Regiospecific Bromination of 2-Phenyl-3*H*-pyrimidin-4-ones

Nilo Zanatta,* Leonardo Fantinel, Liana da S. Fernandes, Ana D. Wouters, Helio G. Bonacorso, Marcos A. P. Martins

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil
Fax +55(55)2208031; E-mail: zanatta@base.ufsm.br

Received 11 June 2008; revised 21 July 2008

Abstract: Three methods for the regiospecific bromination of 2-phenyl-3*H*-pyrimidin-4-ones are presented: bromination of the 5-position of the pyrimidine ring, bromination of the 6-benzylic position and simultaneous bromination of both the 5-position of the pyrimidine ring and 6-benzylic position. Reactions were carried out using simple protocols and the brominated pyrimidines were obtained in good yields.

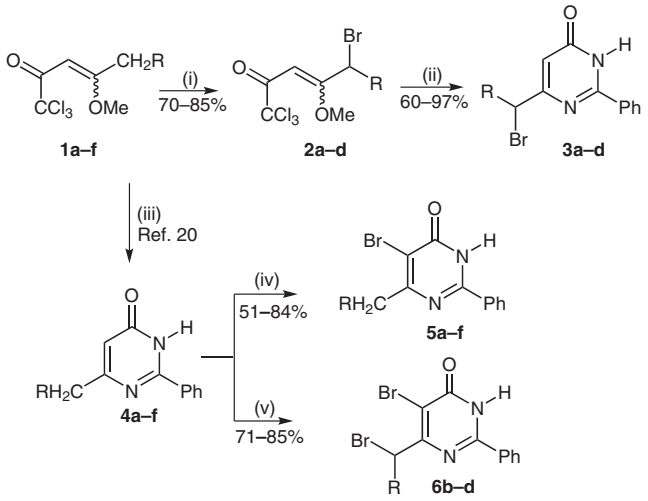
Key words: enones, bromination, bromopyrimidines, pyrimidin-4-ones, 2-phenyl-pyrimidin-4-ones

The introduction of halogen and halogenated groups into organic molecules often confers significant and useful changes in their chemical, physical, and biological properties. For example, 5-fluorouracil is a well-known antitumor agent.[1] In addition, 5-halosubstituted pyrimidines exhibit analgesic, antiinflamatory,[2] agrochemical fungicidal,[3] and herbicidal[4] activity, as well as acting as modulators of voltage-gated ion channels.[5] Furthermore, halogenated pyrimidines have been utilized as intermediates for a variety of synthetic transformations of related compounds of biological interest.[6] It has been shown that 5-halouracil derivatives undergo palladium-catalyzed cross-coupling reactions with vinyl ketones[7] and with alkynes,[8] to give 5-alkanyl- and 5-alkynyl-uracil, respectively. Moreover, halopyrimidines may be used in Suzuki coupling reactions[9] and to generate reactive organometallic intermediates by metalation.[10] Therefore, new methods for the convenient synthesis of 5-halopyrimidine derivatives are of current interest in synthetic chemistry.

Bromination of the 5-position of pyrimidines has been carried out with bromine/acetic anhydride,[11] bromine/water,[12] bromine/dimethylformamide,[13] *N*-bromosuccinimide,[14] and with lithium bromide in the presence of ceric ammonium nitrate (CAN).[15] Bromination of other positions of the pyrimidinone ring has been carried out with phosphorus tribromide[16] through substitution of the carbonyl oxygen by the bromine atom.

Although many methods for the bromination of the pyrimidine ring can be found, the corresponding benzylic halogenation has been less explored because over-bromination is a major problem.[17] Recently, a convenient and regiospecific method for mono- and di-bromination of the benzylic position of pyrimidines using the halogen-containing building block approach has been reported.[17a,18] In the present paper, we present three methods for the regiospecific bromination of 2-phenyl-3*H*-pyrimidin-4-ones: bromination of the 5-position of the pyrimidine ring, bromination of the 6-benzylic position and simultaneous bromination of both the 5-position of the pyrimidine ring and the 6-benzylic position.

Scheme 1 outlines the synthetic strategy used for the regiospecific bromination of 2-phenyl-3*H*-pyrimidin-4-ones. Compounds **3a–d** were synthesized through the halogen-containing building block approach as previously reported.[17a,18] Compounds **2c–d** are new. Compounds **3a–d** were obtained by the cyclocondensation reaction of compounds **2a–d** with benzamidine hydrochloride in the presence of sodium hydride, in anhydrous THF, according to Scheme 1. Compounds of type **3** are important intermediates in the preparation of compounds with potential antitumoral and/or antiviral activities.[19]



R = H (**a**), Me (**b**), Et (**c**), *n*-Pr (**d**), *i*-Pr (**e**), Ph (**f**)

Scheme 1 *Reagents and conditions:* (i) 1. Br_2, CH_2Cl_2, 1 h, 25 °C; 2. py, 1 h, 0 °C; (ii) benzamidine hydrochloride, NaH, THF, 16 h, reflux; (iii) benzamidine hydrochloride, 1 M NaOH, CH_2Cl_2, 15 min, r.t.; (iv) Br_2, MeOH, 5 min, r.t.; (v) NBS, MCPBA, $CHCl_3$, 16 h, r.t.

Compounds **5a–f** were prepared through the bromination of the pyrimidines **4a–f** using bromine in methanol. The synthesis of pyrimidines **4a–f** has been recently reported.[20] Compounds **5** are intermediates in the synthesis of the Bromacil© analogue, which is an important herbicide used for total weed and brush control on non-crop land.[21]

SYNTHESIS 2008, No. 21, pp 3492–3496
Advanced online publication: 16.10.2008
DOI: 10.1055/s-0028-1083178; Art ID: M02908SS

Compounds **6b–d** were obtained through the bromination of pyrimidines **4b–d** with two equivalents of *N*-bromosuccinimide (NBS), in chloroform, in the presence of a catalytic amount of 3-chloroperoxybenzoic acid, under conditions which are typical for free-radical reactions.[17b,22] However, bromination of the 5-ring position, seems to be carried out by aromatic electrophilic substitution. When bromination was carried out with one equivalent of NBS, a mixture of ring and benzylic brominated products was obtained. Alternatively, compounds of type **6** could be obtained through bromination of compounds **3** using bromine in methanol (reaction conditions *iv*, Scheme 1). This, however, would take three reaction steps instead of two. The reaction of compound **4a** failed to give compound **6a** through method *v*. Compounds **6** are important chemical intermediates for the preparation of novel inhibitors of human thymidine phosphorylase (TP).[23] The optimized reaction conditions and yields for the synthesis of compounds **3** are presented in Table 1; those obtained from the synthesis of compounds **5** and **6** are presented in Table 2. All products described in this paper, except **3a**, are new and were fully characterized by GC-MS, ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis.

Table 1 Optimized Reaction Conditions and Yields for the Synthesis of Compounds **3**

Entry	Compd	Method[a]	Yield (%)[b]	Product
1	**2a**	A	60	**3a**
2	**2b**	A	60	**3b**
3	**2c**	A	97	**3c**
4	**2d**	A	74	**3d**

[a] Method A: PhC(=NH)NH$_2$·HCl, THF, 0 °C then reflux, 16 h.
[b] Yield after purification.

Table 2 Optimized Reaction Conditions and Yields for the Synthesis of Compounds **5** and **6**

Entry	Compd	Method[a]	Yield (%)[b]	Product
1	**4a**	B	70	**5a**
2	**4b**	B	69	**5b**
3	**4c**	B	73	**5c**
4	**4d**	B	84	**5d**
5	**4e**	B	51	**5e**
6	**4f**	B	60	**5f**
7	**4b**	C	71	**6b**
8	**4c**	C	85	**6c**
9	**4d**	C	85	**6d**

[a] Method B: Br$_2$, MeOH, r.t., 5 min; Method C: NBS (2 equiv), CHCl$_3$, MCPBA (15 mol%), r.t., 16 h.
[b] Yield after purification.

In summary, we have synthesized a number of useful brominated 2-phenyl-3*H*-pyrimidin-4-ones through regiospecific halogenations. It has been demonstrated that it is possible to regiospecifically brominate the 5-pyrimidine ring position and the 6-benzylic position, as well as to simultaneously brominate both positions, using simple protocols and rendering good yields. The bromopyrimidines obtained are useful intermediates for the synthesis of potential biologically active compounds through an immense variety of nucleophilic and nucleophilic heteroaromatic substitution reactions and metal-catalyzed cross-coupling reactions.

The synthesis of compounds **1a–f**,[24] **2a**, **2b**,[18] and **4a–f**[20] were reported by our group. All melting points were determined on a Kofler Reichert Thermovar or on a MQAPF-301 apparatus and are uncorrected. The CHN microanalyses were performed on a Perkin–Elmer 2400 elemental analyzer from the Department of Chemistry of the Universidade de São Paulo, São Paulo, SP, Brazil. Mass spectra were recorded using a HP 5973 MSD connected to a HP 6890 GC. The GC was equipped with a split-splitless injector, auto-sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX200 or DPX400 spectrometer in CDCl$_3$ or DMSO-d_6 with TMS as the internal reference.

5-Bromo-1,1,1-trichloro-4-methoxyalk-3-en-2-ones 2c–d; General Procedure

To a solution of 1,1,1-trichloro-4-methoxyalk-3-en-2-one **1c–d** (50 mmol) in CH_2Cl_2 (30 mL), a solution of Br_2 (50 mmol) in CH_2Cl_2 (20 mL) was added. The mixture was stirred for 1 h at 25 °C, cooled to 0 °C and pyridine (50 mmol) was added. After 1 h, the reaction mixture was washed with HCl (15%, 30 mL) and with H_2O (2 × 50 mL). The organic phase was dried with $MgSO_4$ and the solvent was removed yielding the compounds **2c–d**. Subsequent purification was not required for compounds **2c–d**. For the synthesis of compounds **2a–b**, see Martins et al.[18]

5-Bromo-1,1,1-trichloro-4-methoxyhex-3-en-2-one (2c)

Yield: 70%; oil.

GC-MS (EI, 70 eV): *m/z* (%) = 322 (1) [M$^+$], 324 (2) [M + 2], 326 (1) [M + 4], 205 (100), 207 (100), 125 (36), 111 (45), 69 (24).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3 H, CH$_3$), 2.04 (quint, *J* = 7.4 Hz, 2 H, CH$_2$), 3.88 (s, 3 H, OCH$_3$), 5.82 (t, *J* = 7.4 Hz, 1 H, CH), 6.01 (s, 1 H, H-3).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.1 (CH$_3$), 28.4 (CH$_2$), 46.8 (CH), 57.0 (OCH$_3$), 90.5 (C-3), 97.4 (C-1), 177.1 (C-4), 179.6 (C-2).

Anal. Calcd for $C_8H_{10}BrCl_3O_2$: C, 29.62; H, 3.11. Found: C, 30.11; H, 2.73.

5-Bromo-1,1,1-trichloro-4-methoxyhep-3-en-2-one (2d)

Yield: 85%; oil.

GC-MS (EI, 70 eV): *m/z* (%) = 336 (1) [M$^+$], 338 (2) [M + 2], 340 (1) [M + 4], 219 (100), 221 (100), 139 (20), 111 (65).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 1.42 (sext, *J* = 7.2 Hz, 2 H, CH$_2$), 1.96–2.06 (m, 2 H, CH$_2$), 3.88 (s, 3 H, OCH$_3$), 5.92 (t, *J* = 7.2 Hz, 1 H, CH), 5.99 (s, 1 H, H-3).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.3 (CH$_3$), 20.7 (CH$_2$), 36.8 (CH$_2$), 44.9 (CH), 56.9 (OCH$_3$), 90.3 (C-3), 97.4 (C-1), 177.2 (C-4), 179.6 (C-2).

Anal. Calcd for $C_9H_{12}BrCl_3O_2$: C, 31.94; H, 3.57. Found: C, 31.64; H, 3.22.

6-Bromoalkyl-2-phenylpyrimidin-4(3*H*)-ones 3a–d; General Procedure

To a solution of benzamidine hydrochloride (0.16 g, 1.0 mmol) in anhydrous THF (10 mL), stirred in an ice-bath, NaH (36.0 mg, 1.5 mmol) was added. To this mixture, a solution of enone **2a–d** (1.0 mmol) in anhydrous THF (1.0 mL) was added dropwise through an addition funnel. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to r.t. and then refluxed for 16 h. At the end of the reaction, NaCl was filtered off and the solvent was removed with a rotary evaporator. Products **3a–d** were purified by recrystallization from MeOH or hexane–$CHCl_3$ (1:3).

6-(Bromomethyl)-2-phenylpyrimidin-4(3*H*)-one (3a)

Yield: 60%; mp 132–135 °C (MeOH).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.47 (s, 2 H, CH_2), 6.52 (s, 1 H, H-5), 7.48–7.63 and 8.09–8.14 (2 m, 5 H, Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 62.2 (CH_2), 109.8 (C-5), 127.8, 128.3, 131.6, 131.9 (Ph), 157.5 (C-6), 163.9 (C-2), 167.1 (C-4).

GC-MS (EI, 70 eV): *m*/*z* (%) = 264 (59) [M^+], 157 (29), 104 (100), 77 (38), 51 (21).

Anal. Calcd for $C_{11}H_9BrN_2O$: C, 49.84; H, 3.42; N, 10.57. Found: C, 50.04; H, 3.53; N, 10.78.

6-(1-Bromoethyl)-2-phenylpyrimidin-4(3*H*)-one (3b)

Yield: 60%; mp 176–177 °C ($CHCl_3$–hexane, 3:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.03 (d, *J* = 7.0 Hz, 3 H, CH_3), 4.96 (q, *J* = 7.0 Hz, 1 H, CH), 6.56 (s, 1 H, H-5), 7.51–7.57 and 8.22–8.27 (2 m, 5 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8 (CH_3), 47.2 (CH), 109.5 (C-5), 127.9, 129.0, 131.7, 132.3 (Ph), 157.2 (C-2), 165.5 (C-4), 167.8 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 278 (20) [M^+], 280 (20) [M + 2], 199 (100), 104 (64), 97 (40), 77 (24).

Anal. Calcd for $C_{12}H_{11}BrN_2O$: C, 51.66; H, 3.97; N, 10.04. Found: C, 51.64; H, 3.90; N, 10.37.

6-(1-Bromopropyl)-2-phenylpyrimidin-4(3*H*)-one (3c)

Yield: 97%; mp 175–176 °C ($CHCl_3$–hexane, 3:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.28 (quint, *J* = 7.2 Hz, 2 H, CH_2), 4.69 (t, *J* = 7.2 Hz, 1 H, CH), 6.52 (s, 1 H, H-5), 7.53–7.56, 8.23–8.27 (m, 5 H, Ph), 13.09 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (CH_3), 30.1 (CH_2), 55.0 (CH), 110.4 (C-5), 127.9, 129.0, 131.7, 132.3 (Ph), 157.2 (C-2), 165.6 (C-4), 167.0 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 292 (2) [M^+], 294 (2) [M + 2], 266 (30), 264 (30), 213 (100), 186 (31), 104 (51), 77 (24).

Anal. Calcd for $C_{13}H_{13}BrN_2O$: C, 53.26; H, 4.47; N, 9.56. Found: C, 53.00; H, 4.66; N, 9.76.

6-(1-Bromobutyl)-2-phenylpyrimidin-4(3*H*)-one (3d)

Yield: 74%; mp 152–153 °C ($CHCl_3$–hexane, 3:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.49 (sext, *J* = 7.4 Hz, 2 H, CH_2), 2.22 (q, *J* = 7.4 Hz, 2 H, CH_2), 4.77 (t, *J* = 7.4 Hz, 1 H, CH), 6.51 (s, 1 H, H-5), 7.54–7.56, 8.23–8.27 (m, 5 H, Ph), 13.11 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4 (CH_3), 21.0 (CH_2), 38.7 (CH_2), 53.0 (CH), 110.0 (C-5), 127.9, 129.0, 131.4, 132.3 (Ph), 157.3 (C-2), 165.6 (C-4), 167.2 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 306 (2) [M^+], 308 (2) [M + 2], 266 (52), 264 (52), 227 (100), 104 (47), 77 (20).

Anal. Calcd for $C_{14}H_{15}BrN_2O$: C, 54.74; H, 4.92; N, 9.12. Found: C, 54.71; H, 4.93; N, 9.12.

5-Bromo-2-phenylpyrimidin-4(3*H*)-ones 5a–f; General Procedure

To a solution of pyrimidinone **4a–f** (1.0 mmol) in MeOH (20 mL), Br_2 (2.72 g, 1.7 mmol) was added under vigorous stirring at r.t. for 5 min. Compounds **5a–f** precipitated in the reaction vessel after partial evaporation of the solvent in the rotary evaporator. The products were collected by filtration and purified by recrystallization from MeOH.

5-Bromo-6-methyl-2-phenylpyrimidin-4(3*H*)-one (5a)

Yield: 70%; mp 160–161 °C (MeOH).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.48 (s, 3 H, CH_3), 7.50–7.62, 8.06–8.10 (m, 5 H, Ph).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 24.2 (CH_3), 110.0 (C-5), 128.0, 128.7, 131.1, 132.0 (Ph), 155.0 (C-2), 159.2 (C-6), 161.4 (C-4).

GC-MS (EI, 70 eV): *m*/*z* (%) = 264 (75) [M^+], 266 (75) [M + 2], 185 (7), 130 (23), 104 (100), 77 (71).

Anal. Calcd for $C_{11}H_9BrN_2O$: C, 49.84; H, 3.42; N, 10.57. Found: C, 49.72; H, 3.38; N, 10.35.

5-Bromo-6-ethyl-2-phenylpyrimidin-4(3*H*)-one (5b)

Yield: 69%; mp 259–260 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23 (t, *J* = 7.4 Hz, 3 H, CH_3), 2.78 (q, *J* = 7.4 Hz, 2 H, CH_2), 7.52–7.62, 8.11–8.13 (m, 5 H, Ph), 13.15 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.0 (CH_3), 29.9 (CH_2), 108.9 (C-5), 127.6, 128.3, 131.1, 131.4 (Ph), 154.9 (C-2), 159.1 (C-4), 165.7 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 278 (97) [M^+], 280 (97) [M + 2], 251 (13), 249 (13), 199 (17), 171 (21), 104 (100), 77 (49).

Anal. Calcd for $C_{12}H_{11}BrN_2O$: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.74; H, 4.43; N, 9.99.

5-Bromo-6-propyl-2-phenylpyrimidin-4(3*H*)-one (5c)

Yield: 73%; mp 228–230 °C (MeOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.82 (sext, *J* = 7.2 Hz, 2 H, CH_2), 2.85 (q, *J* = 7.2 Hz, 2 H, CH_2), 7.49–7.52, 8.19–8.21 (m, 5 H, Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.5 (CH_3), 20.3 (CH_2), 38.9 (CH_2), 110.1 (C-5), 127.4, 128.4, 131.2, 131.4 (Ph), 154.1 (C-2), 160.2 (C-4), 166.2 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 292 (8) [M^+], 294 (8) [M + 2], 266 (100), 264 (100), 213 (9), 104 (67), 77 (36).

Anal. Calcd for $C_{13}H_{13}BrN_2O$: C, 53.26; H, 4.47; N, 9.56. Found: C, 53.43; H, 4.06; N, 9.71.

5-Bromo-6-butyl-2-phenylpyrimidin-4(3*H*)-one (5d)

Yield: 84%; mp 213–215 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.93 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.39 (sext, *J* = 7.2 Hz, 2 H, CH_2), 1.68 (quint, *J* = 7.2 Hz, 2 H, CH_2), 2.77 (t, *J* = 7.2 Hz, 2 H, CH_2), 7.52–7.62, 8.10–8.12 (m, 5 H, Ph), 13.16 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.7 (CH_3), 21.8 (CH_2), 28.9 (CH_2), 36.2 (CH_2), 109.9 (C-5), 127.9, 128.6, 131.4, 131.9 (Ph), 155.0 (C-2), 159.3 (C-4), 164.7 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 306 (2) [M$^+$], 308 (2) [M + 2], 266 (100), 264 (100), 227 (10), 104 (83), 77 (45).

Anal. Calcd for $C_{14}H_{15}BrN_2O$: C, 54.74; H, 4.92; N, 9.12. Found: C, 55.15; H, 4.65; N, 9.32.

5-Bromo-6-isobutyl-2-phenylpyrimidin-4(3*H*)-one (5e)
Yield: 51%; mp 236–238 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.97 (d, *J* = 7.0 Hz, 6 H, 2 × CH_3), 2.24 (m, 1 H, CH), 2.68 (d, *J* = 7.0 Hz, 2 H, CH_2), 7.53–7.61, 8.09–8.11 (m, 5 H, Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.3 (2 × CH_3), 27.3 (CH), 45.1 (CH_2), 110.8 (C-5), 127.9, 128.7, 131.4, 131.9 (Ph), 154.8 (C-2), 159.3 (C-4), 164.0 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 306 (5) [M$^+$], 308 (5) [M + 2], 266 (100), 264 (100), 227 (8), 104 (84), 77 (48).

Anal. Calcd for $C_{14}H_{15}BrN_2O$: C, 54.74; H, 4.92; N, 9.12. Found: C, 54.52; H, 4.56; N, 9.08.

5-Bromo-6-phenyl-2-phenylpyrimidin-4(3*H*)-one (5f)
Yield: 60%; mp 305–306 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.51–7.79, 8.14–8.16 (m, 10 H, 2 × Ph), 13.31 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 109.4 (C-5), 127.8, 127.9, 128.6, 128.9, 129.5, 131.5, 131.9, 138.0 (Ph), 154.9 (C-2), 159.8 (C-6), 161.1 (C-4).

GC-MS (EI, 70 eV): *m*/*z* (%) = 326 (68) [M$^+$], 328 (69) [M + 2], 300 (21), 298 (21), 247 (56), 104 (100), 77 (76).

Anal. Calcd for $C_{16}H_{11}BrN_2O$: C, 58.74; H, 3.39; N, 8.56. Found: C, 59.10; H, 3.30; N, 8.54.

5-Bromo-6-(1-bromoalkyl)-2-phenylpyrimidin-4(3*H*)-ones 6b–d; General Procedure
To a solution of pyrimidinone **4b–d** (1.0 mmol) in $CHCl_3$ (20 mL), NBS (3.56 g, 2.0 mmol) and MCPBA (15 mol%) were added under stirring and the reaction was continued at r.t. for 16 h. The solvent was evaporated by rotary evaporator and the solids were washed with cold H_2O to remove succinimide and benzoic acid residues. Products were dried in a desiccator under phosphorous pentoxide and then recrystallized ($CHCl_3$–MeOH, 3:1).

5-Bromo-6-(1-bromoethyl)-2-phenylpyrimidin-4(3*H*)-one (6b)
Yield: 71%; mp 253–255 °C ($CHCl_3$–MeOH, 3:1).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.98 (d, *J* = 6.8 Hz, 3 H, CH_3), 5.54 (q, *J* = 6.8 Hz, 1 H, CH), 7.52–7.64, 8.14–8.17 (m, 5 H, Ph), 11.06 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.0 (CH_3), 67.1 (CH), 109.1 (C-5), 127.7, 128.4, 128.6, 131.6 (Ph), 155.0 (C-2), 159.2 (C-4), 165.8 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 328 (55) [M$^+$ – 28], 330 (100), 332 (55), 314 (70), 212 (35), 268 (19), 266 (38), 264 (19), 252 (22), 250 (44), 248 (22), 170 (45), 168 (45), 90 (70), 63 (60).

Anal. Calcd for $C_{12}H_{10}Br_2N_2O$: C, 40.26; H, 2.82; N, 7.82. Found: C, 40.60; H, 2.52; N, 8.25.

5-Bromo-6-(1-bromopropyl)-2-phenylpyrimidin-4(3*H*)-one (6c)
Yield: 85%; mp 234–236 °C ($CHCl_3$–MeOH, 3:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.97 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.22–2.35 (m, 2 H, CH_2), 5.29 (t, *J* = 7.2 Hz, 1 H, CH), 7.53–7.64, 8.13–8.15 (m, 5 H, Ph), 13.29 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.6 (CH_3), 28.2 (CH_2), 53.3 (CH), 109.7 (C-5), 127.3, 128.2, 130.8, 131.6 (Ph), 155.2 (C-2), 158.8 (C-4), 160.8 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 370 (2) [M$^+$], 372 (4) [M + 2], 374 (2) [M + 4], 346 (25), 344 (50), 342 (25), 293 (45), 291 (45), 266 (40), 264 (40), 104 (100), 77 (60).

Anal. Calcd for $C_{13}H_{12}Br_2N_2O$: C, 41.97; H, 3.25; N, 7.83. Found: C, 42.36; H, 3.16; N, 7.83.

5-Bromo-6-(1-bromobutyl)-2-phenylpyrimidin-4(3*H*)-one (6d)
Yield: 85%; mp 209–211 °C ($CHCl_3$–MeOH, 3:1).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.93 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.39 (sext, *J* = 7.2 Hz, 2 H, CH_2), 2.26 (q, *J* = 7.2 Hz, 2 H, CH_2), 5.38 (t, *J* = 7.2 Hz, 1 H, CH), 7.54–7.64, 8.13–8.16 (m, 5 H, Ph), 13.34 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.8 (CH_3), 18.3 (CH_2), 37.2 (CH_2), 70.7 (CH), 108.6 (C-5), 128.1, 128.6, 131.4, 132.0 (Ph), 155.5 (C-2), 159.4 (C-4), 165.3 (C-6).

GC-MS (EI, 70 eV): *m*/*z* (%) = 340 (1) [M$^+$ – 44], 342 (2), 344 (1), 302 (25), 300 (100), 298 (72), 263 (50), 261 (16), 234 (38), 104 (80), 77 (42).

Anal. Calcd for $C_{14}H_{14}Br_2N_2O$: C, 43.55; H, 3.65; N, 7.26. Found: C, 43.85; H, 3.69; N, 7.41.

Acknowledgment

The authors thank the Fundação de Apoio à Pesquisa do Estado do Rio Grande do Sul (FAPERGS-PRONEX) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq - Universal grant No. 476634/06-7), for financial support and CAPES (L. Fantinel, A. D. Wouters) and CNPq (L. da S. Fernandes) for the fellowships.

References

(1) Miyashita, O.; Matsumura, K.; Shimatzu, H.; Hashimoto, N. *Chem. Pharm. Bull.* **1981**, *29*, 3181.
(2) Senda, S.; Hirota, K.; Otani, O. *Yakugaku Zasshi* **1974**, *94*, 571; *Chem. Abstr.* **1974**, *81*, 91464.
(3) Minn, K.; Braun, P.; Sachse, B.; Wicke, H. *Ger. Offen.* 4029654, **1992**; *Chem. Abstr.* **1992**, *117*, 171466.
(4) (a) Bucha, H. C.; Loux, H. M.; Harrod, J. E. *Science* **1962**, *137*, 537. (b) Loux, H. M.; Luckenbaugh, R. W.; Soboczenski, E. J. US Patent 3529953, **1963**; *Chem. Abstr.* **1963**, *147*, 316460.
(5) Wilson, D. M.; Martinborough, E.; Neubert, T. D.; Termin, A. P.; Gonzales, J. E.; Zimmermann, N. US Patent 2005049247, **2005**; *Chem. Abstr.* **2005**, *142*, 114092.
(6) (a) Bradshaw, T. K.; Hutchinson, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43. (b) Long, R. A.; Robins, R. K.; Townsend, L. B. *J. Org. Chem.* **1967**, *32*, 2751.
(7) (a) Wada, A.; Ohki, K.; Nagai, S.; Kanatomo, S. *J. Heterocycl. Chem.* **1991**, *28*, 509. (b) Wada, A.; Yasuda, H.; Kanatomo, S. *Synthesis* **1988**, 771.
(8) (a) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854. (b) De Clercq, E.; Descamps, J.; Balzarini, J.; Giziewicz, J.; Barr, P. J.; Robins, M. J. *J. Med. Chem.* **1983**, *26*, 661.

(9) (a) Yamamoto, Y.; Seko, T.; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734. (b) Havelková, M.; Hocek, M.; Cesnek, M.; Dvorac, D. *Synlett* **1999**, 1145. (c) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829. (d) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125.
(10) (a) Grible, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. (b) Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139.
(11) Visser, D. W. In *Synthetic Procedures in Nucleic Acid Chemistry*, Vol. 1; Zorbach, W. W.; Tipson, R. S., Eds.; Wiley: New York, **1968**, 409.
(12) (a) Fukuhara, T. K.; Visser, D. W. *J. Biol. Chem.* **1951**, *190*, 95. (b) Beltz, R. E.; Visser, D. W. *J. Am. Chem. Soc.* **1955**, *77*, 736.
(13) Duval, J.; Ebel, J. P. *Bull. Soc. Chim. Biol.* **1964**, *46*, 1059.
(14) Brammer, K. W. *Biochim. Biophys. Acta* **1963**, *72*, 217.
(15) (a) Sugiyama, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2847. (b) Asakura, J.; Robins, M. J. *Tetrahedron Lett.* **1988**, *29*, 2855. (c) Asakura, J.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 4928.
(16) Ondi, L.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 3714.
(17) (a) Zanatta, N.; Flores, D. C.; Madruga, C. C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2006**, *47*, 573. (b) Strekowski, L.; Wydra, L.; Janda, L.; Harden, D. B. *J. Org. Chem.* **1991**, *56*, 5610. (c) Kaptein, B.; Barf, G.; Kellogg, R. M.; Van Bolhuis, F. *J. Org. Chem.* **1990**, *55*, 1890.
(18) Martins, M. A. P.; Sinhorin, A. P.; da Rosa, A.; Flores, A. F. C.; Wastowski, A. D.; Pereira, C. M. P.; Flores, D. C.; Beck, P.; Freitag, R. A.; Brondani, S.; Cunico, W.; Bonacorso, H. G.; Zanatta, N. *Synthesis* **2002**, 2353.
(19) (a) Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357. (b) Garg, R.; Gupta, S. P.; Gao, H.; Babu, M. S.; Debnath, A. K.; Hansch, C. *Chem. Rev.* **1999**, *99*, 3525. (c) Botta, M.; Occhionero, F.; Nicoletti, R.; Mastromarino, P.; Conti, C.; Magrini, M.; Saladino, R. *Bioorg. Med. Chem.* **1999**, *7*, 1925.
(20) Zanatta, N.; Fantinel, L.; Lourega, R. G.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2008**, 358.
(21) Tomlin, C. D. S. In *The Pesticide Manual*, 14th ed.; British Crop Protection Council: UK, **2006**, 112.
(22) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, 1103.
(23) (a) Reigan, P.; Edwards, P. N.; Gbaj, A.; Cole, C.; Barry, S. T.; Page, K. M.; Ashton, S. E.; Luke, R. W. A.; Douglas, K. T.; Stratford, I. J.; Jaffar, M.; Bryce, R. A.; Freeman, S. *J. Med. Chem.* **2005**, *48*, 392. (b) Yano, S.; Kazuno, H.; Suzuki, N.; Emura, T.; Wierzba, K.; Yamashita, J.-I.; Tada, Y.; Yamada, Y.; Fukushima, M.; Asao, T. *Bioorg. Med. Chem.* **2004**, *12*, 3431. (c) Yano, S.; Kazuno, H.; Sato, T.; Suzuki, N.; Emura, T.; Wierzba, K.; Yamashita, J.-I.; Tada, Y.; Yamada, Y.; Fukushima, M.; Asao, T. *Bioorg. Med. Chem.* **2004**, *12*, 3443. (d) Klein, R. S.; Lenzi, M.; Lim, T. H.; Hotchkiss, K. A.; Wilson, P.; Schwartz, E. L. *Biochem. Pharmacol.* **2001**, *62*, 1257. (e) Corelli, F.; Botta, M.; Lossani, A.; Pasquini, S.; Spadari, S.; Focher, F. *Farmaco* **2004**, *59*, 987.
(24) Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fisher, P. *Synthesis* **1991**, 483.