
Scheme 2.

### The Mechanism of the Biginelli Reaction

Despite the importance and current interest in dihydropyrimidines of the Biginelli type, the mechanism of the classical three-component Biginelli condensation has not been elucidated with certainty [12]. Early work by Folkers and Johnson suggested that *N,N'*-benzylidenebis-urea, *i.e.* the primary bimolecular condensation product of benzaldehyde and urea, is the first intermediate in this reaction [16]. In 1973 Sweet and Fissekis proposed that a carbenium ion, produced by an acid-catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate, is the key intermediate and is formed in the first and limiting step of the Biginelli reaction [17]. We reinvestigated the mechanism in 1997 [18] using <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (CD<sub>3</sub>OH/HCl) and have established that the first step in this reaction involves the acid-catalyzed

formation of an *N*-acyliminium ion intermediate of type 7 from the aldehyde and urea component. Interception of the iminium ion 7 by ethyl acetoacetate, possibly through its enol tautomer, produces an open-chain ureide 8 which subsequently cyclizes to dihydropyrimidine 5 (Scheme 2) [18].

aryl UP-antagonist



aryl DOWN-agonist

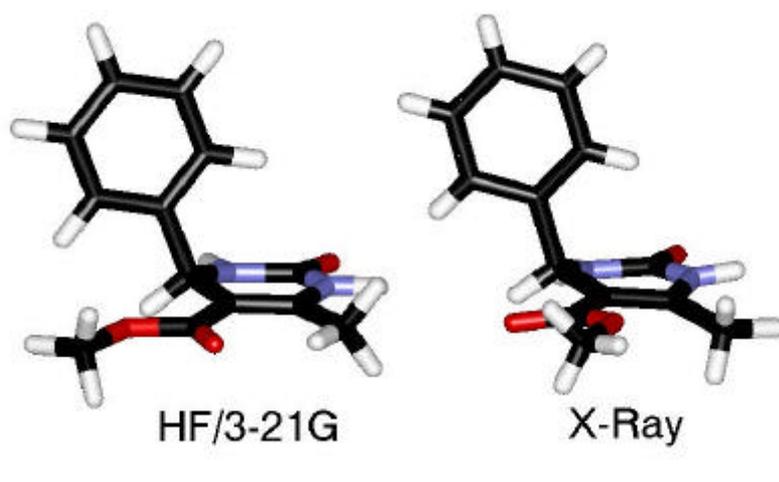
**Figure 2.** Proposed receptor-bound geometry of DHP/DHPM calcium channel modulators [9].

The classical three-component Biginelli condensation is usually carried out in alcoholic solution containing a few drops of concentrated hydrochloric or sulfuric acid as catalyst, although other systems such as THF/HCl, dioxane/HCl, or acetic acid/HCl have also been employed [12]. One major drawback of the classical Biginelli protocol is the low yield that is frequently encountered when using sterically more demanding aldehydes or 1,3-dicarbonyl compounds [12]. In order to promote conditions that would favor the formation of an *N*-acyliminium ion intermediate we have recently performed Biginelli condensations using polyphosphate ester (PPE) as solvent

[19], a reaction medium that has previously been employed in iminium ion-based condensations [19, 20]. Using PPE as a solvent in Biginelli's one-pot protocol (30–50 °C, 12–24 h), a significant increase in the yields of DHPMs was observed, especially for systems that give only moderate yields using traditional Biginelli conditions [21]. We are currently exploring the use of PPE and other related media in the Biginelli condensation.

### Conformational Studies

In 1995 a detailed structure-activity profile for a series of DHPM calcium channel modulators was reported by Rovnyak et al. [9] leading to a new binding-site model for DHP/DHPM analogues. By performing pharmacological studies with uniquely designed single-enantiomer DHPMs, it was established that calcium channel modulation (antagonist *versus* agonist activity) is dependent on the absolute configuration at C4, whereby the orientation of the C4-aryl group (*R*- or *S*-configuration) acts as a "molecular switch" between antagonist (aryl-group up) and agonist (aryl-group down) activity (Figure 2) [9]. Furthermore, in the receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like dihydropyrimidine/pyrimidine ring, with the 4-aryl substituent (X) preferring the synperiplanar (relative to C4-H) orientation [9]. A cis-carbonyl ester orientation (with respect to the C5–C6 dihydropyrimidine double-bond) was also found mandatory for optimum calcium channel modulatory activity (Figure 2). Importantly, only the "left-hand side" of the DHP/DHPM molecule has been proposed to be essential for activity [9].



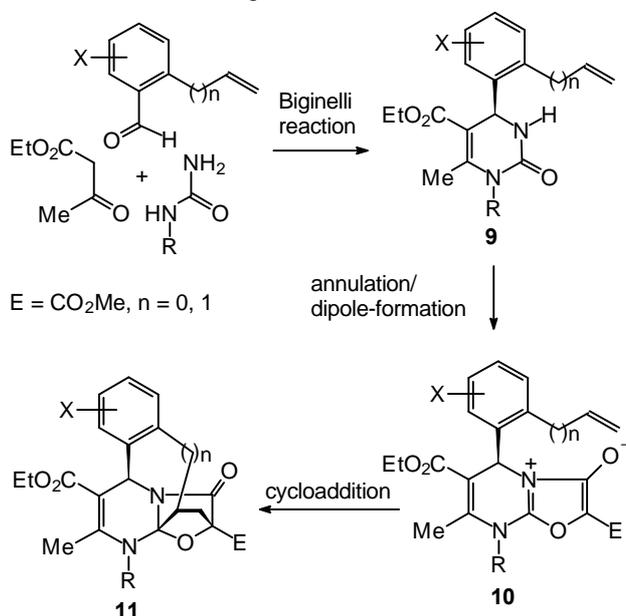
**Figure 3.** Comparison of an ab initio optimized geometry (HF/3-21G) and the solid state geometry of a DHPM derivative. Note the different orientation (*cis versus trans*) of the ester group, a result of crystal packing forces [22].

In a recent publication [22] we reported the first computational study on the geometry and conformational hypersurface of a series of DHPM derivatives. The results of *ab initio* (HF/3-21G) and semiempirical molecular orbital calculations (AM1, PM3) were compared with geometries obtained by X-ray crystallographic studies. All computational treatments predict the lowest energy conformer to be identical with the putative bioactive, receptor-bound conformation shown in Figure 2, although the energy differences between individual conformers and the rotational barriers are generally low. A slight preference for the required *cis* ester conformation (*versus* the *trans* ester form, see Figures 2 and 3) is predicted by all computational methods (0.5-1.5 kcal/mol). Energy differences between aryl conformers (X in *syn* versus *anti* orientation, see Figure 2) were only notable for *ortho* substitution with the *anti* conformation being 1.5-3.6 kcal/mol higher in energy. In general, the conformational features previously reported for DHP calcium modulators [23,24] were also preserved for DHPMs. The most notable difference between DHPs and DHPMs, however, is the extreme flattening of the boat-type dihydropyrimidine ring around N1 as a result of the amide-type bonds present in these heterocycles. A critical comparison of the computational methods indicated that the PM3 Hamiltonian does not reproduce DHPM geometries adequately. On the other hand there is good qualitative agreement with the results obtained by the *ab initio* (HF/3-21G) and AM1 methods, with the results obtained by X-ray crystallography (Figure 3).

In a related study we showed [25] that for the calculated ring conformation (ring pucker) in DHPMs a strong dependence on the computational procedure is observed. RHF, MP2, and B3LYP calculations with basis sets lacking polarization functions on first row heavy atoms (*e.g.* 6-31G) lead to planar ring geometries, whereas inclusion of polarization functions (*e.g.* 6-31+G\*\*) yields puckered boat conformations. With MP2 in particular, unrealistically strong deviations from planarity are predicted, in sharp contrast to the results obtained by X-ray crystallographic studies which yield nearly planar geometries [25].

In the context of our computational studies on DHPM conformers we have developed synthetic methodology leading toward novel types of conformationally restricted dihydropyrimidine derivatives of type **11** that closely mimic the recently proposed receptor-bound conformation of DHP/DHPM calcium channel modulators shown in Figure 2 [26]. The strategy towards these polycyclic dihydropyrimidines is outlined in Scheme 3 and involves an intramolecular 1,3-dipolar cycloaddition reaction of an *o*-alkenylaryl tethered dihydropyrimidine-fused isomünchnone dipole (**10** → **11**) as the key step. The solid-state

structure of model compound **11** (R = Me, X = H, n = 0) shown in Figure 4 demonstrates that the geometry of this conformationally restricted DHPM derivative is very similar to the receptor-bound conformation proposed in the recent binding-site model for DHP/DHPM calcium channel modulators (Figure 2).



Scheme 3.

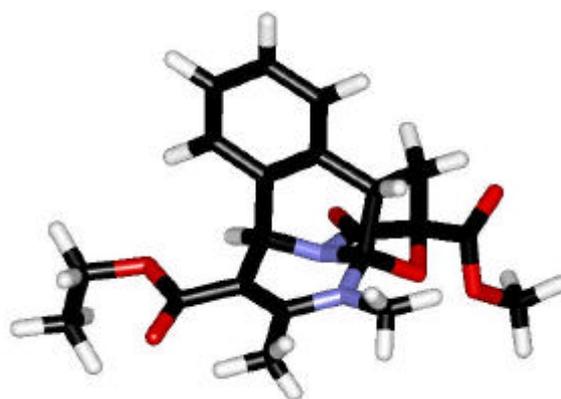
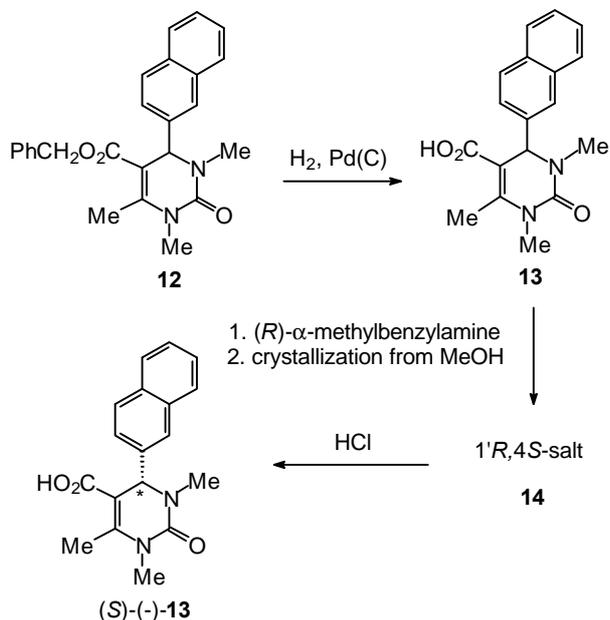


Figure 4. Solid-state structure of **11** (R = Me, X = H, n = 0) [26].

The aryl group in **11** is "tied" into the axial position, is perpendicular to and (nearly) bisecting the boat-like dihydropyrimidine ring. Any additional substituent on the aromatic ring (*i.e.* X in **11**) would be forced into the synperiplanar orientation relative to C4-H. Importantly, by using this cycloaddition protocol all manipulations on the

DHPM system occur on the non essential "right-hand" side of the molecule, thereby not interfering with the receptor sensitive groups on the "left-hand" side (Figure 2). The synthesis of analogues of **11** (R = H), suitable for pharmacological testing is currently under way.



Scheme 4.

### Enantiomerically Pure Dihydropyrimidines

In contrast to DHPs of the Hantzsch type, DHPMs are inherently asymmetric and therefore usually obtained as racemic mixtures. Whereas stereochemical issues in DHPs are well documented [23], the chirality of DHPMs was neglected for many decades. Since individual enantiomers of DHPMs **4** have opposing pharmacological effects on the calcium channel (Figure 2) [9], access to enantiomerically pure DHPMs is an important requirement for the development of cardiovascular drugs of this structural type. Some years ago we obtained enantiomerically pure DHPMs by resolution of the corresponding racemic 5-carboxylic acids (*i.e.* **13**) via fractional crystallization of diastereoisomeric  $\alpha$ -methylbenzyl-ammonium salts (*i.e.* **14**) [27]. The absolute configuration of DHPM **13** was proven by single-crystal X-ray analysis of a suitable diastereoisomeric salt [27]. This and related [5-7] methods, however, involve multi-step reaction sequences giving rise to only moderate overall yields of enantiomerically pure DHPMs. In the absence of an asymmetric synthesis of DHPMs, methodology for efficient enantioseparations is highly desirable.

Due to recent advances in chromatographic enantio-separation techniques, enantioselective HPLC and related methods (*i.e.* simulated moving bed chromatography) have gained importance in the preparation of single-enantiomer

drugs and intermediates [28]. In a recent publication we reported the successful chromatographic enantioseparation of DHPM derivatives of type **4** using a variety of commercially available chiral stationary phases (CSPs) in normal- and reversed-phase analytical HPLC [29]. Out of 29 racemic DHPM analogues all but one were separated on at least one of the eight CSPs tested with separation coefficients ranging from 1.08 to 8.67. For polycyclic DHPMs **11** for example, the use of Chiralcel OD-H as CSP and 2-propanol/n-heptane as mobile phase has proved to be an effective method for enantioseparation (Figure 5).

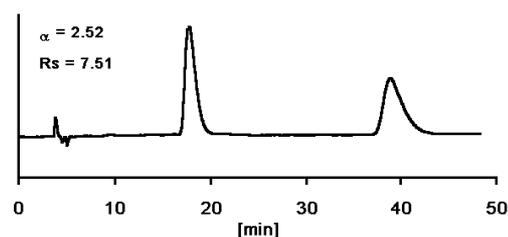


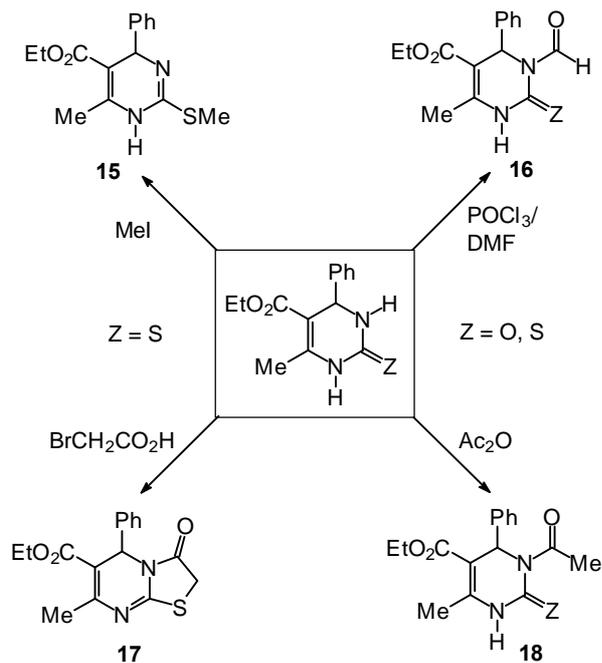
Figure 5. Enantioseparation of **11** (R = Me, X = H, n = 0) on Chiralcel OD-H [29].

### Synthetic Studies

Given the recent DHP/DHPM binding-site model by Rovnyak et al. shown in Figure 2 [9] it is not surprising that DHPMs of type **4** show a similar pharmacological profile to classical DHP analogues **1-3** since the receptor-sensitive "left-hand sides" of both heterocyclic ring systems are identical (Scheme 1). However, from the synthetic point of view, the DHPM system has more flexibility as compared to classical DHP calcium channel modulators. Dihydropyrimidines (DHPMs) are inherently asymmetric and have the advantage that the (thio)amide moiety embedded in the dihydropyrimidine ring clearly defines the "right-hand side" of the molecule and thus allows a selective functionalization of this biologically less important (non-essential) side of DHPMs (see Figure 2), a process that is more troublesome in the DHP series [10,30]. Some years ago we reported a variety of reactions that take advantage of this structural feature (Scheme 5) [31]. Bioavailability, solubility and basicity of DHPMs are some of the factors that may be controlled by such simple "right-hand side" functionalizations.

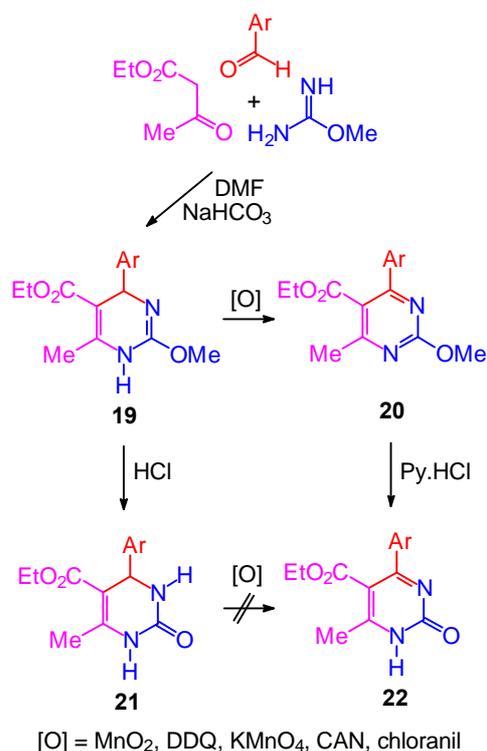
The first step in the metabolism of classical DHP drugs is an oxidative process leading to the corresponding pyridines with complete loss of activity [32]. In contrast to DHPs where aromatization to pyridines is typically an easy process [30], the dehydrogenation of DHPMs (**21**  $\rightarrow$  **22**) is more difficult and no general and practical synthetic procedure has been disclosed [12]. However, we have recently reported that 2-methoxy-1,4-dihydro-pyrimidines

of type **19** can readily be obtained by condensation of ethyl acetoacetate, *O*-methylisourea, and an appropriate aldehyde [33]. 1,4-Dihydropyrimidines **19** could then be oxidized by a variety of methods (Scheme 6) to pyrimidines **20** which can be subsequently *O*-demethylated to give the desired pyrimidin-2-ones **22** by treatment with pyridine hydrochloride. The resistance of DHPMs **21** towards oxidation may explain the prolonged duration of antihypertensive activity as compared to classical DHP drugs of the nifedipine-type.

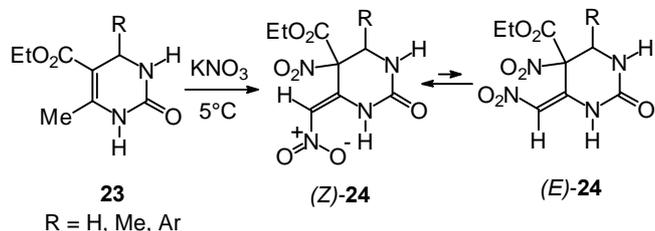


Scheme 5.

In the context of DHPM oxidation we also studied the reaction of **23** with nitric acid and related reagents. Correcting earlier work [34], it was shown that the action of potassium nitrate in concentrated sulfuric acid on DHPMs **23** results in the formation of 5-nitro-4-nitro-methylidene-5-pyrimidinecarboxylates **24** [35]. Single-crystal X-ray analysis established the structure of **24** (R = H) and demonstrated that in the solid state the intramolecular hydrogen-bonded *Z* isomer is preferred, whereas NMR spectra indicate that in solution hexahydropyrimidines **24** can exist in both *Z* and *E* forms, depending on the solvent used. In more polar solvents such as DMSO ca. 10% of the *E* isomer was observed, whereas in less polar solvents such as acetone the *Z* isomer is the only one observed.

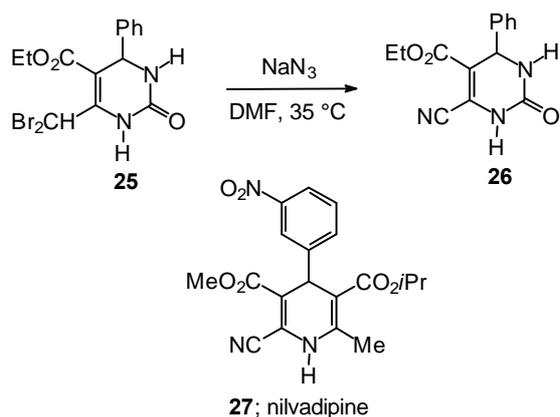


Scheme 6.

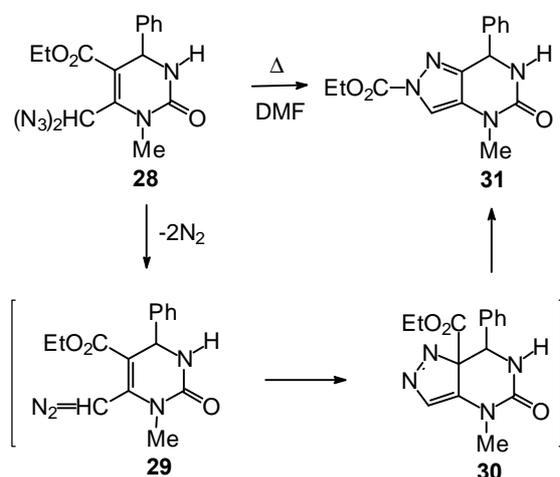


Scheme 7.

Functionalization of the C6 methyl group in DHPMs of type **4** is readily achieved by bromination with elemental bromine, and many subsequent nucleophilic displacement reactions of the resulting mono- or dibromo-methyl pyrimidines have been reported [12]. In a rather unusual and unexpected reaction we discovered that a cyano functionality can be introduced into DHPMs by treatment of 6-dibromomethyl(pyrimidines) such as **25** with sodium azide (Scheme 8) [36]. The resulting DHPMs of type **26** are formed in high yield and can be considered as structural analogues of the DHP calcium channel antagonist nilvadipine (**27**).

**Scheme 8.**

In contrast to the reaction shown in Scheme 8, the N1-methyl analogue of **25** produces the expected diazido derivative **28** when treated with sodium azide [36]. Thermolysis of geminal diazide **28** at 155 °C in DMF produces pyrazolo[4,3-d]pyrimidine **31** in good yield [37,38]. The possible mechanism of this transformation is shown in Scheme 9 and involves decomposition of the diazide **28** to vinyl diazo derivative **29**, which undergoes spontaneous 1,5-electrocyclization to 3H-pyrazole **30**. Subsequent migration of the ester substituent from the tetrahedral carbon to N2 (thermal van Alphen-Hüttel rearrangement) yields pyrazolo[4,3-d]pyrimidine **31**. The structure of **31** confirming the position of the ester group at N2 was established by an X-ray analysis [37].

**Scheme 9**

Since the last chemistry of DHPMs was reviewed in 1993 a considerable number of publications and patents dealing with this heterocyclic system has appeared in the literature. Due to space limitations only part of this material could be discussed herein; additional references are given in [39].

## Outlook

Although largely ignored for over a century the Biginelli dihydropyrimidine synthesis has experienced a comeback in recent years. The present popularity of "Biginelli compounds" (DHPMs) is mainly due to their close structural relationship to the clinically important calcium channel modulators of the nifedipine-type, and the recent discovery of the dihydropyrimidine-5-carboxylate core in biologically active marine natural products. Nevertheless the scope and potential of this multicomponent reaction is still unknown to many organic chemists, and many challenges both in the area of synthetic organic and medicinal chemistry remain. It is hoped that this report will further stimulate interest in the chemistry and biology of this class of heterocycles.

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