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Microwave-mediated regioselective synthesis of novel pyrimido[1,2-*a*]pyrimidines under solvent-free conditions

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Abstract—Ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylates readily react, under microwave irradiation and solvent-free conditions, with 3-formylchromone or diethyl (ethoxymethylene)malonate to yield novel pyrimido[1,2-*a*]pyrimidines. The structure of the final products, deduced from the spectral data and confirmed by X-ray analysis, allows us to suggest reaction pathways.

1. Introduction

In recent years, there has been increasing interest in the design of alkyl 1,4-dihydropyrimidine-5-carboxylates (1,4-DHPMs) and related Biginelli-like compounds[1] which are presented as valuable substitutes[2] for the well-known Nifedipine® and other 1,4-dihydropyridine drugs,[3] clinically used in the treatment of cardiovascular diseases. This interest is illustrated, i.e. by the disclosure of elegant protocols involving solid phase synthesis approaches[4] as well as (solvent-free) preparations under microwave irradiation.[5]

The purpose of the present work is to extend the scope of those studies to 2-amino derivatives, and especially to the evaluation of their synthetic potential for the construction of novel pyrimido[1,2-*a*]pyrimidines, a ring system that can be found in marine-derived natural products such as crambescidin[6] and batzelladine[7] alkaloids.

2. Results and discussion

2.1. Preparation of the starting 2-amino-1,4-DHPMs 2a–e

A recent paper of Milcent[8] describes the synthesis (Scheme 1) of ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylates (**2**) from ethyl 3-aryl-2-benzoylpropenoates (**1**) and guanidine in DMF in the presence of an inorganic base (sodium hydrogen carbonate). This procedure affords the desired heterocycles within reaction times ranging from 8 to 48 h, but reported yields (not optimized) do not exceed 40% because of a competitive reaction yielding diethyl 2,4,6,8-tetraryl-4,6-dihydro-1*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylates (**3**). As these bicyclic derivatives arise from Michael-type condensations between two molecules of ester (**1**) and guanidine,[8] we reasoned that their formation could perhaps be disfavored when starting directly from arylaldehydes, ethyl benzoylacetate, and guanidine. This proposal is verified as the three-component reactions enabled us to obtain derivatives **2a–e** within 3 h in 75–90% yields whereas formation of **3** was not detected.

2.2. Reactions between the 2-amino-1,4-DHPMs 2a–e and 3-formylchromone 4

Diamines are known to react with 3-formylchromone **4** to yield pyrimidines.[9] The reaction initially takes place on the formyl group and is followed by an intramolecular attack of the second amine function on the C-2 atom of the pyrone ring followed by the opening of that ring (Scheme 2). In such a sequence, derivatives **2** are excellent candidates for the preparation of bicyclic systems but, due to the presence of three nitrogen atoms in **2**, formation of two isomeric substances (4-aryl (**5**) or 2-aryl (**6**) derivatives) may be foreseen as illustrated in Scheme 2.

Experimentally we observed (NMR) that only one series of isomers (**5** (**2*H***), see Scheme 2) was obtained when the reactants are heated in boiling ethanol for several hours. However, we felt unsatisfied with those experimental

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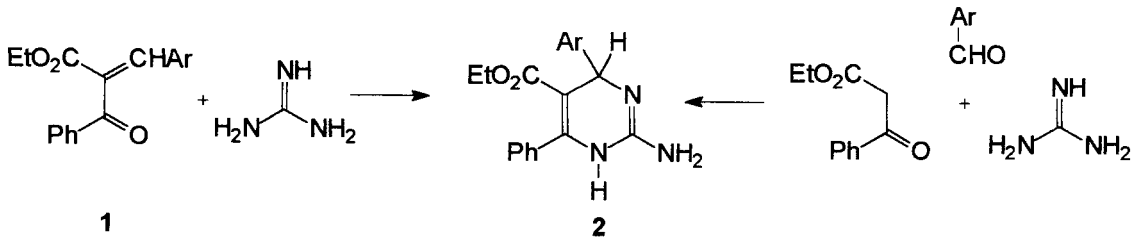
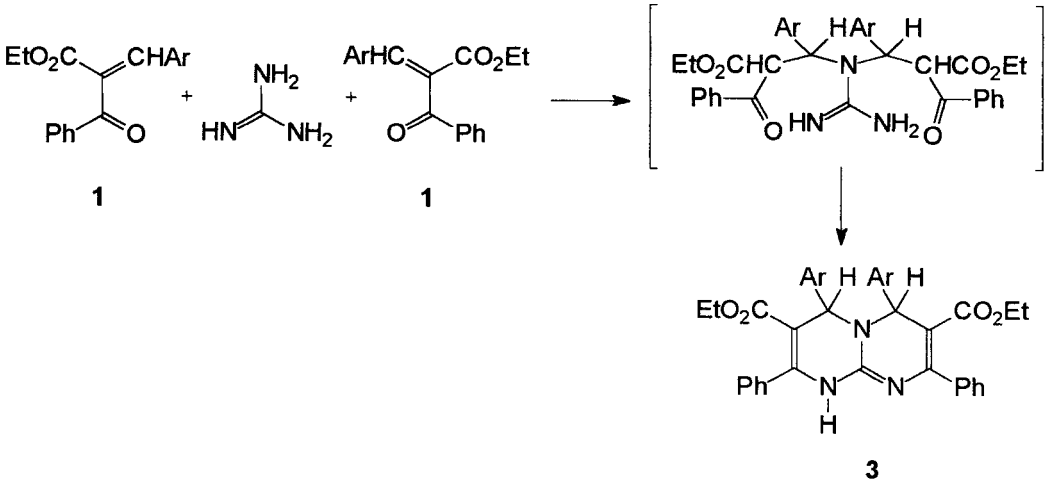
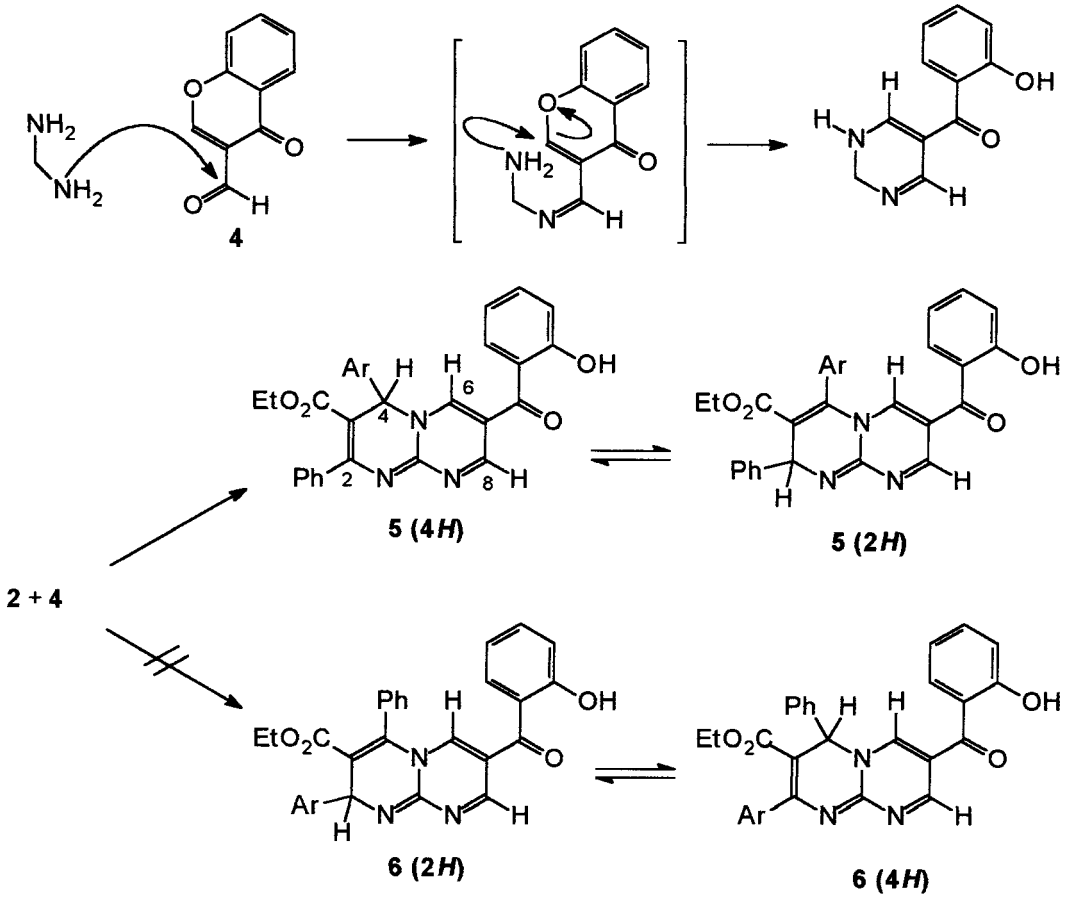


Ar = C_6H_5 (**2a**), 4-(CH_3)-C_6H_4 (**2b**), 4-(OCH_3)-C_6H_4 (**2c**), 4-Cl-C_6H_4 (**2d**), 2-thienyl (**2e**)



Scheme 1. Preparation of compounds **2a–e** and **3**.



Scheme 2. Reactions between 2-amino-1,4-DHPMs (**2**) and 3-formylchromone (**4**).

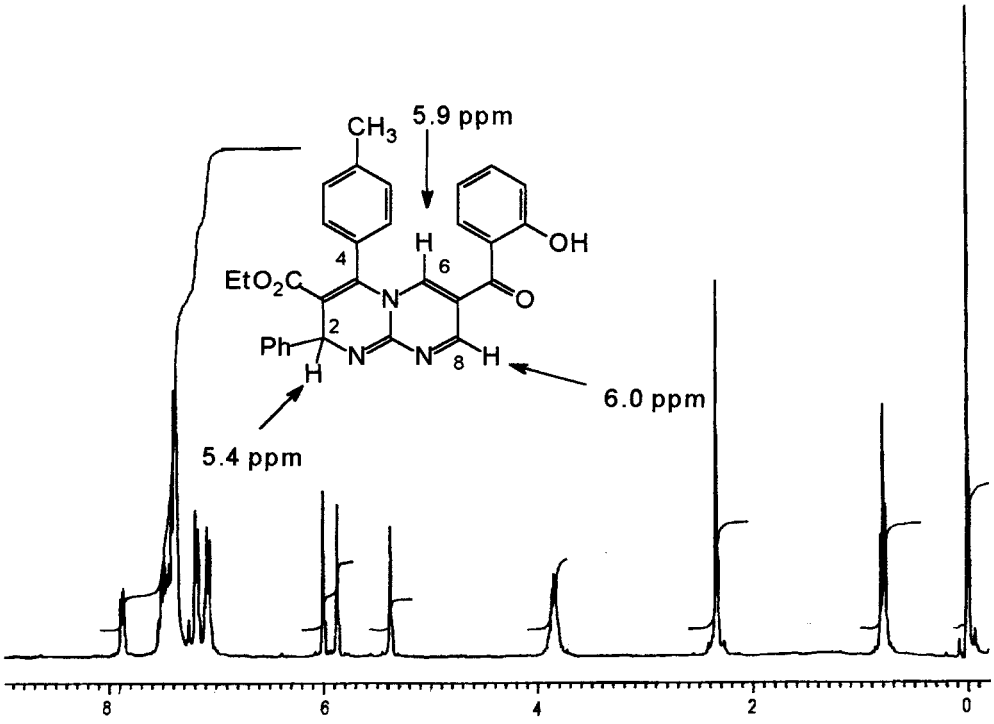


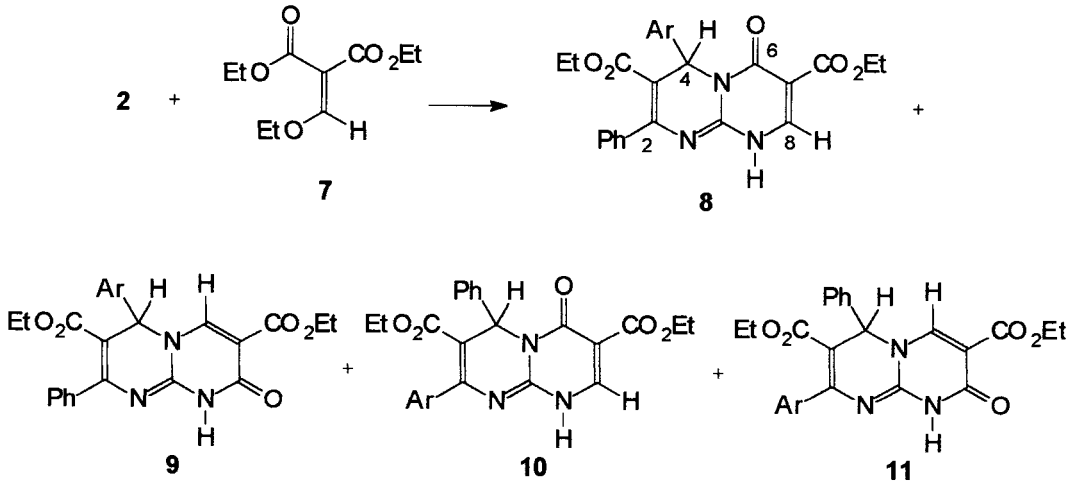
Figure 1. ^{1}H NMR spectrum of compound **5b**.

conditions, and we decided to perform the reactions under microwave irradiation.[10] In that way, we isolated the same final products but advantageously in better yields, under solvent-free conditions, and within a few minutes.

In the ^{1}H NMR spectra (Fig. 1) of the final products, there are three signals (singlet) between 5.0 and 6.5 ppm. The less deshielded signal in this range is located at 5.4 ppm: this is a typical value for ^{1}H chemical shifts observed in the NMR spectra of Biginelli-like 1,4-DHPMs and it allows to attribute the signal to a proton on a sp^3 carbon atom bearing a (hetero)aryl group. As this position is constant whichever, that (hetero)aryl substituent is, structures **5** (**2*H***) or **6** (**4*H***) can be suggested (indeed, as illustrated by the values collected in Table 1, the chemical shift of a Ar–C**H** proton is highly dependent[11] on the nature of the aromatic group: such a dependence is also observed in the spectra of the starting heterocycles (**2**). The second signal (H on a sp^2

Table 1. ^{1}H chemical shifts of CH_3 protons in various Ar–CH_3 compounds

Ar in Ar–CH_3	C_6H_5	4-(CH_3)–C_6H_4	4-(OCH_3)–C_6H_4	4-Cl–C_6H_4	2-thienyl
δ CH_3	2.40	2.30	2.25	2.35	2.55



Scheme 3. Reactions between 2-amino-1,4-DHPMs (**2**) and diethyl (ethoxymethylene)malonate (**7**).

carbon atom) appears around 5.9 ppm when the substituent on the system is a phenyl ring or a substituted phenyl ring, and is shifted downfield to 6.2 ppm when the substituent is a thienyl group. The signal is therefore attributed to the H(6) proton; the signal due to the H(8) proton is located at 6.0 ppm and its position does not vary with the nature of the (hetero)aryl substituent on the system. Those data are consistent with structures **5** (**2*H***) only.

2.3. Reactions between the 2-amino-1,4-DHPMs 2a–e and diethyl (ethoxymethylene)malonate 7

The situation is more complex when derivatives **2** are allowed to react with diethyl (ethoxymethylene)malonate (**7**). Indeed, four series of isomeric pyrimido[1,2-*a*]pyrimidines can be formed (Scheme 3). Once again, when the reactions are conducted in boiling ethanol, or under microwave irradiation, only one series of compounds is obtained. In the ^{1}H NMR spectra, there is no signal between 5.0 and 6.0 ppm. Therefore, the signal due to the proton on the sp^3 carbon atom of the heterocyclic system is highly deshielded when compared with the chemical shifts observed for the starting heterocycles **2** (δ C(4)– *H* in **2**: between 5.2 and 5.6 ppm). Such a deshielding can be explained by the influence of the carbonyl moiety when it is in close vicinity of the considered proton, and is therefore indicating a 6-oxo structure **8** or **10**.

As the chemical shift of this proton varies when going from an aryl substituent (compounds **a**–**d**) to a thienyl substituent (compound **e**), the bicyclic derivatives should belong to series **8**. This conclusion is confirmed by the structure (Fig. 2) obtained from the X-ray analysis of the product, formed by the interaction between **2c** and **7**. According to the X-ray single crystal diffraction study, the pyrimidinone cycle is planar, the exocyclic ester group being twisted from this plane by 26(2)°. The other unsaturated 6-membered ring adopts an asymmetric boat conformation with a planar C2C3N10C9 fragment, the pseudoaxial benzene ring C20–C25 being perpendicular to this fragment. The phenyl substituent attached to C2 is twisted around the C2–C11 bond by 74(2)° to avoid steric interactions with the neighbouring ethoxycarbonyl substituent at C3. In the crystal, molecules **8c** form centrosymmetric dimers via intermolecular hydrogen bonds: N8–H8···N1 [1−*x*, 1−*y*, 1−*z*], N8–H8 0.99(4), H8···N1 1.97(5) Å, ∠N8–H8···N1 170°.

2.4. Reaction pathways

We have not been able to isolate the uncyclized intermediates, neither by reducing microwave irradiation times, nor by performing the syntheses in a solvent at reflux or at room temperature. Anyway, the structure of the final products **5** indicates that they result from the nucleophilic attack of the exocyclic nitrogen atom of **2** on the formyl function of **4** and that the ring closure involves the N(3) nitrogen atom of the pyrimidine cycle. This situation

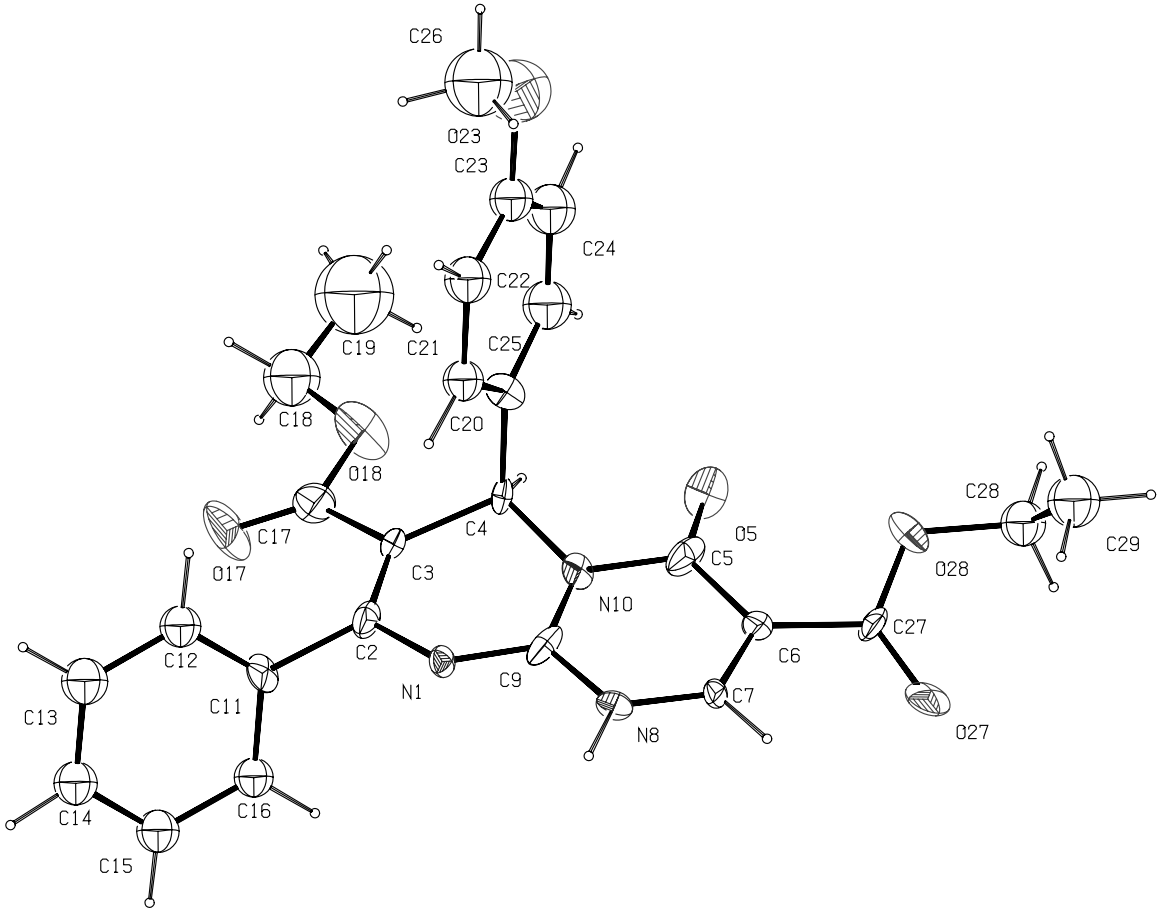


Figure 2. Solid state structure of compound **8c**.

parallels previous results, demonstrating a greater susceptibility of the N(3) atom towards electrophiles, when compared to the N(1) atom.[1a] Similarly, reactions performed from diethyl (ethoxymethylene)malonate involve the same exocyclic and N(3) nitrogen atoms of the starting heterocycles **2**.

3. Conclusion

In this work, we demonstrated that ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylates (**2**) regioselectively react with 3-formylchromone (**4**) or diethyl (ethoxymethylene)malonate (**7**) to afford pyrimido[1,2-*a*]pyrimidines (**5** and **8**, respectively) which had not been described previously. Interestingly, we observed that these bicyclic derivatives can be prepared advantageously in a microwave oven and in the absence of organic solvent, thus contributing to the promotion of economical and environmentally friendly experimental procedures.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained using a Jeol JNP-PM X60 spectrometer (60 MHz for ^{1}H at 1.4 T) and a Bruker AMX-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C at 7 T); chemical shifts (δ) are given in ppm using TMS as internal reference. IR spectra were recorded on a Perkin–Elmer FTIR 1760 K spectrophotometer. Melting points (not corrected) were determined on an electrothermal 9100 apparatus. Solvents are commercially available (Aldrich Co., Acros Organics) and were used without further purification. The elemental analyses were carried out at the Station de Haute Belgique (Libramont-Chevigny, Belgium). Crystallographic data (excluding structure factors) of **7c** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 149469. Copies of the data are available without charge from: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +4412-23336033; e-mail: deposit@ccdc.cam.ac.uk).

4.2. X-Ray structure determination

X-Ray data for crystals **8c** were collected on a CAD4 Enraf-Nonius automatic diffractometer with graphite monochromated λMoKα radiation using $\omega/2\theta$-scan mode in the range $2°\leqslant\theta\leqslant27°$ at 20°C. The stability of the crystal and that of the experimental conditions were checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering three standards. Neither decay, nor absorption correction (μ Mo 0.87 cm^{-1}) was necessary. Corrections for Lorentz and polarization effects were applied.

Crystals **8c**, $C_{26}H_{25}O_6N_3$ (colorless, needles, 0.4×0.1×0.1 mm^3), M 475.51, F(000) 500, triclinic. Twenty-five centered reflections were used to determine unit cell dimensions: a 7.147(3) Å, b 11.969(3) Å, c 14.874(6) Å, α 75.93(2)°, β 81.98(2)°, γ 81.95(2)°, V 1214.7(8) Å^3, d_{calcd} 1.30 g/cm^3, Z 2, space group $P1bar$. A total of 5342 reflections were measured, of which only 992 were with $I > 3\sigma$.

The phase problem was solved by direct methods using the program SIR.[12] The structure was developed by difference-Fourier calculations interspersed with cycles of full-matrix least-squares refinements. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located from difference-Fourier maps and added to structure factor calculations with fixed positional and thermal parameters. The final agreement factors are R 0.088, R_w 0.099. All calculations were carried out using the MolEn package.[13]

4.3. Synthesis

4.3.1. Preparation of the starting 2-amino-1,4-DHPMs 2a–e. A mixture of aldehyde (20 mmol), ethyl benzoylacetate (4.2 g, 3.8 mL, 22 mmol), guanidine hydrochloride (2.3 g, 24 mmol), and sodium hydrogen carbonate (6.7 g, 80 mmol) in DMF (40 mL) was stirred at 70°C for 3 h. After cooling, the mixture was poured onto crushed ice. The precipitate was filtered and thoroughly washed with water. Compounds (Yield) **2a** (75%), **2b** (85%), **2c** (75%), and **2d** (85%) have been described in the literature.[8]

4.3.2. Ethyl 2-amino-1,4-dihydro-6-phenyl-4-(2-thienyl)-pyrimidine-5-carboxylate 2e. Yield: 85%. Mp (EtOH): 223–225°C. IR (KBr): 3395, 3357, 1673 cm^{-1}. ^{1}H NMR (DMSO): 0.7 (t, 3H, J=7 Hz, CH_3), 3.8 (q, 2H, J=7 Hz, CH_2), 5.6 (s, 1H, H(4)), 6.7–7.5 (m, 10H, Ph, thienyl, and NH_2). ^{13}C NMR (DMSO): 13.6, 47.4, 53.2, 58.2, 98.1, 123.1, 124.5, 126.5, 126.8, 127.2, 128.1, 150.4, 155.1, 160.0, 165.6. Anal. Calcd for $C_{17}H_{17}N_3O_2S$ (327.40): C, 62.37; H, 5.23; N, 12.84. Found: C, 62.27; H, 4.88; N, 12.65.

4.3.3. Reactions between the 2-amino-1,4-DHPMs 2a–e and 3-formylchromone 4 in ethanol. A mixture of ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylate **2** (1.5 mmol) and 3-formylchromone **4** (0.27 g, 1.5 mmol) in ethanol was heated under reflux for 4 h. After cooling, the precipitate was filtered and recrystallized. Compounds (Yield): **5a** (70%), **5b** (80%), **5c** (80%), **5d** (80%), **5e** (60%).

4.3.4. Reactions between the 2-amino-1,4-DHPMs 2a–e and 3-formylchromone 4 under microwave irradiation. A mixture of ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylate **2** (1.5 mmol) and 3-formylchromone **4** (0.27 g, 1.5 mmol) was irradiated for 20 min in a domestic microwave oven (Whirlpool AKL260, 400 W). The solid was recrystallized. Yields exceed 95%.

4.3.5. Ethyl 7-(2-hydroxybenzoyl)-2,4-diphenyl-2*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate 5a. Mp (EtOH): 225–226°C. IR (KBr): 3500–2500, 1697, 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.7 (t, 3H, J=7 Hz, CH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 5.4 (s, 1H, H(2)), 5.9 (s, 1H, H(6)), 6.0 (s, 1H, H(8)), 7.0–8.0 (m, 15H, Ar, and OH). ^{13}C NMR ($CDCl_3$): 13.5, 57.4, 60.2, 82.9, 103.3, 108.6, 119.2, 122.3, 124.1, 127.4, 127.6, 128.3, 128.5, 129.2, 130.2, 135.0, 135.7, 139.5, 140.2, 141.4, 146.9, 149.1,

155.9, 164.8, 179.6. Anal. Calcd for $C_{29}H_{23}N_3O_4$ (477.52): C, 72.94; H, 4.86; N, 8.80. Found: C, 72.63; H, 4.85; N, 8.35.

4.3.6. Ethyl 7-(2-hydroxybenzoyl)-4-(4-methylphenyl)-2-phenyl-2*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate 5b. Mp (EtOH): 223–224°C. IR (KBr): 3500–2500, 1687, 1669 cm^{-1}. ^1H NMR ($CDCl_3$): 0.8 (t, 3H, J=7 Hz, CH_3), 2.3 (s, 3H, $ArCH_3$), 3.8 (q, 2H, J=7 Hz, CH_2), 5.4 (s, 1H, H(2)), 5.9 (s, 1H, H(6)), 6.0 (s, 1H, H(8)), 7.0–8.0 (m, 14H, Ar, and OH). ^{13}C NMR ($CDCl_3$): 14.0, 21.8, 57.7, 60.7, 83.4, 104.0, 109.2, 118.6, 123.1, 124.7, 127.9, 128.2, 128.8, 129.1, 130.4, 130.7, 135.6, 136.3, 137.1, 139.7, 141.6, 147.1, 149.6, 156.5, 165.4, 180.2. Anal. Calcd for $C_{30}H_{25}N_3O_4$ (491.54): C, 73.31; H, 5.13; N, 8.55. Found: C, 73.26; H, 5.36; N, 8.88.

4.3.7. Ethyl 7-(2-hydroxybenzoyl)-4-(4-methoxyphenyl)-2-phenyl-2*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate 5c. Mp (EtOH): 222–224°C. IR (KBr): 3500–2500, 1689, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): 0.8 (t, 3H, J=7 Hz, CH_3), 3.8 (s, 3H, OCH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 5.4 (s, 1H, H(2)), 5.8 (s, 1H, H(6)), 6.0 (s, 1H, H(8)), 6.8–8.0 (m, 14H, Ar, and OH). ^{13}C NMR ($CDCl_3$): 13.4, 55.3, 56.9, 60.6, 84.2, 103.5, 108.5, 114.5, 117.2, 123.0, 124.1, 127.4, 128.2, 128.4, 128.7, 128.9, 130.1, 131.5, 135.0, 135.7, 146.0, 148.9, 155.8, 160.2, 164.9, 179.6. Anal. Calcd for $C_{30}H_{25}N_3O_5$ (507.55): C, 71.00; H, 4.97; N, 8.28. Found: C, 70.67; H, 5.08; N, 7.98.

4.3.8. Ethyl 4-(4-chlorophenyl)-7-(2-hydroxybenzoyl)-2-phenyl-2*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate 5d. Mp (EtOH): 228–229°C. IR (KBr): 3500–2500, 1685, 1669 cm^{-1}. ^1H NMR ($CDCl_3$): 0.8 (t, 3H, J=7 Hz, CH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 5.4 (s, 1H, H(2)), 5.9 (s, 1H, H(6)), 6.0 (s, 1H, H(8)), 7.0–8.0 (m, 14H, Ar, and OH). ^{13}C NMR ($CDCl_3$): 13.4, 56.7, 60.3, 82.7, 103.0, 108.6, 117.9, 122.6, 123.9, 127.4, 128.1, 128.5, 128.9, 129.4, 130.2, 135.0, 135.1, 135.8, 137.9, 140.0, 147.2, 148.7, 155.8, 164.7, 179.4. Anal. Calcd for $C_{29}H_{22}ClN_3O_4$ (511.97): C, 68.04; H, 4.33; N, 8.21. Found: C, 67.95; H, 4.54; N, 8.29.

4.3.9. Ethyl 7-(2-hydroxybenzoyl)-2-phenyl-4-thienyl-2*H*-pyrimido[1,2-*a*]pyrimidine-3-carboxylate 5e. Mp (EtOH): 254–257°C. IR (KBr): 3500–2500, 1696, 1666 cm^{-1}. ^1H NMR ($CDCl_3$): 0.8 (t, 3H, J=7 Hz, CH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 5.4 (s, 1H, H(2)), 6.0 (s, 1H, H(8)), 6.2 (s, 1H, H(6)), 6.9–7.9 (m, 13H, Ar, thienyl, and OH). ^{13}C NMR ($CDCl_3$): 13.5, 52.8, 60.3, 82.8, 103.4, 108.7, 118.1, 122.6, 124.0, 126.6, 126.7, 126.9, 127.4, 128.2, 128.5, 130.2, 135.1, 135.7, 140.0, 142.1, 147.5, 148.6, 155.9, 164.6, 179.4. Anal. Calcd for $C_{27}H_{21}N_3O_4S$ (483.54): C, 67.07; H, 4.38; N, 8.69. Found: C, 67.19; H, 4.02; N, 8.67.

4.3.10. Reactions between the 2-amino-1,4-DHPMs 2a–e and diethyl (ethoxymethylene)malonate 7 in ethanol. A mixture of ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylate **2** (1.5 mmol) and diethyl (ethoxymethylene)malonate **7** (0.32 g, 0.30 mL, 1.5 mmol) in ethanol (10 mL) was heated under reflux for 8 h. After evaporation of the solvent, the residue was recrystallized. Compounds (Yield): **8a** (50%), **8b** (50%), **8c** (45%), **8d** (60%), **8e** (40%).

4.3.11. Reactions between the 2-amino-1,4-DHPMs 2a–e and diethyl (ethoxymethylene)malonate 7 under microwave irradiation. A mixture of ethyl 2-amino-4-aryl-1,4-dihydro-6-phenylpyrimidine-5-carboxylate **2** (1.5 mmol) and diethyl (ethoxymethylene)malonate **7** (0.32 g, 0.30 mL, 1.5 mmol) was irradiated for 10 min in a domestic microwave oven (Whirlpool AKL260, 400 W). The solid was recrystallized. Yields exceed 95%.

4.3.12. Diethyl 6,9-dihydro-6-oxo-2,4-diphenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate 8a. Mp (CH_3CN): 241–243°C. IR (KBr): 3400–2400 (br), 1718, 1708, 1664 cm^{-1}. ^1H NMR ($CDCl_3$): 0.9 (t, 3H, J=7 Hz, CH_3), 1.4 (t, 3H, J=7 Hz, CH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 4.3 (q, 2H, J=7 Hz, CH_2), 6.7 (s, 1H, H(8)), 7.0 (s, 1H, H(4)), 7.3–7.7 (m, 11H, Ar, and NH). ^{13}C NMR ($CDCl_3$): 13.6, 14.5, 52.7, 60.6, 60.7, 104.3, 110.1, 127.7, 128.5, 128.7, 128.9, 130.6, 133.2, 139.7, 145.2, 151.5, 156.5, 157.8, 163.2, 163.6. Anal. Calcd for $C_{25}H_{23}N_3O_5$ (445.47): C, 67.41; H, 5.20; N, 9.43. Found: C, 67.04; H, 5.11; N, 9.29.

4.3.13. Diethyl 6,9-dihydro-4-(4-methylphenyl)-6-oxo-2-phenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate 8b. Mp (CH_3CN): 255–257°C. IR (KBr): 3400–2500 (br), 1720, 1705, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): 0.9 (t, 3H, J=7 Hz, CH_3), 1.4 (t, 3H, J=7 Hz, CH_3), 2.3 (s, 3H, $Ar-CH_3$), 3.9 (q, 2H, J=7 Hz, CH_2), 4.3 (q, 2H, J=7 Hz, CH_2), 6.7 (s, 1H, H(8)), 7.0 (s, 1H, H(4)), 7.2–7.6 (m, 10H, Ar, and NH). ^{13}C NMR ($CDCl_3$): 13.6, 14.5, 21.2, 52.5, 60.6, 60.7, 104.4, 110.0, 127.6, 128.5, 128.6, 129.5, 130.5, 133.2, 136.9, 138.8, 145.0, 151.5, 156.5, 157.8, 163.2, 163.1. Anal. Calcd for $C_{26}H_{25}N_3O_5$ (459.50): C, 67.96; H, 5.48; N, 9.15. Found: C, 67.99; H, 5.28; N, 8.96.

4.3.14. Diethyl 6,9-dihydro-4-(4-methoxyphenyl)-6-oxo-2-phenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate 8c. Mp (CH_3CN): 253–255°C. IR (KBr): 3400–2400 (br), 1715, 1708, 1664 cm^{-1}. ^1H NMR ($CDCl_3$): 0.9 (t, 3H, J=7 Hz, CH_3), 1.4 (t, 3H, J=7 Hz, CH_3), 3.8 (s, 3H, OCH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 4.3 (q, 2H, J=7 Hz, CH_2), 6.7 (s, 1H, H(8)), 7.0 (s, 1H, H(4)), 6.9–7.7 (m, 10H, Ar, and NH). ^{13}C NMR ($CDCl_3$): 13.6, 14.5, 52.3, 55.3, 60.5, 104.4, 110.0, 114.2, 128.5, 128.7, 129.2, 130.5, 131.9, 133.3, 144.9, 151.4, 156.5, 157.7, 159.9, 163.2, 163.6. Anal. Calcd for $C_{26}H_{25}N_3O_6$ (475.50): C, 65.68; H, 5.30; N, 8.84. Found: C, 65.55; H, 5.14; N, 8.66.

4.3.15. Diethyl 6,9-dihydro-4-(4-chlorophenyl)-6-oxo-2-phenyl-4*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate 8d. Mp (CH_3CN): 263–265°C. IR (KBr): 3400–2450 (br), 1715, 1708, 1664 cm^{-1}. ^1H NMR ($CDCl_3$): 0.9 (t, 3H, J=7 Hz, CH_3), 1.3 (t, 3H, J=7 Hz, CH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 4.3 (q, 2H, J=7 Hz, CH_2), 6.7 (s, 1H, H(8)), 7.0 (s, 1H, H(4)), 7.2–7.6 (m, 10H, Ar, and NH). ^{13}C NMR ($CDCl_3$): 13.6, 14.5, 52.4, 60.6, 103.9, 110.3, 128.4, 128.7, 129.1, 129.2, 130.7, 133.1, 134.8, 138.3, 145.3, 151.4, 156.2, 157.9, 163.1, 163.5. Anal. Calcd for $C_{25}H_{22}ClN_3O_5$ (479.92): C, 62.57; H, 4.62; N, 8.76. Found: C, 62.83; H, 4.64; N, 8.37.

4.3.16. Diethyl 6,9-dihydro-6-oxo-2-phenyl-4-(2-thienyl)-4*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate 8e. Mp (EtOH): 225–227°C. IR (KBr): 3400–2400 (br), 1716, 1703, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): 0.9 (t, 3H, J=7 Hz, CH_3), 1.4 (t, 3H, J=7 Hz, CH_3), 3.9 (q, 2H, J=7 Hz, CH_2), 4.3 (q, 2H, J=7 Hz, CH_2), 6.7 (s, 1H, H(8)), 7.3 (s, 1H, H(4)), 7.0–7.6 (m, 9H, Ph, thienyl, and NH). ^{13}C NMR ($CDCl_3$): 13.7, 14.5, 47.6, 60.8, 103.9, 110.1, 126.0, 127.2, 127.4, 128.5, 128.7, 130.7, 133.0, 142.0, 145.8, 151.0, 156.4, 157.8, 163.2, 163.3. Anal. Calcd for $C_{23}H_{21}N_3O_5S$ (451.50): C, 61.19; H, 4.69; N, 9.31. Found: C, 61.15; H, 5.05; N, 9.27.

References

1. (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963. (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, in press.
2. (a) Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satoh, F.; Morita, M.; Noguchi, T. *J. Med. Chem.* **1989**, *32*, 2399–2406. (b) Atwal, K. S.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. *J. Med. Chem.* **1990**, *33*, 1510–1515. (c) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629–2635. (d) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806–811.
3. (a) Bossert, F.; Meyer, H.; Wehinger, E. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762–769. (b) Goldmann, S.; Stoltefuss, J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1559–1578.
4. (a) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819–7822. (b) Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 49–51.
5. (a) Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799–1803. (b) Stadler, A.; Kappe, C. O. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1363–1368.
6. Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828–3839.
7. (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182–1188. (b) Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512–1519. (c) McDonald, A. I.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 1520–1528.
8. Milcent, R.; Malanda, J.-C.; Barbier, G.; Vaissermann, J. *J. Heterocycl. Chem.* **1997**, *34*, 329–336.
9. (a) Ghosh, C. K.; Mukhopdhyay, K. K. *J. Indian Chem. Soc.* **1978**, *55*, 52–55. (b) Ghosh, C. K.; Mukhopdhyay, K. K. *J. Indian Chem. Soc.* **1978**, *55*, 386–388. (c) Ito, K.; Maruyama, J. *J. Heterocycl. Chem.* **1988**, *25*, 1681–1687. (d) Sabitha, G. *Aldrichim. Acta* **1996**, *29*, 15–25.
10. Informations about microwave-mediated organic synthesis may be found, i.e. on the following web sites:http://www-ang.kfunigraz.ac.at/~kappeco; http://www.umh.ac.be/~orgafs.
11. Pouchert, C. J.; Behnke, J. *The Aldrich library of ^1H and ^{13}C FT NMR spectra*; Aldrich Chemical: Milwaukee (MI, USA), 1992.
12. Altamore, A.; Cascarano, G.; Giacovazzo, C.; Virerbo, D. *Acta Crystallogr.* **1991**, *A47*, 744–748.
13. Straver, L.; Schierbeek, A. J.; MolEN. Structure determination system. Nonius B.V. **1994**.