ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA

VOL. LVIII, 8 SECTIO AA 2003

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

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The paper presents synthesis of pyrimido[4,5-d]pyrimidine sulfonamido-derivatives using various methods to reach the final product.

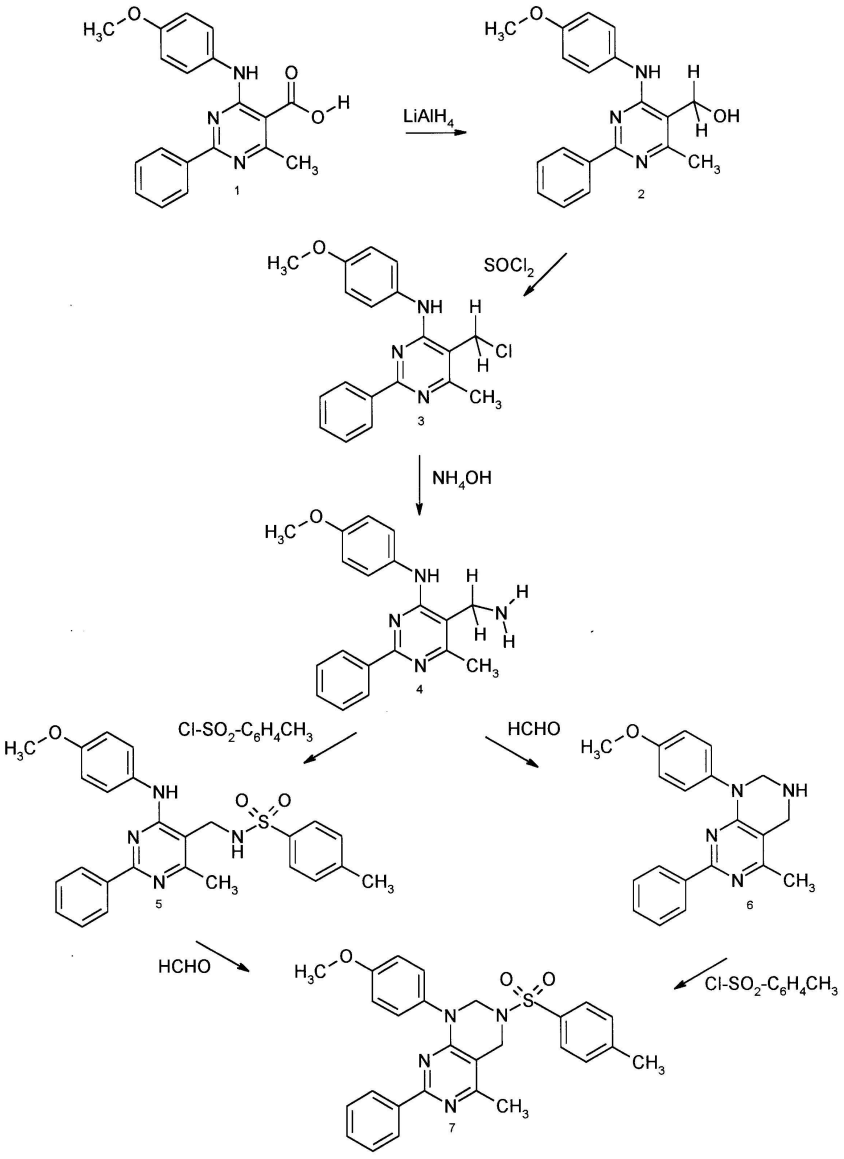
1. INTRODUCTION

Our earlier works on synthesis and biological properties of the pyrimidine ring proved that this system is extremely biologically active. The derivatives prepared showed the 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 to prepare pyrimidopyrimidine derivatives and to subject them to microbiological examinations. On synthesizing new pyrimidine derivatives it was found quite unexpectedly that pyrimido[4,5-d]pyrimidine sulfonamidoderivatives may be prepared by two different independent methods.

2. SYNTHESIS

In our studies the substrate was 6-methyl-4-(4'-methoxyphenylamino)-2-phenyl-5-pyrimidinecarboxylic acid (**1**) (5) which was reduced with lithium aluminium hydride ($LiAlH_4$) yielding 5-hydroxymethyl-6-methyl-4-(4'-methoxyphenylamino)-2-phenylpyrimidine (**2**) (3). Compound 2 was treated with thionyl chloride ($SOCl_2$) yielding 5-chloromethyl-6-methyl-4-(4'-methoxyphenylamino)-2-phenylpyrimidine (**3**), (4). Chloroderivative **3** was heated with 25% ammonia solution yielding 5-aminomethyl-6-methyl-4-(4'-methoxyphenylamino)-2-phenylpyrimidine (**4**) (8). Aminoderivative 4 was condensed with tosyl chloride, yielding 6-methyl-4-(4'-methoxyphenylamino)-5-(4'-methylphenyl)sulfonamidomethyl-2-phenylpyrimidine (**5**) (8). Sulfonamide **5** formed was cyclized in the Mannich reaction to 5-methyl-1-(4'-methoxyphenyl)-7-phenyl-3-N-tosyl-1,2,3,4-tetrahydropyrimido[4,5-d]

pyrimidine (**7**). Compound **7** was prepared by reversing the sequence of the two last synthesis stages: first, aminoderivative **4** was cyclized to the pyrimido[4,5-d]pyrimidine **6** system (9) in the Mannich reaction and then by condensing tosyl chloride with the pyrimido [4,5-d]pyrimidine system, once again compound **7** was obtained.



Scheme 1

3. CHEMIA

Melting points were determined in a Kofler apparatus.

^{1}H NMR spectra were recorded on BS-487-C-60 Mhz Tesla spectrometer. Infrared (IR) apectra were recorded in nujol with Specord-80 Spectrophotometer, at Elemental Laboratory of Medical Academy in Wrocław. Elemental analyses indicated by the symbols were with in +/- 0.4 of the theoretical volues.

5-Hydroxymethyl-4-(4'-Methoxyphenylamino)-6-methyl-2-phenyl-pyrimidine (2)

4 g (0.012 mole) of 4-(4'-methoxyphenylamino)-6-methyl-2-phenyl-5-carboxypyrimidinic acid (**1**) was dissolved in 100 ml THF and treated slowly with portions of lithium aluminium hydride ($LiAlH_4$) until a vigorous reaction stops. After five hours the reaction mixture was poured into 500 ml cold water and extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. The solution was filtered off, condensed and residual recrystallized from methanol, yielding 3.8 g (73.68%) of compound, m.p.153-155^{o}C.

$C_{19}H_{19}N_3O_2$ (321)

Calc.	C 71.03 %	H 5.91 %	N 13.08 %
Found.	71.42	5.52	13.42

I.R. (KBr): ν 3550 cm^{-1} (NH), 1200 cm^{-1} (OH).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ= 1.12 (s 1H CH_3); 1.55 (s, 3H CH_3); 2.90 (s, 2 H CH_2); 3.15 (s, 1H NH); 5.30 (s, 1H OH); 7.10-8.45 (m 13 H aromat).

5-Chloromethyl-4-(4'-methoxyphenylamino)-6-methyl-2-phenylpyrimidine (3)

4 g (0.012 mole) of 5-hydtoxymethyl-4-(4'-methoxyphenylamino)-6-methyl-2-phenylpyrimidine (**2**) was dissolved in 100 ml benzene and treated slowly with thionyl chloride ($SOCl_2$). The mixture was heated up under reflux for 3 hours. Then the reaction mixture was condensed by distilling off excess $SOCl_2$. The oily residue was recrystallized from $CHCl_3$ yielding 3.9 g (92.8%) of compound, m.p. 217-219^{o}C.

$C_{19}H_{18}N_3OCl$ (339)

Calc.	C 67.26 %	H 5.31%	N 12.39 %	Cl 10.32 %
Found.	67.42	5.52	12.42	10.28

I.R. (KBr): ν 3550 cm^{-1} (NH), 1200 cm^{-1} (NH).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ= 1.12 (s 1H CH_3); 1.55 (s, 3H CH_3); 2.90 (s, 2 H CH_2); 3.15 (s, 1H NH); 7.50-8.65 (m 13 H aromat).

5-Aminomethyl-4-(4'-methoxyphenylamino)-6-methyl-2-phenylpyrimidine (4)

4 g (0.012 mole) of 5-Chloromethyl-4-(4'-methoxyphenylamino)-6-methyl-2-phenylpyrimidine (**3**) was dissolved in 100 ml THF and treated with 50 ml of 25% aqueous NH_4OH solution. The mixture was heated up under reflux for 8 hours. Then the reaction mixture was poured into 100 ml water and extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. Dried solution was filtered off, condensed and purified in a chromatographic column resolving the reaction mixture with chloroform on silica gel 60 (35-70 mesh ASTM) yielding 3.1 g (82.2%) of compound, m.p.123-125°C.

$C_{19}H_{20}N_4O$ (320)

Calc.	C 71.25 %	H 6.25 %	N 17.50 %
Found.	71.42	6.52	17.42

I.R. (KBr): ν 3650 cm^{-1} (NH), 1268 cm^{-1} (NH).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ= 1.22 (s 1H CH_3); 1.45 (s, 3H CH_3); 1.85 (s, 2H NH_2); 2.85 (s, 2 H CH_2); 3.15 (s, 1H NH); 7.55-8.95 (m 13 H aromat).

4-(4'-Methoxyphenylamino)-6-methyl-5-(4'-methylphenyl)sulfamoyl-2-phenylpyrimidine (5)

4 g (0.012 mole) of 5-aminomethyl-4-(4'-methoxyphenylamino)-6-methyl-2-phenylpyrimidine (**4**) was dissolved in 100 ml THF and treated with 2 g of tosyl chloride (p-toluenesulfonic chloride). The mixture was heated up under reflux for 8 hours. Then the reaction mixture was cooled down and poured into 100 ml cold water. The aqueous solution was extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. Dried solution was filtered off, condensed and purified in a chromatographic column resolving the reaction mixture with chloroform on silica gel 60 (35-70 mesh ASTM) yielding 3.5 g (62.6%) of compound, m.p.193-195°C.

$C_{26}H_{26}N_4O_3S$ (474)

Calc.	C 65.82 %	H 5.48 %	N 11.81 %
Found.	65.62	5.52	11.52

I.R. (KBr): ν 3650 cm^{-1} (NH), 1268 cm^{-1} (NH).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.12 (s, 1H Alkil-NH); 1.22 (s 1H CH_3); 1.45 (s, 3H CH_3); 1.60(s, 1H CH_3); 2.85 (s, 2 H CH_2); 3.15 (s, 1H Aryl-NH); 7.55-8.95 (m 13 H aromat).

1-(4'-Methoxyphenyl)-5-methyl-7-phenyl-1,2,3,4-pyrimido[4,5-d]pyrimidine (6)

4 g (0.0012 mol) of 5-aminomethyl-4-(4-methoxyphenylamino)-6-methyl-2-phenylpyrimidine **(4)** was dissolvend in 50 ml THF and treated with 1 ml HCl

and 20 ml of 40% formic aldehyde. The mixture was heated for 5 hours. Later the reaction mixture was cooled down, neutralized with 25% NH_4OH, diluted with 200 ml of distilled water and extracted three times with $CHCl_3$. Chloroform extracts were combined and dried over $MgSO_4$. Dried solution was filtered off, condensed and purified in a chromatographic column resolving the reaction mixture with chloroform on silica gel 60 (35-70 mesh ASTM) yielding 3.4 g (82.6%) crystal of m.p. 185-187 ^{0}C was obtained.

$C_{20}H_{20}N_4O$ (332)

Calc. C 72.29 % H 6.02 % N 16.87 %

Found. 72.52 6.42 16.62

I.R. (KBr): ν 1240 cm^{-1} (NH).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.40 (s, 3H CH_3); 1.65 (s, 3H CH_3); 1.80 (s, 1H NH); 2.85-2.90 (s,s, 2H CH_2, 2 H CH_2); 7.20-8.55 (m 13 H aromat).

1-(4'-Methoxyphenylamino)-5-methyl-3-(4'-methylphenyl)sulfon-7-phenyl-1,2,3,4-pyrimido[4,5-d]pyrimidine (7) (Method I)

4.0 g (0.008 mole) of 4-(4'-methoxyphenylamino)-6-methyl-5-(4'-methylphenyl)sulfamoylmethyl-2-phenylpyrimidine (**5**), (8) was dissolved in 50 ml THF and treated with 2.0 g of tosyl chloride. The mixture was heated up for 8 hours under reflux. Then the reaction mixture was cooled down and poured into 200 ml water. The solution was extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. The filtrate was condensed and purified in a chromatographic column on silica gel 60 (35-70 mesh ASTM) in the chloroform/acetone 3:1 mixture, yielding 2.5 g (60.9 %) związku o t.t. 205-207 ^{0}C.

$C_{27}H_{26}N_4O_3S$ (460)

Calc. C 66.67 % H 5.35 % N 11.52 %

Found. 66.52 5.52 11.42

I.R. (KBr): ν 1140 cm^{-1} (SO_2).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.30 (s, 3H CH_3); 1.55 (s, 3H CH_3); 1.85 (s, 3H CH_3); 2.85-2.90 (s,s, 2H CH_2, 2 H CH_2); 7.20-8.55 (m 13 H aromat).

1-(4'-Methoxyphenylamino)-5-methyl-3-(4'-methylphenyl)sulfon-7-phenyl-1,2,3,4-pyrimido[4,5-d]pyrimidine (7) (Method II)

4 g (0.012 mole) of 1-(4'-methoxyphenylamino)-5-methyl-7-phenyl-1,2,3,4-pyrimidino[4,5-d]pyrimidine (**6**) (9) was dissolved in 100 ml THF and treated with 2 g of tosyl chloride (p-toluenesulfonic chloride). The mixture was heated up under reflux for 8 hours. Then the reaction mixture was cooled down and poured into 200 ml cold water. The aqueous solution was extracted three times with 50 ml chloroform. Chloroform extracts were combined and dried over $MgSO_4$. Dry solution was filtered off, condensed and purified in a

chromatographic column resolving the reaction mixture on silica gel 60 (35-70 mesh ASTM) yielding 3.8 g (64.9%) of compound, m.p.205-207°C.

$C_{27}H_{26}N_4O_3S$ (460)

Calc.	C 66.67 %	H 5.35 %	N 11.52 %
Found.	66.52	5.52	11.42

I.R. (KBr): ν 1140 cm^{-1} (SO_2).

^{1}H-N.M.R.($CDCl_3$/TMS_{int}): δ = 1.35 (s, 3H CH_3); 1.60 (s, 3H CH_3); 1.95 (s, 3H CH_3); 2.85-2.90 (s,s, 2H CH_2, 2 H CH_2); 7.20-8.60 (m 13 H aromat).

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