ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA

VOL. LVIII, 7 SECTIO AA 2003

Synthesis of pyrimido[4,5-d]pyrimidine derivatives

J. Cieplik
Department of Organic Chemistry, Medical Academy,
Grodzka 9, 50-137 Wrocław, Poland

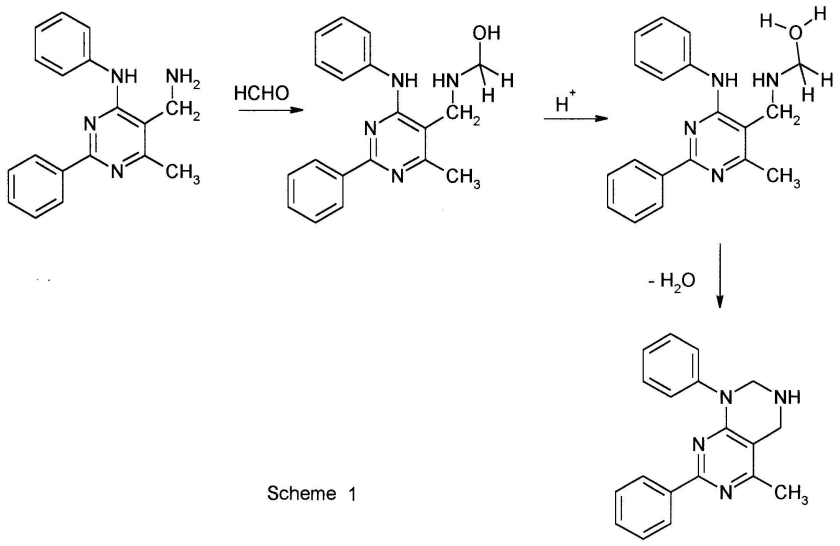
The paper presents synthesis of pyrimido[4,5-d]pyrimidine derivatives where identical structures have been obtained by different methods

1. INTRODUCTION

Our earlier works on synthesis and biological properties of the pyrimidine ring proved that this system is extremely biologically active. The derivatives prepared showed both cytostatic (1,2), immunomodulative (3,4) and, above all, antibacterial (5,6,7,8) properties. Therefore, it was advisable to carry out a number of syntheses in order to prepare pyrimidopyrimidine derivatives and to subject them to microbiological examinations. During synthesis of new pyrimidine derivatives it was found quite unexpectedly that the pyrimido[4,5-d] pyrimidine **3** system may be prepared by two independent different methods.

2. SYNTHESIS

In our studies the substrate was 6-methyl-2-phenyl-4-phenylamino-5-chloromethylpyrimidine (**1**) which was treated with 25% aqueous NH_4OH solution yielding 2-phenyl-4-phenylamino-6-methyl-5-aminomethylpyrimidine (**2**) (9). 4,5-Diaminoderivative of pyrimidione (**2**) prepared was cyclized with 40% aqueous formaldehyde solution and THF. According to the hypothetical mechanism of the Mannich reaction a cyclization process to 5-methyl-1,7-diphenyl-1,2,3,4-tetrahydropyrimido [4,5-d]pyrimidine occurred. An identical result was obtained by treating compound **2** with ethyl orthoformate (scheme 1).



Scheme 1

Treating compound 1 (4) with suitable aliphatic and aromatic amines yielded 5-alkylderivatives and 5-arylderivatives of pyrimidine which have been later cyclized according to the Mannich reaction to form new pyrimido[4,5-d] pyrimidine derivatives **6,7** (scheme 2).

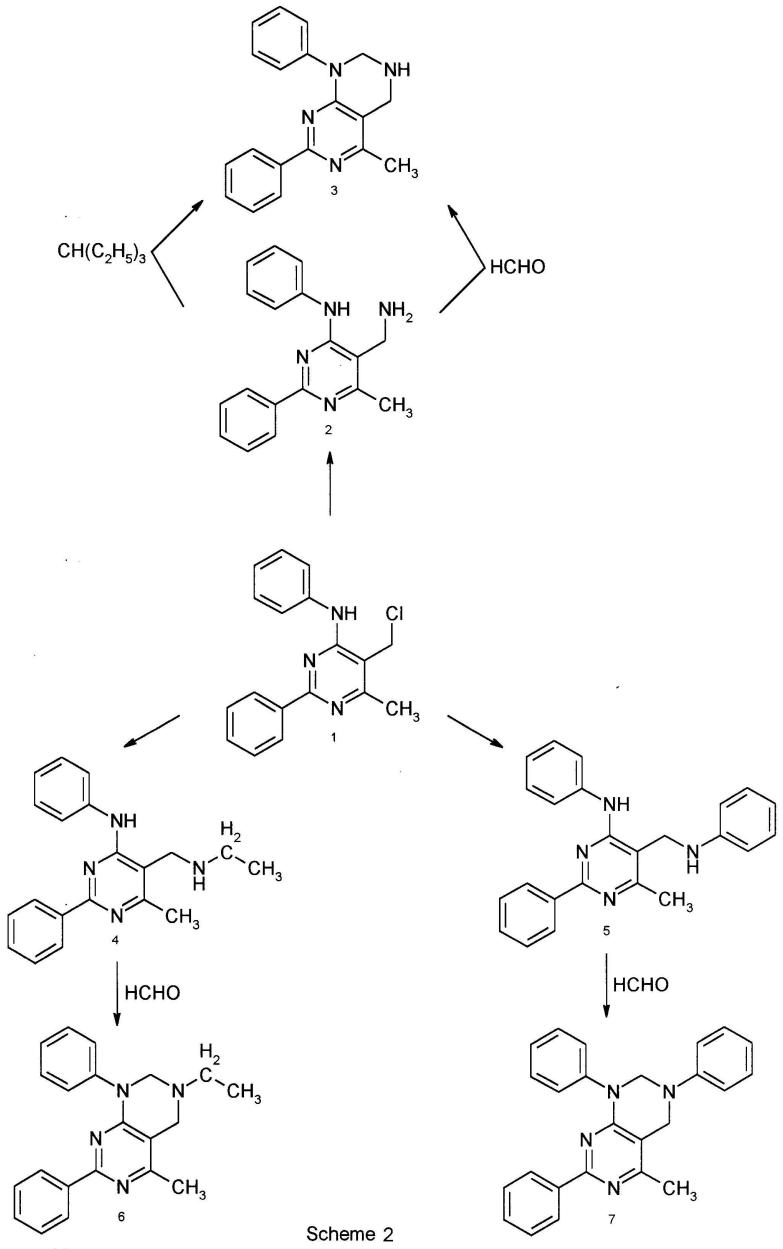
Melting points were determined in Köfler apparatus.

^{1}H NMR spectra were recorded on BS-487-C-80 Mhz Tesla spectrometer. Infra-red (IR) spectra were recorded in nujol with a Specord spectrophotometer, at Elemental Laboratory of Medical Academy in Wrocław. Elemental analises indicated by the symbols were within +/- 0.4 of the theoretical volues.

1,7-Diphenyl-5-methyl -1,2,3,4-tetrahydropyrimido[4,5-d]pyrimidine (3)

(Method I). 4 g (0.014 mole) of 5-aminomethyl-6-methyl-2-phenyl-4-phelaminopyrimidine (**2**) was dissolved in 50 ml of THF and treated with 20 ml of 40% aqueous formaldehyde solution and 1 ml HCl. The mixture was heated under reflux for 7 hours. Then the reaction mixture was cooled down and poured into 100 ml H_2O.

The aqueous solution was neutralized with NH_4OH and extracted three times with chloroform. Chloroform extracts were combined and dry with anhydrous magnesium sulphate. The oily mixture was purified in a chromatographic column with chloroform and the Rf 9/10 fraction was collected.



Scheme 2

The yield was 3.5 g (84.0 %), o t.t. 225-227 ^{0}C.
$C_{19}H_{18}N_4$ (302)
Calc. C 75.50 % H 5.96 % N 18.54 %
Found. 75.52 5.82 18.62
I.R. (KBr): ν 3550 cm^{-1} (NH), 1275 cm^{-1} (NH).
^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.12 (s, 1H NH), 1.55 (s, 3H CH_3), 2.85-2.90 (s, 4 H CH_2, CH_2), 7.20-8.55 (m, 10 H aromat).

1,7-Diphenyl-5-methyl -1,2,3,4-tetrahydropyrimido[4,5-d]pyrimidine (3)

(Method II). 4 g (0.014 mole) of 5-aminomethyl-6-methyl-2-phenyl-4-phenylaminopyrimidine (**2**) was mixed with 50 ml of ethyl orthoformate. Then the reaction mixture was cooled down and poured into 100 ml H_2O. The aqueous solution was extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. The filtrate was condensed. The oily mixture was purified with chloroform in a chromatographic column and the Rf 9/10 fraction was collected. The yield was 2.9 g (71.1%), o t.t. 225-227 ^{0}C.
$C_{19}H_{18}N_4$ (302)
Calc. C 75.50 H 5.96 N 18.54
Found. 75.82 5.72 18.58
I.R. (KBr): ν 3550 cm^{-1} (NH), 1275 cm^{-1} (NH).
^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.12 (s, 1H NH), 1.55 (s, 3H CH_3), 2.85-2.90 (s, 4 H CH_2, CH_2), 7.20-8.55 (,m 10 H aromat).

5-Ethylaminomethyl-6-methyl-2-phenyl-4-phenylaminopyrimidine (4).

4 g (0.013 mole) of 5-chloromethyl-6-methyl-2-phenyl-4-phenylaminopyrimidine (**1**) was dissolved in 50 ml THF and treated with 20 ml ethylamine. The mixture was heated under reflux for 3 hours while being vigorously agitated. The the reaction mixture was cooled down and poured into 200 ml of water. The aqueous solution was extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. The filtrate was condensed. The oily residue was purified with chloroform in a chromatographic column and the Rf 6/10 fraction was collected. The yield was 3.1 g (76.2%), m.p.121-123^{0}C.
$C_{20}H_{22}N_4$ (318)
Calc. C 75.47 H 6.91 N 17.61
Found. 75.52 6.82 17.42
I.R. (KBr): ν 3522 cm^{-1} (NH), 1285 cm^{-1} (NH).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.15 (s, 1H NH), 1.25 (t, 3 H CH_3), 1.55 (s, 3H CH_3), 2.60 (q, 2H CH_2), 3.25 (s, 2H CH_2), 3.50 (s, 1H NH), 7.20-8.55 (m, 10 H aromat).

6-Methyl-2-phenyl-4-phenylamino-5-phenylaminomethylpyrimidine (5).

4 g (0.013 mole) of 5-chloromethyl-6-methyl-2-phenyl-4-phenylaminopyrimidine (**1**) was dissolved in 50 ml THF and treated with 20 ml of aniline. The mixture was vigorously agitated while being heated under reflux for 5 hours. Then the reaction mixture was cooled down and poured into 200 ml water. The aqueous solution was extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. The filtrate was condensed. The oily residue was purified with chloroform in a chromatographic column and the Rf 7/10 fraction was collected. The yield was 3.4 g (71,8 %) o t.t. 148-150 ^{0}C.

$C_{24}H_{22}N_4$ (366)

Calc.	C 78.69	H 6.01	N 15.30
Found.	78.52	6.22	15.42

I.R. (KBr): ν 3532 cm^{-1} (NH), 1265 cm^{-1} (NH).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.20 (s, 1H NH), 1.65 (s, 3H CH_3), 3.35 (s 2H CH_2), 3.60 (s, 1H NH), 7.50-8.75 (m, 10 H aromat).

3-Ethyl-1,7-diphenyl-5-methyl-1,2,3,4-tetrahydropyrimido[4,5-d] pyrimidine (6).

4 g (0.013 mole) of 5-Ethylaminomethyl-6-methyl-2-phenyl-4-phenylaminopyrimidine (4) was dissolved in 50 ml of THF and treated with 20 ml of 40% aqueous formaldehyde solution and with 1 ml HCl. The mixture was heated under reflux for 7 hours. Then the reaction mixture was cooled down and poured into 200 ml H_2O. The aqueous solution was neutralized with NH_4OH and extracted three times with 50 ml of chloroform. Chloroform extracts were combined and dried over $MgSO_4$. The filtrate was condensed. The oily mixture was purified with chloroform in a chromatographic column and the Rf 9/10 fraction was collected. The yield was 3.5 g (84.3%), m.p. 104-106^{o}C.

$C_{21}H_{22}N_4$ (330)

Calc.	C 76.36 %	H 6.67 %	N 16.97 %
Found.	76.52	6.82	16.62

I.R. (KBr): ν 3520 cm^{-1} (NH), 1238 cm^{-1} (NH)

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.15 (t, 3H CH_3), 1.55 (s, 3H CH_3), 2.65 (q, 2H CH_2), 2.85-2.90 (s, 4 H CH_2, CH_2), 7.50-8.65 (m, 10 H aromat).

5-Methyl-1,3,7-triphenyl-1,2,3,4-tetrahydropyrimido[4,5-d]pyrimidine (7).

4 g (0.013 mole) of 2,4-diphenyl-6-methyl-5-phenylaminomethyl-pyrimidine (5) was dissolved in 50 ml of THF and treated with 20 ml of 40% aqueous formaldehyde solution and 1 ml HCl. Then mixture was heated under reflux for 7 hours. Then the reaction mixture was cooled down and poured into 200 ml water. The aqueous solution was neutralized with NH_4OH and extracted three time with 50 ml chloroform. Chloroform extracts were combined anddried over $MgSO_4$. The oily mixture was purified with chloroform in a chromatographic column and the Rf 9/10 fraction was collected. The yield was 3.4 g (82.3 %), m.p.168-170^{o}C.

$C_{25}H_{22}N_4$ (378)

Calc.	C 79.36	H 5.82	N 14.81
Found.	79.52	5.86	14.42

I.R. (KBr): ν 3545 cm^{-1} (NH), 1275 cm^{-1} (NH)

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ= 1.55 (s, 3H CH_3), 2.85-2.90 (s, 4 H CH_2, CH_2), 7.50-8.65 (m, 18 H aromat).

REFERENCES

[1] Machoń Z., Cieplik J.: Synthesis of Furo[3,4-d]purimidine Derivatives via Reaction of 4-Methylpyrimidine-5-carboxylic Acids with Thionyl Chloride. Synthesis, **2**,142, 1986.

[2] Machoń Z., Cieplik J.: Synthesis and antineoplastic effects of furo[3,4-d] pyrimidine derivatives. Pol. J. Pharmacol. Pharm. **40**, 201, 1988.

[3] Cieplik J., Machoń Z., Zimecki M., Wieczorek Z.: Synthesis and biological properties of 5-Hydroksymethylpyrimidines. Arch. Imm.-Ther. Exp. , **41**, 11, 1993.

[4] Cieplik J., Machoń Z., Zimecki M., Wieczorek Z.: Synthesis and immunomodulatory activity of 6-methyl-2-phenyl-5-substituted pyrimidines. Il Farmaco **50**, 131, 1995.

[5] Machoń Z., Cieplik J.: Synthesis and antibacterial activity of 2-phenyl- pyrimidine and pyrimidine[1,3]oxazines. Eur. J. Med. Chem-Chim. Ther., **19**, 4, 359, 1984.

[6] Pluta J., Flendrich M., Cieplik J.: Synthesis and biological activity of some pyrimidine derivatives. J. Boll. Chim. Farmaceutico-Anno 1996, **135**, 239, 1996.

[7] Cieplik J., Pluta J., Meler G.: Synthesis and biological investigation of pyrimidine derivatives. Arch. Pharm. Pharm. Med. Chem. **330**, 237, 1997.

[8] Cieplik J., Pluta J., Gubrynowicz O.: Sci Pharm. **68**, 333, 2000.

[9] Cieplik J., Pluta J., Gubrynowicz O.: Sci Pharm. **70**, 245, 2002.

CURRICULUM VITAE

J. Cieplik was born in Kępno Wielkopolskie. There he attended an elementary and later a secondary school. Next, he graduated from the pharmaceutics at the Medical University in Wrocław in 1976, when he started his scientific career at the Institute of Organic Chemistry. There he presented his doctoral dissertation entitled "Synthesis of 2-phenylpyrimidine derivatives with potential biological activities". In 1993 he was offered a scientific scholarship at the Technological University of Vienna, Institute of Organic Chemistry where he worked on the synthesis of quinolone derivatives having antibacterial properties. In 1996 he was granted the first degree of specialization in Pharmaceutics. In 2000 he was awarded a Golden Cross of Merit for his pedagogical work.

He is the author of 17 original papers, 7 review articles, one monographic paper entitled "Biologically active pyrimidines used in therapy" and eight patents. His scientific achievements were presented at several scientific conferences, both at home and abroad. Now he is bringing to an end his dissertation for obtaining a degree of assistant professor entitled "Synthesis and biological properties of pyrimidine and pyrimido[4,5-d]pyrimidine derivatives".