Development of an Efficient and Straightforward Methodology Toward the Synthesis of Molecularly Diverse 2,6-Disubstituted 3,4-Dihydropyrimidin-4(3*H*)-ones

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Abstract: A simple and efficient methodology toward the synthesis of highly molecularly diverse 2,6-disubstituted 3,4-dihydropyrimidin-4(3*H*)-ones of type **3** has been developed. The methodology is based on a selective O-alkylation reaction with *i*-PrOH under Mitsunobu conditions followed by a nucleophilic heteroaromatic *ipso*-substitution of sulfones **20** and subsequent acidic hydrolysis of the isopropoxy group.

Key words: 4(3*H*)-pyrimidinones, 4-isopropoxypyrimidines, selective O-alkylation, Mitsunobu reaction, *ipso*-substitution, selective acidic hydrolysis

Pyrimidin-4(3*H*)-ones of type **1** (Figure 1), are valuable scaffolds in different areas of research. Thus for instance, it has been described recently, that members of this class of compounds display potent and selective activity as non-nucleoside HIV-1 reverse transcriptase inhibitors.[1,2] Other members of this family of compounds have found utility as herbicides[3] and leishmanicides.[4] In addition, these types of substrates have served as suitable models to conduct studies on self-association[5] and their application to supramolecular synthesis.[6]

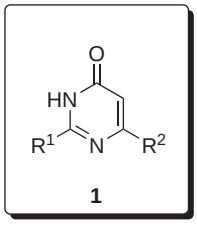

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Figure 1 The structure of pyrimidin-4(3*H*)-ones

In connection with our ongoing studies dealing with the development of efficient methodologies that could readily be adapted for the combinatorial and/or parallel synthesis, in solution and/or on solid supports of relevant core structures with potential therapeutic interest,[7–11] we needed to make use of a number of different molecularly diverse 4-pyrimidinones of type **1** to incorporate this structural motif into different types of libraries.[12]

Despite the wide variety of synthetic approaches available for the construction of the 4-pyrimidinone nucleus, the most direct and widely used methodology toward these type of substrates involves the cyclocondensation reaction between a bidentate nucleophilic fragment (e.g. urea, thiourea, guanidines or amidines) with 1,3-dicarbonyl derivatives (e.g. β-keto esters and related synthetic equivalents).[13] However, this method has some limitations due to the lack of availability of the corresponding bidentate fragments. This limitation prevents the introduction of a high degree of molecular diversity over the 2-position in these derivatives. To circumvent this problem, the alternative approach based on the nucleophilic displacement of alkylsulfanyl groups with different nucleophiles in 2-alkylsulfanylpyrimidones of type **2** has been used. However, due to the poor attitude of alkylsulfanyl groups as efficient leaving groups in these type of systems, this approach needs from harsh reaction conditions yielding the products **3** in generally low yields.[4,14] Activation of the thioether moiety through oxidation to sulfoxide **4** or sulfone **5** to facilitate nucleophilic displacement does not also solve the problem since **4** and/or **5** are too labile and the corresponding pyrimidine-2,4-diones **6** are obtained instead (Scheme 1).[15]

Within this context, we wished to identify and to develop a general, simple and efficient methodology that could afford collections of molecularly diverse 4-pyrimidinones of type **1** that in addition would allow the introduction of a wide variety of substitution patterns over the heterocyclic nucleus.

Recently, we reported on the synthesis of novel 2,6-disubstituted 4-alkoxypyrimidines starting from 2-alkylsulfanylpyrimidones of type **2**.[12] The method is based on a selective O-alkylation reaction in basic medium with sterically demanding alkylating agents like α-haloketones **7** and benefits from the key role played by the thioether linkage in a double sense. On the one hand the steric effect exerted by the bulky thioether moiety placed at the 2-position in pyrimidones of type **2** is likely to be responsible for the observed high selectivity toward the formation of the O-alkylation products. On the other hand, this sulfur linkage, serves as an efficient means for introducing additional molecular diversity through nucleophilic displacement of the corresponding activated sulfones **9** (Scheme 2).

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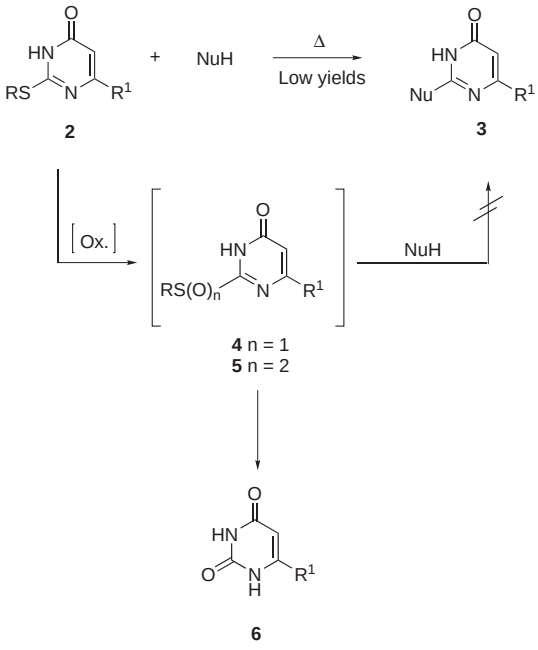
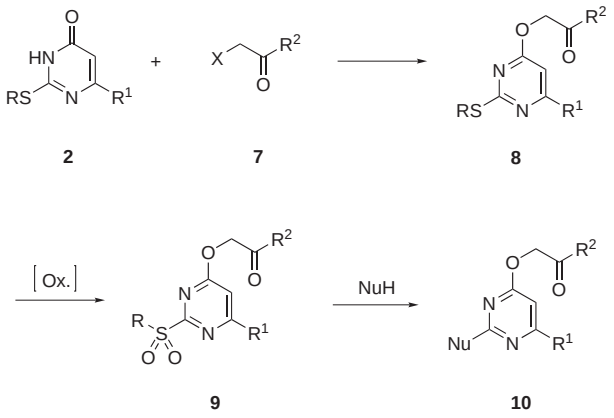


2 **3** **6**

Scheme 1

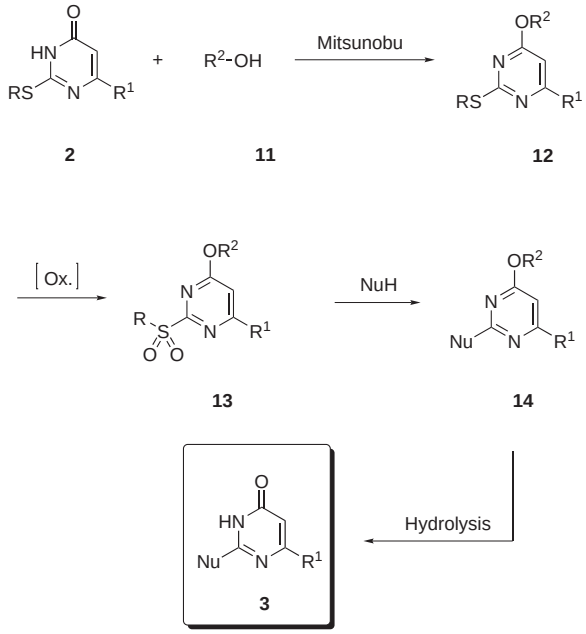


2 **7** **8** **9** **10**

Scheme 2

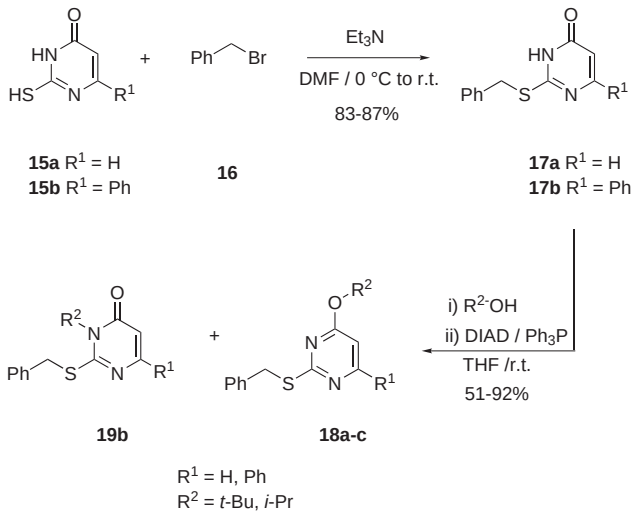
Based on these results, we reasoned that in complete analogy with the above-mentioned results, alkylation reaction with bulky aliphatic alcohols under Mitsunobu conditions should also lead selectively to O-alkylated pyrimidines **12**. Oxidation of the thioether moiety to the corresponding stable pyrimidine sulfone derivatives **13**, followed by nucleophilic *ipso*-substitution reaction with different nucleophiles and subsequent mild hydrolysis of the 4-alkoxy group would allow the formation of collections of target 4-pyrimidinones of type **3** (Scheme 3).

Consistent with this goal, *t*-BuOH and *i*-PrOH were initially selected as bulky aliphatic alcohols. Thus, starting from the readily available 2-sulfanylpyrimidin-4(3*H*)-ones **15a**,**b**, alkylation of the sulfanyl group with benzyl bromide in DMF in the presence of Et_3N afforded the corresponding pure thioether derivatives **17a**,**b** in 83–87% yield. Then, reaction with *t*-BuOH or *i*-PrOH under Mitsunobu conditions led to the formation of the corresponding 4-alkoxypyrimidine derivatives **18a**–**c** (Scheme 4, Table 1 and Table 2).



2 **11** **12** **13** **14** **3**

Scheme 3



15a R^1 = H, **15b** R^1 = Ph — **16** — **17a** R^1 = H, **17b** R^1 = Ph

19b **18a-c**

Scheme 4

The use of *t*-BuOH as alkylating reagent in the Mitsunobu reaction proceeded as expected with total selectivity affording exclusively the corresponding O-alkylated product **18a**. However, this reaction proceeded only in moderated yields (51%), and as much as a 48% of unreacted starting material **17a** was recovered from the reaction mixture (Table 1, entry 3). Better results were obtained however by using *i*-PrOH as alkylating reagent. The Mitsunobu reaction did proceed in high yields and with a high degree of selectivity, affording 4-isopropoxypyrimidines **18b**,**c** (Table 1, entries 4 and 6). Only in the case of **17a**, the formation of the corresponding N-alkylat-

Table 1 2-Benzylthiopyrimidin-4(3*H*)-ones **17a**,**b**, **19b** and 4-Alkoxypyrimidines **18a–c**

Entry	Product[a]	R^1	R^2	Yield (%)	Mp (°C)
1	**17a**	H	–	83	174–175
2	**17b**	Ph	–	85	243–244
3	**18a**	H	*t*-Bu	51	53–54
4	**18b**	H	*i*-Pr	88	colorless oil
5	**18c**	Ph	*i*-Pr	92	81–82
6	**19b**	H	*i*-Pr	4	94–95

[a] Satisfactory microanalyses obtained: C ±0.27, H ±0.28, N ±0.22, S ±0.25.

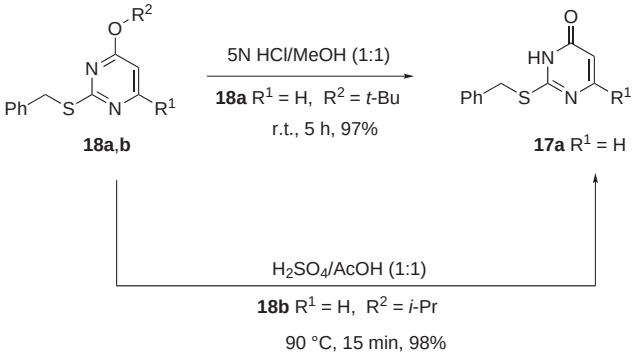
ed product **19b** was also detected, but in very small amounts (<4%) (Table 1, Entry 6).

Having established a good and highly selective methodology for the synthesis of 4-alkoxypyrimidines of type **18** via a Mitsunobu reaction type, before proceeding with our initially planned synthetic route toward pyrimidinones of type **3**, we focused our attention in the search for mild and reliable reaction conditions that could selectively cleave the 4-alkoxy group. Thus, we found that when 4-*tert*-butoxypyrimidine **18a** was treated with a 1:1 mixture of 5 N HCl/MeOH at room temperature for 5 hours, pyrimidinone **17a** was obtained quantitatively. When these conditions were applied to 4-isopropoxypyrimidine **18b**, the hydrolysis to **17a** proved to be unsuccessful. However, by treating **18b** with a 1:1 mixture of H_2SO_4–AcOH at 90 °C, the hydrolysis was essentially completed after 15 minutes (Scheme 5).

Table 2 MS, IR and NMR Data of 2-Benzylthiopyrimidin-4(3*H*)-ones **17a**,**b, 19b** and 4-Alkoxypyrimidines **18a**–**c**

Product	MS *m/z* (%)	IR (KBr) cm^{-1}	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
17a	220 ([M + 2]$^+$, 14), 219 ([M + 1]$^+$, 100), 218 (17), 185 (4), 167 (5), 165 (5)[a]	3030, 2790, 2698, 2620, 1664, 1557, 1457, 1275, 1227, 1177, 976, 930, 822, 707	4.50 (s, 2 H, PhCH_2S), 6.23 (d, 1 H_{pyrim}, *J* = 5.8), 7.40–7.50 (m, 5 H_{arom}), 8.01 (d, 1 H_{pyrim}, *J* = 5.6), 12.19 (br, 1 H, NH)[b]	33.7 (t, CH_2), 110.1 (d, CH_{pyrim}), 127.3, 128.5, 129.0 (3 d, 5 CH_{arom}), 137.1 (s, C_{arom}), 154.3 (d, CH_{pyrim}), 162.7 (s, C_{pyrim})[b]
17b	295 ([M + 1]$^+$, 37), 285 (95), 284 (14), 283 (100), 192 (40), 155 (19), 154 (81), 138 (27), 137 (50), 136 (80)[a]	2796, 2738, 2675, 1660, 1567, 1461, 1380, 1238, 1207, 1060, 987, 930, 840, 780, 700	4.64 (s, 2 H, PhCH_2S) 6.70 (s, 1 H_{pyrim}), 7.30–7.50 (m, 8 H_{arom}), 8.05–8.10 (m, 2 H_{arom}), 12.51 (br, 1 H, NH)[b]	33.8 (t, CH_2), 103.9 (d, CH_{pyrim}), 126.9, 127.3, 128.5, 128.7, 128.9, 130.6 (6 d, 10 CH_{arom}), 136.0, 137.4 (2 s, 2 C_{arom}), 160.3, 162.1, 163.9 (3 s, C_{pyrim})[b]
18a	274 ([M]$^{+\cdot}$, 12), 219 (40), 217 (99), 186 (44), 184 (100), 158 (32), 140 (51), 123 (25), 121 (49), 96 (49), 91 (89)[c]	3053, 2975, 2953, 1562, 1427, 1332, 1202, 1154, 973, 850, 687	1.61 (s, 9 H, *t*-C_4H_9), 4.45 (s, 2 H, PhCH_2S), 6.34 (d, 1 H_{pyrim}, *J* = 5.8), 7.30–7.50 (m, 5 H_{arom}), 8.23 [d, 1 H, *J* = 5.6, H(6)$_{pyrim}$]	28.3 (q, 3 CH_3), 35.3 (t, CH_2), 82.0 (s, C), 105.8 (d, CH_{pyrim}), 127.1, 128.5, 128.8 (3 d, 5 CH_{arom}), 137.0 (s, C_{arom}), 156.9 (d, CH_{pyrim}), 168.6, 170.4 (2 s, 2 C_{pyrim})
18b	261 ([M + 1]$^+$, 16), 260 (M$^+$, 75), 219 (18), 218 (81), 217 (32), 186 (34), 185 (100), 158 (33), 141 (20), 140 (32)[c]	3032, 2981, 2932, 1599, 1439, 1380, 1324, 1106, 979, 825, 707	1.38 [d, 6 H, *J* = 6.0, CH(CH_3)$_2$], 4.44 (s, 2 H, PhCH_2S), 5.40 (m, 1 H, *J* = 6, CH), 6.37 (d, 1 H_{pyrim}, *J* = 5.6), 7.30–7.50 (m, 5 H_{arom}), 8.24 (d, 1 H_{pyrim}, *J* = 5.6)	421.7 (q, 2 CH_3), 35.2 (t, CH_2), 69.4 (d, CH), 104.4 (d, CH_{pyrim}), 127.0, 128.4, 128.8 (3 d, 5 CH_{arom}), 137.5 (s, C_{arom}), 157.1 (d, CH_{pyrim}), 168.2, 171.0 (2 s, 2 C_{pyrim})
18c	336 ([M]$^{+\cdot}$, 90), 294 (97), 293 (40), 261 (100), 172 (64), 171 (42), 103 (28), 91 (99), 77 (22)[c]	3060, 2971, 2926, 1566, 1533, 1490, 1147, 1400, 1265, 1211, 1097, 993, 839, 690	1.38 [d, 6 H, *J* = 6.2, CH(CH_3)$_2$], 4.54 (s, 2 H, PhCH_2S), 5.46 (m, 1 H, *J* = 6.2, CH), 6.77 (s, 1 H_{pyrim}), 7.20–7.70 (m, 8 H_{arom}), 8.0–8.05 (s, 2 H_{arom})	21.9 (q, 2 CH_3), 35.4 (t, CH_2), 69.5 (d, CH), 99.7 (d, CH_{pyrim}), 127.0, 128.4, 128.5, 128.7, 128.8, 130.5 (6 d, 10 CH_{arom}), 136.8, 138.0 (2 s, 2 C_{arom}), 164.6, 169.4, 170.8 (3 s, 3 C_{pyrim})
19b	260 ([M]$^{+\cdot}$, 3), 186 (7), 185 (39), 171 (6), 170 (11), 169 (100)[c]	3062, 2971, 2936, 1682, 1576, 1491, 1403, 1305, 1230, 1183, 1136, 1067, 924, 827, 706	1.63 [d, 6 H, *J* = 6.6, CH(CH_3)$_2$], 4.43 (s, 2 H, PhCH_2S), 4.67 (m, 1 H, CH), 6.15 (d, 1 H_{pyrim}, *J* = 6.2), 7.30–7.50 (m, 5 H_{arom}), 7.71 (d, 1 H_{pyrim}, *J* = 6.2)	19.0 (q, 2 CH_3), 37.3 (t, CH_2), 58.0 (d, CH), 112.0 (d, CH_{pyrim}), 127.7, 128.6, 129.3 (3 d, 5 CH_{arom}), 135.6 (s, C_{arom}), 150.8 (d, CH_{pyrim}), 161.9, 162.6 (2 s, 2 C_{pyrim})

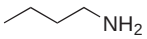
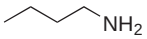
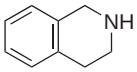
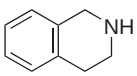
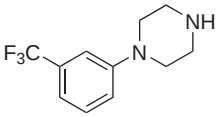
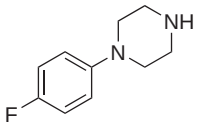
[a] Taken in the FAB$^+$ mode.
[b] NMR recorded in DMSO-d_6.
[c] Taken in the EI (70 eV) mode.



Scheme 5

With this good procedure in our hands for selective O-alkylation of 2-benzylthiopyrimidin-4(3*H*)-ones of type **17** with *i*-PrOH under Mitsunobu conditions and subsequent acidic hydrolysis, we then proceeded to complete our initial plans for the synthesis of collections of molecularly diverse pyrimidinones of type **3**. Thus, when **18b**,**c** were treated with 2.5 equivalents of *m*-CPBA, the corresponding sulfones **20a**,**b** were obtained in good yields (79–88%). These sulfones of type **20** were allowed to react in dioxane at 60 °C with a variety of N-nucleophiles (primary and secondary amines, **21a**–**d**) affording the corresponding *ipso*-substitution products **22a**–**f** in good yields (80–89%). Following acidic hydrolysis under the previously developed conditions of H_2SO_4–AcOH (1:1) at 90 °C yielded the corresponding target compounds **23a**–**f** also in good yields (84–88%) (Scheme 6, Tables 3– 6).

Table 3 4-Alkoxypyrimidine Sulfones **20a**,**b** and 4-Alkoxypyrimidines **22a**–**f** Prepared

Product[a]	R^1	R^2R^3NH	Yield (%)	Mp (°C)
20a	H	–	79	100–101
20b	Ph	–	88	124–125
22a	H		89	colorless oil
22b	Ph		82	colorless oil
22c	H		86	colorless oil
22d	Ph		85	colorless oil
22e	Ph		86	104–105
22f	H		80	57–58

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.26, N ±0.30.

Table 4 MS, IR and NMR Data of Pyrimidines **20a**,**b** and **22a**–**f**

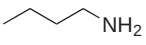
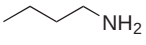
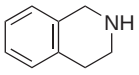
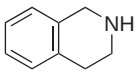
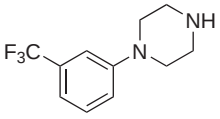
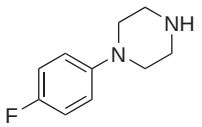
Product	MS *m*/*z* (%)	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
20a	293 ([M + 1]$^+$, 100), 294 (16), 295 (6), 251 (32), 188 (9), 187 (69), 185 (13), 165 (5)[a]	3079, 2986, 2939, 2886, 1584, 1530, 1451, 1319, 1246, 1128, 978, 842, 774, 706	1.38 [d, 6 H, *J* = 6.2, CH(CH_3)$_2$], 4.75 (s, 2 H, PhCH_2S), 5.48 (m, 1 H, *J* = 6.2, CH), 6.82 (d, 1 H_{pyrim}, *J* = 5.8), 7.30–7.55 (m, 5 H_{arom}), 8.54 (d, 1 H_{pyrim}, *J* = 5.8)	21.5 (q, 2 CH_3), 57.5 (t, CH_2), 71.6 (d, CH), 111.7 (d, CH_{pyrim}), 126.8 (s, C_{arom}), 128.6, 128.7, 131.1 (3 d, 5 CH_{arom}), 157.5 (d, CH_{pyrim}), 164.4, 169.7 (2 s, 2 C_{pyrim})
20b	368 ([M]$^{\cdot+}$, 67), 303 (58), 262 (63), 261 (95), 171 (68), 129 (40), 116 (38), 103 (62), 102 (40), 91 (100)[a]	3033, 2980, 2937, 2904, 1587, 1522, 1453, 1417, 1311, 1251, 1213, 1131, 978, 869, 776	1.43 [d, 6 H, *J* = 6.2, CH(CH_3)$_2$], 4.88 (s, 2 H, PhCH_2S), 5.66 (m, 1 H, *J* = 6.0, CH), 6.99 (s, 1 H_{pyrim}), 7.20–7.55 (m, 8 H_{arom}), 8.0–8.1 (m, 2 H_{arom})	21.7 (q, 2 CH_3), 57.3 (t, CH_2), 71.6 (d, CH), 106.0 (d, CH_{pyrim}), 127.1 (s, C_{arom}), 127.2, 128.2, 128.7, 128.8, 131.3, 131.6 (6 d, 10 CH_{arom}), 135.0 (s, C_{arom}), 164.7, 165.5, 170.9 (3 s, 3 C_{pyrim})
22a	210 ([M + 1]$^+$, 16), 209 (M$^+$, 75), 194 (16), 180 (31), 167 (81), 166 (100), 153 (61), 152 (43)[b]	3262, 2967, 2871, 1588, 1531, 1464, 1428, 1366, 1298, 1235, 1109, 981, 800	0.97 (t, 3 H, *J* = 7.2, CH_3), 1.35 [d, 6 H, *J* = 6.4, CH(CH_3)$_2$], 1.40–1.70 (m, 4 H, 2 CH_2), 3.42 (q, 2 H, *J* = 6.6, CH_2), 5.10 (br, 1 H, NH), 5.30–5.35 (m, 1 H, *J* = 6.4, CH), 5.94 (d, 1 H_{pyrim}, *J* = 5.6), 8.00 (d, 1 H_{pyrim}, *J* = 5.8)	13.8 (q, CH_3), 20.1 (t, CH_2), 21.8 (q, 2 CH_3), 31.8, 41.1 (2 t, 2 CH_2), 68.2 (d, CH), 97.5 (d, CH_{pyrim}), 158.0 (d, CH_{pyrim}), 162.6, 169.4 (2 s, 2 C_{pyrim})
22b	286 ([M + 1]$^+$, 1), 244 (100), 243 (7), 242 (5), 201 (6), 188 (6), 187 (7)[a]	3436, 3269, 2962, 2930, 2868, 1583, 1447, 1387, 1321, 1211, 1106, 770, 696	1.00 (t, 3 H, *J* = 7.2, CH_3), 1.40 [d, 6 H, *J* = 6.2, CH(CH_3)$_2$], 1.40–1.70 (m, 4 H, 2 CH_2), 3.52 (q, 2 H, *J* = 6.8, CH_2), 5.13 (br, 1 H, NH), 5.40–5.45 (m, 1 H, *J* = 6.4, CH), 6.40 (s, 1 H_{pyrim}), 7.30–7.50 (m, 3 H_{arom}), 7.75–8.00 (m, 2 H_{arom})	13.8 (q, CH_3), 20.1 (t, CH_2), 21.9 (q, 2 CH_3), 31.9, 41.2 (2 t, 2 CH_2), 68.6 (d, CH), 93.3 (d, CH_{pyrim}), 128.8, 128.5, 130.0 (3 d, 5 CH_{arom}), 137.5 (s, C_{arom}) 162.2, 164.9, 170.6 (3 s, 3 C_{pyrim})

Table 4 MS, IR and NMR Data of Pyrimidines **20a**,**b** and **22a–f** (continued)

Product	MS *m/z* (%)	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
22c	270 ($[M]^{+}$, 15), 269 (78), 228 (5), 227 (41), 226 (100), 212 (25)[b]	2979, 2927, 2844, 1580, 1497, 1445, 1342, 1299, 1238, 1088, 939, 799, 745	1.38 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 2.89 (t, 2 H, *J* = 5.8, CH_2), 4.08 (t, 2 H, *J* = 5.8, CH_2), 5.00 (s, 2 H, CH_2), 5.40–5.45 (m, 1 H, *J* = 6.2, CH), 5.99 (d, 1 H_{pyrim}, *J* = 5.8), 7.25–7.40 (m, 4 H_{arom}), 8.13 (d, 1 H_{pyrim}, *J* = 5.8)	21.9 (q, 2 CH_3), 28.9, 41.4, 46.2 (3 t, 3 CH_2), 68.2 (d, CH), 96.9 (d, CH_{pyrim}), 126.1, 126.2, 126.4, 128.5 (4 d, 4 CH_{arom}), 134.3, 135.2 (2 s, 2 C_{arom}), 157.8 (d, CH_{pyrim}), 161.4, 169.0 (2 s, 2 C_{pyrim})
22d	346 ($[M + 1]^{+}$, 1), 304 (100), 303 (19), 200 (17), 172 (9), 171 (14)[a]	3063, 3023, 2978, 2929, 2841, 1569, 1493, 1453, 1321, 1259, 1210, 1100, 979, 769, 695	1.44 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 3.01 (t, 2 H, *J* = 6.0, CH_2), 4.20 (t, 2 H, *J* = 6.0, CH_2), 5.07 (s, 2 H, CH_2), 5.45–5.50 (m, 1 H, *J* = 6.4, CH), 6.44 (s, 1 H_{pyrim}), 7.20–7.30 (m, 4 H_{arom}), 7.40–7.50 (m, 3 H_{arom}), 8.05–8.10 (m, 2 H_{arom})	22.0 (q, 2 CH_3), 29.0, 41.5, 46.3 (3 t, 3 CH_2), 68.3 (d, CH), 92.6 (d, CH_{pyrim}), 126.0, 126.1, 126.5, 126.9, 128.4, 128.6, 129.8 (7 d, 9 CH_{arom}), 134.6, 135.4, 138.3 (3 s, 3 C_{arom}), 161.6, 165.2, 170.3 (3 s, 3 C_{pyrim})
22e	442 ($[M]^{+}$, 12), 255 (13), 243 (21), 242 (89), 212 (19), 201 (26), 200 (100), 172 (23), 170 (24), 145 (13)[b]	2983, 2901, 2847, 1536, 1503, 1446, 1381, 1340, 1280, 1223, 1162, 1112, 962, 778, 698	1.43 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 3.37 (t, 4 H, *J* = 5.0, CH_2), 4.12 (t, 4 H, *J* = 5.0, CH_2), 5.41 (m 1 H, *J* = 6.0, CH), 6.46 (s, 1 H_{pyrim}), 7.15–7.45 (m, 7 H_{arom}), 7.95–8.05 (m, 2 H_{arom}).	22.0 (q, 2 CH_3), 43.7, 48.8 (2 t, 4 CH_2), 68.5 (d, CH), 93.2 (d, CH_{pyrim}), 112.5, 116.1, 119.0 (3 d, 3 CH_{arom}), 124.3 (s, CF_3), 126.9, 128.5, 129.6, 130.0 (4 d, 6 CH_{arom}), 131.5, 138.0, 151.6 (3 s, 3 C_{arom}), 161.7, 165.3, 170.4 (3 s, 3 C_{pyrim})
22f	316 ($[M]^{+}$, 17), 179 (23), 166 (73), 151 (27), 150 (22), 136 (24), 124 (100), 122 (32), 95 (27)[b]	2981, 2888, 2851, 2814, 1573, 1504, 1446, 1337, 1229, 1150, 1100, 1009, 949, 811	1.39 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 3.18 (t, 4 H, *J* = 5.2, CH_2), 3.98 (t, 4 H, *J* = 5.2, CH_2), 5.35 (m, 1 H, *J* = 6.2, CH), 5.99 (d, 1 H_{pyrim}, *J* = 5.6), 6.90–7.10 (m, 4 H_{arom}), 8.09 (d, 1 H_{pyrim}, *J* = 5.6)	21.8 (q, 2 CH_3), 43.8, 50.4 (2 t, 4 CH_2), 68.3 (d, CH), 97.5 (CH_{pyrim}), 115.6, 118.3 (2 d, 4 CH_{arom}), 148.1, 157.4 (2 s, 2 C_{arom}), 157.9 (d, CH_{pyrim}), 161.7, 169.2 (2 s, 2 C_{pyrim}).

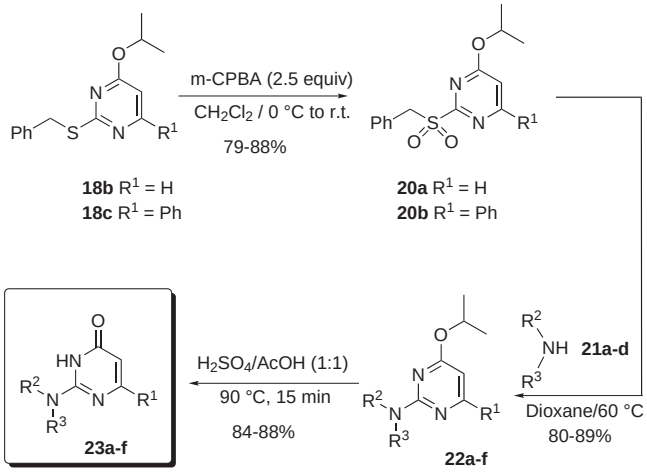
[a] Taken in the FAB^+ mode.
[b] Taken in the EI (70 eV) mode.

Table 5 2-Aminopyrimidin-4(3*H*)-ones **23a–f** Prepared

Product[a]	R	R^2R^3NH	Yield (%)	Mp (ºC)
23a	H		87	116–117
23b	Ph		86	180–181
23c	H		86	121–122
23d	Ph		84	183–184
23e	Ph		88	223–224
23f	H		84	227–228

[a] Satisfactory microanalyses obtainesd: C ±0.18, H ±0.21, N ±0.26.

With the aim of expanding this simple but efficient methodology toward molecularly diverse pyrimidinones of type **3**, we next addressed the problem of introducing at the 2-position in the heterocyclic nucleus other groups different than amines as in the case of compounds of type **23**. To achieve this goal, we then studied the nucleophilic *ipso*-substitution reaction of sulfones **20** with C-nucleophiles and O-nucleophiles and the subsequent hydrolysis. Thus, when compounds **20a**,**b** were prompted to react with methylmagnesium bromide (**24**) as C-nucleophile in diethyl ether at room temperature, the corresponding substitution products **25a**,**b** were obtained in 65–75% yields.



Scheme 6

Table 6 MS, IR and NMR Data of 2-Aminopyrimidin-4(3*H*)-ones **23a–f**

Product	MS *m/z* (%)[a]	IR (KBr) cm^{-1}	^1H NMR (DMSO-d_6/TMS) δ, *J* (Hz)	^{13}C NMR (DMSO-d_6/TMS) δ
23a	168 ([M + 1]$^+$, 100), 166 (3), 138 (2), 125 (2)	3157, 2956, 2931, 1665, 1613, 1613, 1577, 1475, 1350, 1294, 976, 801, 702	0.98 (t, 3 H, *J* = 7.2, CH_3), 1.30–1.60 (m, 4 H, 2 CH_2), 3.22 (t, 2 H, *J* = 6.0, CH_2), 5.60 (d, 1 H_{pyrim}, *J* = 6.6), 6.80 (br, 1 H, NH), 7.65 (d, 1 H_{pyrim}, *J* = 6.6), 11.0 (br, 1 H, NH)	13.7 (q, CH_3), 19.5, 31.0, 39.9 (3 t, 3 CH_2), 102.6 (d, CH_{pyrim}), 155.3 (d, CH_{pyrim}), 163.2 (s, C_{pyrim})
23b	244 ([M + 1]$^+$, 100), 243 (6), 242 (5), 201 (6), 188 (6), 187 (7)	3296, 3167, 2925, 2868, 1666, 1612, 1459, 1413, 1293, 974, 814, 698	1.03 (t, 3 H, *J* = 7.2, CH_3), 1.05–1.80 (m, 4 H, 2 CH_2), 3.60 (q, 2 H, *J* = 6.4, CH_2), 6.15 (br, 1 H, NH), 6.26 (s, 1 H_{pyrim}), 7.35–7.50 (m, 3 H_{arom}), 8.00–8.05 (m, 2 H_{arom}), 11.90 (br, 1 H, NH)	13.7 (q, CH_3), 19.5, 31.0, 39.9 (3 t, 3 CH_2), 97.3 (d, CH_{pyrim}), 126.6, 128.4, 129.9 (3 d, 5 CH_{arom}), 137.4 (s, C_{arom}), 154.5, 161.9, 163.5 (3 s, 3 C_{pyrim})
23c	227 ([M]$^{\cdot+}$, 100), 226 (41), 132 (52), 104 (38), 96 (49)	3102, 3021, 2928, 2868, 1658, 1568, 1490, 1445, 1369, 1208, 972, 807, 754	2.95 (t, 2 H, *J* = 5.8, CH_2), 3.94 (t, 2 H, *J* = 5.8, CH_2), 4.86 (s, 2 H, CH_2), 5.76 (d, 1 H_{pyrim}, *J* = 6.2). 7.2 (m, 4 H_{arom}), 7.84 (d, 1 H_{pyrim}, *J* = 6.2)	28.7, 41.8, 45.9 (3 t, 3 CH_2), 100.6 (d, CH_{pyrim}), 126.1, 126.2, 126.4, 128.4 (4 d, 4 CH_{arom}), 133.5, 134.6 (2 s, 2 C_{arom}), 156.4 (d, CH_{pyrim}), 164.3 (s, C_{pyrim})
23d	304 ([M + 1]$^+$, 100), 303 (19), 302 (36), 200 (17), 174 (6), 172 (9), 171 (12)	3057, 3019, 2954, 2927, 1644, 1570, 1491, 1448, 1384, 1232, 973, 748, 696	3.09 (t, 2 H, *J* = 5.8, CH_2), 4.10 (t, 2 H, *J* = 5.8, CH_2), 5.02 (s, 2 H, CH_2), 6.34 (s, 1 H_{pyrim}). 7.10–7.45 (m, 7 H_{arom}), 8.05–8.10 (m, 2 H_{arom}), 12.1 (br, 1H, NH)	27.9, 41.9, 46.0 (3 t, 3 CH_2), 95.4 (d, CH_{pyrim}), 126.1, 126.3, 126.4, 126.7, 128.4, 128.5, 130.1 (7 d, 9 CH_{arom}), 133.6, 134.7, 137.3 (3 s, 3 C_{arom}), 156.0, 162.4, 166.2 (3 s, 3 C_{pirim})
23e	401 ([M + 1]$^+$, 2), 339 (18), 291 (15), 205 (16), 203 (17), 191 (36), 189 (29), 177 (30), 165 (64)	3096, 2988, 2904, 2853, 1649, 1578, 1496, 1448, 1377, 1283, 1230, 1159, 1121, 955, 779, 696	3.44 (t, 4 H, *J* = 5.0, CH_2), 4.07 (t, 4 H, *J* = 5.0, CH_2), 6.38 (s,1 H_{pyrim}), 7.15–7.50 (m, 7 H_{arom}), 8.00–8.05 (m, 2 H_{arom}), 12.2 (br, 1H, NH)	43.8, 47.3 (2 t, 4 CH_2), 95.7 (d, CH_{pyrim}), 111.2, 114.9, 119.0 (3d, 3 CH_{arom}), 124.5 (s, CF_3), 126.7, 128.5, 130.2, 130.3 (4 d, 6 CH_{arom}), 130.4, 137.3, 151.1 (3 s, 3 C_{arom}), 162.5, 166.5, 172.1 (3 s, 3 C_{pyrim})
23f	275 ([M + 1]$^+$, 100), 274 (32), 273 (24), 154 (18), 150 (32), 138 (35), 137 (38), 136 (29)	3100, 2970, 2921, 2830, 1660, 1567, 1505, 1308, 1225, 1158, 970, 823	3.23 (t, 4 H, *J* = 5.0, CH_2), 3.88 (t, 4 H, *J* = 5.0, CH_2), 5.82 (d, 1 H_{pyrim}, *J* = 6.0), 7.15–7.25 (m, 4 H_{arom}), 7.87 (d, 1 H_{pyrim}, *J* = 6.0), 11.38 (br, 1H, NH)	44.3, 49.2 (2 t, 4 CH_2), 101.4 (d, CH_{pyrim}), 115.7, 118.0 (2 d, 4 CH_{arom}), 148.1, 156.7 (2 s, 2 C_{arom}), 156.9 (d, CH_{pyrim}), 165.5 (s, C_{pyrim})

[a] Taken in the FAB$^+$ mode.

Acidic hydrolysis under standard conditions afforded pyrimidinones **26a**,**b** in good yields. Analogous sequence using acetylide **27** in THF at –10 °C also afforded 4-isopropoxypyrimidines **28a**,**b** in good yields, although the subsequent hydrolysis gave final products **29a**,**b** in only moderate yields (Scheme 7, Tables 7 and 8).

In a similar fashion, when sulfones **20a**,**b** were allowed to react with different phenols **30a**,**b** in the presence of Cs_2CO_3 in dioxane at 60 °C, the corresponding 2-aryloxy-4-isopropoxypyrimidines **31a–d** were isolated in good yields. In addition, when compounds of type **31** were treated with a 1:1 mixture of H_2SO_4–AcOH at 90 °C during 15 min. the selective cleavage of the 4-isopropoxy group took place affording to 2-aryloxypyrimidinone derivatives **32a–d** in also good yields. (Scheme 8, Tables 9 and 10).

In summary, we have developed a simple and efficient methodology that allows the facile synthesis of a collection of 2,5-disubstituted pyrimidin-4(3*H*)-ones of type **3** with a high degree of molecular diversity. This methodology is based on the key role played by the 2-thioalkyl moiety in **17** in two ways. Due to the steric demand imposed by the thioether linkage, the O-alkylation reaction with bulky aliphatic alcohols under Mitsunobu conditions can

Table 7 Pyrimidines **25** and **28** and Pyrimidin-4(3*H*)-ones **26** and **29** Prepared

Entry	Product[a]	R^1	Yield (%)	Mp (°C)
1	**25a**	H	61	colorless oil
2	**25b**	Ph	75	colorless oil
3	**26a**	H	78	204–205
4	**26b**	Ph	82	240–241
5	**28a**	H	79	colorless oil
6	**28b**	Ph	97	colorless oil
7	**29a**	H	30	168–169
8	**29b**	Ph	38	188–189

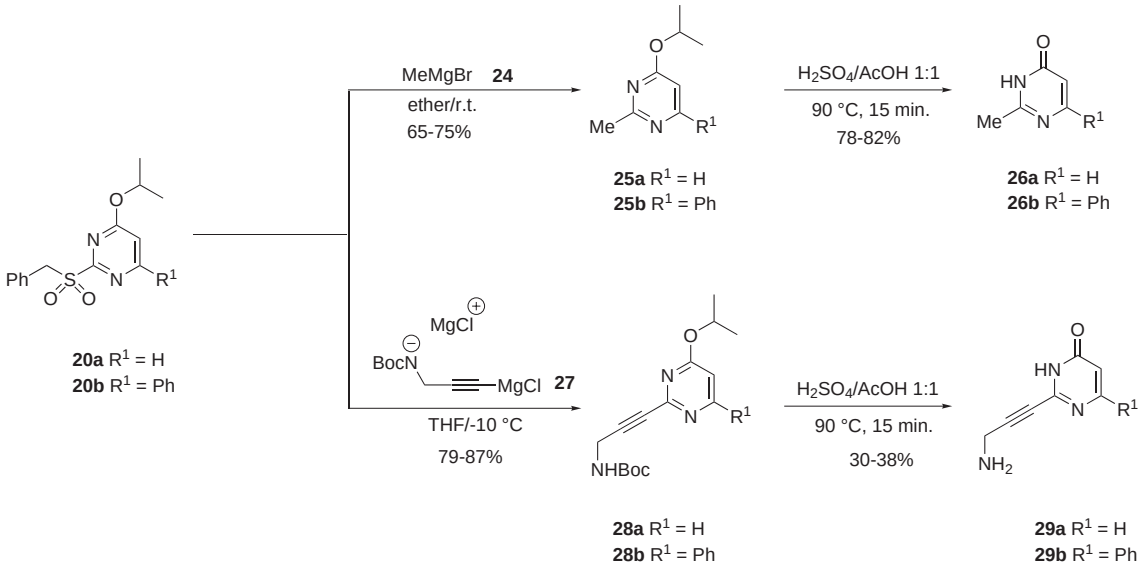
[a] Satisfactory microanalyses obtained: C ±0.22, H ±0.29, N ±0.26.

Table 8 MS, IR and NMR Data of Pyrimidines **25** and **28**, and 2-Substituted Pyrimidin-4(3*H*)-ones **26** and **29**

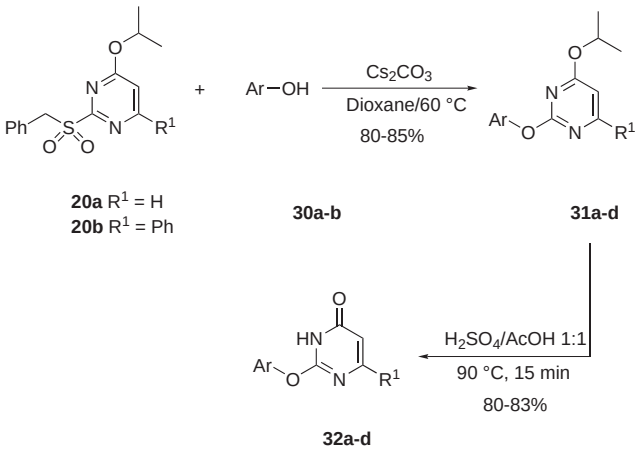
Product	MS *m/z* (%)[a]	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
25a	152 ($[M]^{+\cdot}$, 6), 111 (21), 110 (83), 95 (35), 94 (100), 93 (27), 82 (71), 69 (32)	2980, 2934, 1576, 1451, 1313, 1110, 1035, 986, 968, 829	1.37 [d, 6 H, *J* = 6.4, $CH(CH_3)_2$], 2.57 (s, 3 H, CH_3), 5.40 (m, 1 H, *J* = 6.4, CH), 6.45 (d, 1 H_{pyrim}, *J* = 5.8), 8.29 (d, 1 H_{pyrim}, *J* = 5.8)	21.7, 25.9 (2 q, 3 CH_3), 68.7 (d, CH), 105.6 (d, CH_{pyrim}), 156.9 (d, CH_{pyrim}), 167.9, 168.6 (2 s, 2 C_{pyrim})
25b	228 ($[M]^{+\cdot}$, 31), 213 (94), 187 (36), 186 (92), 185 (100), 170 (94), 158 (83), 129 (87), 128 (66), 104 (72), 102 (94)	2980, 2932, 1584, 1549, 1452, 1391, 324, 1210, 1111, 1052, 926, 695	1.42 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 2.70 (s, 3 H, CH_3), 5.49 (m, 1 H, *J* = 6.2, CH), 6.88 (s, 1 H_{pyrim}), 7.40–7.50 (m, 3 H_{arom}), 8.00–8.05 (m, 2 H_{arom})	21.9, 26.2 (2 q, 3 CH_3), 68.8 (d, CH), 100.9 (d, CH_{pyrim}), 127.0, 128.7, 130.1 (3 d, 5 CH_{arom}), 137.5 (s, C_{arom}), 164.9, 168.0, 169.8 (3 s, 3 C_{pyrim})
26a	110 ($[M]^{+\cdot}$, 100), 95 (5), 93 (3), 82 (32), 81 (9)	3088, 3007, 2926, 2849, 2766, 1681, 1602, 1467, 1422, 1307, 1219, 1096, 978, 929, 850	2.36 (s, 3 H, CH_3), 6.23 (d, 1 H_{pyrim}, *J* = 6.0), 7.89 (d, 1 H_{pyrim}, *J* = 6.0), 12.50 (br, NH)[b]	21.3 (q, CH_3), 112.8 (d, CH_{pyrim}), 154.4 (d, CH_{pyrim}), 160.0, 162.3 (2 s, 2 C_{pyrim})[b]
26b	186 ($[M]^{+\cdot}$, 100), 185 (64), 158 (25), 117 (19), 104 (33), 89 (13), 77 (16)	2990, 2868, 2845, 1655, 1612, 1184, 1120, 858, 781, 693	2.38 (s, 3 H, CH_3), 6.72 (s, 1 H_{pyrim}), 7.40–7.50 (m, 3 H_{arom}), 8.00–8.05 (m, 2 H_{arom}), 12.40 (br, NH)[b]	21.7 (q, CH_3), 106.8 (d, CH_{pyrim}), 126.9, 128.8, 130.5 (3 d, 5 CH_{arom}), 136.5 (s, C_{arom}), 159.3, 160.7, 163.2 (3 s, 3 C_{pyrim})[b]
28a	291 ($[M]^{+\cdot}$, 2), 191 (56), 190 (27), 176 (21), 149 (94), 148 (100), 133 (21), 121 (94), 120 (53)	3297br, 2980, 2934, 1714, 1574, 1421, 1375, 1319, 1236, 1157, 1105, 1105, 982, 934, 830	1.39 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 1.56 (s, 9 H, t-C_4H_9) 2.18 (t, 1 H, *J* = 2.4, NH), 4.68 (d, 2 H, *J* = 2.4, CH_2), 5.38 (m, 1 H, *J* = 6.2, CH), 6.40 (d, 1 H_{pyrim}, *J* = 5.8), 8.37 (d, 1 H_{pyrim}, *J* = 5.8)	21.8, 28.2 (2 q, 5 CH_3), 37.1 (t, CH_2), 69.6 (d, CH), 70.2, 80.4, 82.1 (3 s, 3 C), 104.1 (d, CH_{pyrim}), 152.6 (s, C=O), 157.8 (d, CH_{pyrim}), 159.2, 169.2 (2 s, 2 C_{pyrim})
28b	267 ($[M + 1]^+$, 21), 266 (70), 252 (17), 225 (37), 224 (100), 182 (36)	3297br, 2980, 2933, 1712, 1581, 1554, 1498, 1454, 1434, 1390, 1368, 1329, 1249, 1215, 1157, 1104, 995, 935, 854	1.44 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 1.61 (s, 9 H, t-C_4H_9) 2.20 (t, 1 H, *J* = 2.4, NH), 4.80 (d, 2 H, *J* = 2.4, CH_2), 5.48 (m, 1 H, *J* = 6.2, CH), 6.84 (s, 1 H_{pyrim}), 7.45–7.50 (m, 3 H_{arom}), 8.05–8.10 (m, 2 H_{arom})	22.0, 28.3 (2 q, 5 CH_3), 37.2 (t, CH_2), 69.6 (d, CH), 70.2, 80.6, 81.9 (3 s, 3 C), 99.1 (d, CH_{pyrim}), 127.0, 128.7, 130.5 (3 d, 5 CH_{arom}), 136.9 (s, C_{arom}), 153.1 (s, C=O), 159.2, 165.1, 170.4 (3 s, 3 C_{pyrim})
29a	150 ($[M + 1]^+$, 20), 149 ($[M]^{+\cdot}$, 100), 121 (25)	3117, 2957, 2869, 1649, 1589, 1508, 1459, 1382, 1302, 818	1.90–1.95 (m, 1 H, NH), 2.50-2.60 (m, 2 H, CH_2), 6.0 (d, 1 H_{pyrim}, *J* = 6.0), 6.79 (s, 1 H, NH), 8.19 (d, 1 H_{pyrim}, *J* = 6.0), 12.0 (br s, 1 H, NH)[b]	29.3 (t, CH_2), 73.9, 81,7 (2 s, C≡C), 107.4, 157.2 (2 d, 2 CH_{pyrim}), 161.8, (s, C_{pyrim}), 162.1 (s, C=O)[b]
29b	225 ($[M]^{+\cdot}$, 100), 224 (45), 207 (41), 197 (58), 196 (22), 129 (30), 102 (38), 77 (30)	3354, 3209, 3068, 2971, 2932, 2845, 1665, 1618, 1452, 1418, 1285, 1254, 984, 826, 721	3.25–3.30 (m, 1 H, NH), 4.25–4.30 (m, 2 H, CH_2), 6.32 (s, 1 H_{pyrim}), 6.94 (t, 1 H, *J* = 6.0, NH), 7.5–7.6 (m, 3 H_{arom}), 8.1–8.15 (m, 2 H_{arom}), 11.10 (br s, 1 H, NH)[b]	30.0 (t, CH_2), 73.1, 81.3 (2 s, C≡C), 98.2 (d, CH_{pyrim}), 126.7, 128.4, 130.1 (3 d, 5 CH_{arom}), 137.0 (s, C_{arom}), 153.9, 161.6, 163.4 (3 s, 3 C_{pyrim})[b]

[a] Taken in the EI (70 eV) mode.
[b] NMR recorded in DMSO-d_6.

be effected with a high degree of selectivity. Furthermore, this thioether linkage at the 2-position in 4-isopropoxypyrimidines of type **18** can be activated through the formation of the corresponding sulfones **20** toward a subsequent nucleophilic heteroaromatic *ipso*-substitution reaction with a wide variety of nucleophiles (e.g. N-, C-, and O-nucleophiles). This latter reaction allows the introduction of additional molecular diversity over the heterocyclic nucleus. Finally the high degree of selectivity observed for the cleavage of the 4-isopropoxy group in pyrimidines of type **22**, **25**, **28** and even in those of type **31** is of remarkable importance for the successful accomplishment of the synthesis of pyrimidinones of type **3**. The methodology described herein should also be useful for the synthesis of more elaborated, biologically relevant pyrimidine-4(3*H*)-one derivatives. Synthetic studies along this line are being pursued in our laboratory and the results will be published in due course.

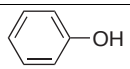
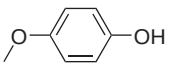
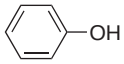
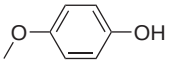


Scheme 7



Scheme 8

Table 9 Pyrimidines **31** and 2-Aryloxypyrimidin-4(3*H*)-ones **32** Prepared

Product[a]	R^1	ArOH	Yield (%)	mp (°C)
31a	H		80	colorless oil
31b	Ph		80	68–69
31c	H		89	colorless oil
31d	Ph		85	85–86
32a	H		81	203–204
32b	Ph		80	263–264
32c	H		82	240–241
32d	Ph		83	202–203

[a] Satisfactory microanalyses obtained: C ±0.24, H ±0.30, N ±0.19.

All commercially available chemicals were used as purchased, except DMF that was dried over activated molecular sieves (4 Å) and THF and Et_2O that were dried over Na/benzophenone prior to use. All reactions were run under a positive pressure of dry N_2. Melting points (capillary tube) were measured with an electrothermal digital melting point apparatus IA 9100 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Bruker DPX200 Advance instrument with TMS as the internal standard. MS spectra were recorded on a VG Quattro instrument in the positive ionisation FAB mode, using 3-NBA or 1-thioglycerol as the matrix or in a Thermo Quest 2000 series apparatus for the EI (70 eV) mode. Elemental analyses were performed on an apparatus from Thermo instruments, model EA1110-CHNS. Analytical TLC was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). Flash-chromatography purifications were performed on silica gel 60 (230–400 mesh, Merck).

2-Thiobenzylpyrimidin-4(3*H*)-ones 17a,b; General Procedure

To a suspension of the corresponding 2-mercaptopyrimidin-4(3*H*)-one **15a**,**b** (1 equiv) in anhyd DMF (3 mL/mmol) was added Et_3N (1.2 equiv). The mixture was stirred at r.t. for 15–20 min. Benzyl bromide (1.2 equiv) was added, and the mixture was stirred at r.t. for an additional 4 h. After this period, the white solid that precipitated was collected by filtration and washed sequentially with small portions of H_2O, MeOH and Et_2O and then dried in high vacuum. Compounds **17a**,**b** were obtained with enough purity to be used in the next step without further purification (Tables 1 and 2).

Mitsunobu Reaction of 17a,b; 4-Alkoxypyrimidines 18a–c and Pyrimidinone 19b; General Procedure (Mitsunobu)

A solution of diisopropyl azodicarboxylate (DIAD, 1.2 equiv) in anhyd THF (1 mL/mmol) was added dropwise at r.t. to a THF solution (2 mL/mmol) of Ph_3P (1.2 equiv), the appropriate 2-benzylthiopyrimidine **17a**,**b** (1 equiv) and *t*-BuOH or *i*-PrOH (1.2 equiv). The reaction mixture was stirred at r.t. during 2 h. The solvent was evaporated under reduced pressure, and the crude mixture separated by flash chromatography to give the products **18a–c** and **19b** (Tables 1 and 2).

Oxidation of 18b,c to Sulfones 20a,b; General Procedure

To a cooled (0 °C) solution of the corresponding pyrimidine derivatives **18b**,**c** (1 equiv) in CH_2Cl_2 (5 mL/mmol), was added *m*-CPBA (2.5 equiv) in small portions. The mixture was stirred at 0 °C for 2 h, diluted with CH_2Cl_2 (20 mL per mmol) and washed with aq sat. $NaHCO_3$ solution (2 × 5 mL/mmol) and brine (5 mL/mmol). The

Table 10 MS, IR and NMR Data of Pyrimidines **31** and 2-Aryloxypyrimidin-4(3*H*)-ones **32**

Product	MS *m/z* (%)	IR (KBr) cm^{-1}	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
31a	230 ($[M]^{+}$, 6), 189 (12), 188 (74), 187 (23), 173 (10), 172 (73), 146 (34), 145 (100), 144 (26) [a]	2981, 2930, 1584, 1564, 1491, 1456, 1383, 1275, 1209, 1045, 692	1.34 [d, 6 H, *J* = 6.4, $CH(CH_3)_2$], 5.28 (m, 1 H, *J* = 6.4, CH), 6.41 (d, 1 H_{pyrim}, *J* = 5.6), 7.20–7.50 (m, 5 H_{arom}), 8.20 (d, 1 H_{pyrim}, *J* = 5.6)	21.6 (q, 2 CH_3), 69.9 (d, CH), 103.7 (d, CH_{pyrim}), 121.7, 125.2, 129.3 (3 d, 5 CH_{arom}), 152.9 (s, C_{arom}), 158.5 (d, CH_{pyrim}, 165.0, 170.9 (3 s, 3 C_{pyrim})
31b	306 ($[M]^{+}$, 24), 305 (57), 264 (69), 263 (62), 248 (68), 222 (57), 221 (61), 192 (100), 103 (60)[a]	2979, 2929, 1588, 1551, 1489, 1455, 1358, 1321, 1211, 1065, 936, 767, 689	1.34 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 5.28 (m, 1 H, *J* = 6.2, CH), 6.84 (s, 1 H_{pyrim}), 7.30–7.50 (m, 8 H_{arom}), 7.95–8.00 (m, 2 H_{arom})	21.8 (q, 2 CH_3), 69.9 (d, CH), 98.6 (d, CH_{pyrim}), 121.9, 124.8, 127.0, 128.7, 129.1, 130.6 (6 d, 10 CH_{arom}), 136.5, 153.2 (2 s, 2 C_{arom}), 165.0, 166.4, 171.9 (3 s, 3 C_{pyrim})
31c	260 ($[M]^{+}$, 55), 218 (49), 202 (56), 176 (42), 175 (100), 160 (71), 132 (54), 123 (65), 95 (64)[a]	2983, 2944, 1579, 1507, 1457, 1368, 1330, 1279, 1237, 1205, 1042, 830	1.35 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 3.84 (s, 3 H, CH_3O), 5.34 (m, 1 H, *J* = 6.2, CH), 6.39 (d, 1 H_{pyrim}, *J* = 5.8), 6.95 (d, 2 H_{arom}, *J* = 8.8), 7.14 (d, 2 H_{arom}, *J* = 8.8), 8.19 (d, 1 H_{pyrim}, *J* = 5.8)	21.7, 55.5 (2 q, 3 CH_3), 68.9 (d, CH), 103.6 (d, CH_{pyrim}), 114.4, 122.6 (2 d, 4 CH_{arom}), 146.4, 156.8 (2 s, 2 C_{arom}), 158.5 (d, CH_{pyrim}), 165.4, 171.0 (2 s, 2 C_{pyrim})
31d	336 ($[M]^{+}$, 76), 335 (65), 294 (53), 251 (100), 236 (57), 223 (59), 208 (64), 123 (74), 103 (61)[a]	2975, 2935, 1587, 1505, 1454, 1359, 1317, 1208, 1105, 1066, 1034, 937, 828, 770	1.35 [d, 6 H, *J* = 6.2, $CH(CH_3)_2$], 3.87 (s, 3 H, CH_3O), 5.30 (m, 1 H, *J* = 6.2, CH), 6.83 (s, 1 H_{pyrim}), 6.97 (d, 2 H_{arom}, *J* = 9.0), 7.22 (d, 2 H_{arom}, *J* = 9.0), 7.95–8.00 (m, 2 H_{arom})	21.8, 55.6 (2 q, 3 CH_3), 69.6 (d, CH), 98.5 (d, CH_{pyrim}), 114.8, 122.7, 127.0, 128.7, 130.6 (5 d, 9 CH_{arom}), 136.5, 146.8, 156.6 (3 s, 3 C_{arom}), 165.3, 166.4, 171.9 (3 s, 3 C_{pyrim})
32a	189 ($[M + 1]^{+}$, 100), 154 (12), 138 (8), 137 (15), 136 (21), 133 (8), 139 (7)[b]	3080, 1645, 1621, 1582, 1536, 1495, 1363, 1266, 1198, 828, 785, 742	6.12 (d, 1 H_{pyrim}, *J* = 6.4), 7.10–7.60 (m, 5 H_{arom}), 7.74 (d, 1 H_{pyrim}), 12.70 (br, NH)[c]	108.5 (d, CH_{pyrim}), 121.8, 125.8, 129.6 (3 d, 5 CH_{arom}), 151.5 (s, C_{arom}), 154.0 (d, CH_{pyrim}), 158.9, 165.0 (2 s, 2 C_{pyrim})[c]
32b	264 ($[M]^{+}$, 54), 263 (21), 221 (26), 194 (26), 193 (100), 180 (21), 116 (29), 103 (44), 89 (25), 77 (56)[a]	3060, 2995, 2847, 2750, 1669, 1615, 1580, 1533, 1488, 1323, 1202, 973, 775	6.74 (s, 1 H_{pyrim}), 7.30–7.55 (m, 8 H_{arom}), 7.80–7.85 (m, 2 H_{arom}), 12.75 (br, NH)[c]	102.4 (d, CH_{pyrim}), 121.7, 125.7, 126.6, 128.8, 129.5, 130.6 (6 d, 10 CH_{arom}), 135.8, 151.8 (2 s, 2 C_{arom}), 158.7, 161.4, 166.0 (3 s, 3 C_{pyrim})[c]
32c	218 ($[M]^{+}$, 18), 185 (23), 175 (37), 167 (36), 149 (100), 124 (20), 109 (25)[a]	3081, 3043, 2957, 2711, 2590, 2533, 1649, 1606, 1540, 1496, 1360, 1247, 1196, 1035, 831	3.87 (s, 3 H, CH_3O), 6.17 (d, 1 H_{pyrim}, *J* = 6.4), 7.06 (d, 2 H_{arom}, *J* = 9.0), 7.26 (d, 2 H_{arom}, *J* = 9.0), 7.80 (d, 1 H_{pyrim}, *J* = 6.4), 12.80 (br, NH)[c]	55.4 (q, CH_3O), 108.5 (d, CH_{pyrim}), 114.5, 122.7 (2 d, 4 CH_{arom}), 144.8 (s, C_{arom}), 153.9 (d, CH_{pyrim}), 156.9 (s, C_{arom}), 159.0, 164.7 (2 s, 2 C_{pyrim})[c]
32d	294 ($[M]^{+}$, 85), 251 (100), 208 (41), 207 (50), 149 (35), 124 (85), 116 (41), 109 (57), 103 (70), 89 (35), 77 (71)[a]	2922, 2841, 2750, 1673, 1613, 1500, 1451, 1321, 1242, 1198, 1034, 973, 774	3.42 (s, 3 H, CH_3O), 6.80 (s, 1 H_{pyrim}), 7.12 (d, 2 H_{arom}, *J* = 7.8), 7.36 (d, 2 H_{arom}, *J* = 7.8), 7.40–7.50 (m, 3 H_{arom}), 7.95–8.00 (m, 2 H_{arom}), 12.80 (br, NH)[c]	55.4 (q, CH_3O), 102.5 (d, CH_{pyrim}), 114.4, 119.6, 122.6, 126.6, 128.6, 130.5, (5 d, 9 CH_{arom}), 135.8, 145.0, 156.7 (3 s, 3 C_{arom}), 158.5, 161.3, 165.6 (3 s, 3 C_{pyrim})[c]

[a] Taken in the EI (70 eV) mode.
[b] Taken in the FAB^+ mode.
[c] NMR recorded in DMSO-d_6.

separated organic layer was dried ($MgSO_4$), filtered and evaporated. The resulting crude material was purified by flash chromatography (*n*-hexane–EtOAc; Tables 3 and 4).

ipso-Substitution Reaction of Sulfone Derivatives 20a,b with Primary and Secondary Amines; 4-Alkoxypyrimidines 22a–f; General Procedure

To a solution of the corresponding pyrimidinyl sulfone **20a**,**b** (1 mmol) in dioxane (3 mL) was added the corresponding primary or secondary amine **21a**–**d** (1.1 mmol). The reaction mixture was stirred well and heated at 80 °C during 15 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane–EtOAc) to afford pure **22a**–**f**. (Tables 3 and 4).

Removal of the 4-Isopropoxy Group with H_2SO_4–AcOH; Pyrimidin-4(3*H*)-ones 23a–f, 26a,b, 29a,b and 32a–d; General Procedure

The appropriate 4-isopropoxypyrimidine **22**, **25** and **28** (1 equiv) was added to a mixture of AcOH (2 mL per mmol) and conc. H_2SO_4 (2 mL per mmol). The reaction mixture was stirred at 90 °C for 15 min. After cooling, the mixture was neutralized with aq 5 N NaOH

and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine and the separated organic layer was dried (MgSO4), filtered and eliminated under reduced pressure to afford the corresponding pure pyrimidinones **23**, **26** and **32** (Tables 5– 10).

***ipso*-Substitution Reaction of Sulfones 20a,b with MeMgBr; General Procedure**

To a cooled (0 °C) solution of the corresponding pyrimidinyl sulfone **20a**,**b** (1 mmol) in anhyd Et_2O (3 mL) was added dropwise a solution of MeMgBr (**24**; 1.1 mmol, 0.37 mL, 3 M in Et_2O) at 0 °C under N_2. After stirring for 1 h at 0 °C, the mixture was diluted with Et_2O (20 mL) and washed with H_2O (2 × 10 mL) and brine (10 mL). The separated organic layer was dried ($MgSO_4$), filtered and evaporated to give a residue with was purified by flash chromatography using *n*-hexane–EtOAc as eluent (Tables 7 and 8).

***ipso*-Substitution Reaction of Sulfones 20a,b with Acetylide 27; General Procedure**

To a cooled (–10 °C) solution of *N*-Boc-propargylamine (1.1 mmol) in anhyd THF (1.5 mL) was added dropwise a solution of *i*-PrMgCl (1.1 mL, 2 M in THF, 2.2 mmol). After stirring for 30 min at –15 °C, a solution of the corresponding sulfone **20a**,**b** (1 mmol) in THF (2 mL) was added. The resulting mixture was stirred from –10 °C to r.t. for 4 h. The mixture was evaporated to dryness, and the residue was acidified with aq 2 M HCl and extracted with EtOAc. The organic phase was separated, washed with brine (10 mL), dried ($MgSO_4$) and evaporated to give a crude material **28a**,**b** that was purified by flash chromatography using *n*-hexane–EtOAc as eluent (Tables 7 and 8).

***ipso*-Substitution Reaction of Sulfones 20a,b with Phenols 30a,b; General Procedure**

To a solution of the corresponding phenol **30a**,**b** (1.05 mmol) in 1,4-dioxane (3 mL) was added Cs_2CO_3 (1.1 mmol). The reaction mixture was stirred at r.t. for 15–20 min. Then, the appropriate sulfone **20a**,**b** (1 mmol) was added. The mixture was stirred at 60 °C for 3 h and then evaporated until dryness. The resulting crude material was acidified with aq 2 M HCl and extracted with EtOAc. The organic phase was separated, washed with brine (10 mL), dried ($MgSO_4$) and evaporated to give a crude material **31a–d** that was purified by flash chromatography using *n*-hexane–EtOAc as eluent (Tables 9 and 10).

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