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# Preparation of N-1 Substituted Thieno[3,4-d]pyrimidine-2,4-diones

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# PREPARATION OF *N*-1 SUBSTITUTED THIENO[3,4-*d*]PYRIMIDINE-2,4-DIONES

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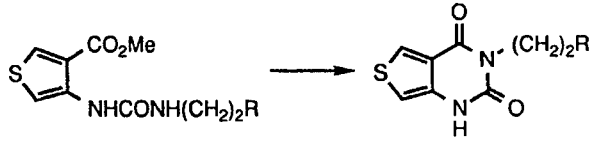
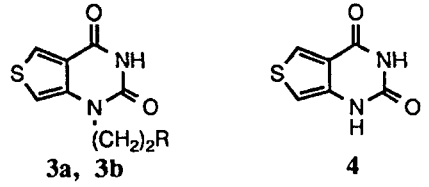
**Abstract** — The preparation of *N*-1 substituted thieno[3,4-*d*]pyrimidine-2,4-diones is presented. The key feature of this synthesis is the use of a 2,4-dimethoxybenzyl protecting group at *N*-3 that was readily removed in methanesulfonic acid.

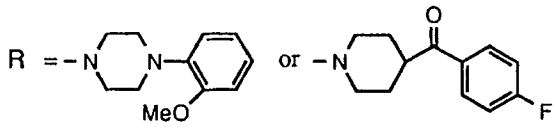
Over the last few years we have been interested in the preparation of pharmacologically novel molecules that contain the thieno[3,4-*d*]pyrimidine-2,4-dione ring system[1-3]. This synthetic strategy involved the preparation of the suitably substituted urea ester (*e.g.* **1a, 1b**) followed by ring closure to form the pyrimidine ring system **2**. To further explore the SAR of this interesting ring system, we decided to switch the substituent pattern from the *N*-3 position of **2** to the *N*-1 position. We report here the preparation of **3a** and **3b** as representative examples of the title compounds.




**1a, 1b** **2a, 2b**




**3a, 3b** **4**

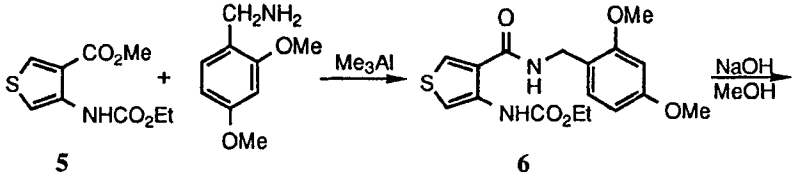



a b

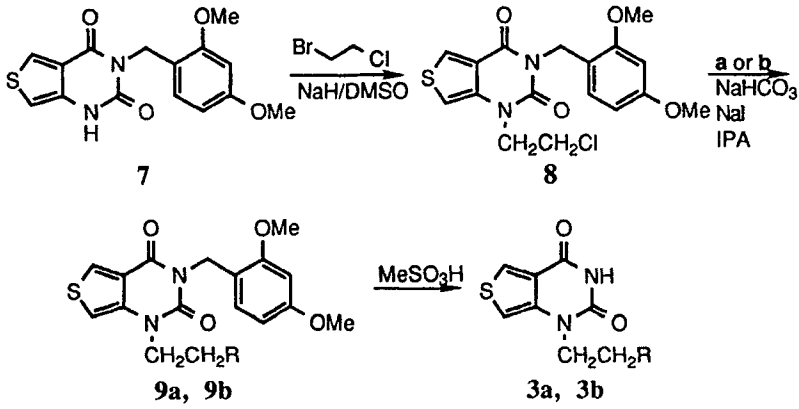
We first attempted the direct approach, *i.e.* selective alkylation of thieno[3,4-*d*]pyrimidine-2,4-dione (**4**)[4]. This approach produced a mixture of both monoalkylated materials as well as the bisalkylated product. With this failure (and a few others) we turned our attention to finding a suitable protecting group for the *N*-3 position that could be easily removed after *N*-1 derivatization. A 3-benzyl compound was prepared (vida supra); however, removal of this group by hydrogenolysis did not work. A 3-(3,4-dimethoxybenzyl) compound was also prepared but it could not be removed with acid[5]. As a last choice, we prepared the 3-(2,4-dimethoxybenzyl) compound and found that this protecting group could be removed at the appropiate time by mild acid treatment[6].

The synthesis of the target molecule started with the urethane **5**[2]. This material was treated with 2,4-dimethoxybenzylamine in the presence of trimethylaluminum to produce the amide **6**[2,7]. This intermediate was readily cyclized to the thieno[3,4-*d*]pyrimidine compound **7** using NaOH/MeOH in nearly quantitative yield. The *N*-1 position was then alkylated with 1-bromo-2-chloroethane in DMSO/NaH and the chloro moiety of **8** was displaced by amine **a** or **b** in refluxing 2-propanol using $NaHCO_3$ as the base and a catalytic amount of NaI. The final step was readily accomplished by stirring a methanesulfonic acid solution of **9** at rt for 16 h.

This report demonstrates a general chemoselective method for functionalizing the *N*-1 position of the pyrimidine-2,4-dione nucleus and specifically the preparation of novel *N*-1 substituted thieno[3,4-*d*]pyrimidine-2,4-diones.




5 6




7 8 9a, 9b 3a, 3b

## Experimental

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1430 instrument. Proton nmr spectra were recorded at 90 MHz on a Varian EM 390 spectrometer with the chemical shifts reported in δ downfield from tetramethylsilane as internal standard. For compounds **3a**, **3b** and **9a**, **9b** the proton nmr spectra were recorded at 300.1 MHz on a Bruker AC 300 spectrometer. The elemental analyses were run on either a Perkin-Elmer 240C or 2400 instruments. All spectra are in agreement with the structures cited. Standard flash column techniques were employed to purify crude reaction mixtures using 230-400 mesh E. Merck silica gel under positive nitrogen pressure. The yields are not optimized and are for isolated product.

Ethyl [4-[[(2,4-dimethoxyphenylmethyl)amino]carbonyl]thiophen-3-yl]carbonate (**6**).

A toluene solution (300 ml) of 2,4-dimethoxybenzylamine (20.9 g, 0.125 mmol) at 10°C under nitrogen was slowly treated with 2*N* $Me_3Al$ in toluene (68.8 ml, 0.138 mmol). The reaction solution was warmed to rt for 30 min and then recooled to 10°C and treated with urethane **5** (28.6 g, 0.125 mmole). After the mixture had been stirred for 3 days at rt, it was cooled to 0°C and carefully quenched with 2*N* HCl. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic phase was washed with 2*N* HCl, water and brine. The organic layer was dried ($MgSO_4$) and condensed *in vacuo* to produce 42.5 g of white solid. This material was crystallized from $CH_2Cl_2$/hexane/ether to afford pure **6** (31.1 g)

as a white solid. The filtrate was purified by flash column chromatography using 50-60% ether in hexane. There was obtained an additional 5.8 g (36.9 g total, 81%) of **6**. A portion of **6** was recrystallized from $CH_2Cl_2$/ether to afford a white solid; mp 123–126°C; IR (KBr) 3400, 1715, 1640, 1530, 1510, 1285, 1225, 1205, 1025, 820, and 775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.27 (t, $J$ = 7 Hz, 3H, $CH_2CH_3$), 3.75 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 4.15 (q, $J$ = 7 Hz, 2H, $CH_2CH_3$), 4.47 (d, $J$ = 5.5 Hz, 2H, benzylic $CH_2$), 6.43-6.63 (m, 3H, $H_{arom}$ and $NHCH_2$), 7.20 (d, $J$ = 10 Hz, 1H, H6 phenyl), 7.45 (d, $J$ = 3 Hz, 1H, H2 thiophene), 7.60 (d, $J$ = 3 Hz, 1H, H5 thiophene) and 9.90 (s, 1H, NHCO); Anal. calc'd for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69. Found: C, 56.13; H, 5.51; N, 7.70.

3-(2,4-Dimethoxyphenylmethyl)thieno[3,4-*d*]pyrimidine-2,4-dione (**7**).

A solution of 12.5 *N* NaOH (11.5 ml, 0.144 mol) in methanol (475 ml) was treated with urethane **6** and stirred at 50°C for 5 h. The white mixture was cooled in an ice bath and acidified to pH 3 with 2*N* HCl. The white solid was collected and dried to afford **7** (29 g, 95%). A portion of this material was crystallized from DMF/MeOH to produce **7** as a white solid; mp 276–277°C; IR (KBr) 3200, 1720, 1650, 1505, 1465, 1205, 1030, 830, 770, 750 and 670 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 3.70 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 4.88 (br s, 2H, benzylic $CH_2$), 6.37 (dd, $J$ = 3, 7.5 Hz, 1H, H5 phenyl), 6.53 (d, $J$ = 3 Hz, H3 phenyl), 6.67 (d, $J$ = 7.5 Hz, 1H, H6 phenyl), 6.83 (d, $J$ = 3 Hz, 1H, H7 thienopyrimidine), 8.37 (d, $J$ = 3 Hz, 1H, H5 thienopyrimidine) and 11.28 (s, 1H, NH); Anal. calc'd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.40; H, 4.42; N, 8.93.

1-(2-Chloroethyl)-3-(2,4-dimethoxyphenylmethyl)thieno[3,4-*d*]pyrimidine-2,4-dione (**8**).

To a mixture of **7** (5.09 g, 16 mmol) in DMSO (80 ml) under nitrogen was slowly added 60% NaH (1.28 g, 32 mmol). After the effervescence had stopped, the mixture was treated with 1-bromo-2-chloroethane (4.0 ml, 48 mmol) and warmed to 30°C for 4.5 h. The reaction was quenched with water, and a white precipitate was collected. The filtrate was extracted with EtOAc and this extract was combined with a $CH_2Cl_2$ solution of the above white solid. This organic phase was washed with water and brine and dried ($MgSO_4$). Solvent removal afforded **8** (6.26 g, quantitative). A portion of this material was crystallized from $CH_2Cl_2$/hexane to produce **8** as a white solid; mp 154.5–156°C; IR (KBr) 3120,

1700, 1655, 1570, 1510, 1385, 1210, 1030 and 770 cm-1; 1H NMR (DMSO-$d_6$) δ 3.66 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.83 (t, $J$ = 6 Hz, 2H, $CH_2Cl$), 4.27 (t, $J$ = 6 Hz, 2H, $ClCH_2CH_2N$), 4.90 (br s, 2H, benzylic $CH_2$), 6.33 (dd, $J$ = 3, 7.5 Hz, 1H, H5 phenyl), 6.50 (d, $J$ = 3 Hz, H3 phenyl), 6.70 (d, $J$ = 7.5 Hz, 1H, H6 phenyl), 7.30 (d, $J$ = 3 Hz, 1H, H7 thienopyrimidine) and 8.43 (d, $J$ = 3 Hz, 1H, H5 thienopyrimidine); Anal. calc'd for $C_{17}H_{17}ClN_2O_4S$: C, 53.61; H, 4.50; N, 7.36. Found: C, 53.74; H, 4.49; N, 7.37.

General Procedure for the Preparation of Compound **9**.

A mixture of the chloroethyl compound **8** (1 eq), $NaHCO_3$ (4-5 eq), NaI (0.5-0.75 eq) and amine in 2-propanol (2.6 *M*) was warmed to reflux for 12 to 17 h under nitrogen. Water was added and the 2-propanol was removed *in vacuo*. The aqueous mixture was extracted with $CH_2Cl_2$ and the combined extract was washed with brine and dried ($MgSO_4$). Solvent removal produced the crude product which was purified by flash silica gel chromatography using 0.5-3% MeOH in $CH_2Cl_2$.

3-(2,4-Dimethoxyphenylmethyl)-1-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-thieno[3,4-*d*]pyrimidine-2,4-dione (**9a**).

Isolated as a tan foam in 78% yield after column chromatography. A portion of this material was dissolved in acetone and converted to its oxalate salt. This white solid was recrystallized from $CH_2Cl_2$/ether; mp 114–117°C; IR (KBr) 3450, 3105, 1700, 1660, 1580, 1500, 1390, 1210, 1025 and 750 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 3.03 (br s, 10H, $CH_2N$), 3.67 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 4.24 (m, 2H, $CH_2NCO$), 4.96 (s, 2H, benzylic $CH_2$), 6.35 (dd, $J$ = 2.2, 8.4 Hz, 1H, H5 dimethoxyphenyl), 6.56 (d, $J$ = 2.2 Hz, 1H, H3 dimethoxyphenyl), 6.77 (d, $J$ = 8.4 Hz, 1H, H6 dimethoxyphenyl), 6.87-6.98 (m, 4H, methoxyphenyl), 7.38 (d, $J$ = 3.2 Hz, H7 thienopyrimidine) and 8.53 (d, $J$ = 3.1 Hz, 1H, H5 thienopyrimidine) (Note: $(CO_2H)_2$ was a slight rise in the baseline δ 4.5-6.0); Anal. calc'd for $C_{28}H_{32}N_4O_5S \cdot C_2H_2O_4$: C, 57.50; H, 5.47; N, 8.94. Found: C, 57.52; H, 5.56; N, 8.85.

1-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]-3-(2,4-dimethoxyphenylmethyl)-thieno[3,4-*d*]pyrimidine-2,4-dione (**9b**).

Isolated as a tan oil in 80% yield after column chromatography. This material was twice crystallized from $CH_2Cl_2$/ether/hexane to produce **9b** as a cream-colored solid; mp 86–88°C; IR (KBr) 3060, 2900, 1675, 1630, 1550, 1360, 1180, 1000, 830 and 800 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.77-1.85 (m, 4H, piperidine $CH_2$), 2.20-

2.27 (m, 2H, piperidine $CH_2$), 2.72 (t, $J$ = 7.0 Hz, 2H, $CH_2CH_2$-N piperidine), 3.04-3.08 (m, 2H, piperidine $CH_2$), 3.13-3.25 (m, 1H, piperidine CH), 3.77 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 4.12 (t, $J$ = 7.0 Hz, 2H, $CH_2NCO$), 5.18 (s, 2H, benzylic $CH_2$), 6.40 (dd, $J$ = 2.4, 8.3 Hz, 1H, H5 dimethoxyphenyl), 6.45 (d, $J$ = 2.3 Hz, 1H, H3 dimethoxyphenyl), 6.70 (d, $J$ = 3.3 Hz, 1H, H7 thienopyrimidine), 6.93 (d, $J$ = 8.3 Hz, 1H, H6 dimethoxyphenyl), 7.13 (t, $J$ = 8.6 Hz, 2H, H3 and H5 benzoyl), 7.95 (dd, $J$ = 5.4, 8.9 Hz, 2H, H2 and H6 benzoyl) and 8.25 (d, $J$ = 3.3 Hz, 1H, H5 thienopyrimidine); Anal. calc'd for $C_{29}H_{30}FN_3O_5S \cdot 0.5\ H_2O$: C, 62.13; H, 5.57; N, 7.50. Found: C, 62.07; H, 5.61; N, 7.24.

General Procedure for the Preparation of Compound **3**.

The dimethoxybenzyl compound **9** (1 eq.) was dissolved in methanesulfonic acid (0.03–0.07 *M*) at rt. The solution slowly turned a purple color and after stirring at ambient temperature for 16 h the solution was poured into ice-water. The pH of the aqueous mixture was adjusted to 10 with concentrated $NH_4OH$. The white precipitate was collected and redissolved in $CH_2Cl_2$/MeOH. This organic solution was quickly washed with water and brine and dried (MgSO4). Solvent removal produced a quantitative amount of crude product.

1-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl]-thieno[3,4-*d*]pyrimidine-2,4-dione (**3a**).

Isolated as a tan solid (26%) after crystallization from MeOH/$CH_2Cl_2$; mp 244–247°C; IR (KBr) 3200, 3070, 1710, 1675, 1580, 1500, 1240, 1030, and 760 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 2.62 (br s, 6H, methylene), 2.93 (br s, 4H, methylene), 3.77 (s, 3H, $OCH_3$), 4.01 (t, $J$ = 7.0 Hz, 2H, $CH_2NCO$), 6.86-6.94 (m, 4H, $H_{arom}$), 7.21 (d, $J$ = 3.2 Hz, H7 thienopyrimidine), 8.43 (d, $J$ = 3.2 Hz, 1H, H5 thienopyrimidine) and 11.21 (s, 1H, NH); Anal. calc'd for $C_{19}H_{22}N_4O_3S$: C, 59.05; H, 5.74; N, 14.50. Found: C, 59.03; H, 5.69; N, 14.01.

1-[2-[4-(4-Fluorobenzoyl)piperidin-1-yl]ethyl]thieno[3,4-*d*]pyrimidine-2,4-dione (**3b**).

Isolated as a tan solid (28%) after column chromatography using 0.5-5% MeOH in $CH_2Cl_2$. This material was crystallized from MeOH/$CH_2Cl_2$; mp 205.5–209°C; IR (KBr) 3050, 1680, 1580, 1580, 1485, 1285, 1205, 1170, 975, 855 and 750 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.80-1.88 (m, 4H, piperidine $CH_2$), 2.23-

2.31 (m, 2H, piperidine $CH_2$), 2.73 (t, $J$ = 7.2 Hz, 2H, $CH_2C\underline{H_2}$-N piperidine), 3.04-3.13 (m, 2H, piperidine $CH_2$), 3.16-3.30 (m, 1H, piperidine CH), 4.10 (t, $J$ = 7.2 Hz, 2H, $CH_2NCO$), 6.76 (d, $J$ = 3.2 Hz, 1H, H7 thienopyrimidine), 7.14 (t, $J$ = 8.6 Hz, 2H, H3 and H5 benzoyl), 7.96 (dd, $J$ = 5.4, 8.9 Hz, 2H, H2 and H6 benzoyl), 8.26 (d, $J$ = 3.3 Hz, 1H, H5 thienopyrimidine) and 8.45 (s, 1H, NH); Anal. calc'd for $C_{20}H_{20}FN_3O_3S$: C, 59.84; H, 5.02; N, 10.47. Found: C, 59.90; H, 5.13; N, 10.34.

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