Polymer-assisted synthesis of ethyl 2-amino-4,6-diarylpyrimidine-5-carboxylates

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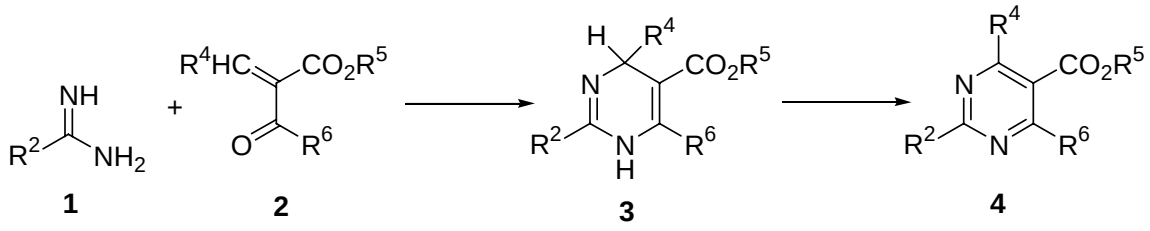
Abstract
Nine novel ethyl 2-amino-4,6-diarylpyrimidine-5-carboxylates have been synthesized in modest to good yields by a five-step procedure that involves building of the heterocyclic moiety on a solid support derived from Merrifield's resin and final displacement with an amine.

Keywords: Biginelli compounds, Merrifield's resin, oxidation, pyrimidine, solid-phase synthesis

Introduction

Recently we focused our attention on derivatives of pyrimidine-5-carboxylic acid, [1] some of them exhibiting antihypertensive, [2] antiviral, [3] antianoxis, [4] and antilipid peroxidation [4] activities. In addition, this cyclic system can be found in the crambine alkaloids.[5] Such subtances (**4**, Scheme 1) are readily available by the Atwal modification [6] of the Biginelli [7] multi-component reaction, *i.e.* interaction between an amidine-like compound **1** and a 2-alkylidene-3-ketoester **2**, followed by an oxidation of the intermediate 1,4 dihydropyrimidine **3**.



Scheme 1. Preparation of derivatives of pyrimidine-5-carboxylic acid.

Among the pyrimidines **4**, products bearing an amino group in position 2 (R^2 = -NRR') are poorly described in the literature probably because of the lack of straightforward synthetic methods. Indeed, the amino moiety can be introduced during the ring formation process with an appropriate guanidine (**1**, R^2 = -NRR') but the approach is of restricted interest because of the limited availability of substituted guanidines. The amino moiety can also be introduced by displacement of a good leaving group with an amine after construction of the heterocycle **3** or **4**. However, to the best of our knowledge, that strategy has been seldom exploited to access the title compounds. In this paper we wish to report on the preparation of the target substances from alkyl 2-(alkylthio)pyrimidine-5-carboxylates bound to a solid support through the thio group, reasoning that an aminolysis reaction could effect the cleavage from the polymer while inducing the expected functionalities in position 2.

Results and Discussion

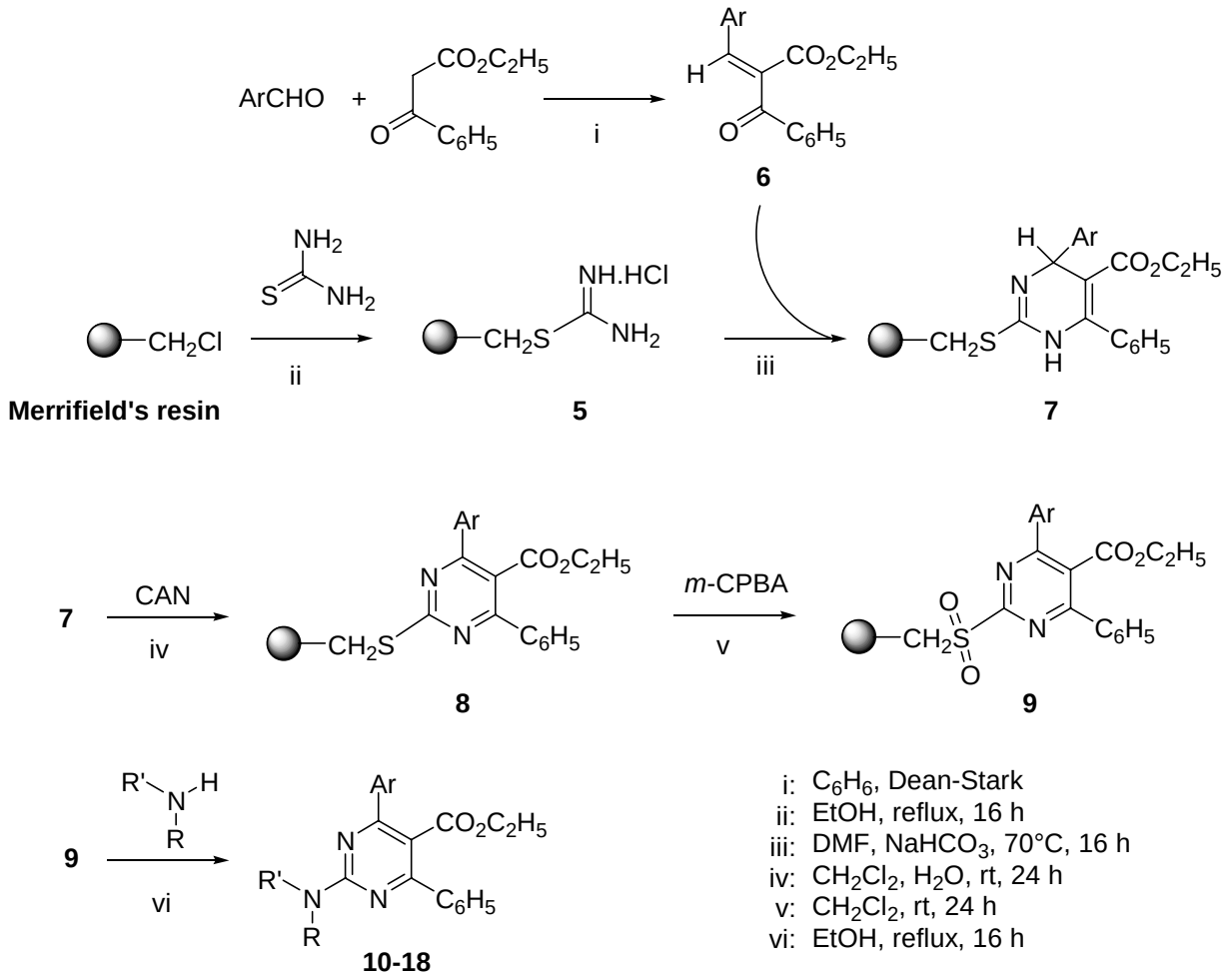
Our strategy (Scheme 2) started by the modification of the Merrifield's resin into **5** by reaction with thiourea. Condensation of **5** with a pre-formed [8] ethyl 3-aryl-2-benzoylpropenoate (**6**) gave the polymer-supported 1,4-dihydropyrimidine **7**, which was oxidized by treatment with ceric ammonium nitrate [1a, 9] to afford **8**. The formation of the polymer-bound compounds was followed on line by infrared spectroscopy. Disappearance [10] of the C-Cl band at 1264 cm^{-1} and appearance of a broad absorption [11] around 3435 cm^{-1} are indicative for the fixation of the thiourea. The presence of a carbonyl peak at 1680 cm^{-1} suggests the incorporation of the ester moiety (in **7**) and that band is shifted to 1720-1730 cm^{-1} in the corresponding aromatic derivative (**8**). Inspection of the infrared spectra revealed that construction of the 1,4-dihydropyrimidine system on the polymer was the crucial step that determined the overall yield. We also observed that reacting together the solid **5**, an aldehyde, and a β-ketoester (the Hideg modification [12] of the Biginelli synthesis) was a less attractive method, as formation of by-products in solution occurred more rapidly than the interaction with the solid reagent.

Disappointingly, we found that displacement of the alkylthio group in **8**, by an amine, was a slow process. Therefore, we turned towards the concept described by Obrecht [11, 13] who suggested transforming the alkylthio group into the more labile sulfone by treatment with *meta*-chloroperoxybenzoic acid. It was not possible to convert **7** into **9** directly, thus justifying the use of two oxidants. Finally, the cleavage from the resin was readily accomplished with various aliphatic or aromatic primary and secondary amines in boiling ethanol. Overall yields (not optimized), based on the chlorine content of the Merrifield's resin, ranged from 35 to 75 % as indicated in the Table.

Table. Nature of the substituents in compounds **10** – **18** and overall yields

Cpd	Ar	R	R'	Overall Yield (%) *
10	Ph	Me	Me	75
11	Ph	Ph	H	35
12	Ph	4-Cl-Ph	H	55
13	Ph	4-(Ome)-Ph	H	65
14	Ph	$-(CH_2)_4-$		50
15	Ph	$-(CH_2)_2-O-(CH_2)_2-$		40
16	Ph	But	H	70
17	4-(NO_2)-Ph	Me	Me	65
18	4-(Ome)-Ph	Me	Me	70

*: not optimized.



Scheme 2. Procedure used to prepare compounds **10** – **18**.

Conclusions

In this paper we present our preliminary results on a simple strategy to access the title compounds. From these results, it can be anticipated that the sequence might be suitable for a combinatorial approach. Indeed substituents R^4 and R^6 could be independently modified, as well as the nature of the ester group (R^5). However, to reach that goal, each step remains to be carefully optimized, and particular attention must be dedicated to the construction of the 1,4-dihydropyrimidine skeleton on the support, as, in our hands, that reaction appeared to be highly sensitive to small variations in the experimental conditions.

Experimental Section

General Procedures. ^{1}H and ^{13}C NMR spectra were obtained using 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 1760K spectrometer. Melting points (not corrected) were determined on a Electrothermal 9100 apparatus. Solvents are commercially available (Aldrich Co, Acros Organics) and were used without further purification. Yields were calculated on the Cl content of the Merrifield's resin. Elemental analyses were performed at the Station de Haute-Belgique, Libramont-Chevigny, Belgium.

Ethyl 2-dimethylamino-4,6-diphenylpyrimidine-5-carboxylate (10). Heating under reflux for 16 h a mixture of Merrifield's resin (5 g; 2.0 meq of chlorine per g) and thiourea (3,8 g; 50 mmol) in ethanol (40 mL) yielded **5** (IR: 3435; 1635; 1418; 1019; 754 cm^{-1}). Heating under reflux for 24 h a mixture of **5**, ethyl 3-aryl-2-benzoylpropenoate [8] (**6**; 40 mmol), and sodium hydrogenocarbonate (3.36 g; 40 mmol) in DMF (50 mL) yielded **7** (Ar = Ph, IR: 3285; 1679; 1490; 1446; 1068 cm^{-1}). An aqueous solution (40 mL) of ceric ammonium nitrate (21.92 g; 40 mmol) was slowly added to a suspension of **7** in dichloromethane (20 mL); stirring the mixture at rt for 16 h yielded **8** (Ar = Ph, IR: 1723; 1510; 1489; 1211; 1055 cm^{-1}). Stirring at rt for 24 h a mixture of **8** and *m*-CPBA (6.90 g; 40 mmol) in dichloromethane (50 mL) yielded **9** (Ar = Ph, IR: 1728; 1536; 1221; 1119; 695 cm^{-1}). A mixture of **9** and N,N-dimethylamine (40% in water, 6.3 mL; 50 mmol) in ethanol (10 mL) was heated under reflux for 16 h. After filtration, the solvents were removed under reduced pressure and the residue was recrystallized from a mixture of ethanol and water (3/1) to afford **10**. M.p.: 172-4 °C. IR (KBr): 3060; 2979; 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.89 (t, J = 7 Hz, 3 H); 3.29 (s, 6 H); 3.96 (q, J = 7 Hz; 2 H); 7.42 (m, 6 H); 7.67 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): 13.3; 31.0; 61.2; 114.9; 128.0; 128.3; 129.9; 139.1; 161.4; 166.3; 169.2 ppm.
$C_{21}H_{21}N_3O_2$, 347.41, calc. C, 72.60; H, 6.09; N, 12.10. Found C, 72.09; H, 6.11; N, 11.98.

Ethyl 2-phenylamino-4,6-diphenylpyrimidine-5-carboxylate (11) was prepared according to the procedure described for **10**, using aniline for the displacement.
M.p. (EtOH): 172-4 °C. IR (KBr): 3398; 3055; 2980; 1718 cm^{-1}. ^1H NMR ($CDCl_3$): 0.91 (t, J = 7 Hz, 3 H); 4.00 (q, J = 7 Hz, 2 H); 7.02 (t, J = 11 Hz, 1 H); 7.30-7.51 (m, 10 H); 7.62-7.78 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): 13.4; 61.5; 117.3; 119.1; 128.1; 128.4; 128.8; 129.8; 138.1; 139.1; 158.9; 166.1; 168.6 ppm. $C_{25}H_{21}N_3O_2$, 395.46, calc. C, 75.90; H, 5.35; N, 10.63. Found C, 75.57; H, 5.40; N, 10.98.
Ethyl 2-(4-chlorophenyl)amino-4,6-diphenylpyrimidine-5-carboxylate (12) was prepared according to the procedure described for **10**, using 4-chloroaniline for the displacement.
M.p. ($EtOH/H_2O$ – 2/1): 226-8 °C. IR (KBr): 3404; 3066; 2984; 1716 cm^{-1}. ^1H NMR ($CDCl_3$): 0.91 (t, J = 7 Hz, 3 H); 3.99 (q, J = 7 Hz, 2 H); 7.30-7.53 (m, 8 H); 7.69 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): 13.4; 61.6; 117.6; 120.4; 127.4; 128.1; 128.4; 128.7; 129.9; 137.7; 137.9; 158.7; 166.1; 168.5 ppm. $C_{25}H_{20}ClN_3O_2$, 429.91, calc. C, 69.85; H, 4.69; N, 9.78. Found C, 70.09; H, 4.41; N, 10.08.
Ethyl 2-(4-methoxyphenyl)amino-4,6-diphenylpyrimidine-5-carboxylate (13) was prepared according to the procedure described for **10**, using 4-methoxyaniline for the displacement.
M.p. (EtOH): 186-7 °C. IR (KBr): 3399; 3057; 2979; 1714 cm^{-1}. ^1H NMR ($CDCl_3$): 0.90 (t, J = 7 Hz, 3 H); 3.80 (s, 3 H); 3.98 (q, J = 7 Hz, 2 H); 6.89 (d, J = 11 Hz, 2 H); 7.38-7.53 (m, 8 H); 7.60-7.76 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): 13.4; 55.4; 61.4; 114.0; 116.9; 121.2; 128.1; 128.3; 129.7; 132.3; 138.3; 155.4; 159.2; 166.2; 168.7 ppm. $C_{26}H_{23}N_3O_2$, 425.49, calc. C, 73.39; H, 5.45; N, 9.88. Found C, 73.09; H, 5.11; N, 9.98.
Ethyl 4,6-diphenyl-2-(pyrrolidin-1-yl)pyrimidine-5-carboxylate (14) was prepared according to the procedure described for **10**, using pyrrolidine for the displacement.
M.p. ($EtOH/H_2O$ - 3/2): 248-50 °C. IR (KBr): 3061; 2977; 1715 cm^{-1}. ^1H NMR ($CDCl_3$): 0.89 (t, J = 7 Hz, 3 H); 2.01 (m, 4 H); 3.71 (m, 4 H); 3.92 (q, J = 7 Hz, 2 H); 7.42 (m, 6 H); 7.65 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): 13.7; 25.7; 47.1; 61.4; 114.1; 128.3; 128.4; 129.6; 139.4; 159.6; 166.0; 169.7 ppm. $C_{23}H_{23}N_3O_2$, 373.45, calc. C, 73.97; H, 6.21; N, 11.25. Found C, 74.22; H, 6.18; N, 11.57.
Ethyl 2-(morpholin-4-yl)-4,6-diphenylpyrimidine-5-carboxylate (15) was prepared according to the procedure described for **10**, using morpholine for the displacement.
M.p. ($EtOH/H_2O$ - 1/1): 232-4 °C. IR (KBr): 3065; 2980; 1717 cm^{-1}. ^1H NMR ($CDCl_3$): 0.94 (t, J = 7 Hz, 3 H); 3.77 (m, 4 H); 3.94 (m, 8 H); 7.44 (m, 6 H); 7.63 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): 13.4; 44.2; 61.3; 66.9; 114.9; 128.1; 128.2; 129.5; 138.7; 160.4; 165.8; 169.1 ppm. $C_{23}H_{23}N_3O_3$, 389.45, calc. C, 70.93; H, 5.95; N, 10.79. Found C, 70.58; H, 6.23; N, 11.05.
Ethyl 2-butylamino-4,6-diphenylpyrimidine-5-carboxylate (16) was prepared according to the procedure described for **10**, using butylamine for the displacement.
M.p. ($EtOH/H_2O$ - 1/1): 198-9 °C. IR (KBr): 3397; 3065; 2980; 1717 cm^{-1}. ^1H NMR ($CDCl_3$): 0.87 (t, J = 7 Hz, 3 H); 0.96 (t, J = 7 Hz, 3 H); 1.33-1.76 (m, 4 H); 3.53 (t, J = 7 Hz, 2 H); 3.96 (q, J = 7 Hz, 2 H); 7.42 (m, 6 H); 7.62 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): 13.4; 13.8; 20.0; 31.7;

41.0; 61.2; 115.2; 128.0; 128.2; 129.5; 138.6; 161.4; 166.4; 169.0 ppm. $C_{23}H_{25}N_3O_2$, 375.47, calc. C, 73.58; H, 6.71; N, 11.19. Found C, 73.25; H, 6.51; N, 11.58.

Ethyl 2-dimethylamino-4-(4-nitrophenyl)-6-phenylpyrimidine-5-carboxylate (17) was prepared according to the procedure described for **10**, using 4-nitrobenzaldehyde as the aldehyde component and dimethylamine for the displacement.

M.p. (EtOH): 275-7 °C. IR (KBr): 3068; 2980; 1719; 1519; 1345 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92 (t, J = 7 Hz, 3 H); 3.31 (s, 6 H); 3.94 (q, J = 7 Hz, 2 H); 7.47 (m, 3 H); 7.62 (m, 2 H); 7.80 (d, J = 11 Hz, 2 H); 8.24 (d, J = 11 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): 13.4; 37.0; 61.4; 113.4; 123.3; 128.2; 128.3; 129.3; 129.6; 138.7; 145.3; 148.2; 160.9; 163.7; 166.4; 168.8 ppm. $C_{21}H_{20}N_4O_4$, 392.41, calc. C, 64.28; H, 5.14; N, 14.28. Found C, 64.12; H, 5.11; N, 14.49.

Ethyl 2-dimethylamino-4-(4-methoxyphenyl)-6-phenylpyrimidine-5-carboxylate (18) was prepared according to the procedure described for **10**, using 4-methoxybenzaldehyde as the aldehyde component and dimethylamine for the displacement.

M.p. (EtOH): 158-9 °C. IR (KBr): 3054; 2969; 1714 cm^{-1}. ^1H NMR ($CDCl_3$): 0.92 (t, J = 7 Hz, 3 H); 3.31 (s, 6 H); 3.85 (s, 3 H); 3.97 (q, J = 7 Hz, 2 H); 6.96 (d, J = 11 Hz, 2 H); 7.38-7.47 (m, 3 H); 7.60-7.69 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): 13.8; 37.2; 55.6; 61.4; 113.6; 113.8; 128.4; 129.5; 130.1; 131.6; 139.5; 161.0; 161.3; 165.1; 165.8; 170.1 ppm. $C_{22}H_{23}N_3O_3$, 377.44, calc. C, 70.01; H, 6.14; N, 12.72. Found C, 69.84; H, 6.11; N, 11.96.

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