Molecules **2007**, *12*, 2546-2558

molecules

ISSN 1420-3049

www.mdpi.org/molecules

Full Paper

Hantzsch Synthesis of 2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(*o*-methoxyphenyl)-1,4-dihydropyridine; a Novel Cyclisation Leading to an Unusual Formation of 1-Amino-2-methoxy-carbonyl-3,5-bis(*o*-methoxyphenyl)-4-oxa-cyclohexan-1-ene

Mirela Filipan-Litvić [1], Mladen Litvić [1,*], Ivica Cepanec [1] and Vladimir Vinković [2]

[1] BELUPO Pharmaceuticals, Inc. R&D, Danica 5, 48000 Koprivnica, Croatia;
E-mail: mirela.filipan-litvic@belupo.hr; E-mail: ivica.cepanec@belupo.hr
[2] Institute Ruđer Bošković, Bijenička c. 54, 10002 Zagreb, Croatia; E-mail: vvink@irb.hr

* Author to whom correspondence should be addressed. E-mail: mladen.litvic@belupo.hr; Tel: (+385) 48 652 458; Fax: (+385) 48 652 461.

Received: 9 November 2007; in revised form: 22 November 2007 / Accepted: 23 November 2007 / Published: 26 November 2007

Abstract: Hantzsch condensation of two equivalents of methyl-3-aminocrotonate with (*m*- and *p*)-methoxybenzaldehyde afforded the expected products 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(*m*-methoxyphenyl)-1,4-dihydropyridine and 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(*p*-methoxyphenyl)-1,4-dihydropyridine, whereas *o*-methoxy-benzaldehyde produced mainly 1-amino-2-methoxycarbonyl-3,5-bis(*o*-methoxy-phenyl)-4-oxa-cyclohexan-1-ene. The structure of the product, not previously reported in the literature, was determined by 1D and 2D NMR spectra and its MS fragmentation. This is the first example of cyclisation leading to a substituted pyran rather than 1,4-DHP under typical Hantzsch reaction conditions. A plausible mechanism for its formation is postulated.

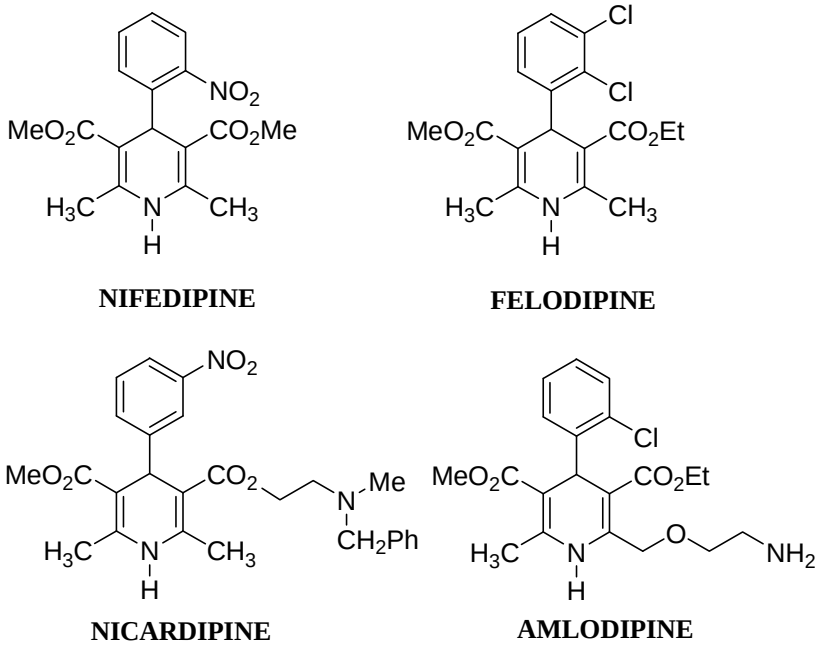
Keywords: Hantzsch condensation, intramolecular Michael addition, deprotonation, substituted pyrane.

Introduction

The first synthesis of a 1,4-dihydropyridines (1,4-DHPs) *via* a three component cyclocondensation reaction of acetoacetic ester, aldehyde and ammonia was reported by Arthur Hantzsch in 1882 [1]. Since then a lot of new variants of original method have been developed, allowing synthesis of different substituted 1,4-DHPs (Scheme 1) [2].

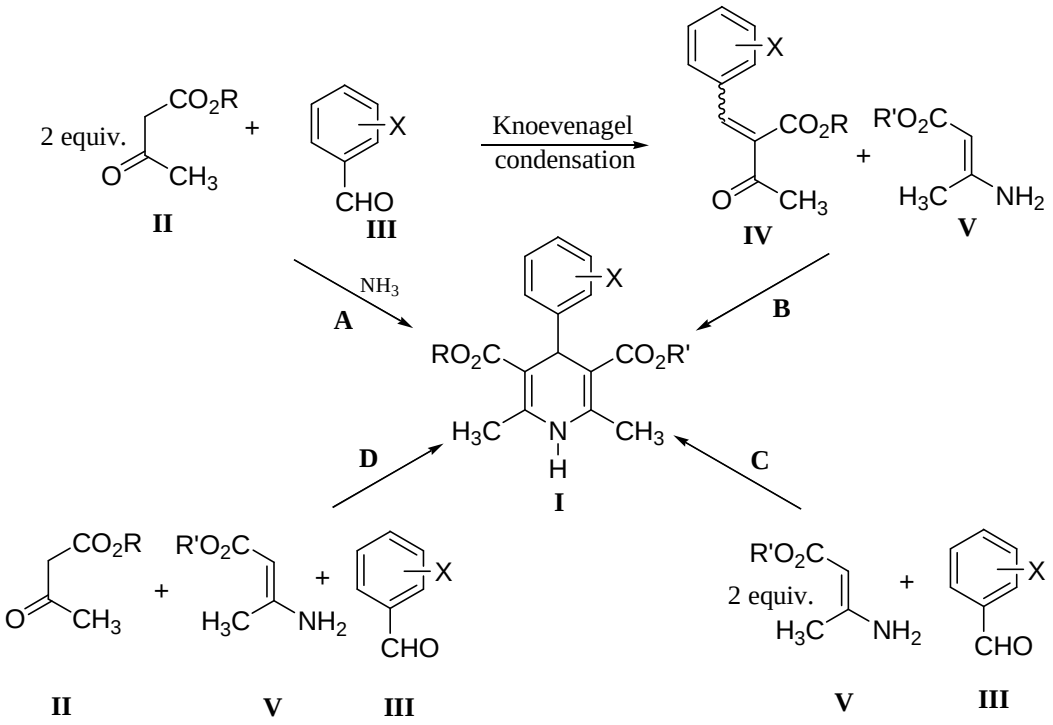
1,4-DHPs have now been recognised as vital drugs in treatment of angina and hypertension. Some of the representatives (nifedipine [3], felodipine [4], nicardipine [5] and amlodipine [6], Figure 1) have been commercialised and it has been proven that their pharmaceutical action is related to binding to voltage dependent L-type of calcium channel and thus decreasing the passage of calcium ions to the cell. The result is relaxation of smooth muscle cells and lowering the blood pressure. Recently, the other mechanism on molecular level have been found and is based on increasing NO release from the intact endothelium [7]. As a result, newly synthesized generations of 1,4-DHPs possess different pharmacological activities such as: anticancer [8], bronchodilating [9], antidiabetic [10], neurotropic [11], antianginal [12] and other pharmacological activities [13].

Figure 1.



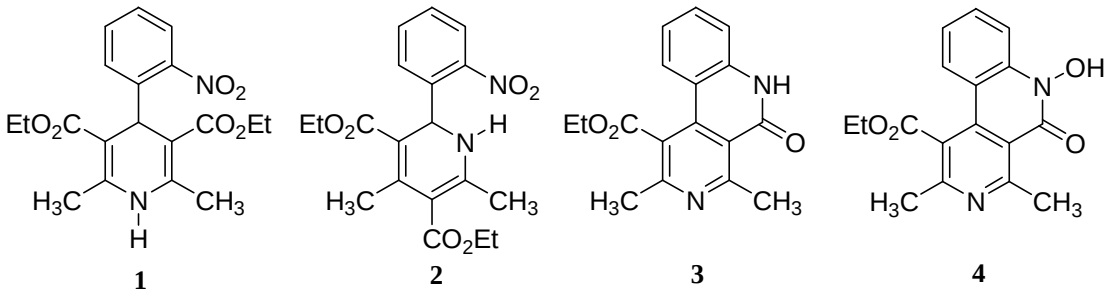
As it can be seen from the Scheme 1, methods **A** and **C** are only convenient for the synthesis of symmetrical, nonchiral 1,4-DHPs (R=R') [14-16], while methods **B** (two step synthesis via Knoevenagel intermediate **IV**) and **D** (three component cyclocondensation) are usually used for the synthesis of 1,4-DHPs having different ester moieties (R≠R') [17-20].

Scheme 1. Most common variants of the Hantzsch 1,4-DHP synthesis.



As one might predict, symmetrical 1,4-DHPs are always formed as impurities in synthesis of nonsymmetrical 1,4-DHPs. However, formation of impurities other than intermediates leading to the 1,4-DHP ring is rarely described in Hantzsch condensations [21]. Thus, Angeles *et. al*. [22] have isolated four different compounds **1**-**4** (Figure 2) from the Hantzsch condensation of 2-nitro-benzaldehyde, NH_4OH and acetoacetic acid ethyl ester. The formation of 1,2-dihydropyridine **2**, cyclic amide **3** and substituted hydroxamic acid **4** is possibly due to steric hindrance as well as the oxidative ability of the nitro group in the *ortho*- position. Similar observations have not yet been published for other substituents (OCH_3, Cl, CH_3 etc.).

Figure 2.



Görlitzer *et. al*. [23] have studied the dimerisation of *o*-nitrobenzylideneacetic acid esters and isolated two diastereomeric substituted hexenes which could also be present as impurities in the classical Hantzsch condensation.

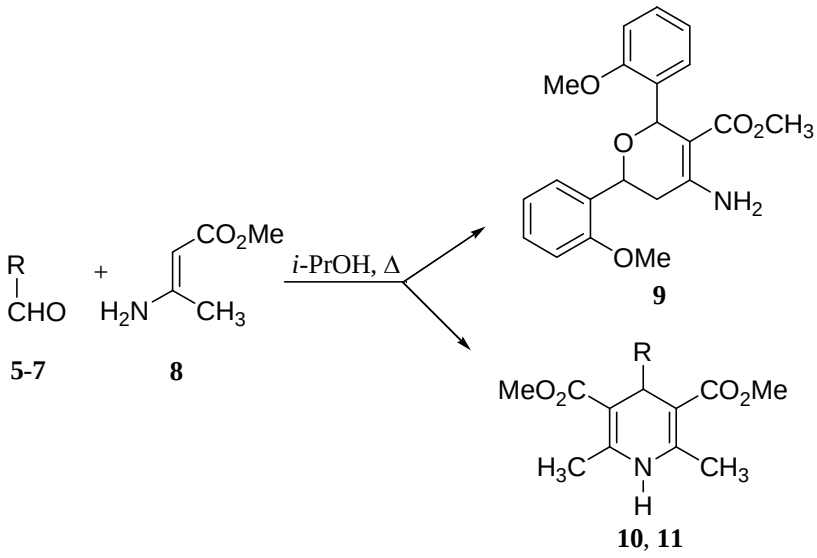
As part of a continuing effort in our laboratory toward the development of new methods for the synthesis and aromatization of 1,4-DHPs [24], we required gram scale samples of some substituded

1,4-DHPs having a OCH_3 group in the *ortho*-, *meta*- and *para*- position on the aromatic ring. Taking into account a wide variety of methods for 1,4-DHP synthesis, as well as our previous experience in Hantzsch 1,4-DHP synthesis [25], we decided to use method **C** (Scheme 1) as most convenient for synthesis when employing sterically demanded *ortho*-substituted benzaldehydes as starting material.

Results and Discussion

The Hantzsch condensation of all three (*o*-, *m*- and *p*)-methoxybenzaldehyde isomers **5-7** with two equivalents of methyl-3-aminocrotonate (**8**) was carried out at reflux temperature in isopropanol as solvent (Scheme 2). According to our previous experience with the chemistry of 1,4-DHPs the latter solvent was proven to be better than other alcohols (such as ethanol, methanol, etc.) due to the easier crystallisation of the product from the cold reaction mixture. With respect to other methods, method **C** (Scheme 1) has been rarely mentioned in the modern literature as the method of choice for synthesis of simple 1,4-DHPs although it has some advantages over the other methods such as the amount of water formed in the reaction (one mol compared to three moles in method **A**), which is a key factor in Hantzsch 1,4-DHP syntheses employing sterically demanding benzaldehydes [25]. The reactions were monitored by TLC (9:1 CH_2Cl_2/AcOEt as eluent) until the disappearance of the starting benzaldehydes and methyl-3-aminocrotonate (**8**). In the cases of the (*m*- and *p*)-methoxybenzaldehydes **6**, **7** the reactions were completed after 23 and 17 h respectively (Table 1). As expected the reaction with the sterically demanding *o*-methoxybenzaldehyde (**5**) was much slower and was complete after 84 h. To our surprise, a quite intensive methyl-3-aminocrotonate (**8**) spot of was still present at the end of reaction but not traces of **5** were noted.

Scheme 2.



5-7 **8** **9** **10**, **11**

The all reaction mixtures were cooled to room temperature to obtain crystalline products which were collected by filtration. The products thus obtained were analysed by TLC, IR, MS and NMR (^1H and ^{13}C) spectroscopy to determine their structures. The corresponding *m*- and *p*-methoxy derivatives **10** and **11** were prepared in 28.8 % and 15.3 % yields, respectively.

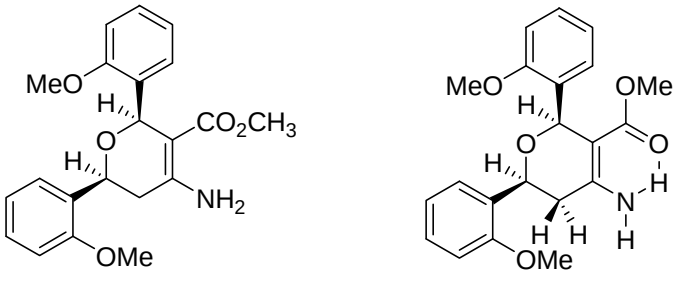
Table 1. The results of Hantzsch condensation of (*o*-, *m*- and *p*)-methoxybenzaldehydes **5**-**7** with methyl-3-aminocrotonate (**8**).

Entry	R	Product	Reaction time[h][a]	Yields after crystallisation [%]	mp	R_f (TLC)
1	*o*-$MeOC_6H_4$	**9**	84	25.6	170.0 - 171.5	0.11[b]
2	*m*-$MeOC_6H_4$	**10**	23	28.8	168.0 - 170.5	0.39[c]
3	*p*-$MeOC_6H_4$	**11**	17	15.3	172.5 - 175.0	0.47[c]

[a] Determined by TLC; [b] CH_2Cl_2/MeOH, 9:1 as eluent; [c] CH_2Cl_2/AcOEt, 9:1 as eluent.

Although the majority of the products were soluble in the mother liquors, the purities of crystals were very high (>98 %), which was sufficient for further testing. To our surprise the product **9** obtained with *o*-methoxybenzaldehyde (**5**) had much higher polarity (Table 1) than was expected [R_f (CH_2Cl_2/MeOH, 9:1) = 0.11], compared to similar 1,4-DHP derivatives [R_f (CH_2Cl_2/MeOH, 9:1) > 0.90], which suggested formation of a product of different structure than 1,4-DHP. By careful assignment of the ^{1}H- and ^{13}C-NMR spectra the structure **9** was elucidated. The ^{1}H-NMR spectrum (aromatic region) showed incorporation of two molecues of *o*-methoxybenzaldehyde (**5**) and one molecule of methyl-3-aminocrotonate (**8**). An interesting observation was made in the aliphatic region for $CDCl_3$ and DMSO-d_6 solutions. Two diastereotopic protons (at position 5) are clearly seen only in DMSO-d_6 solution, suggesting a rigid structure **9B** (Figure 3) with an intramolecular hydrogen bond. Additional proof are the two different shifts of the NH protons. Contrary to **9B**, the flexible structure **9A** is present in $CDCl_3$ solution, where the NH_2 group gives a broad signal at 2.2 ppm and the diastereotopic protons appear as one signal at 2.5 ppm. To our surprise, from NOESY spectra it was clearly proved that the two aromatic rings occupy the *syn*- position. However, it cannot be claimed that only the *syn*-conformer is exclusively formed in the reaction. Rather, it is more likely that the *anti*-conformer is more soluble in the reaction mixture in comparison to the *syn*- one and hence the crystalline product is exclusively the *syn*-conformer.

Figure 3.

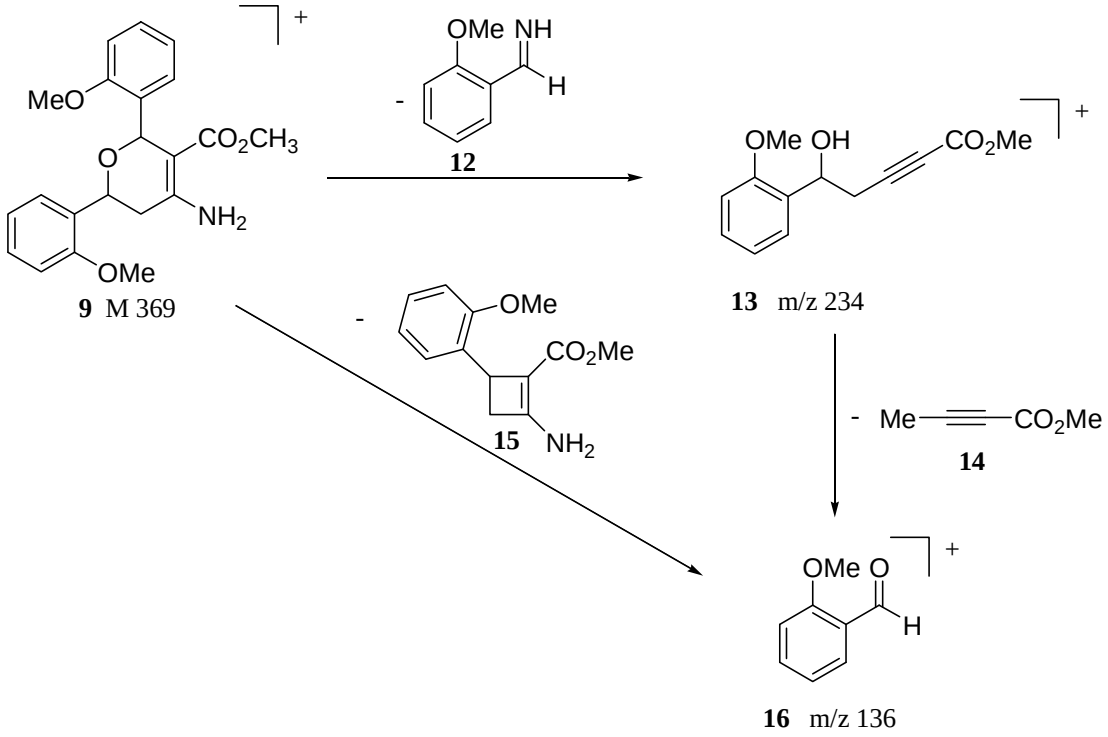


9A **9B**

According to MS spectra the high intensity of the molecular ion (m/z = 369, 79 %) indicates the stability of structure **9**. Plausible fragmentation pathways, which are consistent with the spectral data, together with the structures which are suggested for fragment ions, are shown in Scheme 3.

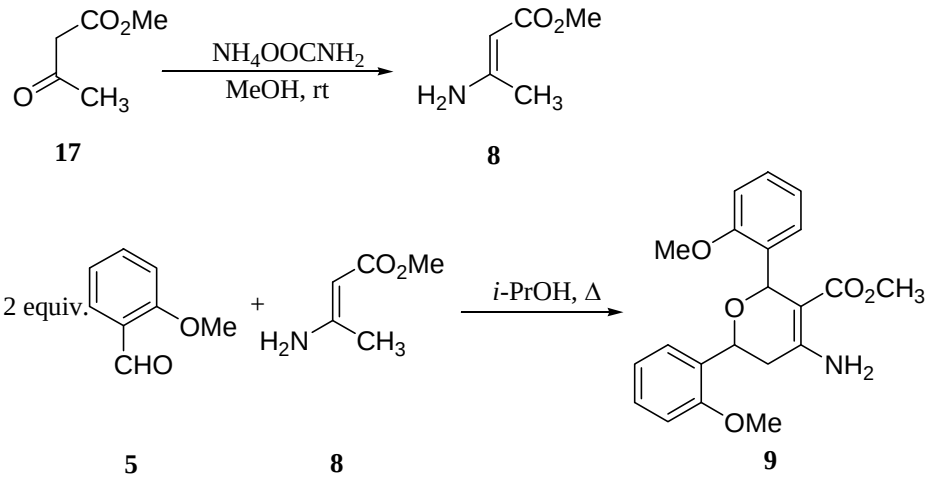
After formation of the molecular ion, fragment ion 13 (m/z 234, 100 %) is formed by unexpected elimination of *o*-methoxybenzaldimine (**12**). This process starts with intramolecular addition of the amino group to the more reactive benzylic position in the molecule, followed by elimination of **12**. Further fragmentation involves the elimination of one molecule of methyl-2-butynoate (**14**) and the formation of **16**, a radical cation of *o*-methoxybenzaldehyde (**16**) at m/z 136 (19 %). The second pathway involves one step elimination of a substituted cyclobutane molecule **15** to form the radical cation **16**.

Scheme 3.



Additional proof for the structure **9** was obtained by performing the reaction with two equivalents of *o*-methoxybenzaldehyde (**5**) and one equivalent of freshly prepared methyl-3-aminocrotonate (**8**), (Scheme 4).

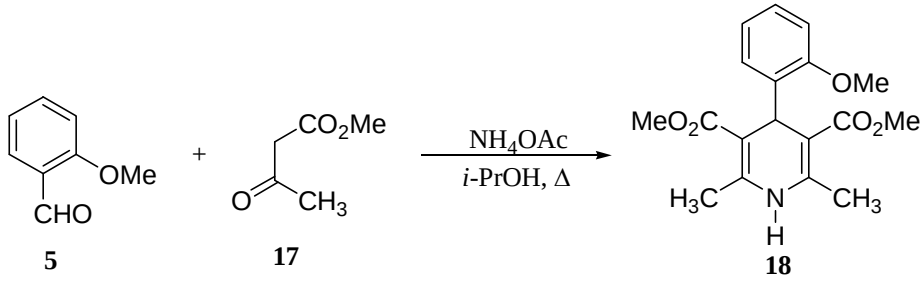
Scheme 4.



The latter compound was prepared by the method developed in our laboratory, via the reaction of methyl acetoacetate (**17**) and ammonium carbamate in methanol at room temperature [26]. The crude **8** of high purity (>99%) was then subjected to reaction with **5** for the same time as original reaction (84 h). After crystallisation from reaction mixture the product **9** was obtained in good yield (51 %). These findings clearly indicate that two molecules of *o*-methoxybenzaldehyde (**5**) were incorporated in the molecule. Additionally, the purity of methyl-3-aminocrotonate (**8**) also plays an important role in the overall yield of the product.

As mentioned above, *o*-methoxy-substituted-1,4-DHP **18** is proven to be formed in the reaction according to Scheme 2, but only as a mixture with unreacted methyl-3-aminocrotonate (**8**) and other impurities (by TLC analysis). A chromatographic separation, due to the small differences in the R_f values, was not convenient for its isolation from the mother liquor and therefore we decided to synthesize it employing different Hantzsch conditions (Scheme 5).

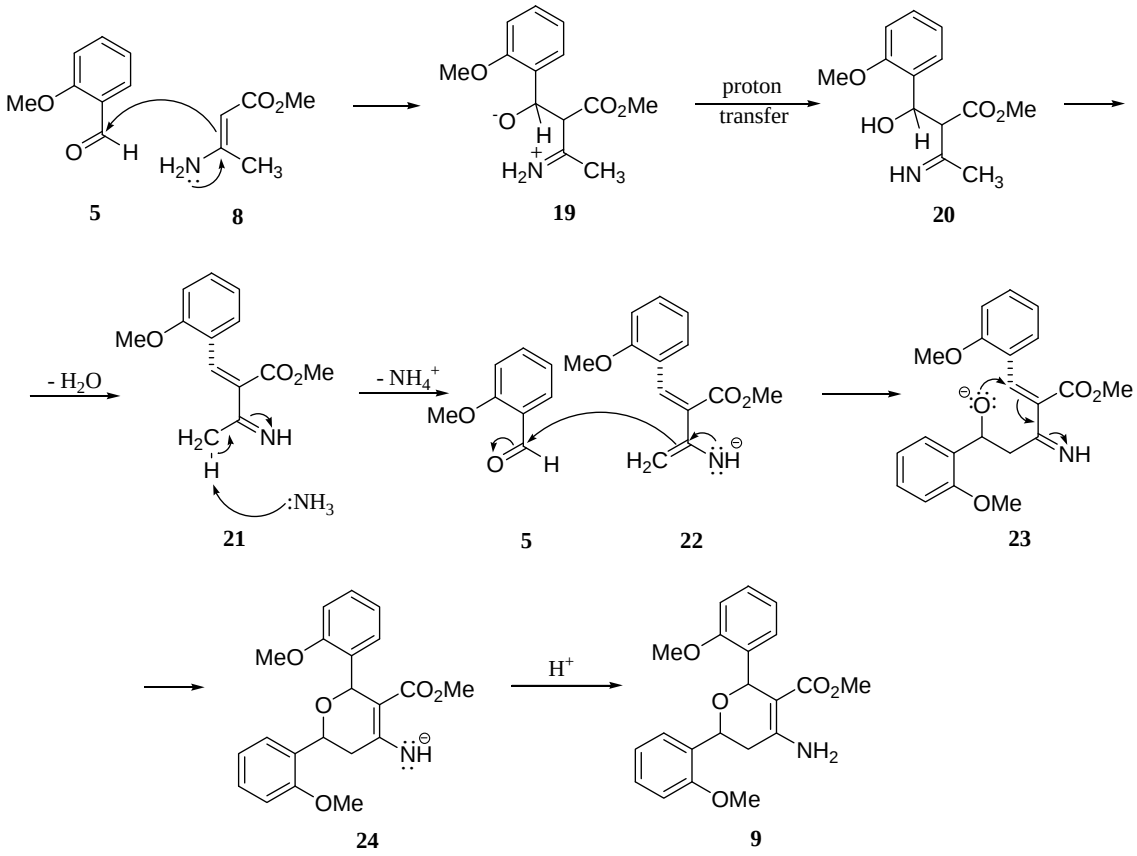
Scheme 5.



Thus, two equivalents of methyl acetoacetate (**12**), ammonium acetate and 2-methoxybenzaldehyde (**5**) were subjected to reaction in refluxing isopropanol during 22 h to give the expected 1,4-DHP **18** in 37.8 % yield after crystalization from methanol. It is interested to note that even a trace of impurity **9** was observed in this reaction. It seems that its formation is characteristic only for Hantzsch method C, Scheme 1. To prove this hypothesis we look at the mechanism of its formation according to reaction condition in Scheme 2. The plausible mechanism is presented in Scheme 6.

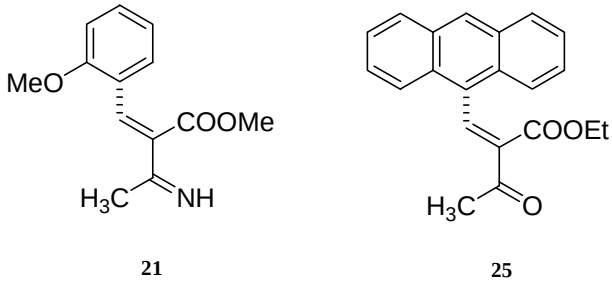
The mechanism involves initial nucleophilic attack on *o*-methoxybenzaldehyde (**5**) by methyl-3-aminocrotonate (**8**) to form the ionic intermediate **19**, which upon proton tranfer gives the iminoalcohol **20**. In the next step dehydration leads to formation of the imino-Knoevenagel intermediate **21**. These types of compounds have been described by Kim *et. al*. [27] as metastable intermediates in the aza-Diels-Alder condensation, a key step in the synthesis of the antyhypertensive drug amlodipine. As one could predict, the next step would be Michael addition of a second molecule of methyl-3-amino-crotonate (**8**) to **5**, according to the proven and accepted mechanism for the Hantzsch condensation [28]. However, due to steric hindrance by the influence of methoxy group in the *ortho*- position, as well as its electron donating ability, the carbon-carbon double bond is poorly reactive towards Michael addition. Similarly, anthracene-9-carbaldehyde is easily converted to Knoevenagel intermediate **25** employing Hantzsch reaction conditions, but at this stage the reaction is stopped although sufficient amounts of acetoacetate ester and ammonia are present in the reaction medium [29]. For this reason, 9-anthryl-1,4-DHPs have not been prepared so far in Hantzsch condensations.

Scheme 6.



According to TLC analysis of the reaction mixture the formation of 1,4-dihydropyridine **18** is also observed, suggesting that intermediate **21** (Figure 4) is not as completely unreactive as the 9-anthryl-analogue **25**. However, the presence of higly basic ammonia in the reaction mixture (refluxing *i*-PrOH) causes deprotonation of the methyl group rather than Michael addition of the second molecule of methyl-3-aminocrotonate (**8**). Thus formed carbanion **21**, in which the negative charge is delocalised and stabilised by interacting with the double bonds and electronegative nitrogen and oxygen atoms in the molecule is highly nucleophillic and reacts with a second molecule of *o*-methoxybenzaldehyde (**5**) to yield intermediate **23**, which upon fast intramolecular Michael addition and protonation gives the final product **9**.

Figure 4.



In summary, the main reasons that determined formation of **9** rather than the expected 1,4-DHP **18** are: a) the steric hindrance and electron donating ability of the *o*-methoxy group; b) the presence of basic ammonia formed in reaction; c) the slow bimolecular Michael addition of methyl-3-amino-crotonate (**8**) to the imino-Knoevenagel intermediate **21**.

Conclusions

We believe that this type of side product formation is characteristic of Hantzsch condensations employing two equivalents of alkyl-3-aminocrotonates and substituted benzaldehydes, but the amounts formed may vary drastically, depending on the nature of the substituents present on the aromatic ring. The preliminary experiments with benzaldehydes having Cl, CH_3, and OEt on the *ortho*- position have shown formation of traces of impurities with similar polarities as **9** (TLC), but the amounts were not sufficient for their isolation by crystallisation. Further attempts to isolate analytical samples for structure determination are now in progress and the results will be published elsewhere in due course.

Experimental

General

IR Spectra were recorded on a Perkin-Elmer 297 instrument. ^{1}H- and ^{13}C-NMR spectra were recorded using a Bruker 600 spectrometer in the solvents indicated (referenced to the residual ^{1}H signals in the deuterated solvents) using TMS as internal standard. Chemical shifts are reported in ppm (δ scale), coupling constant (*J*) values are given in Hertz (Hz). Electron impact (EI) mass spectra were recorded using a LC-MS (2795, Waters Micromass Q-ToF) instrument operated at 3.0 kV ionization energy. Elemental analyses were done by the Central Analytical Service (CAS) at the Ruđer Bošković Institute, Zagreb. Melting points were measured on a Büchi Melting Point B 540 apparatus and are uncorrected. Thin layer chromatography (TLC) analyses were performed on Merck aluminium plates coated with silica gel (60 F_{254}). Compounds were visualised by ultra-violet irradiation at 254 and 366 nm.

General procedure for the Hantzsch condensation

To a solution of corresponding substituted benzaldehyde **5**-**7** (0.2 mol) in *i*-PrOH (50 mL) methyl-3-aminocrotonate (**8**, 46.05 g, 0.4 mol) was added at once. The reaction mixture was heated at reflux temperature for the time indicated in Table 1, and then cooled to rt. The obtained crystals of products **9**-**11** were filtered, washed with *i*-PrOH (3 x 20 mL) and dried in vacuum to constant weight.

1-Amino-2-methoxycarbonyl-3,5-bis(o-methoxyphenyl)-4-oxa-cyclohexan-1-ene (**9**). Pale yellow crystals; yield: 9.47 g (25.6 %); R_f (CH_2Cl_2/MeOH, 9:1)=0.11; mp 170.0–171.5 °C; IR (KBr): ν=3530, 3399, 3298, 3214, 3075, 2959, 2944, 1658, 1622, 1602, 1585, 1542, 1488, 1459, 1441, 1417, 1364, 1341, 1310, 1293, 1263, 1242, 1186, 1162, 1124, 1099, 1071, 1053, 1026, 999, 968, 947, 929, 888, 862, 844, 812, 795, 783, 757, 641, 596, 572, 528 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=2.20 (br., s, 2H, NH_2),

2.50 (d, 2H, CH_2, *J*=6.8 Hz), 3.50 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.84 (s, 3H, $COOCH_3$), 4.10 (t, 1H, CH, *J*=7.5 Hz), 5.50 (s, 1H, CH), 6.76 (d, 1H, arom., *J*=8.2 Hz), 6.85–6.92 (m, 2H, arom.), 6.96 (d, 1H, arom., *J*=7.4 Hz), 7.16–7.24 (m, 3H, arom.), 7.46 (dd, 1H, arom., J_1=7.5, J_2=1.5); ^{13}C-NMR ($CDCl_3$): δ=36.42, 44.44, 50.53, 50.56, 55.13, 55.31, 91.89, 110.07, 110.24, 110.64, 119.48, 120.88, 125.93, 127.61, 128.01, 128.83, 131.78, 132.57, 156.70, 157.16, 157.64, 169.47; MS (3.0 kV, EI,): m/z (%) for $C_{21}H_{23}NO_5$: 369 (79), 234 (100), 136 (19); anal. calcd. for $C_{21}H_{23}NO_5$: C 68.28, H 6.28, N 3.79, O 21.66; found: C 68.37, H 6.39, N 3.61.

2,6-Dimethyl-3,5-dimethoxycarbonyl–4-(m-methoxyphenyl)-1,4-dihydropyridine (**10**). Yellow crystals; yield: 19.06 g (25.6 %); R_f (CH_2Cl_2/AcOEt, 9:1)=0.39; mp 168.0–170.5 °C; IR (KBr): ν=3348, 3241, 3091, 3029, 3004, 2953, 2837, 1704, 1651, 1626, 1606, 1580, 1486, 1449, 1434, 1380, 1346, 1317, 1296, 1263, 1219, 1181, 1157, 1134, 1120, 1099, 1047, 1016, 964, 949, 895, 871, 810, 775, 752, 735, 716, 682, 637, 584, 563 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=2.28 (s, 6H, CH_3), 3.65 (s, 6H, $COOCH_3$), 3.75 (s, 3H, OCH_3), 5.00 (s, 1H, CH), 6.23 (s, 1H, NH), 6.68 (dd, 1H, arom., J_1 = 8.1 Hz; J_2 = 1.9 Hz), 6.82–6.88 (m, 2H, arom.), 7.13 (t, 1H, arom., *J* = 7.9 Hz); ^{13}C-NMR ($CDCl_3$): δ=19.12, 38.98, 50.80, 54.84, 103.18, 110.65, 113.72, 119.91, 128.73, 144.54, 148.85, 159.13, 167.98; Anal. calcd. for $C_{18}H_{21}NO_5$: C 65.24, H 6.39, N 4.23, O 24.14; found: C 65.1, H 6.5, N 4.3.

2,6-Dimethyl-3,5-dimethoxycarbonyl–4-(p-methoxyphenyl)-1,4-dihydropyridine (**11**). Pale yellow crystals; yield: 10.10 g (15.3 %); R_f (CH_2Cl_2/AcOEt, 9:1)=0.47; mp 172.5–175.0 °C; IR (KBr): ν=3365, 3096, 3001, 2950, 2838, 1680, 1653, 1613, 1512, 1486, 1431, 1377, 1336, 1302, 1256, 1229, 1174, 1147, 1128, 1093, 1049, 942, 843, 817, 805, 787, 745, 665, 631, 604, 587, 546, 525 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=2.33 (s, 6H, CH_3), 3.65 (s, 6H, $COOCH_3$), 3.75 (s, 3H, OCH_3), 4.94 (s, 1H, CH), 5.67 (s, 1H, NH), 6.75 (d, 2H, arom.; *J*=8.5 Hz), 7.18 (d, 2H, arom., *J*=8.5 Hz); ^{13}C-NMR ($CDCl_3$): δ=19.29, 38.24, 50.80, 54.95, 103.78, 113.21, 128.40, 139.81, 143.97, 157.76, 168.01; Anal. calcd. for $C_{18}H_{21}NO_5$: C 65.24, H 6.39, N 4.23, O 24.14; found: C 65.3, H 6.2, N 4.2.

Synthesis of 1-amino-2-methoxycarbonyl-3,5-bis(o-methoxyphenyl)-4-oxa-cyclohexan-1-ene (**9**). To a solution of methyl acetoacetate (**12**, 5.40 mL, 5.81 g, 50 mmol) in methanol (50 mL) ammonium carbamate (NH_4OOCNH_2, 3.90 g, 50 mmol) was added at once. The resulting suspension was stirred at room temperature untill all solid material was dissolved (about 15 min). After that the solvent was evaporated off to yield white crystals of crude **8** (yield quantitative) which was suspended in *i*-PrOH (40 mL). To the resultant suspension *o*-methoxybenzaldehyde (**5**, 12.08 mL, 13.62 g, 100 mmol) were added dropwise during 15 min and after that the reaction mixture was heated under reflux temperature for 84 h with stirring. After cooling to room temperature the suspesion was cooled in refrigerator (-18°C) for 12 h. The obtained crystals were filtered, washed with cold *i*-PrOH (2 x 10 mL) and dried in vacuum to constant weight to give 9.42 g (51.0 %) of **9** as a yellow crystals. The analytical data were in accordance with the sample obtained according to Scheme 2.

Synthesis of 2,6-dimethyl-3,5-dimethoxycarbonyl–4-(o-methoxyphenyl)-1,4-dihydropyridine (**18**). To a suspension of ammonium acetate (0.05 mol, 3.85 g) in *i*-PrOH (50 mL), methyl acetoacetate (**17**, 0.1 mol; 11.61 g, 10.75 mL) and *o*-methoxybenzaldehyde (**5**, 0.05 mol, 6.81 g, 6.04 mL) were added

dropwise during 15 min. The resultant suspension was heated under reflux temperature for 22 h with stirring. After cooling to room temperature reaction mixture was filtered and evaporated to dryness. The residue was disolved in methanol (25 mL) and the resultant clear solution was cooled in refrigerator (-18°C) for 12 h. The obtained crystals were filtered, washed with cold methanol (2 x 5 mL) and dried in vacuum to constant weight to give 6.27 g (37.8 %) of **18** as a yellow crystals, R_f (CH_2Cl_2/AcOEt, 9:1)=0.46; mp 129.0–131.5 °C; IR (KBr): ν= 3337, 3068, 2993, 2945, 2837, 1706, 1683, 1651, 1584, 1489, 1464, 1433, 1381, 1353, 1335, 1310, 1288, 1212, 1143, 1128, 1096, 1051, 1028, 942, 857, 837, 823, 799, 786, 760, 687, 640, 591 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=2.24 (s, 6H, CH_3), 3.61 (s, 6H, $COOCH_3$), 3.78 (s, 3H, OCH_3), 5.29 (s, 1H, CH), 6.28 (s, 1H, NH), 6.78–6.90 (m, 2H, arom.), 7.07–7.16 (m, 2H, arom.); ^{13}C-NMR ($CDCl_3$): δ=18.78, 34.60, 50.63m, 55.29, 102.40, 110.71, 120.05, 127.09, 129.47, 134.98, 144.16, 156.69, 168.47; Anal. calcd. for $C_{18}H_{21}NO_5$: C 65.24, H 6.39, N 4.23, O 24.14; found: C 65.4, H 6.1, N 4.1.

Acknowledgements

The authors wish to express their gratitude to Belupo Pharmaceuticals Inc. for financial support of this research.

References

1. Hantzsch, A. Condensationprodukte aus Aldehydammoniak und ketoniartigen Verbindungen. *Chem. Ber*. **1881**, *14*, 1637–1638.
2. a) Eisner, U.; Kuthan, J. The Chemistry of Dihydropyridines. *Chem. Rev.*, **1972**, *72*, 1–42; b) Stout, D. M.; Meyers, A. I. Recent Advances in the Chemisty of Dihydropyridines. *Chem. Rev.* **1982**, *82*, 223–243; c) Sausinš, A.; Duburs, G. Synthesis of 1,4-Dihydropyridines by Cyclocondensation Reactions. *Heterocycles*, **1988**, *27*, 269–289; d) Kuthan, J.; Kurfürst, A. Development in Dihydropyridine Chemistry. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191–261; e) Zolfigol, M. A.; Salehi, P.; Safaiee, M. An Efficient and Eco-Friendly Procedure for the Synthesis of Hantzsch Ethyl 1,4-Dihydro-2,6-Dimethylpyridine-3,5-Dicarboxylates Under Mild and Green Conditions. *Lett. Org. Chem*. **2006**, *3*, 153-156; f) Zolfigol, M. A.; Salehi, P.; Khorramabadi-Zad, A.; Shayegh, M. Iodine-catalysed synthesis of novel Hantzsch *N*-hydroxyethyl 1,4-dihydropyridines under mild conditions. *J. Mol. Catal. A: Chem*. **2007**, *261*, 88-92; g) Zolfigol, M. A.; Safaiee, M. Synthesis of 1,4-Dihydropyridines under Solvent-free Conditions. *Synthesis*, **2004**, 827-828.
3. *The Merck Index, 12th edition*; Merck Research Laboratories: Rahway, NJ, **1996**; p. 1121.
4. Boström, S. L.; Ljung, B.; Mårdh, S.; Forsen, S.; Thulin, E. Interaction of the antihypertensive drug felodipine with calmodulin. *Nature* **1981**, *292*, 777–778.
5. Iwanami, M.; Shibanuma, T.; Fujimoto, M.; Kawai, R.; Tamazawa, K.; Takenaka, T.; Takahashi, K.; Murakami, M. Synthesis of New Water-soluble Dihydropyridine Vasodilatators. *Chem. Pharm. Bull.* **1979**, *27* 1426-1440.

6. Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Stubbs, J. K.; Burges, R. A.; Gardiner, D. G.; Blackburn, K. J. Long-Acting Dihydropyridine Calcium Antagonists. 1. 2-Alkoxymethyl Derivatives Incorporating Basic Substituents. *J. Med. Chem.* **1986**, *29*,1696-1702.
7. Berkels, B.; Roesen, R.; Dhein, S.; Fricke, U.; Klaus, W. Dihydropyridine Calcium Antagonist-Induced Modulation of Endothelial Function: A Reviw. *Cardiovasc. Drug Rev.* **1999**, *17*, 179-186.
8. Tsuruo, T.; Iida, H.; Nojiri, M.; Tsukagoshi, S.; Sakurai, Y. Circumvention of Vincristine and Adriamycin Resistance in Vitro and in Vivo by Calcium Influx Blockers. *Cancer Res.* **1983**, *43*, 2905-2910.
9. Chapman, R. W.; Danko, G.; Siegels, M. I. Effect of Extra- and Intracellular Calcium Blockers on Histamine and Antigen-Induced Bronchospasm in Guinea Pigs and Rats. *Pharmacology* **1984**, *29*, 282-291.
10. Malaise, W. J.; Mathias, P. C. F. Stimulation of Insulin Release by Organic Calcium-Agonist. *Diabetologia* **1985**, *28*, 153-156.
11. Krauze, A.; Germane, S.; Eberlins, O.; Sturms, I.; Klusa, V.; Duburs, G. Derivatives of 3-cyano-6-phenyl-4-(3'-pyridyl)pyridine-2(1H)-thione and their neurotropic activity. *Eur. J. Med. Chem.* **1999**, *34*, 301-310.
12. Peri, R.; Padmanabhan, S.; Singh, S.; Rutledge, A.; Triggle, D. J. Permanently Charged Chiral 1,4-Dihydropyridines: Molecular Probes of L-Type Calcium Channels. Synthesis and Pharmacological Characterization of Methyl (ω-Trimethylalkylammonium) 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5- pyridinedicarboxylate Iodide, Calcium Channel Antagonists *J. Med. Chem.* **2000**, *43*, 2906-2914.
13. Zhou, X.; Zhang, L.; Tseng, E.; Scott-Ramsay, E.; Schentag, J. J.; Coburn, R. A.; Morris, M. E. New 4-aryl-1,4-dihydropyridines and 4-arylpyridines as P-glycoprotein inhibitors. *Drug. Metab. Dispos.* **2005**, *33*, 321-328.
14. Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. "Hantzsch-Type" Dihydropyridine Hypotensive Agents. *J. Med. Chem.* **1974**, *17*, 956–965.
15. Meyer, H.; Bossert, F.; Horstmann, H. Dihydropyridine, II. Synthese Von 1,4-Dihydropyridinen mit Brückenkopf-N-atom. *Liebigs Ann. Chem*. **1977**, 1888–1894.
16. Phillips, A. P. Hantzsch's Pyridine Synthesis. *J. Am. Chem. Soc*. **1949**, *71*, 4003-4007.
17. Meyer, H.; Bossert, F.; Wehinger, E.; Stoepel, K.; Vater, W. Synthese und vergleichende pharmakologische Untersuchungen von 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridin-3,5-dicarbonsäuereestern mit nicht-identischen Esterfunktionen. *Arzneim. Forsch. (Drug Res.)* **1981**, *31*, 407–409.
18. Wong, W. C.; Chiu, G.; Wetzel, J. M.; Marzabadi, M. R.; Nagarathnam, D.; Wang, D.; Fang, J.; Miao, S. W.; Hong, X.; Forray, C.; Vaysse, P. J. J.; Branchek, T. A.; Gluchowski, C. Identification of a Dihydropyridine as a Potent α_{1a} Adrenoreceptor-Selective Antagonist That Inhibits Phenylephrine-Induced Contraction of the Human Prostate. *J. Med. Chem.* **1998**, *41*, 2643–2650.
19. Nagarathnam, D.; Wetzel, J. M.; Miao, S. W.; Marzabadi, M. R.; Chiu, G.; Wong, W. C.; Hong, X.; Fang, J.; Forray, C.; Branchek, T. A.; Heydorn, W. E.; Chang, R. S. L.; Broten, T.; Schorn, T.

W.; Gluchowski, C. Design and Synthesis of Novel α_{1a} Adrenoreceptor-Selective Antagonist for the Treatment of Benign Prostatic Hyperplasia. *J. Med. Chem.* **1998**, *41*, 5320–5333.

20. Khadilkar, B. M.; Jaisinghani, H. G.; Saraf, M. N.; Desai, S. K. Synthesis and pharmacological studies of new derivatives of dimethyl-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylate. *Ind. J. Chem.* **2001**, *40B*, 82–86.
21. Wang, G.-W.; Miao, C.-B. Environmentally benign one-pot multi-component approaches to the synthesis of novel unsymmetrical 4-arylacridiones. *Green Chem.* **2006**, *8*, 1080-1095.
22. Angeles, E.; Santillán, H.; Martínez, I.; Ramírez, A.; Velásquez, A.; López-Castañares, R.; Martínez, R. Rearrangement of *o*-Nitrobenzaldehyde in the Hantzsch Reaction. *Molecules* **2001**, *6*, 683-693.
23. Görlitzer, K.; Fabian, J.; Trittmacher, J. Dimere aus *o*-Nitrobenzylidenacetessigestern. *Pharmazie* **2005**, *60*, 571-573.
24. Litvić, M.; Cepanec, I.; Filipan, M.; Kos, K.; Bartolinčić, A.; Druškovič, V.; Tibi, M. M.; Vinković, V. Mild, Selective and High-Yield Oxidation of Hantzsch 1,4-Dihydropyridines with Lead(IV) Acetate. *Heterocycles* **2005**, *65*, 23–36.
25. Litvić, M.; Cepanec, I.; Vinković; V. A convenient Hantzsch synthesis of 1,4-dihydropyridines using tetraethyl orthosilicate. *Heterocycl. Commun.* **2003**, *9*, 385–390.
26. Litvić, M.; Filipan, M.; Pogorelić, I.; Cepanec, I. Ammonium carbamate; mild, selective and efficient ammonia source for the preparation of β-amino-α,β-unsaturated esters at room temperature. *Green Chem*. **2005**, *7*, 771–774.
27. Kim, S. C.; Choi, K. M.; Cheong, C. S. Synthesis of Amlodipine Using Aza Diels-Alder Reaction. *Bull. Kor. Chem. Soc.* **2002**, *23*, 143–144.
28. Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. The Mechanism of the Hantzsch Pyridine Synthesis: A Study by ^{15}N and ^{13}C Spectroscopy. *Tetrahedron* **1986**, *42*, 5729–5738.
29. Treibs, W.; Beger, J. 4-Aryl-3-carboxy-pyridine als ausgangssubstanzen für *N*-methyl-1,2-benzisoazalene. *Liebigs Ann. Chem.* **1962**, *652*, 192-203.

Sample Availability: Available from the authors.