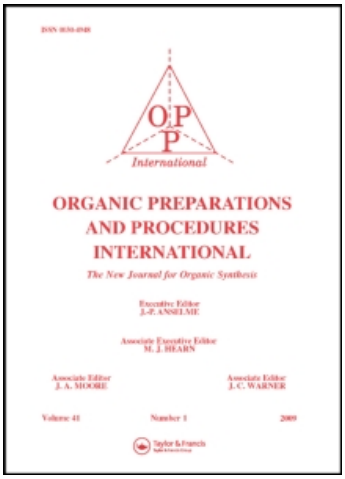

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Sai-Hay Yiu[a]; Edward E. Knaus[a]
[a] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

To cite this Article Yiu, Sai-Hay and Knaus, Edward E.(1996) 'AN IMPROVED SYNTHESIS OF HIGH-PURITY FELODIPINE', Organic Preparations and Procedures International, 28: 1, 91 — 95
To link to this Article: DOI: 10.1080/00304949609355911
URL: http://dx.doi.org/10.1080/00304949609355911

ORGANIC PREPARATIONS AND PROCEDURES INT., 28 (1), 91-95 (1996)

AN IMPROVED SYNTHESIS OF HIGH-PURITY FELODIPINE

Sai-hay Yiu and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta, Edmonton, Alberta, Canada T6G 2N8

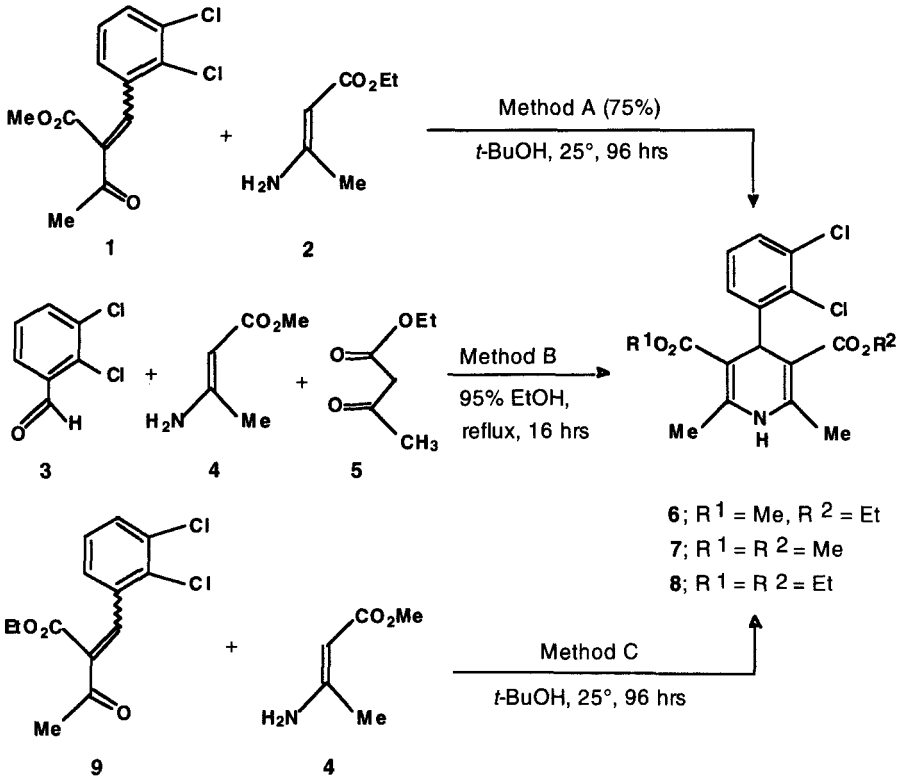
The 1,4-dihydropyridine (DHP) calcium channel antagonist (CCA) felodipine (**6**) is a potent vasodilator that is used clinically as an antihypertensive drug.[1] Due to its significant selectivity towards vascular smooth muscle, relative to myocardial tissue, felodipine unlike other CCAs does not exhibit cardiac side-effects.[2] Felodipine can be prepared readily using the classical Hantzsch reaction,[3] or modified Hantzsch reactions,[4] such as reaction of methyl 2-(2,3-dichlorobenzylidene)acetoacetate (**1**) with ethyl 3-aminocrotonate (**2**) in *t*-BuOH for 96 hours at 25° (75%, Scheme 1, Method A)[5]. The formation of symmetrical diester side-products is a limitation of the Hantzsch reaction.[6] While this study was in progress, an alternative low environmental impact method to prepare felodipine was reported which involved the condensation of **1** with **2** in the presence of an activated alumina catalyst without solvent (53% yield).[7] As part of a project involving the design and synthesis of novel chemical delivery systems, we required an efficient, yet versatile, synthesis of high-purity felodipine, which is amenable to large scale synthesis. We now describe a simple method for the preparation of ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (**13**) which can be readily converted to high-purity felodipine or coupled to a brain-selective chemical delivery system (CDS).

The initial Hantzsch reaction investigated (Scheme 1, Method B) involved the condensation of 2,3-dichlorobenzaldehyde (**3**), methyl 3-aminocrotonate (**4**) and ethyl acetoacetate (**5**) in 95% EtOH at reflux temperature for sixteen hours. Purification of the reaction product(s) by silica gel column chromatography and recrystallization from EtOAc-hexane gave a product (43% yield) which appeared as a single spot on TLC analysis. However, HPLC analysis showed that the two undesired symmetrical dimethyl (**7**) and diethyl (**8**) esters were also present together with the desired product felodipine (**6**) where the ratio of **6** : **7** : **8** was 65.67 : 23.71 : 10.61.

A modified Hantzsch reaction involving the reaction of ethyl 2-(2,3-dichlorobenzylidene) acetoacetate (**9**) with methyl 3-aminocrotonate (**4**, Scheme 1, Method C) in t-BuOH at 25° for 96 hours yielded a product(s) in 20.6% total yield that was shown by HPLC analysis to consist of a mixture of **6**, **7** and **8** in a ratio of 96.64 : 1.57 : 1.78, respectively. The formation of **7** and **8** in this latter reaction may be due to a very limited hydrolysis of ethyl 2-(2,3-dichlorobenzylidene)acetoac-

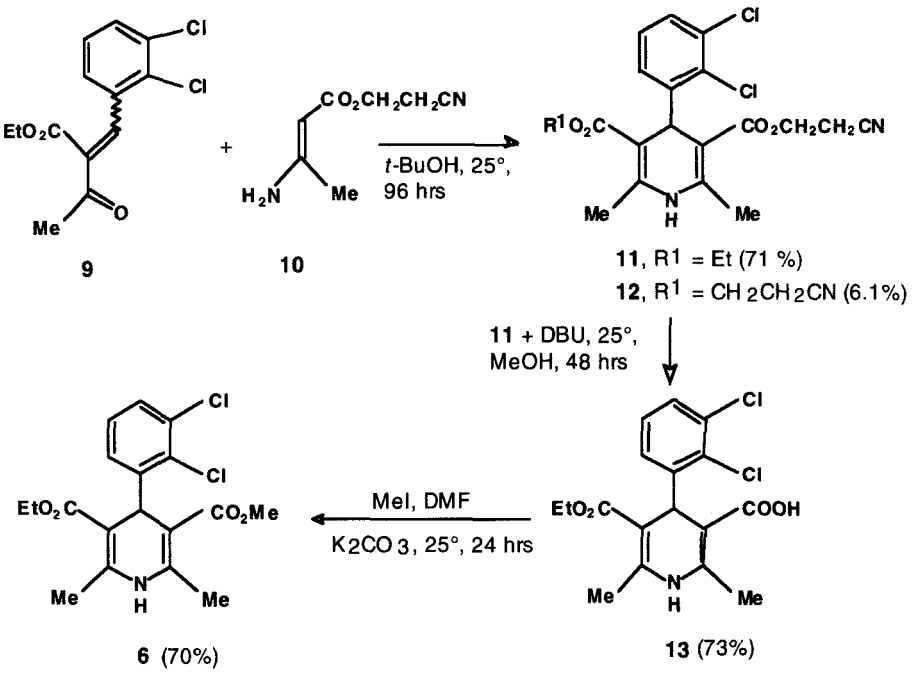
etate (**9**) to 2,3-dichlorobenzaldehyde (**3**) and ethyl acetoacetate (**5**) by water that is produced in the Hantzsch condensation reaction.

The difficulty in separating felodipine (**6**) from the undesired symmetrical dimethyl (**7**) and diethyl (8) esters by conventional TLC, or silica gel column chromatography, is due to their similar polarity. It was envisaged that the use of a more polar ester substituent such as a 3-(2-cyanoethyl)



Scheme 1

ester, that could be readily converted to the carboxyl analog using a non-nucleophilic base promoted β-elimination reaction of acrylonitrile, would circumvent this problem. Thus, condensation of ethyl 2-(2,3-dichlorobenzylidene)acetoacetate (**9**) with 2-cyanoethyl 3-aminocrotonate (**10**) afforded a mixture of the unsymmetrical 3-(2-cyanoethyl) 5-ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (**11**, 71%) and symmetrical 3,5-*bis*-(2-cyanoethyl) product (**12**, 6.1%) that were readily separated by silica gel column chromatography (Scheme 2). Cleavage of the unsymmetrical ester **11** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave 3-ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (**13**, 73%) which was converted to high-purity felodipine by reaction with iodomethane in 70% yield. HPLC analysis indicated that felodipine prepared using this procedure contained a trace quantity of the symmetrical



Scheme 2

dimethyl ester **7** where the ratio of **6** : **7** was 99.29 : 0.71. The formation of **7** in this latter methylation reaction must be due to transesterification of the ethyl ester moiety to a methyl ester substituent, in spite of the fact that dry DMF was used as solvent.

In conclusion, an efficient method for the synthesis of high-purity (99.29%) felodipine has been developed that does not contain the symmetrical diethyl ester **8**. Furthermore, the carboxylate compound **13** is a versatile reactant that can be used to prepare other primary or secondary alkyl ester products, or it can be coupled to a chemical delivery system to improve tissue biodistribution and/or pharmacokinetic properties.

EXPERIMENTAL SECTION

Mps were determined using a capillary melting point apparatus and are uncorrected. IR spectra were obtained using a Nicolet 5DX-FT spectrometer. Nuclear magnetic resonance spectra (^{1}H NMR) were acquired using a Bruker AM-300 spectrometer. Ethyl 3-aminocrotonate (**2**), methyl 3-aminocrotonate (**4**) and ethyl acetoacetate (**5**) were purchased from the Aldrich Chemical Co. (E/Z)-Ethyl 2-(2,3-dichlorobenzylidene)acetoacetate (**9**)[8] and 2-cyanoethyl 3-aminocrotonate (**10**)[9] were prepared using literature procedures.

High-performance liquid chromatography (HPLC) was performed using a Waters HPLC system comprised of two Model 510 pumps, Model U6K injector, Model 486 tunable absorbance detector and Millennium 2010 software. A Waters analytical dimethyloctadecylsilyl Nova Pak C

reverse phase silica gel column (3.9 x 150 mm) using acetonitrile-water (1:1, v/v) as eluent with a flow rate of 1.0 mL/min and UV detection at 350 nm was used for the analytical studies. The retention times of **6**, **7** and **8** were 6.8, 9.8 and 14.0 min, respectively. The ratio of products **6-8** were calculated from the relative areas under the respective peaks.

3-(2-Cyanoethyl) 5-ethyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (11) and 3,5-Di-(2-cyanoethyl) 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (12).- A mixture of ethyl 2-(2,3-dichlorobenzylidene) acetoacetate (**9**, 5.74 g, 20 mmol), 2-cyanoethyl 3-aminocrotonate (**10**, 3.08 g, 20 mmol) in dry *t*-BuOH (25 mL) was stirred at 25° for 96 hrs. Removal of the solvent *in vacuo* and purification of the residue by silica gel column chromatography using EtOAc-hexane (3:7, v/v) as eluent yielded **11** as a yellow oil (6.04 g, 71%) and **12** (0.46 g, 6%), respectively. **Product 11**: IR (film): 3344 (NH), 2256 (CN), 1719 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ (7.32 (dd, J = 7.7, J = 1.6 Hz, 1H, aryl H-4), 7.27 (dd, J = 7.7, J = 1.6 Hz, 1H, aryl H-6), 7.10 (t, J = 7.7, 1H, aryl H-5), 5.86 (br s, 1H, N*H*), 5.45 (s, 1H, H-4), 4.24 (t, J = 6.4 Hz, 2H, $CO_2CH_2CH_2$), 4.09 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.66 (t, J = 6.4 Hz, 2H, CH_2CN), 2.33 and 2.31 (two s, 3H each, C-2 and C-6 CH_3), 1.19 (t, J = 7.0 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{20}H_{20}Cl_2N_2O_4$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.55; H, 4.66; N, 6.45

Product 12 as colorless needles, mp 156-157° (CH_2Cl_2-hexane): IR (KBr): 3336 (NH), 2258 (CN), 1697 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32 (dd, J = 7.7, 1.6 Hz, 1H, aryl H-4), 7.29 (dd, J =7.7, J = 1.6 Hz), 1H, aryl H-6), 7.12 (t, J = 7.7 Hz, 1H, aryl H-5), 6.15 (br s, 1H, N*H*), 5.44 (s, 1H, H-4), 4.25 (m, 4H, CO_2CH_2), 2.67 (t, J = 6 Hz, 4H, CH_2CN), 2.33 (s, 6H, C-2 and C-6 Me).

Anal. Calcd for $C_{21}H_{19}Cl_2N_3O_4$: C, 56.26; H, 4.27; N, 9.37. Found: C, 55.88; H, 4.04; N, 9.18

Ethyl 1,4-Dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3-5-pyridinedicarboxylate (13).- 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 4.41 g, 29 mmol) was added to a solution of **11** (4.09 g, 12 mmol) in MeOH (50 mL) and the reaction was allowed to proceed at 25° for 48 hrs with stirring prior to adjustment of the pH to 1 using *2N* HCl. The resulting yellow precipitate was filtered, washed successively with water (3 x 35 mL) and ether (3 x 25mL), and the pale yellow product was dried *in vacuo* (2.6 g, 72.7%), mp 184-185° (dec), IR (KBr): 2900-3600 (COOH), 3397 (NH), 1676 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ (11.65 (br s, 1H, COO*H*, exhanges with D_2O), 8.79 (s, 1H, N*H*, exchanges with D_2O), 7.38 (dd, J = 7.7, J = 2.1 Hz, 1H, aryl H-4), 7.29 (dd, J =7.7, J = 2.1 Hz, 1H, aryl H-6), 7.23 (t, J = 7.7 Hz, 1H, aryl H-5), 5.29 (s, 1H, H-4), 3.94 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.22 (s, 6H, C-2 and C-6 CH_3), 1.07 (t, J = 7.0 Hz, 3H, CH_2CH_3).

Anal. Calcd for $C_{17}H_{17}Cl_2NO_4$: C, 55.15; H, 4.63; N, 3.78. Found: C, 55.28; H, 4.42; N, 3.80

3-Ethyl 5-methyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (6).- Iodomethane (0.84 mL, 13.5 mmol) was added to a solution of **12** (1.0 g, 2.7 mmol) in dry DMF (20 mL) and K_2CO_3 (1.12 g, 8 mmol) and the reaction was allowed to proceed at 25° for 24 hrs with stirring. The reaction mixture was filtered and the solvent from the filtrate was removed *in vacuo* to remove as much DMF as was possible. The residue obtained was dissolved in CH_2Cl_2 (20 mL), washed with water (3 x 25 mL) and this $CHCl_2$ solution was dried (Na_2SO_4). Removal of the solvent *in vacuo* and purification of the product(s) obtained by elution from a silica gel column using EtOAc-

hexane (1:1, v/v) as eluent afforded **6** as colorless needles, which were recrystallized from CH_2Cl_2 and then from diisopropyl ether (0.73 g, 70%), mp 140-141°, lit.[5] mp 145°: IR (KBr): 3362 (NH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ (7.29 (dd, J = 7.7, J = 1.7 Hz, 1H, aryl H-4), 7.24 (dd, J = 1.7, J = 7.7 Hz, 1H, aryl H-6), 7.06 (t, J = 7.7 Hz, 1H, aryl H-5), 5.58 (br s, 1H, N*H*), 5.46 (s, 1H, H-4), 4.07 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.61 (s, 3H, OCH_3), 2.32 and 2.31 (two s, 3H each, C-2 and C-6 CH_3), 1.18 (t, J = 7.1 Hz, 3H, CH_2CH_3).

Anal. Calcd for $C_{18}H_{19}Cl_2NO_4$: C, 56.25; H, 4.98; N, 3.65. Found: C, 56.55; H, 4.69; N, 3.59

Acknowledgement.- We are grateful to the Medical Research Council of Canada (Grant No. MT-8892) for financial support of this research.

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(Received August 8, 1995; in revised form October 13, 1995)