Monatshefte für Chemie 137, 1421–1430 (2006)
DOI 10.1007/s00706-006-0528-7

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

An Easy Synthesis of Pyranopyrimidines

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Received January 31, 2006; accepted February 16, 2006
Published online October 5, 2006

Summary. The one-pot reaction of valerolactone with nitriles in the presence of triflic anhydride affords 2,4-disubstituted pyrano[2,3-*d*]pyrimidines. Subsequent addition of methyl thiocyanate leads to 2,4-bis(methylthio)pyranopyrimidines which can easily be converted into the corresponding methylsulfonyl derivatives. The reaction of these derivatives with different nucleophiles produces a variety of substituted pyranopyrimidines.

Keywords. Cyclizations; Heterocycles; Nucleophilic substitutions.

Introduction

Among the pyranopyrimidines one of the most important classes are the dihydro-5*H*-pyrano[2,3-*d*]pyrimidines **1**. Compounds containing this moiety have interesting biological properties. For example, molecules with a pyrano[2,3-*d*]pyrimidine skeleton fused to a coumarine unit exhibit antibacterial activity and are used as fungicides [1, 2]. In addition, compounds having a chalcone unit attached to the pyranopyrimidine ring are efficient herbicides [3, 4].

The construction of the pyranopyrimidine skeleton has involved multi-step synthetic procedures. For example, substituted pyranopyrimidines can be prepared form benzylidenemalonitrile in a four-step synthesis [5] or from barbituric acid derivatives [6–8]. The reaction of pyrazolinones with cycloalkanones catalyzed by fused sodium acetate gives cycloalkylidene derivatives, which have been subsequently treated with malonitrile and finally cyclized to pyranopyrimidines [9]. Recently, microwave irradiation has been used in the synthesis of pyranopyrimidines from thiobarbituric acid derivatives [10]. Solvent-free conditions have been also applied to the preparation of pyranopyrimidines [11]. Many methods to prepare pyranopyrimidines are reported in literature. In spite of their importance, only a few methods of them involve less than a few steps.

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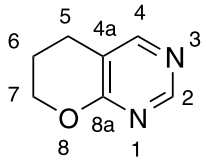


1

Fig. 1. 6,7-Dihydro-5*H*-pyrano[2,3-*d*]pyrimidines and its numbering system

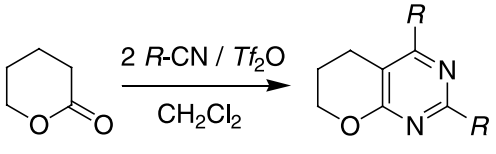
Herein, we wish to report that the one-pot reaction of valerolactone with nitriles in the presence of trifluoromethanesulfonic anhydride (triflic anhydride) affords 2,4-substituted 6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidines.

Results and Discussion

In previous papers we have reported the synthesis of a variety of heterocyclic systems based on the reaction of different carbonyl compounds with nitriles in the presence of triflic anhydride [12–17]. Specifically, the reaction of alicyclic carboxylic esters with nitriles and triflic anhydride [$(CF_3SO_2)O$, Tf_2O] gives the corresponding substituted 4-alkoxypyrimidines [18]. However, the use of lactones as carbonyl starting material was not investigated then.

We have found that the reaction of valerolactone (**2**, tetrahydro-2*H*-pyran-2-one) with different nitriles in the presence of Tf_2O under mild conditions affords 6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidines **3** in moderate yields (Scheme 1).

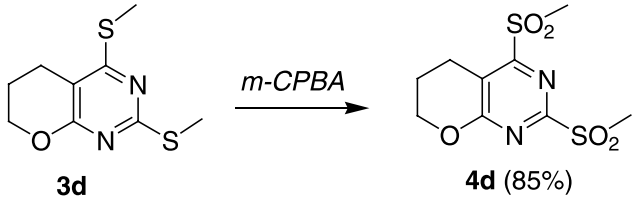
The well-known mechanism of the reaction involves the formation of a triflil-oxycarbenium ion which is trapped by the nitrile to form a nitrilium ion. A second molecule of nitrile reacts with the intermediate giving the corresponding pyrano-pyrimidines after elimination of *Tf*OH and loss of a proton [12]. The higher yields with nitriles bearing electron donating groups can be explained by their increased nucleophilicities. When methyl thiocyanate was used as the nitrile, 2,4-bis(methyl-thio)pyranopyrimidine (**3d**) was obtained. Methylthiopyranopyrimidines can be easily converted into methylsulfonylpyranopyrimidines **4d** by oxidation with



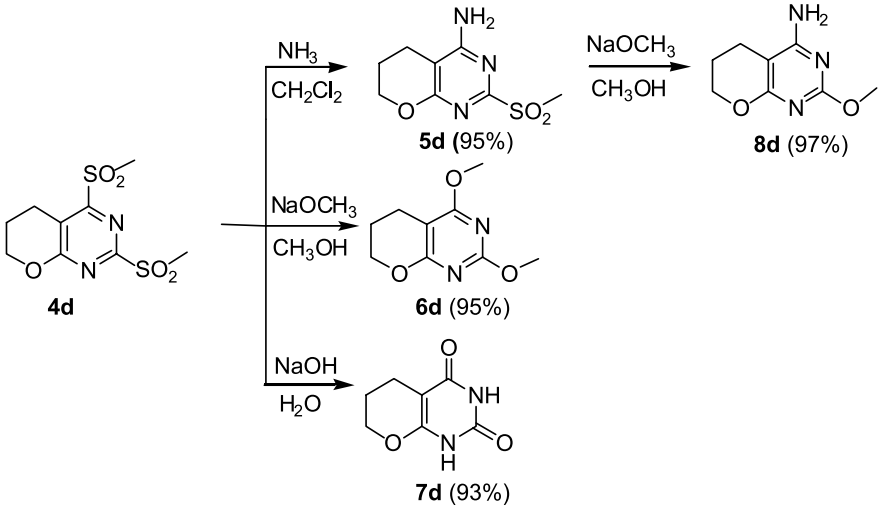
2 **3a–3h**

$R = C_2H_5$	**3a** (45%)
$R = (CH_3)C$	**3b** (40%)
$R = CH_3(CH_2)_7$	**3c** (50%)
$R = CH_3S$	**3d** (48%)
$R = C_6H_5$	**3e** (60%)
$R = 4\text{-}CH_3C_6H_4$	**3f** (54%)
$R = 4\text{-}CH_3OC_6H_4$	**3g** (90%)
$R = 3,4\text{-}(CH_3O)_2C_6H_3$	**3h** (83%)

Scheme 1



Scheme 2



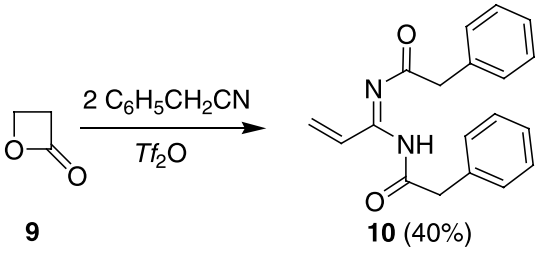
Scheme 3

m-CPBA. Because methylsulfonyl groups can be removed by nucleophilic displacement, these compounds open the route to a variety of substituted pyranopyrimidines otherwise not easily prepared (Scheme 2).

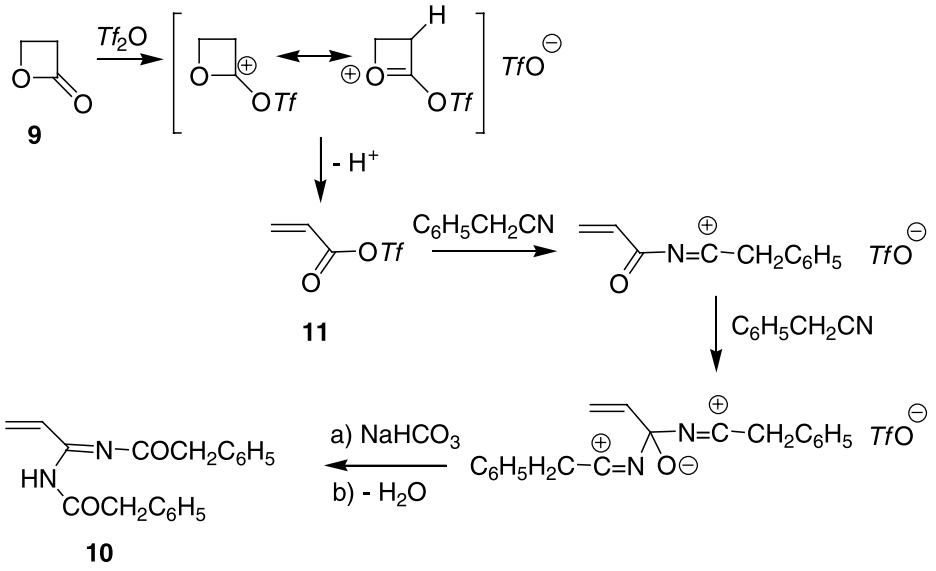
The nucleophilic displacement of one or both methylsulfonyl groups can be controlled either by the nucleophilicity of the reagent or by the reaction conditions. Thus, when **4d** reacts with ammonia only the methylsulfonyl group attached at C4 is removed while the use of sodium methoxide or sodium hydroxide produces the double substitution. Using these procedures, we obtained in good yields differently substituted pyranopyrimidines **5d**–**8d** (Scheme 3).

We attempted to extend this procedure to other lactones such as γ-butyrolactone (dihydrofuran-2(3*H*)-one) and ε-caprolactone (oxepan-2-one) with nitriles in the presence of triflic anhydride. Unfortunately these reactions resulted in very complex product mixtures from which no pyrimidines could be identified. The triflic anhydride probably induces ring openings of these lactones. The reaction with β-propiolactone (**9**) with benzyl cyanide led to **10** (Scheme 4). This can be explained (Scheme 5) by a ring cleavage by triflic anhydride to form ketotriflate **11**. Nucleophilic displacement followed by basic hydrolysis and elimination of water affords **10**.

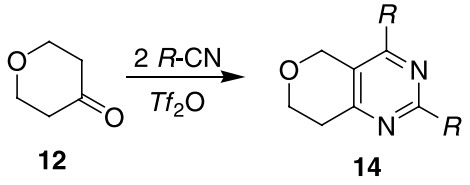
The pyrano[4,3-*d*]pyrimidines are another class of heterocyclic pyrimidines which present interesting biological properties [19]. The results from valerolactone suggested that tetrahydro-4*H*-pyran-4-one **12** may afford these pyrimidines. These



Scheme 4



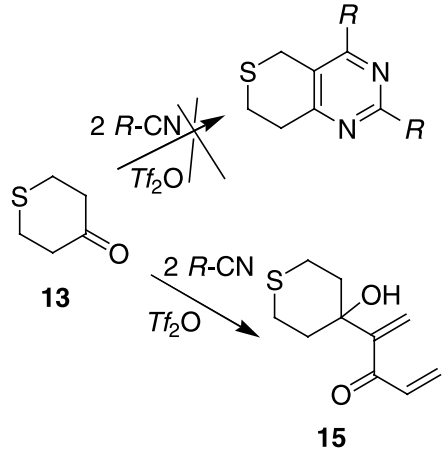
Scheme 5



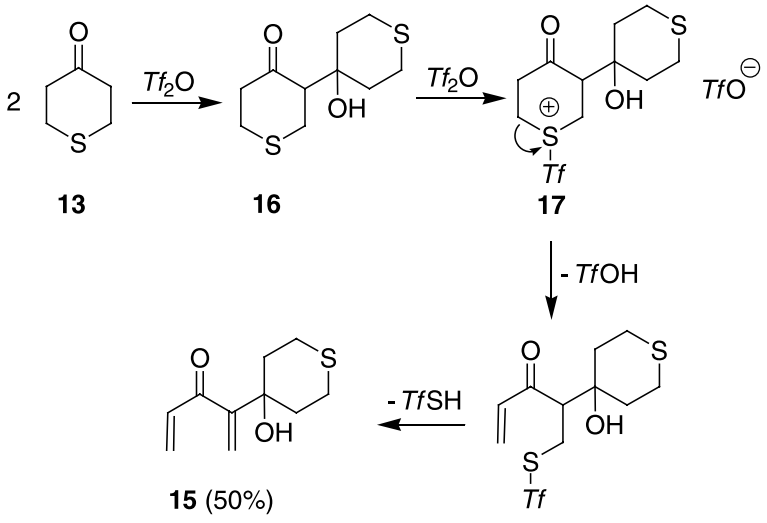
Scheme 6

products (**14**) were obtained in low yields and only when aromatic nucleophiles were used. Reaction of the sulfur analog of **12**, tetrahydro-4*H*-thiopyran-4-one **13** resulted in an aldol condensation product **15**. That the nitrile does not participate in the reaction was verified by repetition of the reaction without the nitrile, and this gave **15** in moderate yield (Scheme 7).

The formation of **15** can be explained (Scheme 8) by an initial aldol condensation of the thiopyranone induced by traces of triflic acid. The corresponding



Scheme 7



Scheme 8

hydroxythiopyranone **16** reacts with triflic anhydride to form **17** which, after two elimination steps, gives **15**. Aldol condensations of various carbonyl compounds induced by triflic acid traces and subsequent steps in these reactions have been reported previously [17, 20, 21].

In conclusion, we report that the one-pot reaction of valerolactone with a variety of nitriles affords 2,4-disubstituted 6,7-dihydro-5*H*-pyrano[2,3-*d*]pyrimidines in moderate yields. The 2,4-bis(methylthio) derivatives can be easily converted into their 2,4-bis(methylsulfonyl) derivatives *via* oxidation. The reaction of the bissulfones with different nucleophiles gives the aminomethoxy, dimethoxy, aminosulfonyl, and dihydroxy substituents. Pyrano[4,3-*d*]pyrimidines can be also prepared from tetrahydro-4*H*-pyran-4-one by reaction with aromatic nitriles albeit in low yields.

Experimental

All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from *Tf*OH and redistilled twice prior to use [22, 23]. Solvents were distilled from an appropriate drying agent before use. Reactions were monitored by TLC. Column chromatography employed silica gel 60 (70–230 mesh). Melting points were determined on a Gallenkamp apparatus in open capillary tubes. The IR spectra were measured with a Shimadzu FTIR 8300 instrument and sample pellets were prepared with spectroscopic grade KBr. NMR spectra were recorded on a Bruker DPX 300 and Bruker Avance 500 at 300 MHz for ^{1}H and 75.47 MHz for ^{13}C and 500 MHz for ^{1}H and 125.72 for ^{13}C. Chemical shifts are given in δ (ppm) to residual $CHCl_3$ (7.26 and 77.0 ppm) and *DMSO* (2.50 and 39.5 ppm). EI mass spectra were carried out at 70 eV on a HP 5989A quadrupole instrument. ESI mass spectra were recorded on a Bruker Esquire with an ion-trap detector. Elemental analyses were carried out with a Perkin-Elmer 2400 CHN apparatus and the results were in good agreement with the calculated values.

General Procedure for the Preparation of 2,4-Disubstituted 6,7-Dihydro-5H-pyrano[2,3-d]pyrimidines ***3***

A mixture of 1.0 g **2** (10.0 mmol) and the corresponding nitrile (40.0 mmol) dissolved in 30 cm^3 CH_2Cl_2 was cooled at −78°C. To this mixture 4.23 g triflic anhydride (15.0 mmol) dissolved in 30 cm^3 CH_2Cl_2 were added. The reaction mixture was stirred at 0°C for 4 days. The reaction was monitored by TLC. The reaction mixture was hydrolyzed by careful addition of saturated aqueous solution of sodium hydrogen carbonate until *pH* was basic. The organic layer was separated, washed with brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by column chromatography using *n*-hexane/ethyl acetate = 7/3 as eluent. The crude product was distilled or recrystallized.

2,4-Diethyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine (**3a**, $C_{11}H_{16}N_2O$)

Destillation afforded 0.86 g (45%) **3a**. Bp 150°C/0.4 torr (kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.19$ (t, $J = 7.6$ Hz, CH_3), 1.25 (t, $J = 7.6$ Hz, CH_3), 2.00 (tt, $J = 6.5$, 5.3 Hz, H-6), 2.62 (q, $J = 7.6$ Hz, $C\underline{H}_2CH_3$), 2.65 (t, $J = 6.5$ Hz, H-5), 2.74 (q, $J = 7.6$ Hz, $C\underline{H}_2CH_3$), 4.29 (t, $J = 5.3$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.84$ (CH_3), 12.25 (CH_3), 20.12 (C-6), 21.17 (C-5), 26.84 ($\underline{C}H_2CH_3$), 31.72 ($\underline{C}H_2CH_3$), 66.76 (C-7), 108.19 (C-4a), 166.46 (C-8a), 169.21 (C-4), 169.99 (C-2) ppm; IR (film): $\bar{\nu} = 2972$, 1578, 1556, 1418 cm^{-1}; MS (70 eV): $m/z = 192$ (M^+, 100), 191 (99), 177 (M-CH_3, 48), 164 (M-C_2H_4, 64).

2,4-Di-tert-butyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine (**3b**, $C_{15}H_{24}N_2O$)

Recrystallization from ethanol afforded 1.0 g (40%) **3b**. Mp 64–65°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ (s, $3CH_3$), 1.38 (s, $3CH_3$), 1.99 (tt, $J = 6.3$, 5.3 Hz, H-6), 2.91 (t, $J = 6.3$ Hz, H-5), 4.33 (t, $J = 5.3$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.89$ (C-6), 23.37 (C-5), 29.40 (CH_3), 29.42 (CH_3), 68.83 (C-7), 108.55 (C-4a), 167.08 (C-8a), 173.27 (C-4), 173.95 (C-2) ppm; IR (KBr): $\bar{\nu} = 2959$, 1568, 1533, 1094 cm^{-1}; MS (ESI): $m/z = 249$ $[M + H]^+$.

2,4-Dioctyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine (**3c**, $C_{23}H_{40}N_2O$)

Destillation afforded 1.80 g (50%) **3c**. Bp 200°C/0.4 torr (kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.77$–0.82 (m, $2CH_3$), 1.20–1.30 (m, $10CH_2$), 1.54–1.73 (m, $2CH_2$), 1.97 (m, CH_2), 2.53–2.72 (m, $3CH_2$), 4.27 (t, $J = 5.1$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.92$ (CH_3), 20.61, 21.50, 22.48, 22.49, 28.23, 29.06, 29.29, 29.31, 29.52, 31.67, 31.71, 34.01, 38.96 (CH_2), 67.04 (C-7), 108.63 (C-4a), 166.76 (C-8a), 168.79 (C-4), 169.35 (C-2) ppm; IR (film): $\bar{\nu} = 2926$, 1578, 1555, 1418 cm^{-1}; MS (70 eV): $m/z = 360$ (M^+, 10), 331 (M-C_2H_5, 11), 317 (M-C_3H_7, 17), 289 (M-C_5H_{11}, 23), 275 (M-C_6H_{13}, 50), 262 (M-C_7H_{14}, 56), 177 (100).

2,4-Bis(methylthio)-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine (**3d**, $C_9H_{12}N_2O_2S_2$)
Recrystallization from *n*-hexane afforded 1.08 g (48%) **3d**. Mp 92–93°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.03$ (tt, $J = 6.3$, 5.2 Hz, H-6), 2.52 (t, $J = 6.3$ Hz, H-5), 2.53 (s, SCH_3), 2.56 (s, SCH_3), 4.32 (t, $J = 5.2$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.63$ (SCH_3), 14.02 (SCH_3), 20.17 (C-6), 21.14 (C-5), 67.42 (C-7), 105.64 (C-4a), 164.61 (C-8a), 168.47 (C-4), 168.90 (C-2) ppm; IR (KBr): $\bar{\nu} = 1556$, 1524, 1340, 1151, 1068 cm^{-1}; MS (70 eV): $m/z = 228$ (M^+, 91), 213 (M-CH_3, 40), 195 (M-SH, 100).

2,4-Diphenyl-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine (**3e**, $C_{19}H_{16}N_2O$)
Recrystallization from *n*-hexane afforded 1.72 g (60%) **3e**. Mp 136–137°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.02$ (tt, $J = 6.3$, 5.1 Hz, H-6), 2.89 (t, $J = 6.3$ Hz, H-5), 4.51 (t, $J = 5.1$ Hz, H-7), 7.44–7.52 (m, Ar–H), 7.71–7.75 (m, Ar–H, 8.47–8.52 (m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.86$ (C-6), 23.49 (C-5), 67.74 (C-7), 110.11 (C-4a), 128.15, 128.24, 129.04, 129.29, 130.36, 137.40, 138.00 (arom), 162.42 (C-8a), 165.95 (arom), 167.76 (C-2) ppm; IR (KBr): $\bar{\nu} = 1545$, 1418, 1350, 700 cm^{-1}; MS (70 eV): $m/z = 288$ (M^+, 100), 287 (M-H, 78), 273 (M-CH_3, 30).

2,4-Bis(4-methylphenyl)-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine (**3f**, $C_{21}H_{20}N_2O$)
Recrystallization from methanol afforded 1.70 g (54%) **3f**. Mp 164–165°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.00$ (tt, $J = 6.3$, 5.1 Hz, H-6), 2.40 (s, CH_3), 2.43 (s, CH_3), 2.85 (t, $J = 6.3$ Hz, H-5), 4.47 (t, $J = 5.1$ Hz, H-7), 7.26 (d, $J = 8.3$ Hz, Ar–H), 7.28 (d, $J = 8.3$ Hz, Ar–H), 7.61 (d, $J = 8.3$ Hz, Ar–H), 8.39 (d, $J = 8.3$ Hz, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.32$ (CH_3), 21.39 (CH_3), 21.89 (C-6), 23.53 (C-5), 67.62 (C-7), 109.56 (C-4a), 128.07, 128.86, 129.04, 128.94, 128.99, 134.75, 135.22, 139.29, 140.41 (arom), 162.35 (C-8a), 165.81, 167.60 (C-2) ppm; IR (KBr): $\bar{\nu} = 1555$, 1400, 1157, 797 cm^{-1}; MS (70 eV): $m/z = 316$ (M^+, 100), 301 (M-CH_3, 30).

2,4-Bis(4-methoxyphenyl)-6,7-dihydro-5H-pyrane[2,3-d]pyrimidine (**3g**, $C_{21}H_{20}N_2O_3$)
Recrystallization from ethanol afforded 3.12 g (90%) **3g**. Mp 135–136°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.99$ (tt, $J = 6.3$, 5.1 Hz, H-6), 2.87 (t, $J = 6.3$ Hz, H-5), 3.86 (s, OCH_3), 3.87 (s, OCH_3), 4.47 (t, $J = 5.1$ Hz, H-7), 6.95 (d, $J = 8.9$ Hz, Ar–H), 7.02 (d, $J = 8.3$ Hz, Ar–H), 7.70 (d, $J = 8.3$ Hz, Ar–H), 8.45 (d, $J = 8.3$ Hz, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.65$ (C-6), 23.36 (C-5), 54.96 (OCH_3), 55.01 (OCH_3), 67.29 (C-7), 108.63 (C-4a), 113.24, 129.41, 130.01, 130.18, 130.40 (arom), 160.19 (C-8a), 161.29, 161.56, 164.86, 167.33 (C-2) ppm; IR (KBr): $\bar{\nu} = 1556$, 1510, 1402, 1250 cm^{-1}; MS (70 eV): $m/z = 348$ (M^+, 100), 333 (M-CH_3, 33).

2,4-Bis(3,4-dimethoxyphenyl)-6,7-dihydro-5H-pyrane[2,3-d]pyrimidine (**3h**, $C_{23}H_{24}N_2O_5$)
Recrystallization from methanol afforded 3.38 g (83%) **3h**. Mp 145–146°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.01$ (tt, $J = 6.2$, 5.2 Hz, H-6), 2.88 (t, $J = 6.2$ Hz, H-5), 3.93–3.98 (bs, 4OCH_3), 4.49 (t, $J = 5.2$ Hz, H-7), 6.93 (d, $J = 8.4$ Hz, Ar–H), 6.96 (d, $J = 8.4$ Hz, Ar–H), 7.33 (d, $J = 1.9$ Hz, Ar–H), 8.04 (d, $J = 1.9$ Hz, Ar–H), 8.13 (dd, $J = 8.4$, 1.9 Hz, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.85$ (C-6), 23.62 (C-5), 55.75 (OCH_3), 55.83 (OCH_3), 55.87 (OCH_3), 67.52 (C-7), 108.90 (C-4a), 110.39, 110.44, 110.66, 112.46, 121.35, 121.97, 130.28, 130.60, 148.57, 148.64, 149.96, 150.98, 161.77, 165.18 (arom), 167.50 (C-2) ppm; IR (KBr): $\bar{\nu} = 1556$, 1516, 1398, 1265, 1140 cm^{-1}; MS (70 eV): $m/z = 408$ (M^+, 100), 393 (M-CH_3, 28), 377 (M-OCH_3, 10), 362 (M-C_2H_6O, 15).

2,4-Bis(methylsulfonyl)-6,7-dihydro-5H-pyrane[2,3-d]pyrimidine (**4d**, $C_9H_{12}N_2O_5S_2$)
To a stirred solution of 0.91 g **3d** (4 mmol) in 10 cm^3 CH_2Cl_2 4.85 g *m-CPBA* (28 mmol) dissolved in 25 cm^3 CH_2Cl_2 were added. The mixture was stirred at room temperature for 4 h. An aqueous solution of $Na_2S_2O_3$ (5%) was added and the layers were shaked and separated. The organic layer was washed with aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by recrystallization in methanol affording 0.95 g (85%) **4d**. Mp 176–177°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.15$ (tt, $J = 6.3$, 5.3 Hz, H-6), 3.31 (t, $J = 6.3$ Hz, H-5) overlapped with

3.31 (s, SO_2CH_3), 3.43 (s, SO_2CH_3), 4.58 (t, $J = 5.3$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.74$ (C-6), 20.28 (C-5), 39.08 (SO_2CH_3), 39.84 (SO_2CH_3), 69.30 (C-7), 116.64 (C-4a), 162.82 (C-8a), 164.16 (C-4), 169.98 (C-2) ppm; IR (KBr): $\bar{\nu} = 1541$, 1331, 1310, 1132 cm^{-1}; MS (70 eV): $m/z = 292$ (M^+, 100), 277 (M–CH_3, 8), 213 (M–SO_2CH_3, 24).

2-(Methylsulfonyl)-6,7-dihydro-5H-pyrane[2,3-d]pyrimidin-4-amine (**5d**, $C_8H_{11}N_3O_3S$)
A continuous stream of NH_3 was bubbled through a solution of 0.43 g **4d** (2.0 mmol) in 30 cm^3 CH_2Cl_2 at room temperature. After 2 h, the solvent was removed and the residue washed with H_2O and recrystallized from methanol giving 0.43 g (95%) **5d**. Mp 96–97°C; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.96$ (tt, $J = 6.3$, 5.0 Hz, H-6), 2.39 (t, $J = 6.3$ Hz, H-5), 3.19 (s, SO_2CH_3), 4.29 (t, $J = 5.0$ Hz, H-7), 7.30 (bs, NH_2) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 18.70$ (C-6), 20.40 (C-5), 38.70 (SO_2CH_3), 67.08 (C-7), 162.41 (C-4a), 163.68 (C-8a), 163.70 (C-4), 165.51 (C-2) ppm; IR (KBr): $\bar{\nu} = 3587$, 3416, 3335, 1585, 1294, 1132 cm^{-1}; MS (70 eV): $m/z = 229$ (M^+, 19), 214 (M-CH_3, 21), 150 (M-SO_2CH_3, 100).

2,4-Dimethoxy-6,7-dihydro-5H-pyrane[2,3-d]pyrimidine (**6d**, $C_9H_{12}N_2O_3$)
A solution containing 0.58 g **4d** (2.0 mmol) and 0.38 g $NaOCH_3$ (6.0 mmol) in 20 cm^3 dry methanol was refluxed for 2 h. After H_2O addition and extraction with CH_2Cl_2, the organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was recrystallized from methanol affording 0.38 g (96%) **6d**. Mp 83–84°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.97$ (tt, $J = 6.4$, 5.2 Hz, H-6), 2.51 (t, $J = 6.2$ Hz, H-5), 3.92 (s, OCH_3), 3.95 (s, OCH_3), 4.31 (t, $J = 5.2$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.65$ (C-6), 21.14 (C-5), 54.07 (OCH_3), 54.47 (OCH_3), 67.64 (C-7), 91.72 (C-4a), 163.01 (C-8a), 168.18 (C-4), 169.79 (C-2) ppm; IR (KBr): $\bar{\nu} = 1578$, 1474, 1356, 1134, 783 cm^{-1}; MS (ESI): $m/z = 197$ $[M + H]^+$.

1,5,6,7-Tetrahydro-2H-pyrano[2,3-d]pyrimidin-2,4(3H)-dione (**7d**, $C_7H_8N_2O_3$)
To 20 cm^3 aqueous NaOH (10%) 0.58 g **4d** (2.0 mmol) were added. The suspension was refluxed for 2 h, then the reaction mixture was acidified with HCl (10%) until *pH* 2 and the solid was collected by filtration and washed with H_2O. Recrystallization from H_2O gave 0.31 g **7d** (93%). Mp 270°C (dec); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 1.82$ (tt, $J = 6.2$, 5.1 Hz, H-6), 2.15 (t, $J = 6.2$ Hz, H-5), 4.22 (t, $J = 5.1$ Hz, H-7), 10.70 (s, NH), 11.19 (s, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 16.43$ (C-6), 20.80 (C-5), 68.35 (C-7), 85.31 (C-4a), 149.84 (C-8a), 157.37 (C-4), 164.40 (C-2) ppm; IR (KBr): $\bar{\nu} = 3447$, 1595 cm^{-1}; MS (70 eV): $m/z = 168$ (M^+, 100), 153 (M-NH, 32), 140 (M-CO, 6).

2-Methoxy-6,7-dihydro-5H-pyrane[2,3-d]pyrimidin-4-amine (**8d**, $C_8H_{11}N_3O_2$)
A solution of 0.45 g **5d** (2.0 mmol) and 0.38 g $NaOCH_3$ (6.0 mmol) in 20 cm^3 dry methanol was refluxed for 2 h. After H_2O addition and extraction with CH_2Cl_2, the organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by recrystallization from methanol affording 0.35 g (97%) **8d**. Mp 150°C (dec); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.04$ (tt, $J = 6.3$, 5.1 Hz, H-6), 2.39 (t, $J = 6.3$ Hz, H-5), 3.89 (s, OCH_3), 4.31 (t, $J = 5.1$ Hz, H-7), 5.29 (bs, NH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.34$ (C-6), 21.34 (C-5), 54.24 (OCH_3), 67.16 (C-7), 87.81 (C-4a), 163.23 (C-8a), 163.71 (C-4), 167.33 (C-2) ppm; IR (KBr): $\bar{\nu} = 3454$, 1647, 1603, 1572, 1371, 1138 cm^{-1}; MS (70 eV): $m/z = 181$ (M^+, 100), 151 (M-CH_2O, 40), 99 (23).

2-Phenyl-N-{1-[(phenylacetyl)amino]prop-2-enylidene}acetamide (**10**, $C_{19}H_{18}N_2O_2$)
Following the general procedure for the synthesis of pyranopyrimidines, the reaction of 1.0 g **9** (13.9 mmol), 6.5 g benzylcyanide (55.6 mmol), and 5.86 g Tf_2O (20.8 mmol) afforded after recrystallization from a mixture of $CHCl_3$ and *n*-hexane, 1.49 g (35%) **10**. Mp 128–129°C; ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 3.83$ (s, CH_2), 3.93 (s, CH_2), 5.88 (dd, $J = 10.2$, 1.5 Hz, =CH), 6.35 (dd, $J = 17.0$, 1.5 Hz, =CH), 6.62 (dd, $J = 17.0$, 10.2 Hz, =CH), 7.27–7.35 (m, Ar–H), 11.00 (s, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 44.09$ (CH_2), 44.13 (CH_2), 127.42, 127.43, 128.75, 128.77, 129.48, 129.53,

129.84, 131.48, 133.14, 133.25, 165.52 (=C and arom), 172.07 (CO), 172.75 (CO) ppm; IR (KBr): $\bar{\nu} = 3265$, 3171, 1728, 1506, 1173 cm^{-1}; MS (ESI): $m/z = 305$ $[M\text{-}H]^-$.

2,4-Diphenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (**14e**, $C_{19}H_{16}N_2O$)
Following the general procedure for the synthesis of pyranopyrimidines, the reaction of 1.0 g tetrahydro-4*H*-pyran-4-one (10.0 mmol), 4.12 g benzonitrile (40.0 mmol), and 4.23 g Tf_2O (15.0 mmol) gave after recrystallization from methanol 1.0 g (35%) **14e**. Mp 128–129°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.15$ (t, $J = 6.0$ Hz, H-8), 4.17 (t, $J = 6.0$ Hz, H-7), 4.85 (s, H-5), 7.46–7.53 (m, Ar–H), 7.61–7.63 (m, Ar–H), 8.48–8.53 (m, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.45$ (C-8), 66.26 (C-5), 67.03 (C-7), 123.96 (C-4a), 128.40, 128.56, 128.63, 128.78, 130.10, 130.92, 137.12 (arom), 162.05 (C-4), 162.96 (C-2), 163.18 (C-8a) ppm; IR (KBr): $\bar{\nu} = 1466$, 1215 cm^{-1}; MS (70 eV): $m/z = 288$ (M^+, 75), 259 (M-C_2H_5, 100).

2,4-Bis(4-methylphenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (**14f**, $C_{20}H_{18}N_2O$)
Following the general procedure for the synthesis of pyranopyrimidines, the reaction of 1.0 g tetrahydro-4*H*-pyran-4-one (10.0 mmol), 4.68 g 4-methylbenzonitrile (40.0 mmol), and 4.23 g Tf_2O (15.0 mmol) afforded, after recrystallization from ethanol, 0.89 g (28%) **14f**. Mp 149–150°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.42$ (s, CH_3), 2.44 (s, CH_3), 3.20 (t, $J = 6.0$ Hz, H-8), 4.15 (t, $J = 5.1$ Hz, H-7), 4.85 (s, H-5), 7.31 (m, Ar–H), 7.54 (m, Ar–H), 8.39 (m, 2H, Ar–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.49$ (CH_3), 21.60 (CH_3), 29.60 (C-8), 64.75 (C-7), 65.94 (C-8), 124.01 (C-4a), 128.86, 129.04, 129.49, 129.57, 133.62, 141.37 (arom), 142.49 (C-4), 160.77 (C-2), 161.65 (C-8a), 165.81, 167.60 (C-2) ppm; IR (KBr): $\bar{\nu} = 1547$, 1217 cm^{-1}; MS (70 eV): $m/z = 316$ (M^+, 81), 301 (M-CH_3, 4), 287 (M-C_2H_5, 100).

2-(4-Hydroxytetrahydro-2H-thiopyran-4-yl)penta-1,4-dien-3-one (**15**, $C_{10}H_{14}O_2S$)
To 1.0 g **12** (9.6 mmol) dissolved in 15 cm^3 CH_2Cl_2 and cooled al −78°C 2.92 g Tf_2O (10.3 mmol) dissolved in 25 cm^3 CH_2Cl_2 were added dropwise. The reaction mixture was stirred 2 h at this temperature and was allowed to stand at −20°C for 2 days. The reaction mixture was hydrolyzed by careful addition of a saturated aqueous solution of $NaHCO_3$ until *pH* was basic. The organic layer was separated, washed with brine, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by column chromatography using *n*-hexane/ethyl acetate = 7/3 as eluent. Recrystallization from methanol afforded 0.46 g (48%) **15**. Mp 59–60°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.86$ (m, CH_2), 2.10 (m, CH_2), 2.35 (m, CH_2), 3.17 (m, CH_2), 5.88 (dd, $J = 10.5$, 1.4 Hz, =CH), 5.93 (d, $J = 2.6$ Hz, =CH_2), 6.26 (dd, $J = 17.1$, 1.4 Hz, =CH), 6.75 (dd, $J = 17.1$, 10.5 Hz, =CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 23.56$ (CH_2), 37.43 (CH_2), 71.42 (C), 123.96, 130.94, 133.86, 152.88, 195.98 (CO) ppm; IR (KBr): $\bar{\nu} = 3447$, 1653, 1425, 1215 cm^{-1}; MS (ESI): $m/z = 237$ $[M + K]^+$, 221 $[M + Na]^+$.

Acknowledgements

We gratefully acknowledge the DGSIC (Spain, grant BQU2002-00406). We also thank the CAIs of the UCM for recording MS and NMR spectra and determining elemental analysis.

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