SYNTHESIS AND AROMATIZATION OF DIHYDRO-PYRIMIDINES STRUCTURALLY RELATED TO CALCIUM CHANNEL MODULATORS OF THE NIFEDIPINE-TYPE [1]

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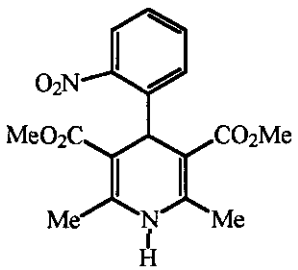
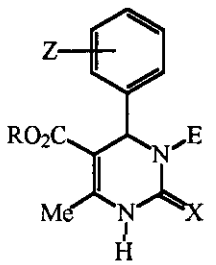
Abstract- A series of 4-substituted ethyl 2-methoxy-6-methyl-1,4-dihydro-pyrimidine-5-carboxylates has been synthesized and was successfully aromatized to the corresponding pyrimidines with various oxidizing reagents. *O*-Demethylation of such pyrimidines provides a simple route to pyrimidinone derivatives which are otherwise difficult to obtain.

Hantzsch 1,4-dihydropyridines of the nifedipine-type (DHPs, *e.g.* **1**) belong to the most studied class of calcium antagonists used in the clinical treatment of hypertension, cardiac arrhythmias, or angor. Despite intensive research efforts and the commercial success of DHPs,[2] these types of calcium channel modulators generally exhibit a rather short duration of antihypertensive activity, thus requiring frequent administrations. In the past years interest has focused on structurally closely related compounds such as dihydropyrimidine-5-carboxylates of type **2** and **3** (DHPMs).[3-13] These aza-analogs show a pharmacological profile very similar to that of DHP calcium channel modulators and several lead- compounds have recently been developed that compare favorable with DHP analogs.[3-10] However, surprisingly little is



1, nifedipine



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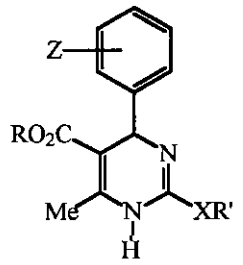

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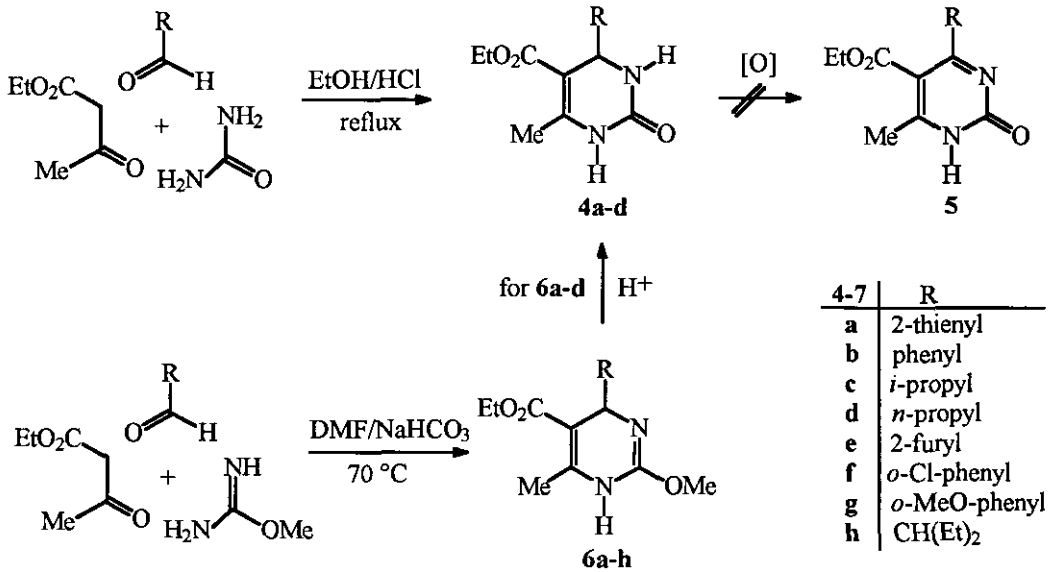
R = alkyl; X = O, S; Z = e.g 2/3-NO_2, 2-CF_3,
E = ester, acyl, amide; R' = alkyl

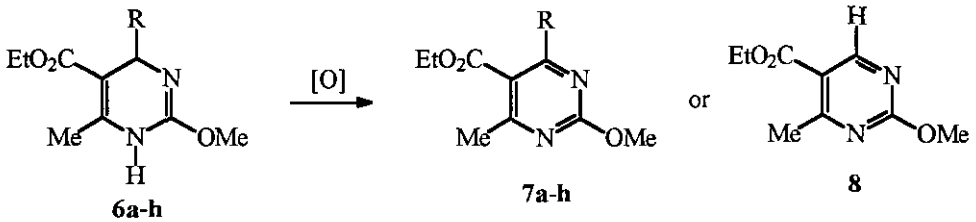
known about the behavior of such partly reduced pyrimidine derivatives towards chemical oxidants. Although several different methods for the dehydrogenation of specific DHPMs exist,[13-16] no general and practical procedure has been disclosed so far. In continuation of our work on the aromatization of Hantzsch dihydropyridines[17-22] we now report a general synthetic method for the preparation of oxidized dihydropyrimidine derivatives derived from DHPMs **2** and **3**.

Compounds (**4a-d**) were prepared by classical acid-catalyzed Biginelli condensation[13] of ethyl acetoacetate, urea, with the appropriate aldehyde component. In agreement with earlier work by Folkers *et al.*,[23] we find that this procedure usually gives good yields (60-70%) for 4-(hetero)aryl derivatives (**4a,b**),but is of poor synthetic value for the preparation of 4-alkyl analogs such as **4c,d** where yields of only up to 15% could be obtained. We have therefore employed the "Hideg-modification"[14] of the Biginelli reaction, *i.e.* the base-catalyzed condensation of ethyl acetoacetate, *O*-methylisourea hydrogen-sulfate, with an appropriate aldehyde, to afford 1,4-dihydropyrimidines of type **6**. This method seems to be of wide applicability as a number of variously substituted dihydropyrimidine derivatives (**6a-h**) could be prepared in good yield (see Experimental). Dihydropyrimidines (**6**) exist in solution as mixtures of 1,4- and 3,4-dihydro tautomers[24-27] as confirmed by ^{1}H and ^{13}C NMR spectroscopy (see Experimental). As shown in Scheme 1 selected 1,4-dihydropyrimidines (**6a-d**) were readily *O*-demethylated by treatment with concd HCl,[28,29] thus providing a simple and general access to DHPMs **4a-d** ("Biginelli compounds") as an alternative to the rather unreliable classical Biginelli condensation.



Scheme 1

All attempts to oxidize (*i.e.* dehydrogenate) dihydropyrimidines (**4a-d**) using a number of different oxidation reagents and conditions failed. In our hands, these DHPMs appeared to be quite stable towards *sodium nitrite in acetic acid* ($NaNO_2$/AcOH, Method A),[30] pyridinium chlorochromate (PCC, Method B),[18,31] cerium ammonium nitrate (CAN, Method C),[32] manganese dioxide (MnO_2, Methods D and E),[14,21,33-35] potassium permanganate, ($KMnO_4$/clay, Method F),[19,36] tetrachloro-1,4-benzoquinone (chloranil, Method G), and 2,6-dichloro-3,5-dicyanobenzoquinone (DDQ, Method H).[21,37,38] In contrast, 1,4-dihydropyrimidines of type **6** were readily dehydrogenated under most of the above conditions to yield the desired pyrimidines (**7a-h**), or in some cases the dealkylated (*i.e.* C4-unsubstituted) pyrimidine (**8**).



6a-h **7a-h** **8**

for R-Key, see Scheme 1

While dihydropyrimidines (**6**) reacted too slowly with $NaNO_2$/AcOH (less than 20 % of conversion after 24 h) and decomposed in the presence of PCC, it appeared that the other oxidation reagents we tested (Methods C, D, E, F, G and H) constitute valuable reagents for the aromatization of dihydropyrimidines of type **6**. As mentioned above, dealkylation occurred using MnO_2 (Methods D and E) for dihydropyrimidines with branched alkyl substituents, *e.g.* **6c**, and was also observed using CAN (Method C) and $KMnO_4$ (Method F) as oxidizing reagents. Similar results were recently reported by Hideg for related 2-*methylthio analogs.*[14] *This dealkylation process is also found in the oxidation of DHPs of the nifedipine-*type but we have demonstrated[21] that in this series the use of a quinone-derived dehydrogenation agent can avoid the expulsion of the branched C4-alkyl substituent. Indeed, this effect can also be observed with dihydropyrimidines of type **6**. Thus, treatment of **6c** with chloranil or DDQ in dichloromethane at room temperature (Methods G and H) yielded exclusively the corresponding pyrimidine (**7c**). Methods C, E, and H afforded the pyrimidines (7) or (**8**) in fair to good yields (30-70%). Therefore, the choice of the most appropriate oxidant can now be made based on criteria such as cost of the reagent, the experimental conditions, or the selectivity of the reaction in the case of DHPMs with a branched C4-alkyl substituent.

Having in hand several efficient procedures for the aromatization of dihydropyrimidine-5-carboxylates of type **6**, it seemed of interest to obtain quantitative data on oxidation rates in order to conduct a comparison with analogous DHP derivatives. A set of dihydropyrimidines (**6**) was therefore oxidized (Table 1) as

described in the Experimental Section. Since all methods employed CH_2Cl_2 as a solvent and all (dihydro)pyrimidine species were soluble in CH_2Cl_2 these reactions could be conveniently monitored by ^1H NMR spectroscopy. In dihydropyrimidines (**6**), the protons of the C6-methyl group gave rise to a singlet at *ca.* 2.30 ppm for the (predominant) 1,4-dihydro tautomer. That signal was shifted to *ca.* 2.50 ppm for the 3,4-dihydro tautomer and appeared at *ca.* 2.60 ppm in the aromatized species (**7a-h**) and (**8**). The composition of the mixtures could be readily determined by monitoring changes in intensities of these methyl group resonances. Side reactions appeared to be neglectable as significant changes in the sum of the measured intensities within the duration of the oxidation processes were not observed. Reactions involving CAN and DDQ were too fast to be monitored by ^1H NMR. Examination of the results presented in Table 1 demonstrates that as a general rule dihydropyrimidines bearing a C4-alkyl group are more sensitive towards oxidants than those having a C4-(hetero)aryl substituent.

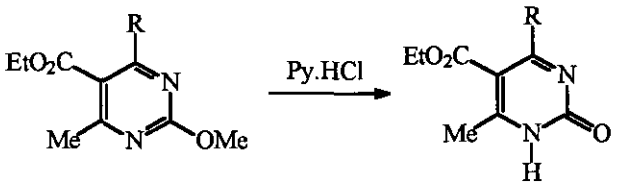
Table 1. Quantitative Data on the Aromatization of DHPMs **6** (for R-Key see Scheme 1).

	Remaining concd (%) of DHPM **6** after (h)				
	0.5	1.0	2.0	3.0	4.0
Method D					
a	100	100	95		90
b	90	80	75		70
c	80	75	70		60
d	85	80	70		65
Method E					
a		50	35	10	0
b		45	20	5	0
c		30	15	0	0
d		10	0	0	0

	Remaining concd (%) of DHPM **6** after (h)						
	0.5	1.0	2.0	4.0	6.0	8.0	18.0
Method F							
a			95	90	85	80	
b			95	90	80	70	
c			90	85	80	70	
d			80	80	75	70	
Method G							
a	90	85	75	70	50	30	5
b	85	80	65	55	50	45	40
c	85	85	75	65	55	30	0
d	75	65	35	20	0	0	0
e	90	85	75	65	35	15	0
f	100	95	80	75	65	55	15
g	90	85	80	55	40	30	10
h	85	75	60	40	20	0	0

Method D: MnO_2, CH_2Cl_2, rt
Method E: MnO_2, CH_2Cl_2, reflux
Method F: $KMnO_4$/clay, CH_2Cl_2/H_2O, rt
Method G: chloranil, CH_2Cl_2, rt

It should be pointed out that from a synthetic point of view, the present study provides an improved procedure for the preparation of DHPMs **4** bearing an alkyl group at C4; compounds that are not readily available by classical Biginelli condensation.[13] In addition, this route also yields access to pyrimidin-2-ones of type **5**, that can generally not be obtained by direct oxidation of the corresponding DHPM derivatives (**4**) (Scheme 1).[13] This was shown by the fact that **7b** and **c**, whereas stable in hydrochloric acid, could be effectively *O*-demethylated by treatment with neat pyridinium hydrochloride[39-41] to yield the



7b,c **5b,c**

for R-Key, see Scheme 1

corresponding pyrimidones (**5b,c**). The structure of pyrimidone (**5b**) was confirmed by comparison with authentic material obtained by oxidation of **4b** with CrO_3/H_2SO_4 as reported by Slavinskaya *et al.*[15]

The results presented in this study indicate that DHPMs of type **4** (Biginelli compounds) are rather resistant towards oxidation, *i.e.* dehydrogenation, whereas 1,4-dihydropyrimidines of type **6** can readily be aromatized by a variety of reagents. Quantitative data demonstrate that pyrimidines bearing a C4-(hetero)aryl group are less sensitive to oxidation than the C4-alkyl analogs. In some cases, where the C4-substituent is a branched alkyl group, aromatization may be accompanied by loss of the C4-substitutent, although this pathway can be prevented if chloranil or DDQ is used as an oxidizing reagent. The results presented here are analogous to our previous work in the DHP series, although DHPs are generally oxidized faster than the corresponding dihydropyrimidines of type **6**. Based on the experimental results described herein it is not surprising that dihydropyrimidine calcium channel modulators of type **2** (DHPMs) are resistant to an oxidative metabolism involving dehydrogenation to pyrimidones of type **5**. Therefore the prolonged duration of antihypertensive activity of DHPMs as compared to classical DHP drugs of the nifedipine-type could be rationalized.

EXPERIMENTAL

All reagents and solvents were commercially available and were used without further purification except for CH_2Cl_2 which was distilled from P_4O_{10} before use. MnO_2, oxidation grade, was kindly supplied by MMM Sedema s.a., Tertre, Belgium. IR spectra were recorded on a Perkin-Elmer FTIR 1760K spectrophotometer. NMR spectra were recorded on a Varian EM 360-L spectrometer (60 MHz for ^1H at 1.4 T) or on a Bruker AMX spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C at 7.0 T). Chemical shifts are reported in ppm relative to TMS as internal standard. Melting points (uncorrected) were determined on a hot-stage microscope. Elemental analyses were performed at the Station de Haute-Belgique (Libramont-Chevigny, Belgium). Compounds (**4a**),[42] (**4b**),[23] and (**5b**)[15] have been described in the literature.

Direct Synthesis of Ethyl 6-Methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (4a-d). A solution of urea (3.0 g, 50 mmol), ethyl 3-oxobutanoate (9.8 g, 9.6 mL, 75 mmol), the appropriate aldehyde (50 mmol) and concd HCl (10 drops) in EtOH (25 mL) was heated under reflux for 4 h. After cooling, the precipitate was filtered and washed with a mixture (1:1) of ethanol and water (for **4a,b**). In the case of alkyl substituted pyrimidines (**4c,d**) the reaction mixture was concentrated under reduced pressure and the so obtained solid residue was filtered and thoroughly washed with water. Yields: **4a**: 70%; **4b**: 60%; **4c**: 10%; **4d**: 15 %.

Ethyl 6-Methyl-4-(1-methylethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c): mp 170-172 °C (H_2O); IR (KBr) 3240, 3122, 1723, 1700, 1683, 1653 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.10 (br s, N1-*H*), 7.40 (br s, N3-*H*), 4.00 (m, OCH_2 and C4-*H*), 2.30 (s, C6-CH_3), 1.10 (m, OCH_2CH_3 and C_3H_7). *Anal.* Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.51; H, 7.63; N, 11.96.

Ethyl 6-Methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d): mp 153-155 °C (H_2O); IR (KBr) 3251, 3121, 1721, 1703, 1673, 1647 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.10 (br s, N1-*H*), 7.50 (br s, N3-*H*), 4.00 (m, OCH_2 and C4-*H*), 2.30 (s, C6-CH_3), 1.10 (m, OCH_2CH_3 and C_3H_7). *Anal.* Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.19; H, 7.73; N, 11.93.

Synthesis of Ethyl 2-Methoxy-6-methyl-1,4-dihydropyrimidine-5-carboxylates (6a-h). A mixture of *O*-methylisourea hydrogensulfate (7.4 g, 60 mmol), ethyl 3-oxobutanoate (6.5 g, 6.4 mL, 55 mmol), the appropriate aldehyde (50 mmol), $NaHCO_3$ (16.8 g, 200 mmol) and DMF (100 mL) was heated at 70 °C for 3 h. After cooling, the mixture was diluted with brine (150 mL) and extracted with ether (2 x 100 mL). The combined organic layers were washed with water (2 x 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on alumina with CH_2Cl_2 to yield the following dihydropyrimidines (most ^1H NMR spectra show line-broadening due to tautomeric equilibria, the ^{13}C NMR spectra are complex due to line splitting and are not presented below).

Ethyl 2-Methoxy-6-methyl-4-(2-thienyl)-1,4-dihydropyrimidine-5-carboxylate (**6a**): 65% yield, mp 102-104 °C (cyclohexane); IR (KBr) 3329, 1685, 1626, 1489 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (br s, N-*H*), 7.10 (m, C5-*H* thienyl), 6.90 (m, C3-*H* thienyl and C4-*H* thienyl), 5.90 (br s, C4-*H*), 4.20 (q, J = 7.0 Hz, OCH_2), 3.80 (br s, OCH_3), 2.30 (br s, C6-CH_3), 1.20 (t, J = 7.0 Hz, OCH_2CH_3). *Anal.* Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99. Found: C, 55.98; H, 5.89; N, 10.00.

Ethyl 2-Methoxy-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylate (**6b**): 60% yield, mp 83-86 °C (cyclohexane); IR (KBr) 3166, 1684, 1511 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.00 (m, Ph and N3-*H*), 6.50 (br s, N-*H*), 5.60 (s, C4-*H*, 1,4-dihydro), 5.40 (br s, C4-*H*, 3,4-dihydro), 4.10 (q, J = 7.0 Hz, OCH_2), 3.80 (br s, OCH_3, 3,4-dihydro), 3.60 (s, OCH_3, 1,4-dihydro), 2.40 (s, C6-CH_3, 3,4-dihydro), 2.20 (s, C6-CH_3, 1,4-dihydro), 1.15 (t, J = 7.0 Hz, OCH_2CH_3), the ratio 1,4-/3,4-dihydro is *ca.* 2:1, the assignments are based on the ^3J[H-N3-C4-H] reported by Duburs.[16] *Anal.* Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.41; H, 6.56; N, 10.21.

Ethyl 2-Methoxy-6-methyl-4-(1-methylethyl)-1,4-dihydropyrimidine-5-carboxylate (**6c**): 45% yield (oil); IR (neat) 3311, 1695, 1680, 1554, 1234 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (br s, N-*H*), 4.30 (br s, C4-*H*), 4.20 (q, *J* = 7.0 Hz, OCH_2), 3.80 (br s, OCH_3), 2.30 (br s, C6-CH_3), 1.70 (m, C4-*H*), 1.30 (t, *J* = 7.0 Hz, OCH_2CH_3), 0.90 (br s, CH-$(CH_3)_2$). *Anal.* Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.57; H, 8.20; N, 11.37.

Ethyl 2-Methoxy-6-methyl-4-propyl-1,4-dihydropyrimidine-5-carboxylate (**6d**): 40% yield (oil); IR (neat) 3313, 1695, 1681, 1554, 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (br s, N-*H*), 4.50 (br s, C4-*H*), 4.20 (q, *J* = 7.0 Hz, OCH_2), 3.80 (br s, OCH_3), 2.30 (br s, C6-CH_3), 1.50 (m, C4-CH_2-CH_2), 1.30 (t, *J* = 7.0 Hz, OCH_2CH_3), 0.90 (t, *J* = 7.0 Hz, CH_3). *Anal.* Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.65; H, 7.99; N, 11.99.

Ethyl 4-(2-Furyl)-2-methoxy-6-methyl-1,4-dihydropyrimidine-5-carboxylate (**6e**): 50% yield, mp 121-124 °C (cyclohexane); IR (KBr) 3293, 1697, 1651, 1491, 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (d, *J* = 3.0 Hz, C5-*H* furyl), 7.10 (br s, N-*H*), 6.30 (t, *J* = 3.0 Hz, C4-*H* furyl), 6.10 (d, *J* = 3.0 Hz, C3-*H* furyl), 5.80 (br s, C4-*H*), 4.20 (q, *J* = 7.0 Hz, OCH_2), 3.80 (br s, OCH_3), 2.30 (br s, C6-CH_3), 1.20 (t, *J* = 7.0 Hz, CH_2CH_3). *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.86; H, 6.14; N, 10.62.

Ethyl 4-(2-Chlorophenyl)-2-methoxy-6-methyl-1,4-dihydropyrimidine-5-carboxylate (**6f**): 60% yield, mp 103-106 °C; IR (KBr) 3304, 1709, 1677, 1494, 1226 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.10 (m, ArH), 6.70 (br s, N3-*H*), 6.10 (br s, N1-*H*), 5.90 (s, C4-*H*, 1,4-dihydro), 5.80 (br s, C4-*H*, 3,4-dihydro), 4.00 (q, *J* = 7.0 Hz, OCH_2), 3.80 (s, OCH_3, 3,4-dihydro), 3.70 (s, OCH_3, 1,4-dihydro), 2.50 (s, C6-CH_3, 3,4-dihydro), 2.30 (s, C6-CH_3, 1,4-dihydro), 1.15 (t, *J* = 7.0 Hz, OCH_2CH_3), the ratio 1,4-/3,4-dihydro is *ca.* 1:2, the assignments are based on the spectrum of **6b**. *Anal.* Calcd for $C_{15}H_{17}N_2O_3Cl$: C, 58.35; H, 5.55; N, 9.07. Found: C, 58.54; H, 5.64; N, 9.21.

Ethyl 2-Methoxy-4-(2-methoxyphenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (**6g**): 55% yield, mp 112-115 °C (cyclohexane); IR (KBr) 3231, 1676, 1558, 1373, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.10 (m, ArH), 5.90 (br s, N-*H*), 5.80 (br s, C4-*H*), 4.10 (q, *J* = 7.0 Hz, OCH_2), 3.90 (s, OCH_3), 3.70 (br s, OCH_3), 2.50 (br s, C6-CH_3), 1.20 (t, *J* = 7.0 Hz, OCH_2CH_3). *Anal.* Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.03; H, 6.60; N, 9.31.

Ethyl 4-(1-Ethylpropyl)-2-methoxy-6-methyl-1,4-dihydropyrimidine-5-carboxylate (**6h**): 50% yield (oil); IR (neat) 3305, 1695, 1621, 1551, 1463, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.20 (br s, N-*H*), 4.50 (br s, C4-*H*), 4.00 (q, *J* = 7.0 Hz, OCH_2), 3.60 (br s, OCH_3), 2.20 (br s, C6-CH_3), 1.50 (m, C4-C*H*), 1.30-0.80 (m, and 2 t, *J* = 7.0 Hz, $(C_2H_5)_2$ and OCH_2CH_3). *Anal.* Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01; N, 10.44. Found: C, 63.00; H, 8.70; N, 10.77.

***O*-Demethylation of Ethyl 2-Methoxy-6-methyl-1,4-dihydropyrimidine-5-carboxylates (6a-d).** A mixture of the corresponding dihydropyrimidine (**6a-d**) (10 mmol), THF (25 mL), MeOH (25 mL) and 3*N* HCl (15 mL) was heated under reflux for 6 h. After cooling, the mixture was extracted with CH_2Cl_2 (2 x 50 mL), the combined organic layer dried over $MgSO_4$, and subsequently concentrated under reduced

pressure to yield dihydropyrimidines (**4a-d**). Yields : **4a**: 60%; **4b**: 75%; **4c**: 70%; **4d**: 65%. These products were identical (TLC, IR, ^{1}H NMR) to dihydropyrimidines obtained by classical Biginelli condensation (see above).

Aromatization of Dihydropyrimidines 6a-h → 7a-h or 8, General Procedures:

Method A: $NaNO_2$ (1.40 g, 20 mmol) was slowly added to a mixture of DHPM **6** (5 mmol) in AcOH (5 mL) while maintaining a temperature of *ca.* 0 °C. The mixture was allowed to warm up to rt and was subsequently stirred for 24 h at rt. Addition of water yielded a solid precipitate that was identified by spectroscopic analysis (^{1}H NMR, IR).

Method B: A mixture of pyridinium chlorochromate (PCC) (45.0 g, 190 mmol) and neutral alumina (200 g) in acetone (200 mL) was concentrated under reduced pressure. A mixture of DHPM **6** (5 mmol) and PCC on alumina (18 g, 14 mmol) was stirred in CH_2Cl_2 (50 mL) at rt for 6 h. The solid material was filtered, washed with CH_2Cl_2 (25 mL), and the so obtained CH_2Cl_2 solution concentrated under reduced pressure. The residue was chromatographed on alumina with CH_2Cl_2 as eluent.

Method C: A solution of cerium ammonium nitrate (CAN) (5.5 g, 10 mmol) in water (10 mL) was slowly added to a solution of DHPM **6** (5 mmol) in CH_2Cl_2 (10 mL). After 15 min, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on alumina with CH_2Cl_2 as eluent.

Method D: A mixture of DHPM **6** (5 mmol) and MnO_2 (2.2 g, 25 mmol) was stirred in CH_2Cl_2 (50 mL) at rt for 24 h. The resulting suspension was filtered on a cake of alumina (20 g) and the inorganic solid was washed with CH_2Cl_2 (3 x 25 mL). The combined organic layers were concentrated under reduced pressure and the residue was chromatographed on alumina using CH_2Cl_2 as eluent.

Method E: Same as Method D, except that the reactions were performed at reflux temperature for 4 h.

Method F: A mixture of $KMnO_4$ (32 g, 200 mmol) and a clay (montmorillonite KSF, 68 g) in acetone (100 mL) was stirred at rt for 30 min. The solvent was evaporated under reduced pressure and the solid residue dried for 1 h at 110 °C. A mixture of DHPM **6** (5 mmol) and $KMnO_4$ on clay (2.5 g, 5 mmol) was stirred in CH_2Cl_2/water (1:1, 25 mL) at rt for 6 h. The solid material was filtered, washed with CH_2Cl_2 (2 x 20 mL), and the organic layer concentrated under reduced pressure. The residue was chromatographed on alumina with CH_2Cl_2 as eluent.

Method G: A mixture of DHPM **6** (5 mmol) and tetrachloro-1,4-benzoquinone (chloranil) (1.2 g, 5 mmol) was stirred in CH_2Cl_2 at rt for the appropriate time given in Table 1. The mixture was filtered on a cake of alumina (20 g) and the inorganic solid was washed with CH_2Cl_2 (2 x 25 mL). The combined organic layers were concentrated under reduced pressure. The residue was chromatographed on alumina with CH_2Cl_2.

Method H: Same as Method G, except that 2,6-dichloro-3,5-dicyanobenzoquinone (DDQ) (1.1 g, 5 mmol) was used instead of chloranil.

Ethyl 2-Methoxy-4-methyl-6-(2-thienyl)-pyrimidine-5-carboxylate (**7a**). Yield: 5% (Method A), 35% (Method C), 50% (Method E), 10% (Method F), 60% (Method G, 24 h), 50% (Method H); mp 77-80 °C (cyclohexane); IR (KBr) 1712, 1548, 1258, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (m, C3-H and C5-*H* thienyl), 7.20 (m, C4-*H* thienyl), 4.40 (q, *J* = 7.0 Hz, OCH_2), 4.10 (s, OCH_3), 2.50 (s, C4-CH_3), 1.30 (t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 169.0, 168.4, 164.7, 157.7, 141.3, 131.2, 129.5, 128.7, 117.9, 62.6, 55.4, 22.9, 14.3. *Anal.* Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06. Found: C, 56.26; H, 4.73; N, 9.73.

Ethyl 2-Methoxy-4-methyl-6-phenylpyrimidine-5-carboxylate (**7b**). Yield: 5% (Method A), 25% (Method C), 60% (Method E), 10% (Method F), 50% (Method G, 24 h), 55% (Method H); oil; IR (neat) 1724, 1557, 1278, 1073 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70-7.40 (m, Ph), 4.30 (q, *J* = 7.0 Hz, OCH_2), 4.10 (s, OCH_3), 2.60 (s, C4-CH_3), 1.10 (t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 169.0, 166.8, 164.9, 138.2, 130.4, 129.9, 128.7, 128.6, 120.3, 61.9, 55.4, 23.1, 13.9. *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.77; H, 5.79; N, 10.29.

Ethyl 2-Methoxy-4-methyl-6-(1-methylethyl)-pyrimidine-5-carboxylate (**7c**). Yield: 40% (Method G, 24 h), 60% (Method H); oil; IR (neat) 1724, 1556, 1254, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.40 (q, *J* = 7.0 Hz, OCH_2), 4.00 (s, OCH_3), 3.10 (m, C*H*-$(CH_3)_2$), 2.50 (s, C4-CH_3), 1.40 (t, *J* = 7.0 Hz, OCH_2CH_3), 1.25 (d, *J* = 6.0 Hz, CH-$(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 175.7, 168.5, 167.8, 165.2, 120.4, 62.0, 55.1, 33.7, 23.3, 22.0, 14.6. *Anal.* Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.84; H, 7.44; N, 11.57.

Ethyl 2-Methoxy-6-methyl-4-propylpyrimidine-5-carboxylate (**7d**). Yield: 5% (Method A), 45% (Method C), 40% (Method E), 10% (Method F), 55% (Method G, 24 h), 55% (Method H); oil; IR (neat) 1724, 1556, 1255, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.40 (q, *J* = 7.0 Hz, OCH_2), 4.00 (s, OCH_3), 2.70 (t, *J* = 7.0 Hz, CH_2-C_2H_5), 2.50 (s, C6-CH_3), 1.80 (m, CH_2-CH_2-CH_3), 1.40 (t, *J* = 7.0 Hz, OCH_2CH_3), 1.00 (t, *J* = 7.0 Hz, $(CH_2)_2CH_3$); ^{13}C NMR ($CDCl_3$) δ 172.2, 168.1, 168.0, 164.7, 120.7, 61.7, 55.0, 38.0, 23.3, 22.3, 14.4, 14.2. *Anal.* Calcd for $C_{12}H_{18}N_2O_3$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.24; H, 7.42; N, 11.58.

Ethyl 4-(2-Furyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (**7e**). Yield: 65% (Method C), 60% (Method E), 50% (Method G, 24 h), 65% (Method H); mp 66-68 °C (cyclohexane); IR (KBr) 1713, 1559, 1261, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (m, C5-*H* furyl), 7.40 (m, C3-*H* furyl), 6.60 (m, C4-*H* furyl), 4.40 (q, *J* = 7.0 Hz, OCH_2), 4.00 (s, OCH_3), 2.50 (s, C6-CH_3), 1.30 (t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 168.5, 168.4, 164.8, 153.6, 151.4, 145.7, 117.1, 114.9, 112.8, 62.2, 55.3, 22.7, 14.5. *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 60.02; H, 5.02; N, 10.26.

Ethyl 4-(2-Chlorophenyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (**7f**). Yield: 45% (Method C), 40% (Method E), 30% (Method G, 24 h), 60% (Method H); mp 65-67 °C (cyclohexane); IR (KBr) 1719, 1558, 1273, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50-7.30 (m, ArH), 4.00 (q, *J* = 7.0 Hz, OCH_2), 4.00 (s, OCH_3), 2.70 (s, C6-CH_3), 0.90 (t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 170.7, 167.2, 164.9, 140.9, 132.3, 130.6, 130.0, 129.4, 127.0, 120.8, 61.8, 55.7, 24.2, 13.9. *Anal.* Calcd for $C_{15}H_{15}N_2O_3Cl$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.58; H, 4.99; N, 9.18.

Ethyl 2-Methoxy-4-(2-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (**7g**). Yield: 65% (Method C), 30% (Method E), 50% (Method G, 24 h), 70% (Method H); mp 79-81 °C; IR (KBr) 1718, 1544, 1255, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (dd, *J* = 8.0 and 1.0 Hz, ArH), 7.40 (dt, *J* = 8.0 and 1.0 Hz, ArH), 7.10 (t, *J* = 8.0 Hz, ArH), 6.90 (d, *J* = 8.0 Hz, ArH), 4.10 (q, *J* = 7.0 Hz, OCH_2), 4.00 (s, OCH_3), 3.80 (s, OCH_3), 2.60 (s, C6-CH_3), 1.10 (t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 169.5, 167.5, 166.3, 165.1, 156.7, 131.4, 131.0, 128.3, 121.3, 121.1, 110.6, 61.2, 55.5, 55.4, 24.0, 14.0. *Anal.* Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.26. Found: C, 63.18; H, 6.39; N, 9.44.

Ethyl 4-(1-Ethylpropyl)-2-methoxy-6-methylpyrimidine-5-carboxylate (**7h**). Yield: 45% (Method G, 24 h), 40% (Method H); oil; IR (neat) 1728, 1557, 1471, 1361, 1248 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.50 (q, *J* = 7.0 Hz, OCH_2), 4.10 (s, OCH_3), 3.00 (m, C4-C*H*), 2.50 (s, C6-CH_3), 1.70-1.20 (m, OCH_2CH_3 and C_2H_5); ^{13}C NMR ($CDCl_3$) δ 175.2, 170.1, 169.8, 169.5, 121.4, 59.2, 54.5, 38.7, 24.2, 15.0, 11.9. *Anal.* Calcd for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.33; N, 10.52. Found: C, 63.33; H, 8.36; N, 10.12.

Ethyl 2-Methoxy-4-methylpyrimidine-5-carboxylate (**8**). Yield: 5% (Method A), 30% (Method C), 60% (Method E), 20% (Method F); oil; IR (neat) 1724, 1551, 1281, 1229 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.90 (s, C4-*H*), 4.20 (q, *J* = 7.0 Hz, OCH_2), 3.80 (s, OCH_3), 2.60 (s, C4-CH_3), 1.40 (t, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 176.3, 172.1, 155.6, 165.0, 119.7, 58.2, 55.6, 22.9, 13.9. *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.40; H, 5.62; N, 13.92.

***O*-Demethylation of Pyrimidines (7b,c).** A mixture of the corresponding pyrimidine (**7b,c**) (2.0 mmol) and pyridinium hydrochloride (2.5 g, 21 mmol) was heated under reflux for 30 min. After cooling, the mixture was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with water (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield the corresponding pyrimidones **5b,c.**

Ethyl 6-Methyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-5-carboxylate (**5b**). Yield: 45%; mp 130-132 °C (EtOH) (lit. mp 130-131 °C[15]); IR (KBr) 3300-2600, 1727, 1705, 1557, 1462, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (m, Ph), 6.30 (br s, N*H*), 4.50 (q, *J* = 7.0 Hz, OCH_2), 2.50 (s, C6-CH_3), 1.00 (t, *J* = 7.0 Hz, OCH_2CH_3).

Ethyl 4-(Methylethyl)-6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (**5c**). Yield: 40%; mp 165-167 °C (EtOH/H_2O); IR (KBr) 3300-2500, 1725, 1712, 1562, 1453, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (br s, N*H*), 4.30 (q, *J* = 7.0 Hz, OCH_2), 3.00 (m, C4-C*H*), 2.40 (s, C6-CH_3), 1.30 (t, *J* = 7.0 Hz, OCH_2CH_3), 1.10 (d, *J* = 6.0 Hz, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 175.2, 172.2, 165.3, 159.7, 112.3, 62.9, 36.2, 20.5, 14.6. *Anal.* Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.60; H, 6.72; N, 12.12.

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