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# Synthesis of 6-Ami NO-5-Nitro-4-Thi Oxopyri Mi Dines

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SYNTHETIC COMMUNICATIONS, 22(9), 1319-1331 (1992)

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# SYNTHESIS OF 6-AMINO-5-NITRO-4-THIOXOPYRIMIDINES

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*ABSTRACT*: The synthesis of 6-amino-5-nitro-4-thioxopyrimidines starting from the C-adducts of nitroketeneaminals and acyl isothiocyanates is described.

The reaction of C-adducts of enaminic compounds and isothiocyanates to form heterocyclic systems has been often described in the literature. Therefore new methods for the synthesis of isothiazole/1-6/, tiophene/7/ and pyrimidine/2-3,5,8-12/ bearing suitable functional groups have been reported.

Particularly pyrimidine derivatives have been synthesized in high yields from the C-adducts of enaminoesters or enaminoketones on treatment with base

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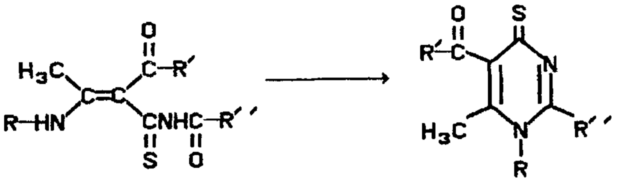

1 2

R = H, $CH_3$, $C_2H_5$, Ph

R′ = $OC_2H_5$, $CH_3$, Ph

R′′ = Ph

FIGURE 1

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or heating in different solvents[2-3,8-11] (FIG. 1), or from the C-adducts of keteneaminals substituted at the β-carbon by the benzoyl group, though in this case longer reaction times are needed and the yields are moderate[5] ( 35-42% ). When the C-adduct is substituted at the β-carbon by a nitro group as in the C-adducts of the nitrovinylamines, the intramolecular cyclization to the pyrimidine ring even occurs with greater difficulty. If acetonitrile is used as solvent, by heating under reflux the nitropyrimidines are obtained in very low yields ( 0,5-17%, from the "in situ" obtained nitrovinylamine - benzoyl isothiocyanate adducts ). However, in DMF at 110 °C for 5 minutes 90-96% yields can be obtained [12] (from the previously isolated C-adducts).

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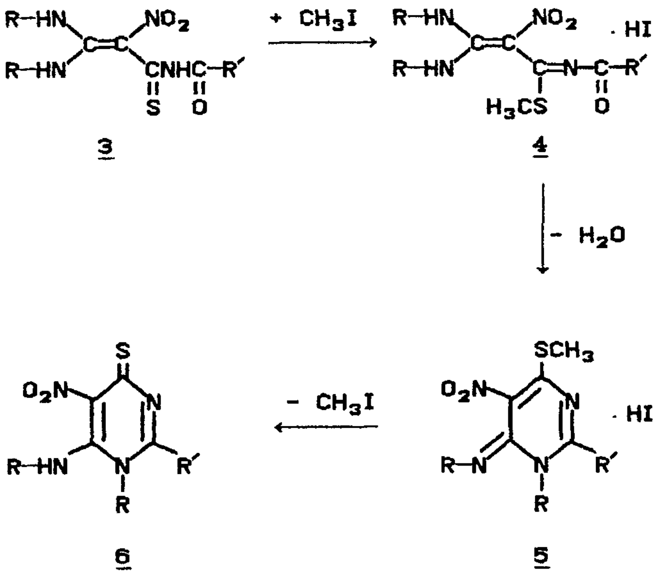
Regarding the importance of the nitropyrimidine derivatives from the biological point of view -- it has been reported their antimitotic activity [13] -- it was our aim to develop a general method for the synthesis of substituted 6-amino-5-nitro-4-thioxopyrimidines from the C-adducts of nitroketeneaminals and acyl isothiocyanates. According to our knowledge these products haven't been reported so far[14-16].

Heating the C-adducts in DMF even at 70 °C was unsuccesful. Many side-products and resins were formed and the desired pyrimidine derivatives were obtained in very low yields (t.l.c.). However, the reaction of the C-adducts with methyl iodide using ethanol as solvent led to the 6-amino-5-nitro-4-thioxopyrimidines.

Evidently by these reaction methyl iodide acts as a catalyst. The acyclic S-methylated derivative 4 is formed as the primary product of the reaction. The activation of the carbonyl C-atom by the -I-effect of the $SCH_3$-group of 4 allows its cyclization to the 6-imino-4-methylthio-5-nitropyrimidine hydroiodide 5. In 5 the C-atom of the methyl group attached to the sulfur atom undergoes a nucleophilic attack by the soft iodid anion with the succeeding loss of methyl iodide and the formation of the 4-thioxo derivative 6 (FIG. 2,TABLE).

The proposed reaction pathway was verified by heating the isolated 5d and 5e in DMF at 100 °C. Compounds 6d



| | R | R′ |
|---|---|---|
| a | $CH_3$ | Ph |
| b | $CH_3$ | Fu |
| c | $CH_3$ | $C_6H_4-Cl\,p$ |
| d | $CH_3$ | $CH=CH-Ph$ |
| e | $CH_3$ | $CH=CH-Fu$ |
| f | $CH_3$ | $CH=CH-C_6H_4-OCH_3p$ |

FIGURE 2

and 6e were obtained. The isolation of the acyclic thiol was carried out starting from 3a and 3c, by treatment with methyl iodide in DMF at room temperature.

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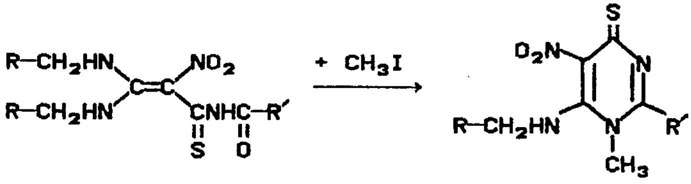

7

8

|   | R | R′ |
|---|---|---|
| a | Ph | Ph |
| b | Ph | Fu |
| c | Fu | Ph |
| d | Fu | Fu |

FIGURE 3

Of great interest resulted the reaction of the N,N'-aralkyldisubstituted C-adducts 7 with methyl iodide. In these cases, instead of the 1-aralkyl-6-aralkylaminopyrimidines 1-methyl-6-aralkylaminopyrimidines 8 were obtained (FIG. 3, TABLE).

The formation of 8 was verified by means of the reaction of the 1-furfurylamino-1-methylamino-2-nitroethene-benzoyl isothiocyanate adduct with methyl iodide. The nitropyrimidine obtained in this way was identical with the one obtained from 7c.

## EXPERIMENTAL

The starting C-adducts 3 and 7 were synthesized according to ref. 6 and 20 using the acyl

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TABLE

6-amino-5-nitro-4-thioxopyrimidine derivatives 6 and 8

| Entry | Yield ( % ) | M.P. ( °C) |
|---|---|---|
| 6a | 65[17-18] | 215-6 |
| 6b | 81 | 209-10 |
| 6c | 54[18] | 253-4 |
| 6d | 63[19] | 216-7 |
| 6e | 65[19] | 187-8 |
| 6f | 75 | 188-9 |
| 8a | 39 | 170-1 |
| 8b | 55 | 188-9 |
| 8c | 69 | 152-3 |
| 8d | 65 | 156-7 |

isothiocyanates obtained "in situ", in acetone, from the corresponding acyl chlorides and $NH_4SCN$. 3 precipitated from the reaction mixtures and 7 were isolated by evaporation of the solvent and crystallization from cold ethanol. The C-adducts were used without further purification and showed the following melting points: 3a: 176-8 °C; 3b: 184-5 °C; 3c: 175-7 °C; 3d: 154-6 °C; 3e: 167-9 °C; 3f: 154-5 °C; 7a: 144-6 °C[21], 7b: 165-6 °C; 7c: 132-4 °C; 7d: 147-8 °C.

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IR spectra were recorded in KBr tablets on a Carl Zeiss SPECORD 71 IR spectrophotometer and $^1$H-NMR spectra in d$_6$-DMSO ( $\delta$, ppm ) on a JEOL FX-90 Q instrument at 90 MHz. The mass spectra were registered on a JEOL JMS DX 30 mass spectrometer at 70 eV.

*1-Methyl-2-aryl(aralkenyl)-6-alkyl(aralkyl)amino-1,4-dihydro-5-nitro-4-thioxopyrimidines 6 and 8; General Procedure:*

To a suspension of 2,17 mmoles of the C-adduct 3 or 7 in 6 mL of absolute ethanol 0,3 mL (4,35 mmoles) of methyl iodide are added. The reaction mixture is refluxed with stirring for 5-6 h (monitored by t.l.c., silicagel 60 F$_{254}$-precoated plates; 0,25 mm; CHCl$_3$-CH$_3$OH 10 : 1). Yellow solids, which precipitate by cooling at room temperature, are filtered, washed with ethanol (2 x 4 mL), and the crude pyrimidine 6 or 8 further purified by recrystallization from DMF.

6a: M.F.: $C_{12}H_{12}N_4O_2S$ (276,3)

| | | | | |
|---|---|---|---|---|
| calcd.: | C: 52,17% | H: 4,35% | N: 20,29% | S: 11,59% |
| obsd.: | C: 51,84% | H: 4,34% | N: 20,43% | S: 11,42% |

IR: 695,740,785,875,955,1090,1150,1185,1245,1345,1415, 1485,1505,1540,1605,3340 cm$^{-1}$

$^1$H-NMR: 2,60 (s,3H,N-CH$_3$); 3,19 (d,3H,HN-CH$_3$); 7,59 (m,3H,H$_{m,p}$-Arom.); 8,46 (m,2H,H$_o$-Arom.); 9,26 (bq,1H,NH)

MS (M$^+$): 276

6b: M.F.: $C_{10}H_{10}N_4O_3S$ (266,3)

calcd.: C: 45,11% H: 3,84% N: 21,04% S: 12,04%

obsd.: C: 45,49% H: 3,85% N: 21,29% S: 11,99%

IR: 775,790,860,905,1005,1080,1140,1195,1235,1260,1325, 1340,1415,1490,1525,1590,1600,3280 $cm^{-1}$

$^1$H-NMR: 2,52 (s,3H,N-$\underline{CH}_3$); 3,11 (d,3H,HN-$CH_3$); 6,75 (dd,1H,$H_4$-Fur.,$J_{3,4}$=3,66 Hz,$J_{4,5}$=1,71 Hz); 7,48 (dd,1H, $H_3$-Fur.,$J_{3,5}$=0,98 Hz); 8,03 (dd,1H,$H_5$-Fur.); 9,24 (bq, 1H,NH)

MS ($M^+$): 266

6c: M.F.: $C_{12}H_{11}N_4O_2SCl$ (310,8)

IR: 770,800,855,960,1025,1090,1100,1190,1255,1295, 1355,1420,1495,1510,1550,1585,1605,1620,3350,3420 $cm^{-1}$

$^1$H-NMR: 2,60 (s,3H,N-$CH_3$); 3,18 (d,3H,HN-$\underline{CH}_3$); 7,57 (d,2H,$H_o$-Arom.$^*$); 8,45 (d,2H,$H_m$-Arom.$^*$); 9,10 (b,1H,NH).

* o,m in relation to the Cl-atom

MS ($M^+$): 310

6d: M.F.: $C_{14}H_{14}N_4O_2S$ (302,3)

IR: 790,975,1075,1110,1220,1240,1320,1340,1385, 1405,1480,1490,1525,1590,1620,3300 $cm^{-1}$

$^1$H-NMR: 2,56 (s,3H,N-$CH_3$); 3,08 (d,3H,HN-$\underline{CH}_3$); 7,05 (d,2H,CH=$^*_\alpha$ ,$J_{\alpha,\beta}$=15,0 Hz); 7,41 (m,3H,$H_{m,p}$-Arom.); 7,70 (m,2H,$H_o$-Arom.); 8,04 (d,2H,CH=$^*_\beta$ ); 9,01 (b,1H,NH).

* $\alpha,\beta$ in relation to the $C_2$-atom of the pyrimidine ring

MS ($M^+$): 302

6e: M.F.: $C_{12}H_{12}N_4O_3S$ (292,3)

IR: 765,785,885,970,1005,1080,1105,1220,1235,1245, 1280,1340,1380,1400,1470,1485,1520,1595,1615,3300 $cm^{-1}$

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$^1$H-NMR: 2,50 (s,3H,N-$CH_3$); 3,07 (d,3H,HN-$\underline{CH_3}$); 6,57 (dd,1H,$H_4$-Fur.,$J_{3,4}$=3,22 Hz,$J_{4,5}$=1,76 Hz); 6,75 (d,1H, $CH=^{*}_{\alpha}$ ,$J_{\alpha,\beta}$=15,82 Hz); 6,93 (dd,1H,$H_3$-Fur.,$J_{3,5}$<1); 7,75 (d,1H,$H_5$-Fur.); 7,79 (d,1H,$CH=^{*}_{\beta}$); 8,93 (b,1H,NH).

* $\alpha,\beta$ in relation to $C_2$-atom of the pyrimidine ring

MS ($M^+$): 292

<u>6f</u>: M.F.: $C_{15}H_{16}N_4O_3S$ (332,4)

calcd.: C: 54,22% H: 4,82% N: 16,87% S: 9,64%

obsd.: C: 54,88% H: 4,86% N: 17,28% S: 9,56%

IR: 840,1025,1160,1180,1245,1275,1285,1305,1355,1375, 1405,1420,1480,1515,1555,1605,1630,1675,3200 $cm^{-1}$

$^1$H-NMR: 2,54 (s,3H,N-$CH_3$); 3,12 (d,3H,HN-$\underline{CH_3}$); 3,82 (s, 3H,$OCH_3$); 6,92 (d,1H,$CH=^{*}_{\alpha}$ ,$J_{\alpha,\beta}$ =15,0 Hz); 6,99 (d,2H, $H_o$-Arom.$^{**}$); 7,72 (d,2H,$H_m$-Arom.$^{**}$); 8,01 (d,1H.$CH=^{*}_{\beta}$); 9,19 (bq,1H,NH). * $\alpha,\beta$ in relation to the $C_2$-atom of the pyrimidine ring; ** o,m in relation to the $OCH_3$-group

MS ($M^+$): 332

<u>8a</u> : M.F.: $C_{18}H_{16}N_4O_2S$ (352,4)

calcd.: C: 61,36% H: 4,55% N: 15,91% S: 9,09%

obsd.: C: 60,66% H: 4,62% N: 15,92% S: 9,33%

IR: 700,705,785,875,1075,1185,1205,1230,1345,1490,1540, 1580,1600,3300 $cm^{-1}$

$^1$H-NMR: 2,60 (s,3H,$CH_3$); 4,84 (d,2H,$CH_2$); 7,10-7,80 (m, 8H,H-Arom.$^{*}$); 8,38 (m,2H,$H_o$-Arom.); 9,60 (t,1H,NH).

* 5H-Arom. of the benzyl group + $2H_m$- + $H_p$-Arom. of the

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phenyl ring attached to the $C_2$-atom of the pyrimidine ring

MS ($M^+$): 352

<u>8b</u>: M. F.: $C_{16}H_{14}N_4O_3S$ (342,4)

IR: 700,755,790,1075,1085,1195,1225,1255,1345,1420, 1490,1530,1580,1600,3290 $cm^{-1}$

$^1$H-NMR: 2,55 (s,3H,$CH_3$); 4,85 (d,2H,$CH_2$); 6,73 (dd,1H, $H_4$-Fur.,$J_{3,4}$=3,66 Hz,$J_{4,5}$=1,71 Hz); 7,11-7,60 (m,6H,H-Arom.+$H_3$-Fur.); 8,03 (dd,1H,$H_5$-Fur.); 9,73 (t,1H,NH)

MS ($M^+$): 342

<u>8c</u>: M. F.: $C_{16}H_{14}N_4O_3S$ (342,4)

calcd.: C: 56,13% H: 4,12% N: 16.36% S: 9,37%

obsd.: C: 56,86% H: 4,30% N: 16,73% S: 9,27%

IR: 710,780,795,885,945,1035,1090,1175,1195,1215,1250, 1265,1305,1365,1440,1510,1555,1610,3340 $cm^{-1}$

$^1$H-NMR: 2,59 (s,3H,$CH_3$); 4,92 (d,2H,$CH_2$); 6,40 (m,2H, $H_3$-Fur.,$H_4$-Fur.); 7,53 (m,1H,$H_5$-Fur.); 7,59 (m,3H,H-Arom.); 8,40 (m,2H,H-Arom.); 9,56 (t,1H,NH).

MS ($M^+$): 342

<u>8d</u>: M. F.: $C_{14}H_{12}N_4O_4S$ (332,3)

IR: 755,795,1010,1070,1075,1195,1235,1255,1330, 1415,1490,1540,1585,1595,3330 $cm^{-1}$

$^1$H-NMR: 2,50 (s,3H,$CH_3$); 4,85 (d,2H,$CH_2$); 6,40 (m,2H, $H_3$-Fur.,$H_4$-Fur.); 6,76 (dd,1H,$H_4$-Fur.*); 7,50 (dd,1H, $H_3$-Fur.* ); 7,58 (m,1H,$H_5$-Fur.); 8,05 (dd,1H,$H_5$- Fur.*); 9,54 (t,1H,NH). * Furan ring attached to the $C_2$- atom of the pyrimidine ring

MS ($M^+$): 332

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/17/. Use of DMF as solvent allowed 75% yield

/18/. Use of DMF and anhydrous $K_2CO_3$, at room temperature, allowed the isolation of the acyclic thiol derivatives 4a and 4c in 77% and 71% yield respectively. 4a: M.P.: 193-4 °C; $^1$H-NMR : 2,23 (s,3H,HN-$CH_3$); 2,61 (s,3H,$SCH_3$); 2,63 (s,3H,HN-$CH_3$); 7,41 (m,3H,$H_{m,p}$- Arom.); 7,89 (m,2H,$H_o$-Arom.); 8,75 (b,2H,2 x NH). 4c : M.P.: 125-7 °C; $^1$H-NMR: 2,25 (s,3H,HN-$CH_3$); 2,66 (s,3H,$SCH_3$); 2,68 (s,3H,HN-$CH_3$); 7,42 (d,2H,$H_o$- Arom.* ); 7,89 ( d,2H,$H_m$-Arom.* ); 8,76 (b,2H, 2 x NH).

* o,m in relation to the Cl-atom

/19/. DMF was used as solvent. The use of ethanol as solvent allowed the isolation of 6-imino-4-methyl

thio-5-nitropyrimidine hydroiodides 5d and 5e in 38% and 68% yield respectively. $^{1}$H-NMR: 5d: 2,76 (s,3H,$CH_3$); 2,95 (s,3H,$SCH_3$); 3,90 (s,3H,=N-$CH_3$); 7,53 (m,3H,$H_{m,p}$-Arom.); 7,66 (d,1H,$CH=^{*}_{\alpha}$,$J_{\alpha,\beta}$=15,2 Hz); 8,00 (m,2H,$H_o$-Arom.); 8,35 (d,1H,$CH=^{*}_{\beta}$). 5e: 2,74 (s,3H,$CH_3$); 2,96 (s,3H,$SCH_3$); 3,86 (s,3H, =N-$CH_3$); 6,83 (dd,1H,$H_4$-Fur.,$J_{3,4}$=3,4 Hz;$J_{4,5}$=1,6 Hz); 7,16 (d,1H,$CH=^{*}_{\alpha}$,$J_{\alpha,\beta}$=15,0 Hz); 7,40 (dd,1H, $H_3$-Fur.,$J_{3,5}$<1); 8,10 (d,1H,$H_5$-Fur.); 8,23 (d,1H, $CH=^{*}_{\beta}$). * $\alpha,\beta$ in relation to the $C_2$-atom of the pyrimidine ring. The =NH-$^{+}$ signal wasn't observed because both spectra were registered until 10 ppm

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